Medicom International Conference Series in Neurology

Check out the EAN 2020 Medicom Podcast

6th EAN Congress

European Academy of Neurology

23-26 MAY 2020

PEER-REVIEWED CONFERENCE REPORT

Long-term safety of ND0612 in Parkinson's disease

Long-term safety of the subcutaneous levodopa/carbidopa solution ND0612 was established in Parkinson's disease patients with motor fluctuations, as demonstrated in the BeyoND study.

read more on PAGE 9

Reassuring real-world safety profile of CGRP inhibitors

The 3 CGRP inhibitors approved for the prevention of migraine —erenumab, fremanezumab, and galcanezumab— showed a reassuring safety profile in a real-world setting.

read more on PAGE 13

CASTING trial: high 2-year NEDA rates

In the CASTING trial of ocrelizumab in multiple sclerosis, the proportion of patients with NEDA at year 2 was high. NEDA was maintained from year 1 over year 2.

read more on PAGE 18

MEDICOM MEDICAL PUBLISHERS

Editor Prof. Hans-Peter Hartung, Heinrich-Heine University Düsseldorf, Germany

Contents

COLOPHON

Editor Prof. Hans-Peter Hartung
Department of Neurology, Heinrich-Heine University Düsseldorf, Germany

Advisory Board Prof. Marinos Dalakas
Thomas Jefferson University, Philadelphia, USA

Prof. Stefan Schwab
University Hospital Erlangen, Germany

Publishing Director Paul Willers
Editorial Manager Lisa Colson
Editorial Coordinators Deirdre Boucherie
Dr Joery Goossens
Medical Writer Michiel Tent
Production Manager Desiree Heijl
Graphic Design MOOZ grafisch ontwerp
ISSN 2468-8762 20:3

MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Main reviewers of this report

Prof. Marinos Dalakas

Biography

Marinos Dalakas is Professor of Neurology and Director of the Neuromuscular Division at the Thomas Jefferson University School of Medicine, Philadelphia, USA since 2007. He is also Professor of Neurology and Director of the Neuroimmunology Unit at the University of Athens Medical School in Greece since 2007.

Prior faculty appointments include Senior Investigator in Neuroimmunology and Neurovirology at National Institutes of Health (NIH) Bethesda, Maryland; Chief of the Neuromuscular Diseases Section, National Institute of Neurological Disorders (NIH NINDS), Bethesda; Chair of Clinical Neuroscience, Neuromuscular Diseases at Imperial College London; and Professor and Chair of Neurology at the University of Athens Medical School.

Dr Dalakas' research interest includes neuroimmunology and neuro-immunotherapies. He has a special interest in autoimmune and viral-related myopathies and neuropathies, demyelinating disorders of the central and peripheral nervous system, CNS-excitability disorders, stiff-person syndrome, autoimmune encephalitis, myasthenia gravis, and intravenous immunoglobulin in neurology.

He has received numerous national and international awards. He is the author or co-author of more than 650 peer- reviewed papers or reviews in high impact Journals. He serves on the Editorial Board of major Neurology Journals, like Neurology and Annals of Neurology. He is the Associate Editor for Neurology, Neuroimmunology, Neuroinflammation and Therapeutic Advances of Neurology.

Conflict of Interest Statement:
Dr Dalakas serves as Associate Editor for Neurology, Neuroimmunology, Neuroinflammation, and TAND. He serves as Chair of the Data Monitoring Committee for chronic inflammatory demyelinating polyneuropathy trials by Octapharma and Takeda. He received a consulting fee from Dysimmune Diseases Foundation and honorarium by writing commentaries for Elsevier and Neurodiem.

Prof. Stefan Schwab

Biography

Stefan Schwab is Professor of Neurology and Director and Chair of the Department of Neurology at the Friedrich-Alexander University Erlangen-Nuremberg, Germany.

Prior to joining the University of Erlangen-Nuremberg, he received his training at the Department of Neurology in Würzburg, Aachen, and Heidelberg, Germany as well as Johns-Hopkins University, Baltimore. In Heidelberg he was an associate Professor and vice-chairman at the Department of Neurology. He initiated several path breaking studies on decompressive surgery in MCA-infarction, as well as on hypothermia in ischaemic stroke.

Dr Schwab's main interest is improving stroke therapy and diagnosis, neurocritical care, and developing new treatment strategies for severe cerebral ischaemia as well as neuroprotection and regulation of blood flow and metabolism. He was several times president of the German Neurocritical care society (DGNI) and has been president of the German Critical Care Society (DIVI). His work was honoured with numerous national and international awards. He is an honorary member of the French Neurological Society, and honorary and visiting professor of Universities in Brazil, Philippines, and Chile.

Dr Schwab has authored and co-authored more than 400 publications in journals as Stroke, Lancet Neurology, JAMA, Annals of Neurology, Neurology, Critical care Medicine, and numerous other prestigious journals. He is the editor of several books and author of more than 40 book chapters.

Conflict of Interest Statement:
Dr Schwab received speakers' honoraria from Boehringer Ingelheim Pharma GmbH & Co.KG, Pfizer Pharma GmbH, Daiichi-Sankyo Deutschland GmbH, and Portola Pharmaceuticals. He serves on the Advisory Board of Boehringer Ingelheim Pharma GmbH & Co. KG and Novartis Pharma GmbH.

Letter from the Editor

Prof. Hans-Peter Hartung

Dear colleagues,

The 6th Congress of the European Academy of Neurology (EAN) was supposed to be held in Paris May 23-May 26, 2020. In the wake of the COVID-19 pandemic, like many other congresses before and after, with little preparation the meeting had to go virtual.

More than 42,500 neurologists registered for this virtual event that highlighted research from all areas of neurology. In response to the COVID-19 pandemic, very recent data were presented on an EAN survey on neurological symptoms. The EAN also has set up a neuroCOVID registry to gather information on clinical characteristics, management, and outcome.

This report tries to provide an overview of the most relevant contributions presented at EAN virtual 2020.

Hans-Peter Hartung, MD FRCP FAAN FANA FEAN
Professor and Chairman

Biography

Prof. Hartung has been chair of the Department of Neurology at Heinrich-Heine University Düsseldorf since 2001. He was also appointed director of the Center for Neurology and Neuropsychiatry in 2012 and Medical Director of the Department of Conservative Medicine.
Prof. Hartung received his undergraduate training at the Universities of Düsseldorf, Glasgow, Oxford, and London. After graduating *magna cum laude* he served an immunology fellowship at the University of Mainz. His clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies.
He has been involved as member of the Steering Committee in numerous international multi-centre therapeutic phase 2 and 3 trials in Multiple Sclerosis, Guillain-Barré Syndrome, and chronic inflammatory demyelinating polyneuropathy.
He is former President of ECTRIMS and is a Fellow of the American Academy of Neurology, Fellow and general assembly member of the EAN, has been chair/member of the management group of the EAN scientific panels on general neurology and multiple sclerosis, amongst others. He is/was also member of the Editorial Board of a number of international journals.

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.

Alzheimer's Disease and Other Dementias

Non-Alzheimer's disease pathophysiology in the elderly

Primary central nervous system pathologies leading to cognitive decline include a variety of only partially known conditions that can coexist to various extents with Alzheimer's disease (AD) pathology. Availability of biomarkers as well as clinical profiling is still limited. In a lecture, Prof. Philip Scheltens (Amsterdam UMC, the Netherlands) focused on suspected non-Alzheimer's disease pathophysiology (SNAP) [1].

Prof. Scheltens explained that SNAP is a biomarker-based concept denoting AD-like neurodegeneration in individuals without β-amyloidosis. Its prevalence is 20-30% in cognitive healthy individuals; it accounts for 20-40% of patients presenting to memory clinics. SNAP may be caused by cerebrovascular disorders, mixed pathologies (dementia with Lewy bodies, frontotemporal lobar degeneration), or non-AD neurodegeneration, such as primary age-related tauopathy (PART) and limbic-predominant age-related TDP-43 encephalopathy (LATE).

In the ATN system of the National Institute on Ageing-Alzheimer's Association (NIA-AA), 8 major AD biomarkers are divided into 3 pathophysiology-based binary categories. "A" refers to the value of a β-amyloid biomarker (amyloid-PET or cerebrospinal fluid [CSF] $A\beta_{1-42}$); "T," the value of a tau biomarker (CSF phosphorylated tau, or tau-PET); and "N," biomarkers of neurodegeneration or neuronal injury ([^{18}F]-fluorodeoxyglucose-PET, structural MRI, CSF total tau, or neurofilament light chain).

AD risk in individuals with SNAP or with A-T-N- is almost equal. In individuals with mild cognitive impairment (MCI), however, SNAP predicts progression to AD, with a highly variable percentage. In a Dutch study, 3-year progression from SNAP with MCI to AD was 24%, 4 times higher than cognitive healthy individuals [2].

Prof. Scheltens argued that the concept of SNAP is still useful, but that it is now referred to as "non-AD pathophysiology". This concept is part of a research framework (see Table) proposed by the NIA-AA to define AD pathologies based on ATN profiles [3].

Table. ATN-profiles and corresponding biomarker categories [3].

ATN-profiles	Biomarker category	
A-T-N-	Normal AD biomarkers	
A+T-N-	AD pathophysiology	AD pathophysiological continuum
A+T-N+	AD pathophysiology	
A+T+N-	AD	
A+T+N+	AD	
A-T+N-	Non-AD pathophysiology	
A-T-N+	Non-AD pathophysiology	
A-T+N+	Non-AD pathophysiology	

1. Scheltens F. Symposium SYMP08, EAN 2020.
2. Vos SJB, et al. Brain. 2015;138(Pt 5):1327-38.
3. Jack Jr CR, et al. Alzheimers Dement. 2018;14(4):535-62.

Novel genetic association with resistance to ERC tau deposition

A novel genetic association with resistance to entorhinal cortex (ERC) tau deposition in older adults has been identified [1]. Results of a genome-wide association study of tau-PET also suggest that tau deposition may have a genetic architecture distinct from known Alzheimer's disease (AD) risk genes.

The study included 754 participants from the Mayo Clinic Study of Aging with genome-wide genotype and regional tau-PET (AV-1451) data. The mean age was 72.4 years, 54.6% were male, and 87.4% were cognitively impaired. A genome-wide association study of tau burden of the ERC (a sensitive marker of early tau deposition) was performed of 515,206 single nucleotide polymorphisms (SNPs) following genotyping with the Illumina GSA array. A post-hoc stratified analysis utilised amyloid-PET positivity (global PiB >1.48) as a discriminator.
A genome-wide significant association was found for rs75546066, in an intergenic region on chromosome 9. The minor allele (A, frequency 2.7%) was associated with lower ERC tau ($P=2.85 \cdot 10^{-8}$; β=-0.49). The effect was stronger in amyloid-negative versus amyloid-positive individuals (β=-0.51 and -0.23, respectively).

The observation that tau deposition may have a genetic architecture distinct from known AD risk genes could have implications for enhanced risk prediction, according to the authors, as well as for therapeutic targeting.

1. Ramanan V, et al. Abstract S4.009, AAN 2020.

News on AD biomarkers

New insights into biomarkers for Alzheimer's disease (AD) were shared in 3 studies.

One study evaluated the ability of EEG alone or with resting state functional MRI (rsfMRI) to characterise mild cognitive impairment (MCI) subjects with an AD-like cerebrospinal fluid (CSF) biomarker profile [1]. A total of 39 AD, 86 MCI, and 86 healthy subjects underwent EEG and/or rsfMRI. MCI subjects were differentiated into phosphorylated tau/$A\beta_{-42}$ ratio ≥0.13 (MCI-ATpos) and <0.13 (MCI-ATneg). In AD patients, delta and theta densities were increased, and alpha2 and beta1 densities decreased. MCI-ATpos individuals had higher theta density than MCI-ATneg individuals. After the application of rsfMRI networks to current source density analysis, the alpha2 band could distinguish MCI-ATpos patients from MCI-ATneg, AD, and healthy individuals. The authors concluded that theta frequency was the most sensitive to AD-like CSF biomarker profile. These results emphasise the role of the alpha2 band as a biomarker for neurodegeneration correlating with disease progression.

A new biomarker that could reflect beta-secretase 1 (BACE1) activity and cognitive alteration in AD patients is Neuregulin1 (Nrg1). Nrg1 is a presynaptic BACE1 substrate that can activate postsynaptic ErbB4 receptors. Neuritic plaques are associated with Nrg1 accumulation in AD [2]. CSF Nrg1 levels were evaluated in 172 individuals: 56 had AD, 21 MCI-AD, 32 non-AD MCI, and 36 non-AD dementia; the other 27 were neurological controls [3]. In AD and MCI-AD patients, CSF Nrg1 concentrations were significantly enhanced. Nrg1 levels correlated positively with tau, phosphorylated tau, $A\beta_{1-40}$, and BACE1 levels, and negatively with Mini-Mental State Examination (MMSE) scores and frontal battery scores. The authors concluded that Aβ-induced neurotoxicity induced synaptic demise with increased CSF BACE1 and Nrg1 levels. They postulate that lack of neuroprotection may be linked to decreased Nrg1 brain levels.

New research supports the systematic use of the concentration ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ ($A\beta_{1-42/1-40}$ ratio) as an amyloid biomarker in diagnosing AD [4]. A French group found significant differences in amyloid status according to the ATN system (A+/A-) in CSF between absolute values of $A\beta_{1-42}$ and of $A\beta_{1-42/1-40}$ ratio. The modification of the amyloid status (A- or A+) after $A\beta_{1-42/1-40}$ ratio calculation was analysed in CSF of 738 subjects with a mean age of 69 years. Of patients deemed A+ after $A\beta_{1-42}$ measurement, 67% became A- after $A\beta_{1-42/1-40}$ ratio calculation (P<0.0001), while 18% of A- subjects became A+ (P<0.0001). These findings confirm the recent suggestion that the $A\beta_{1-42/1-40}$ ratio may be more specific to distinguish AD and should be used when analysing CSF AD biomarkers [5].

1. Agosta F, et al. EPR1001, EAN 2020.
2. Chaudhury AR, et al. J. Neuropathol. Exp. Neurol. 2003;62(1):42-54.
3. Mouton Liger F, et al. EPR2004, EAN 2020.
4. Tisserand C, et al. EPR2009, EAN 2020.
5. Hansson O, et al. Alzheimers Res Ther. 2019;11(1):34.

Diastolic dysfunction novel risk factor for cognitive impairment

Increasing diastolic dysfunction is associated with more difficulty with executive functioning and with increasing cerebral small vessel disease, as demonstrated by white matter hyperintensities on brain imaging. These observations strongly suggest diastolic dysfunction to be a novel, modifiable risk factor for cognitive impairment and dementia [1].

Systolic dysfunction has an important effect on cardiovascular outcomes and is associated with cognitive decline [2]. The relationship between diastolic dysfunction and cognition is undefined, however. To this end, Parker et al. analysed echocardiographic, MRI, and neuropsychological data, collected between 2005-2008 in 1,438 participants >55 years in the Framingham Heart Study Offspring Cohort.

The outcomes demonstrated that an increasing E/E' ratio (early mitral filling/diastolic mitral annular velocity) was associated with increased incident mild cognitive impairment (HR 1.29; 95% CI 1.01-1.66; P<0.043) and an increase in executive function impairment in the Similarities (P<0.002) and Phonemic Fluency (P<0.001) tasks. Participants with moderate-to-severe diastolic dysfunction were more impaired on both tasks (P<0.046 and P<0.023, respectively). In 1,217 participants, those with mild diastolic dysfunction showed a trend towards increased white matter hyperintensities (portion of total cranial volume=0.11±0.07, P<0.105); those with moderate-to-severe diastolic dysfunction had increased white matter hyperintensities (0.30±0.09, P<0.001). The authors noted that these results align well with clinical findings in cerebral small vessel disease, as this usually presents with executive dysfunction.

1. Parker A, et al. Abstract S15.005, AAN 2020.
2. Zuccalà, et al. Am J Med. 2005;118(5):496-502.

Epilepsy

Avoidable epilepsy-related mortality remains high

A nationwide population-based study of secular trends in adult epilepsy-related and potentially avoidable mortality in Scotland demonstrated that (avoidable) epilepsy-related deaths (EPRDs) remain common, particularly in young adults [1]. Despite treatment advances, mortality in epilepsy has not been reduced over time.

The national burden of avoidable EPRDs in adults ≥16 years in Scotland was quantified. The study had a retrospective, sequential cross-sectional design. The 2016 Office for National Statistics' Revised Definition of Avoidable Mortality Causes was used to identify potentially avoidable EPRDs.

International Classification of Disease (ICD-10) G40-41-coded causes of death had the highest positive predictive values for epilepsy diagnosis, at 93%. G40-41 captured 2,149 EPRDs, 1,276 (59%) of which had ≥1 seizure-/epilepsy-related hospital admission during 2009–2016. However, only 516 (24%) of these patients visited a neurology clinic during this period. Mortality rates per 100,000 ranged between 6.8 (95% CI 6.0–7.6) in 2009 and 9.1 (95% CI 8.2–9.9) in 2015. Standardised mortality ratios were higher in adults ≤55 years, peaking at 6.0 (95% CI 2.3–9.7) between ages 16-24 years. Of young adult EPRDs, 78% were deemed potentially avoidable. The most common mechanisms of death were sudden unexpected death in epilepsy, aspiration pneumonia, cardiac arrest, alcohol use, and congenital malformation.

1. Mbizvo G, et al. Abstract O3007, EAN 2020.

How genetic testing can contribute to epilepsy management

As sequencing costs decrease and the clinical relevance of genetics increases, genomic data have now entered the everyday clinical practice of epilepsy management. Therefore, specialists should be able to interpret genetic data and use them to make treatment decisions, argued Dr Guido Rubboli (University of Copenhagen, Denmark) [1].

Applying genetics may contribute to prognosis and improve treatment. It allows for choosing treatments that correct specific metabolic defects, to avoid adverse events that can aggravate the pathogenic defect, and to select anti-epileptic drugs (AEDs) that counteract the functional disturbance caused by a gene mutation. Mutations in *SCN1A, SCN1B, SCN2A, SCN3A, SCN8A,* and *SCN9A* are responsible for a considerable proportion of drug-resistant epilepsy cases with childhood onset. Phenotypic variability can be associated with a single gene and even a single variant. Detailed ("deep") clinical phenotyping may identify subtle or unexpected distinguishing features of specific genes that can help to identify the underlying genetic mechanisms.

Genetic testing for therapeutic decision-making is not only useful in children, but also in adults with epilepsy, as a study by Rubboli and colleagues illustrated [2]. Participants were 200 patients from 18-80 years. A genetic diagnosis could be established in 46/200 patients (23%). *SCN1A*, *KCNT1*, and *STXBP1* accounted for 48% of positive findings. Consequently, gene-specific treatment changes were initiated in 11/46 patients (17%), of which 10 with *SCN1A*. Ten of 11 patients improved either in terms of seizure reduction and/or an increased alertness and general well-being.

Performing genetic testing allows for offering genetic counselling to patients. Genetic counselling is in fact recommended by the International League Against Epilepsy (ILEA) as standard care for all infantile seizures and epileptic encephalopathies.

1. Rubboli G. Session FW16, EAN 2020.
2. Johannesen KM, et al. Epilepsia 2020;00:1-6.

Cenobamate effective in focal epilepsy

Data from 2 international, double-blind, placebo-controlled trials showed that cenobamate, a voltage-gated sodium channel blocker, has consistent, statistically significant, and clinically meaningful antiepileptic efficacy [1]. Treatment-emergent adverse events (AEs) were dose dependent and generally mild or moderate.

The 2 pivotal trials were named C013 and C017. They enrolled adult patients with uncontrolled focal onset seizures (FOS) with ≥3 seizures per month (C013) or ≥8 seizures per 8 weeks (C017). Participants also used 1-3 concomitant

anti-epileptic drugs. In C013 they were randomised to cenobamate 200 mg/day or placebo; in C017 to cenobamate 100, 200, or 400 mg/day, or placebo. Response was defined as ≥50% reduction in seizure frequency from baseline.

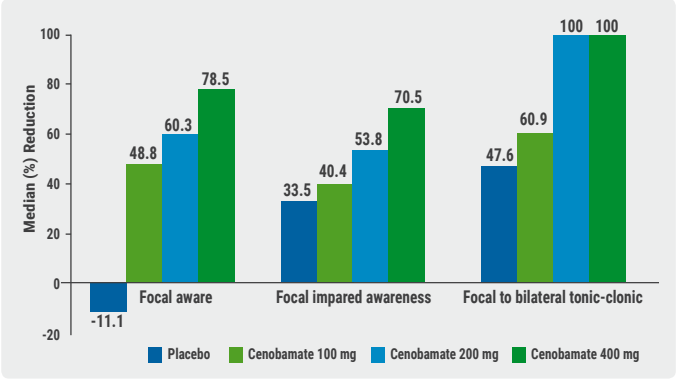
In C013, responder rate in the maintenance phase was significantly higher for cenobamate 200 mg versus placebo (62% vs 33%). Seizure freedom rate was significantly higher as well (28% vs 9%). In C017, ≥50% responder rate during maintenance was significantly higher for all cenobamate dosages (100 mg, 40%; 200 mg, 56%; 400 mg, 64%) versus placebo (26%). In the 200 and 400 mg groups, significantly higher rates of patients achieved seizure freedom (11% and 21%, respectively) versus placebo (1%).

There was a significant reduction across all subtypes of FOS in actively treated patients in both C017 (see Figure) and C013, in which reductions in seizure frequency with cenobamate versus placebo in the maintenance phase were:

- Focal aware (91.5% vs 46.5%);
- Focal impaired awareness (62.0% vs 27.6%);
- Focal to bilateral tonic-clonic (100.0% vs 53.0%).

Cenobamate was generally well tolerated. The most frequently occurring AEs (≥10%) were dizziness, somnolence, headache, fatigue, and diplopia.

Figure. Percent reduction in seizure frequency by seizure type in the maintenance phase (C017 study) [1].



1. Steinhoff BJ, et al. Abstract O3006, EAN 2020.

Sustained seizure reductions with cannabidiol for Lennox-Gastaut syndrome

Add-on cannabidiol (CBD) in patients with Lennox-Gastaut syndrome (LGS) produced sustained seizure reductions, with no new safety concerns [1]. This was concluded from 3-year results of an open-label extension of 2 randomised controlled trials.

LGS is a rare and severe form of epileptic encephalopathy characterised by multiple seizure types, characteristic EEG findings with bursts of slow spike-wave complexes or generalised paroxysmal fast activity, and intellectual impairment. Seizures are often drug-resistant. Efficacy and safety of CBD as an add-on anticonvulsant therapy in LGS were demonstrated in two 14-week phase 3 randomised controlled trials: GWPCARE3 and GWPCARE4 [2,3]. Patients who completed either of these trials could enter the open-label extension trial GWPCARE5. Participants received plant-derived highly purified CBD (Epidiolex® 100 mg/mL oral solution). The primary endpoint was safety.

Of 368 eligible LGS patients, 366 (99%) entered GWPCARE5. Mean age was 16 years; 33% was ≥18 years; 54% was male. At baseline, median monthly quantified seizure frequency was 80 drop seizures and 168 total seizures. During the median follow-up of 150 weeks (range 3 days to 179 weeks), one third of patients (n=119) withdrew. The incidence of adverse events (AEs) and of serious AEs was 96% and 42%, respectively; 12% of AEs led to discontinuation. Most common AEs (≥20%) included diarrhoea, convulsion, pyrexia, somnolence, vomiting, upper respiratory tract infection, and decreased appetite. Increased alanine aminotransferase occurred in 8% of patients. There were 11 deaths; none deemed treatment-related by the investigators. Efficacy outcomes over 156 weeks showed the median monthly drop seizures decreased by 48–71% and the median total seizures by 48–68%.

1. Patel A, et al. Abstract S25.004, AAN 2020.
2. Devinsky O, et al. N Engl J Med. 2018;378(20):1888-97.
3. Thiele EA, et al. Lancet. 2018;391(10125):1085-96.

Prevalence of autoantibodies in epilepsy almost 10%

At clinics in the UK, 9.3% of epilepsy outpatients had potentially pathogenic autoantibodies. The proportion of antibody-positive patients was similar across patients with new-onset focal epilepsy, drug-resistant epilepsy, and seizure-free epilepsy.

The prevalence of autoantibodies among people with epilepsy is not clear; rates between 5-80% have previously been reported. By determining the prevalence of largely pathogenic antibodies in prospectively recruited outpatients with new-onset focal epilepsy, drug-resistant epilepsy, and seizure-free epilepsy, British researchers aimed to provide a prevalence rate that is generalisable to the broader population

of epilepsy patients [1]. They screened collected serum on live cell-based assays for neuronal-surface antibodies (NSAs) to LGI1, CASPR2, contactin-2, DPPX, antibodies to intracellular GAD65, and the $GABA_A$, $GABA_B$, glycine, and NMDA receptors. Overall, autoantibodies were detected in 51/546 (9.3%) epilepsy outpatients:

- new-onset focal epilepsy, 24/232 (10.3%);
- drug-resistant epilepsy, 22/260 (8.5%);
- seizure-free epilepsy, 5/54 (9.3%);
- healthy controls, 0/55 (0%).

New-onset focal epilepsy patients had NSAs only, whereas drug-resistant epilepsy and seizure-free epilepsy cohorts had NSAs and GAD65 antibodies (drug-resistant epilepsy: 11 NSAs, 11 GAD65; seizure-free epilepsy: 2 NSAs, 3 GAD65). In future studies, the pathophysiological role for antibodies in epilepsy should be examined. The authors concluded that the "striking" absence of GAD65 antibodies in new-onset focal epilepsy also warrants explanation.

1. McGinty RN, et al. Abstract O3008, EAN 2020.

Parkinson's Disease

White matter matters in Parkinson's disease

Two studies presented at EAN 2020 demonstrated that longitudinal changes of microstructural white matter (WM) damage are associated with both motor and global cognitive deterioration in Parkinson's disease (PD) [1,2].

In the first study, disruption of WM tracts and cognitive decline was found after deep brain stimulation of the subthalamic nucleus (STN-DBS). The trajectories of electrodes in STN-DBS intersected with tracts involved in different cognitive domains [1].

A group of 51 consecutive PD patients underwent neuropsychological assessment before DBS and 6 months after in on-drug/on-stimulation condition. There was a decline in global cognitive evaluation and in selective cognitive domains including episodic verbal memory, executive functions, and phonemic and semantic verbal fluency. Decline in cued recall in verbal memory correlated with the proportion of lesions of the superior longitudinal fasciculus.

The second study showed that longitudinal evolution of macro- and microstructural damage follows different pathways in PD. Most of all, macroscopic damage, *in vivo* assessed by structural MRI, might provide a sensitive biomarker of disease progression in PD [2].

The 154 participating PD patients received clinical assessment, cognitive evaluation, and an MRI scan once a year over a period of 48 months. At baseline, diffusion tensor imaging (DTI) metrics differed significantly between total and normal appearing WM (NAWM) ($P \leq 0.001$). During follow-up, Unified Parkinson Disease Rating Scale (UPDRS)-III score and WM lesion volume (both $P<0.001$) significantly progressed. Longitudinal differences of mean, axial, and radial diffusivity values significantly correlated with UPDRS-III and Addenbrooke Cognitive Examination total score. Regression analyses showed a significant interaction between axial diffusivity and Mini-Mental State Examination (MMSE) and UPDRS-III score, both in total WM and in NAWM.

The authors concluded that, even though not evident macroscopically, NAWM appeared to be damaged. Microstructural damage at baseline was associated with cognitive and motor status. No such association was found for longitudinal evolution of NAWM microstructural damage.

1. Costentin G, et al. Abstract O1022, EAN 2020.
2. Scamarcia PG, et al. Abstract O3010, EAN 2020.

Sleep disorders mark PD progression

REM sleep behaviour disorder (RBD) and REM sleep without atonia (RWA) increase significantly over time in Parkinson's disease (PD). Both phenomena may therefore be regarded as a progression marker for PD, according to German researchers [1].

In a cohort of *de novo* PD patients, RBD and RWA were analysed using video-supported polysomnography (vPSG). In 158 participants, the proportion of patients with RBD rose

from 25% at baseline to 52% at 6 years. In the subsequent RWA analysis, 31 patients with RBD were included for whom a complete set of 4 vPSG readings (at baseline, 2 years, 4 years, and 6 years) was available. The mean age of this group at baseline was 60 years. Over 6 years, RWA increased from baseline by 0.26 points every 2 years on a logarithmic scale (P<0.001). The rate of RWA rose from 19% at baseline, to 29% at 2 years, 33% at 4 years, and 41% at 6 years (P<0.001). Age was the only independent factor influencing RWA increase (P=0.04). Sex, levodopa equivalent daily dose, Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and benzodiazepine intake did not have any statistical significant influence.

1. Muntean M-L, et al. Abstract O4021, EAN 2020.

Long-term safety of ND0612 in idiopathic PD

ND0612 is a levodopa/carbidopa (LD/CD) solution continuously infused subcutaneously via a pump system. In the phase 2b BeyoND study, long-term safety was established in Parkinson's disease (PD) patients with motor fluctuations [1]. ND0612 was generally well tolerated with no new safety concerns emerging.

Continuous subcutaneous treatment with ND0612 may be more effective in managing motor fluctuations and other symptoms of PD than oral LD/CD, which often becomes less effective as the disease progresses.

The BeyoND study was an open-label, 1-year safety study in PD patients >30 years who were taking ≥4 levodopa doses/day and ≥1 other PD medications. To be included, patients were required to have ≥2 hours of OFF time per day with predictable early-morning OFF periods. Participants received open-label ND0612 for either 16 or 24 hours. They took adjunct oral PD medications as needed. Mean time since PD diagnosis was 9.0±4.7 years, the mean duration of motor fluctuations was 5.3±4.2 years. Of the 214 PD patients enrolled, 124 were appointed to the 16-hour regimen, while 90 received the 24-hour regimen.

ND0612 was generally well tolerated. Local infusion-site reactions were transient and manageable. Reported systemic treatment-emergent adverse events (AEs) were consistent with those expected for levodopa. The most common treatment-emergent AEs were nodules, haematoma, and pain at the infusion site. Overall, less than a quarter of patients discontinued the study due to treatment-emergent AEs, and serious treatment-related AEs were rare. After 12 months, patients could continue treatment with ND0612; some of them are now in their fourth year. Of these participants, additional data is collected in the study extension.

1. Isaacson S, et al. Abstract O3011, EAN 2020.

Directional DBS superior to omnidirectional DBS

Directional deep brain stimulation (DBS) in Parkinson's disease (PD) yielded a wider therapeutic window and a lower therapeutic current strength than conventional omnidirectional DBS in the prospective blinded crossover PROGRESS study [1]. Directional DBS was also preferred by subjects.

Patients receiving subthalamic nucleus DBS for PD received omnidirectional stimulation for 3 months, followed by directional stimulation for another 3 months. Superiority of directional stimulation required a wider therapeutic window in >60% of patients after 3 months (primary endpoint). For non-inferiority of directional stimulation, this percentage was set at 40% (secondary endpoint).

A directional DBS system was implanted in 234 subjects, without intracranial haemorrhages or infections occurring. There were 13 serious adverse events in 12 patients (5.1%). Using directional stimulation, the therapeutic window was wider in 90.7% of patients at 3 months and in 89.3% at 12 months. Mean relative increase in therapeutic window at 3 months was 40% with directional versus omnidirectional stimulation (2.98±1.38 mA and 2.11±1.33 mA, respectively). With directional programming, therapeutic current strength was decreased by 39% after 3 months and by 34% at 12 months. Activation of a single segment increased the therapeutic window in 86.8% of patients at 3 months, and 84.3% at 12 months. After 6 months, 102/193 subjects (53%) blinded to stimulation type preferred the period with directional stimulation, while 50/193 (26%) preferred the omnidirectional period. There was no difference in therapeutic efficacy measured by Unified Parkinson's Disease Rating Scale (UPDRS)-III motor score.

1. Schnitzler A, et al. Abstract O3014, EAN 2020.

Stroke

Benefits of statins to prevent stroke outweigh risks

The benefits of lipid-lowering therapy in the prevention of ischaemic stroke greatly exceed the risk of intracerebral haemorrhage (ICH) that may be associated with statins. This conclusion is based on the outcomes of a new meta-analysis of 19 clinical studies [1].

The association between statins and intracerebral haemorrhage risk is still a matter of controversy. A new review and meta-analysis assessed the safety of statins by weighing risks and benefits in terms of cerebral haemorrhagic and ischaemic events. Included were 19 randomised and non-randomised studies with a total of 35,842 patients who had a history of cardiovascular or cerebrovascular events and had been treated with statins. The primary endpoint was ICH; secondary endpoints were ischaemic stroke and transient ischaemic attack (TIA).

The results could not show a significant association between the risk of combined primary and secondary ICH and statin use (RR 1.03; 95% CI 0.85-1.08). However, a sensitivity analysis had a trend toward a higher risk of secondary ICH among those assigned to statin treatment (OR 1.87; 95% CI 0.91-3.86). The risk of stroke and TIA was a significant 21% lower in subjects assigned to statin treatment (RR 0.79; 95% CI 0.61-0.87). Given the considerably higher incidence rates of ischaemic events, the benefit/risk balance of statin treatment is favourable in this patient population. The authors think that the risk of losing the protection against ischaemic events when withdrawing statin use is probably greater than any harm, even in patients with underlying risk factors for ICH.

1. Ishfaq A, et al. Abstract S9.010, AAN 2020.

Extubation after thrombectomy: the sooner, the better

Early extubation (within 6 hours) after thrombectomy independently predicts a favourable outcome at 3 months in stroke patients, compared to extubation between 6 and 24 hours [1]. Furthermore, pneumonia rates and duration of stay in the neurointensive care/ stroke unit were reduced. Mechanical ventilation in these patients should therefore be shortened as much as safely possible.

In a single-centre study, researchers from the Medical University of Graz (Austria) aimed to assess the clinical impact of the duration of artificial ventilation in stroke patients receiving mechanical thrombectomy under general anaesthesia [1]. They identified all ischaemic stroke patients who had received mechanical thrombectomy for anterior circulation large vessel occlusion under general anaesthesia over a period of 8 years (n=447). Patients were divided into 3 groups, according to ventilation timing: "early" (extubation within 6 hours), "delayed" (6-24 hours), and "late" (>24 hours). The mean age was 69 years, half of patients were female; median ventilation time was 3 hours.

A favourable outcome, defined as modified Rankin Scale scores of 0-2 at 3-months post-stroke, was seen in 188 patients (42.6%) and correlated with shorter ventilation time (P<0.001). In patients extubated ≤24 hours, early extubation was associated with better outcomes than delayed extubation (OR 2.40; 95% CI 1.53-3.76; P<0.001), also in a multivariable analysis (P=0.007). The authors offered a number of possible explanations:

- higher rates of (ventilator-associated) pneumonia;
- impaired cerebral blood flow due possible vasodilatory effects of sedative drugs;
- hyperoxemia, which may occur in ventilated intensive care unit patients;
- delayed early rehabilitation and stroke work-up.

Of 65 patients with late extubation, the most frequent reasons for prolonged intubation were brain oedema (44.6%), impaired consciousness due to other reasons (26.1%), and respiratory insufficiency (15.9%). However, delayed extubations were predicted by non-medical reasons, notably admission outside of core working hours (P<0.001). During neurointensive care, longer ventilation time was strongly associated with a higher rate of pneumonia: 9.6%, 20.6%, and 27.7% in the early, delayed, and late group, respectively (P<0.01).

1. Fandler-Höfler S, et al. Abstract O3036, EAN 2020.

Thrombus location and length predictors of early neurological deterioration

A large retrospective observational study in patients with minor strokes with large vessel occlusion found that thrombus location and length are strong predictors of early neurological deterioration (END) [1]. This may help to select the best candidates for additional endovascular therapy.

Researchers from Paris, France conducted the multicentre observational study MINOR-STROKE in which they included 721 patients with intravenous thrombolysis-treated minor strokes (NIH Stroke Scale/Score [NIHSS] ≤5) with large vessel occlusion intended for intravenous thrombolysis alone, including those patients who eventually received thrombectomy because of END. END was defined as a ≥4-point NIHSS increase within 24 hours after admission. Mean age of participants was 70 years, median NIHSS was 3. Occlusion was located in the internal carotid artery (ICA)-T/L in 3%, in the tandem cervical ICA+middle cerebral artery in 10%, in the proximal M1 in 7%, in the distal M1 in 21%, in the M2 in 54%, and in the basilar artery in 4%. The thrombus was visible in 85% of patients.

END occurred in 12% and was associated with poor outcome after 3 months. In a multivariable analysis, a more proximal occlusion site (P<0.001) and a longer thrombus (P=0.002) were independently associated with END. Rates of END according to occlusion type were the following:

- ICA-T/L, 55%;
- Tandem occlusion, 23%;
- Proximal M1 occlusion, 19%;
- Distal M1 occlusion, 13%;
- Distal M2 occlusion, 5%;
- Basilar artery occlusion, 27%.

In patients with a thrombus length of <6, 6-9, 9-12, and ≥12 mm, respectively, END occurred in 5%, 7%, 15%, and 23%.

1. Seners P, et al. Abstract O2036, EAN 2020.

Endovascular treatment in large vessel occlusion stroke patients treated with OAC

Endovascular treatment appears to be safe and efficacious in patients with large vessel occlusion stroke in patients using oral anticoagulation (OAC). This was suggested by the outcomes of a large-scale retrospective study analysing data from the German Stroke Registry-Endovascular Treatment [1].

Primary outcomes were successful recanalisation, defined as modified thrombolysis in cerebral infarction (mTICI 2b-3), good outcome at 3 months according to modified Rankin scale (mRS; 0-2 or back to baseline), and rates of intracranial haemorrhage (ICH) until hospital discharge.

The analysis included 2,521 stroke patients, of whom 442 (17.6%) were treated with OACs, 201 (8.0%) with vitamin-K antagonists (VKA), and 241 (9.6%) with non-vitamin-K antagonist oral anticoagulants (NOACs). OAC users were older, had more often a history of atrial fibrillation, and had a higher rate of arterial hypertension (see Table).

The rate of mTICI 2b-3 was similar among all 3 groups (82.7%, 85.5%, and 82.7%; P=1.00 and P=0.57). The other main results after 90 days:

- A favourable outcome was less frequent in OAC patients (28.4%, 31.1%, and 40.9%; P<0.005 and P<0.05);
- ICH rates were similar among the 3 groups (12.1%, 12.4%, and 10.4%; P=1.00 and P=0.86);
- OAC status had no influence on good outcome (OR 1.03; 95% CI 0.99-1.08);
- OAC status did not affect ICH risk (OR 1.03; 95% CI 0.94-1.05).

1. Küpper C, et al. Abstract EPR2022, EAN 2020.

Table. Baseline patient, stroke, imaging, and treatment characteristics [1].

Parameter	No OAC	VKA	P-value	NOAC	P-value	Missing values
n (%)	2,079 (82.5)	201 (8.0)	n.a.	241 (9.6)	n.a.	0 (0)
Age, mean ± SD	71.6 ± 13.4	77.6 ± 10.7	<0.005	76.2 ± 10.5	<0.005	0 (0)
Female, n (%)	1,031 (49.6)	114 (56.7)	0.108	127 (52.7)	0.722	0 (0)
Arterial hypertension, n (%)	1,527 (73.7)	170 (85.0)	<0.005	199 (83.6)	<0.005	12 (0.5)
Atrial fibrillation, n (%)	638 (30.9)	177 (88.1)	<0.005	203 (85.3)	<0.005	16 (0.6)
pmRS, median	0 [0, 1]	0 [0, 2]	<0.005	0 [0, 1]	<0.005	90 (3.7%)
NIHSS, median	15 [10, 19]	15 [11, 19]	0.788	16 [12, 20]	<0.005	30 (1.2%)
mTICI 2b-3, n (%)	1,688 (82.7)	162 (82.7)	1	206 (85.5)	0.57	44 (1.7)
ICH until discharge, n (%)	225 (12.1)	25 (12.4)	1	25 (10.4)	0.856	0 (0)
Good outcome, n (%)	755 (40.9)	50 (28.4)	<0.005	64 (31.1)	<0.05	293 (11.6)

OAC, oral anticoagulation; VKA, vitamin-K antagonist; NOAC, non-vitamin-K oral anticoagulant; pmRS, premorbid modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; mTICI, modified thrombolysis in cerebral infarction; ICH, intracranial haemorrhage

Early edoxaban may be safe after cardioembolic stroke

The optimal timing for starting oral anticoagulation after a stroke or transient ischaemic attack (TIA) in patients with nonvalvular atrial fibrillation (NVAF) is unknown. The observational SATES study of early treatment with edoxaban showed early initiation of edoxaban seems to be safe after a cardioembolic stroke [1].

New direct oral anticoagulants (DOACs), of which edoxaban is an example, are recommended for stroke prevention in NVAF patients. SATES was a prospective study to evaluate the safety of initiation within 72 hours of full dose edoxaban in NVAF patients after acute ischaemic stroke. The primary endpoint was safety in terms of any major bleeding in the first 3 months of treatment. Secondary endpoints were incidence of major bleeding, haemorrhagic transformation, and symptomatic haemorrhagic transformation rate, 3±2 days after the start of edoxaban treatment.

A total of 50 patients were enrolled, with a mean age of 77 years and a mean NIH Stroke Scale/Score of 7.8. After 3 months, only one major bleeding (gastrointestinal bleeding) was reported, which resulted in a temporary suspension of edoxaban use; there were also 8 minor bleedings, without recurrence of stroke. There was no major bleeding or symptomatic haemorrhagic transformation in the first 3±2 treatment days; the incidence rate of haemorrhagic transformation was 12% for haemorrhagic infarction (HI)-1 (small petechiae) and 8% for HI-2 (confluent petechiae) without neurological deterioration. All patients continued edoxaban after 3 months.

1. Frisullo G, et al. Abstract O1031, EAN 2020.

Headache and Pain

Small fibre pathology as biomarker for fibromyalgia

Results from a German study add further evidence to the concept of small nerve fibre impairment in fibromyalgia syndrome (FMS) as peripheral contributor to FMS pain [1]. Indications were found for systemic and local microRNA alterations in FMS, that may serve as diagnostic signatures and treatment target.

Skin biopsy, quantitative sensory testing, corneal confocal microscopy, pain-related evoked potentials, and microneurography were applied in 156 FMS patients. Blood samples and keratinocyte cultures from skin punch biopsies were collected to assess potential systemic and local microRNA signatures. MicroRNAs are small molecules that regulate gene expression and may be promising biomarkers to identify and characterise chronic pain types.

In a subgroup of FMS patients, small fibre pathology including morphological, functional, and electrophysiological properties was found. In 98 patients (63%), skin innervation was abnormal and associated with disease severity. In blood and keratinocyte microRNA analysis, 69 and 41 deregulated microRNAs were found, respectively. Potential key pathways presenting themselves were fatty acid synthesis and factor forkhead box protein O1 (FOXO1) signalling in blood, and extracellular matrix receptor signalling in keratinocytes. miR-576-5p was validated as a microRNA that can distinguish between FMS and healthy controls ($P<0.001$), and between FMS and patients with depression with pain that served as disease controls ($P<0.01$). The authors deduced that the extent of small fibre impairment may reflect FMS severity.

1. Evdokimov D, et al. Abstract EPR3053, EAN 2020.

Migraine as a cyclical functional disorder

During a migraine attack induced by nitroglycerin, the whole-brain functional connectivity changes systematically, involving areas well known for their roles in pain modulation and migraine generation [1]. These pilot study results suggest that migraine could be seen as a cyclical functional disorder.

In this Italian study, 5 subjects with episodic migraine were given nitroglycerin, which successfully triggered a migraine attack

without aura in all of them. Subjects subsequently underwent 4 resting state functional MRI (rsfMRI) repetitions during different phases of the attack (baseline, prodromal, full-blown, recovery phase). Brainstem elements involved in the pain circuits (such as the spinal trigeminal nucleus, periaqueductal gray, and dorsal raphe nuclei) and the thalamus were found to exhibit an altered functional coupling within themselves and with the hypothalamus, particularly during the prodromal phase. Whole-brain activity coupling with the left thalamus indicated greater involvement during the full-blown phase.

1. Martinelli D, et al. Abstract O1019, EAN 2020.

Reassuring real-world safety profile of 3 CGRP inhibitors

The 3 calcitonin gene-related peptide (CGRP) inhibitors that have been approved thus far for the prevention of migraine since 2018 —erenumab, fremanezumab, and galcanezumab— showed a reassuring safety profile in a real-world setting [1]. Post-marketing data of the first 6 months following their marketing launch was reported.

Included in this retrospective analysis were adverse events (AEs) that were spontaneously reported to the FDA during the first 6 months post-approval and that were likely to be treatment-related. Many of the reported AEs were injection-site reactions, such as pain, pruritus, rash, and erythema. Migraine, headache, and drug ineffectiveness were reported for all 3 medications. Constipation ranked second for erenumab, but was not in the top 10 of AEs for fremanezumab or galcanezumab. Cardiovascular events were not among the top 10 AEs for any of the products. The top 5 reporting rates (RRs) per 1,000 patients exposed for each of the 3 CGRP inhibitors were:

- erenumab: wrong technique (4.97), constipation (4.90), migraine (4.89), accidental exposure (4.83), and drug ineffectiveness (3.68);
- fremanezumab: headache (1.27), drug ineffectiveness (1.14), migraine (1.01), nausea (0.91), and injection-site pain (0.81);
- galcanezumab: injection-site pain (4.90), under-dose (3.86), headache (3.07), migraine (2.99), and drug ineffectiveness (1.69).

These observations were as expected based upon the clinical trial results. Longer-term safety data, such as those on the approved CGRP inhibitors, has been eagerly awaited, since there are theoretical cardiovascular concerns especially in patients with coronary disease.

1. Silberstein SD, et al. Abstract S58.008, AAN 2020.

Long-term cardiovascular safety of erenumab

In an analysis of 4 randomised trials and their open-label extensions, the safety of erenumab was assessed [1]. The frequency of cardiovascular and cerebrovascular adverse events (AEs) was comparable to that of placebo seen over 12 weeks. There was no increased emergence of AEs in up to 5 years of follow-up.

Dr Stewart Tepper (Geisel School of Medicine, USA) presented the results of the post-hoc analysis of AEs in erenumab users with episodic or chronic migraine with or without a history of aura. During the 12-week double-blind treatment phase, 2,443 patients were treated with erenumab (70 mg/140 mg once monthly) or placebo. Of these, 1,140 (47%) had a history of aura. Dr Tepper noted that vascular risk factors were more prominent in the aura subgroup. At baseline, ≥2 cardiovascular risk factors were present in 35% of patients with aura and 27% of patients without.

Cardiovascular and cerebrovascular AE rates were low throughout the controlled and open-label erenumab exposure of up to 5 years. During that period, these rates were the same among patients with aura (n=6; 0.4/100 patient years) and without aura (n=5; 0.3/100). Hypertension-related AE rates were similar in both subgroups (n=30; 2.3/100 patient-years and n=37; 2.2/100, respectively).

Rates of cardiovascular, cerebrovascular, and hypertension-related AEs, general AEs, and all serious AEs were similar in the placebo and erenumab treatment groups during the double-blind treatment phase, regardless of aura history. Dr Tepper concluded: "This is reassuring data".

1. Tepper SJ, et al. Abstract O1016, EAN 2020.

Real-world data for erenumab in Germany

Based on the assessment of treating physicians, erenumab reduced the burden of migraine and increased the quality of life (QoL) in over 75% of their migraine patients. These were the main results of the TELESCOPE study, providing real-world data for erenumab in Germany [1].

By means of an online survey from July-December 2019, data from 45 headache centres across Germany were collected. The interim analysis included 542 patients. Half of these had episodic migraine, half had chronic migraine. A total of 45 physicians reported that 19% of their patients were currently using monoclonal antibodies. For almost all patients, restricted QoL (100%) and number of mean monthly migraine days (MMD) (98.8%) were the main reasons to start treatment with a monoclonal antibody. Physicians reported that 82.7% of their patients responded to erenumab and that 79.5% were satisfied with it. Erenumab reduced headache intensity in 77.4% of patients, improved QoL in 75.5%, and reduced MMD by half in 66%. Physicians also reported that 69.4% of their patients already had a response after the first injection. Mean change in MMD was -6.3; mean change in acute medication days was -6.4.

1. Straube P, et al. P3.005, AAN 2020.

Eptinezumab in chronic migraine and medication-overuse headache

In the pivotal PROMISE-2 study, eptinezumab was efficacious in patients with chronic migraine and medication-overuse headache (MOH). After 12 weeks, the eptinezumab group had a greater reduction in migraine days than the placebo placebo group. Efficacy was noted from day 1 and sustained through 24 weeks [1].

In PROMISE-2, 1,072 chronic migraine patients participated, 431 of whom had a dual diagnosis of chronic migraine and MOH. Participants were randomised to eptinezumab 100 mg, 300 mg, or placebo for 2 intravenous doses administered every 12 weeks. Eptinezumab is an anti-calcitonin gene-related peptide monoclonal antibody. MOH patients were equally distributed in these 3 groups. During the 28-day baseline period, MOH patients experienced a mean 16.7 migraine days.

Efficacy of eptinezumab versus placebo on day 1 through 7 was lower with eptinezumab than placebo. On baseline, about 60% of participants experienced migraine; on day 1, this rate was 27.8% (100 mg); 30.1% (300 mg); and 45.5% (placebo). In all of the first 12 weeks of intervention, eptinezumab-treated patients experienced greater reductions in monthly migraine days (MMDs) than placebo patients (100 mg, -8.2; 300 mg, -8.5; placebo, -5.2). About twice as many patients in the eptinezumab groups were ≥50% (60.4%; 61.9%; 34.5%) or ≥75% migraine responders (27.3%; 29.9%; 14.5%). Results were similar during weeks 13-24.

1. Diener H-C, et al. Abstract EPR1090, EAN 2020.

Fremanezumab tolerability in cardiovascular patients with migraine

In a pooled analysis of 3 phase 3 trials, fremanezumab treatment over 12 weeks was well tolerated, with a low rate of cardiovascular adverse events (AEs) similar to placebo in migraine patients using cardiovascular medication at baseline [1]. There were no new safety signals over 12 weeks of double-blind treatment.

Fremanezumab is a a fully-humanised monoclonal antibody that selectively targets calcitonin gene-related peptide. The 3 trials included were HALO EM, HALO CM, and FOCUS, in which patients were randomised to subcutaneous quarterly or monthly fremanezumab, or placebo over 12 weeks. Overall, 280/2,842 trial participants were receiving cardiovascular medications at baseline, accounting for 9-11% of every treatment group. The most common type of cardiovascular medications used were agents acting on the renin-angiotensin system (3-4%) and beta blockers (3-4%).

The rates of patients with ≥1 AE were:
- placebo, 53%;
- quarterly fremanezumab (675 mg/placebo/placebo), 66%;
- monthly fremanezumab (675/225/225 mg), 70%;
- monthly fremanezumab (225/225/225 mg), 54%.

The most common AEs were injection site-related (pain, erythema, and induration). Cardiac disorder as well as vascular disorder AEs were infrequent across treatment groups. Their respective AE rates were:
- placebo, <1% and 0%;
- quarterly fremanezumab (675 mg/placebo/placebo), 0% and 1%;
- monthly fremanezumab (675/225/225 mg), 2% and 6%;
- monthly fremanezumab (225/225/225 mg), 0% and 0%.

Results of another pooled analysis showed that fremanezumab treatment over 12 weeks was well tolerated in patients with migraine and concomitant triptan use, with similar cardiovascular tolerability to those who did not use triptans [2].

1. Coppola G, et al. Abstract EPR1092, EAN 2020.
2. Kärppä M, et al. Abstract EPR2065, EAN 2020.

Effects of galcanezumab on health-related quality of life

Patients with treatment-resistant episodic or chronic migraine treated with the calcitonin gene-related peptide inhibitor galcanezumab reported better daily functioning and patient perception of health state, compared with placebo, as well as less disability. This was concluded from results of the CONQUER study [1].

Treatment resistance was defined as previous failure with 2 to 4 standard-of-care migraine preventive medication categories in the past 10 years due to inadequate efficacy and/or safety/tolerability issues. Participants were randomised to galcanezumab 120 mg/month (240 mg loading dose) or placebo for 3 months. Migraine Disability Assessment (MIDAS), European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L), and Migraine-Specific Quality of Life Questionnaire v2.1 (MSQ) scores were collected at baseline and month 3; MSQ as well at month 1 and 2.

In the intent-to treat (ITT) population (n=462), mean improvement with galcanezumab versus placebo on EQ-5D-5L visual analog scale was significant (P=0.03). In the ITT and subpopulations with episodic (n=269) and chronic migraine (n=193), mean improvements from baseline in MSQ total and all domain scores were significantly greater with galcanezumab versus placebo (all P<0.0001), as well as improvements in MIDAS total scores (see Table).

1. Tepper SJ, et al. Abstract EPR3051, EAN 2020.

Unmet needs and pipeline

In a presentation about migraine medication, Prof. Christian Lampl (Headache Medical Center, Austria) argued that, despite recent developments, there is still a need for more treatment options for acute migraine. Prof. Lampl gave an overview of the most important compounds currently in development, including ditants, gepants, and antibodies [1].

Triptans are the gold standard for acute migraine treatment, but have class contraindications that limit their use in patients with cardiovascular diseases. Calcitonin gene-related peptide (CGRP) antagonism does not cause vasoconstriction, making it safe for migraine patients who cannot use triptans. CGRP receptor antagonists (gepants) do not have vasoconstrictive properties either; in phase 2 and 3 trials they have demonstrated similar efficacy to triptans, with fewer side effects.

Three new gepants (rimegepant, ubrogepant, and atogepant) are still in a developmental stage. Results from phase 2 and 3 trials showed they are effective, well tolerated, and safe, especially in terms of liver toxicity.

Apart from CGRP, one of the other members of the CGRP family of neuropeptides is amylin. Prof. Lampl said that targeting neuropeptides such as pituitary adenylate cyclase-activating peptide (PACAP) and amylin, which have similar functions as CGRP, are promising targets for migraine treatment. Clinical trials are planned for the PACAP38 receptor antagonist ALD 1910. The PAC1 receptor antagonist AMG-301 is in phase 2 development for the prevention of migraine.

Therapeutics that are not yet available in Europe but have already been approved by the American FDA are lasmiditan (tablet, acute migraine), ubrogepant (tablet, acute migraine), and rimegepant (tablet and fast dissolving tablet, acute migraine). Vazegepant (nasal spray, acute migraine) is ready to advance into a phase 3 trial. Atogepant (tablet) is in phase 2/3 development for the prevention of migraine.

1. Lampl C. Symposium SYMP09, EAN 2020.

Table. Mean change in health-related QoL measures [1].

Scores, LS mean change (SE)		ITT population		EM subpopulation		CM subpopulation	
		Placebo	Galcanezumab	Placebo	Galcanezumab	Placebo	Galcanezumab
MSQ	Role function-restrictive	10.68 (1.34)	23.21 (1.35)***	11.88 (1.80)	23.39 (1.79)***	6.71 (1.99)	20.61 (2.05)***
	Role function-preventive	7.68 (1.19)	17.53 (1.20)***	8.94 (1.56)	18.44 (1.55)***	5.37 (1.83)	15.27 (1.88)***
	Emotional function	12.01 (1.60)	24.02 (1.61)***	11.58 (2.08)	22.52 (2.06)***	11.09 (2.57)	24.38 (2.63)***
	Total score	10.08 (1.25)	21.67 (1.26)***	10.91 (1.67)	21.70 (1.66)***	7.67 (1.86)	20.17 (1.91)***
MIDAS	Total	-3.30 (3.28)	-21.10 (3.32)***	-2.58 (3.68)	-18.96 (3.63)**	-1.68 (6.19)	-20.27 (6.40)*
EQ-5D-5L	VAS score	-0.09 (1.29)	3.38 (1.31)*	-0.83 (1.63)	2.90 (1.63)	n.a.	n.a.

*P<0.05, **P<0.01, ***P<0.0001 vs placebo. LS, least squares; ITT, intention-to-treat; EM, episodic migraine; CM, chronic migraine; MSQ, Migraine-specific quality of life questionnaire v2.1; MIDAS, Migraine disability assessment; EQ-5D-5L, European quality of life 5-dimensions 5-levels; VAS, visual analog scale.

Multiple Sclerosis

Imaging to evaluate remyelination and neuroprotection

The treatment goals of remyelination and neuroprotection in multiple sclerosis (MS) present new challenges to treatments, and also in finding ways to evaluate these outcome measures. Dr Benedetta Bodini (Sorbonne University, France) discussed the potential of MRI and PET techniques in evaluating myelin repair and neuroprotection in clinical treatment trials [1].

MRI offers very high sensitivity to tissue microstructural damage and generally has a high resolution; PET has the highest possible specificity for single cellular, myelin, or neuronal targets, but at the expense of resolution, which is generally very low.

Dr Bodini gave an overview of MRI techniques that are sensitive to myelin content changes. Magnetisation transfer ratio (MTR) is very sensitive to myelin and has very reasonable acquisition times. However, the signal is affected by oedema and axonal density, as well as by microglia. MTR captures changes in myelin content in single lesions. Dr Bodini said MTR has already been shown to be sensitive to the effects of remyelinating treatment in clinical trials and that sample sizes are very reasonable. She added that inhomogeneous magnetisation transfer (ihMT) can improve MTR because of a higher myelin specificity. Other valuable techniques that can measure myelin changes include diffusion-weighted imaging (DWI), myelin water fraction imaging (MWI), and quantitative susceptibility-weighed imaging (SWI) to measure myelin and iron. As MRI techniques have a suboptimal specificity for myelin *in vivo*, PET holds a special place in imaging de-/remyelination. PET captures clinically relevant remyelination, which is critical to determine disease evolution and disability (see Table 1).

Table 1. Imaging techniques for de- and remyelination: a summary [1].

Technique	Advantages	Limitations
MTR	Early implementation/post-processing, reasonable sample size and acquisition times	Incomplete specificity for myelin, calibration required across and within scanners
DTI	Sensitive to myelin content, measurable recovery	Poor specificity
MWI	High specificity for myelin when corrected, reproducibility across platforms	Long acquisition times, low signal-to-noise ratio
SWI	High spatial resolution, high signal-to-noise ratio	Variable acquisition protocols with different sensitivity, non-local effects
PET	Highest possible specificity for myelin	Low resolution, multidisciplinary expertise required, radiation, expensive

Dr Bodini went on to discuss imaging techniques to measure potential neuroprotection. The most widely used is whole brain atrophy, which is easy to implement and correlates with clinical and cognitive scores. Thalamic atrophy may be a promising primary MRI endpoint for phase 2 trials. Early markers of neuronal damage are N-acetyl-aspartate ^{1}H-MRS (NAA-^{1}H-MRS), advanced DWI, ^{11}C-FMZ, and synaptic vesicle protein.

"A turning point in the search for effective imaging measures of neuroprotection will be the development of imaging strategies to evaluate the key mechanisms leading to neurodegeneration", Dr Bodini argued. One of these mechanisms is energy dysregulation. Different techniques have been developed to investigate different aspects of energy dysregulation, notably ^{23}Na-MRI, ^{31}P-MRS, and diffusion-weighted (DW)-MRS (see Table 2).

Table 2. Imaging techniques for neuroprotection: a summary [1].

Technique	Advantages	Limitations
Global/regional brain atrophy	High clinical relevance, high sensitivity to change	Non-specific measures, captures the final stage of neurodegeneration, measurement variability
NAA-^{1}H-MRS	High specificity for neurons	Limited reproducibility, low spatial resolution
Advanced DWI	Improved specificity for tissue microstructural changes	Additional validation required, challenging multicentre application
^{23}Na-MRI, ^{31}P-MRS, DW-MRS	High specificity for detecting early signs of energy dysfunction	Very low resolution, additional validation required for DW-MRS

Dr Bodini concluded with the following take-home messages:

- MRI and PET should be deployed as outcome measures in future clinical phase 2 trials testing pro-myelinating and neuroprotective MS treatments.
- Future outcome measures will include imaging techniques of mechanisms leading to neurodegeneration.
- PET should be used in the future to validate single MRI sequences or a combination of multiple MRI measurements to improve MRI specificity for myelin and neurons.

1. Bodini B. Symposium SYMP04, EAN 2020.

MRI-based clustering of MS patients

MRI-based clustering of multiple sclerosis (MS) patients is feasible and contributes to demonstrating disease heterogeneity. Researchers from IRCCS San Raffaele (Italy) identified 5 hierarchical clusters of MS patients

with homogeneous underlying pathophysiology by using advanced MRI techniques [1]. They think this is useful for personalised medicine.

A cohort of 115 MS patients along with 44 age- and sex-matched healthy controls underwent brain and cervical cord 3T MRI with pulse sequences. Of the MS cohort, 57 patients had relapsing-remitting MS, 12 primary progressive MS, and 46 secondary progressive MS. Lesions, atrophy, and microstructural damage were assessed. A complete neurological assessment with Expanded Disability Status Scale (EDSS) rating was performed as well.

Five clusters of MS patients were identified: "early", "intermediate-cord", "intermediate-cortical", "intermediate-late-lesion", and "late". Early patients showed similar MRI metrics as healthy controls (except lesions), low EDSS, and short disease duration. Compared with early patients, intermediate patients were characterised by altered MRI metrics, higher EDSS, and longer disease duration (P<0.01). Intermediate-cord patients stood out by high cord T2-lesion volume (LV), except versus late patients (P<0.001). The intermediate-cortical group had relatively low cortical thickness (P<0.001), except versus intermediate-late-lesion and late patients. Intermediate-late-lesion patients had a longer disease duration, a higher brain T2-LV, and deep grey matter (GM) atrophy, except compared with late patients (P<0.01). Of all groups, the late patients had the worst corticospinal-tract diffusion-tensor metrics and cord/brain atrophy (P<0.01); they also had higher EDSS and disease duration than the intermediate-cord and the intermediate-cortical patients (P<0.01).

The authors suggest that intermediate-cord patients could be divided into 2 groups that differ in cord GM atrophy and cortical thickness (P<0.01), the impaired group including mostly progressive phenotypes and higher EDSS. They believe the intermediate-cord group is best suited to study neuroprotective and regenerative strategies.

1. Bonacchi R, et al. Abstract O2029, EAN 2020.

Serum NfL predicts long-term clinical outcomes in MS

Higher serum levels of neurofilament light chain (NfL) close to the time of multiple sclerosis (MS) disease onset is a sensitive marker for subsequent relatively poor clinical outcomes. This is suggested by results of a prospective cohort study with over 15 years of follow-up [1]. The authors claim that these patients may benefit from a more aggressive initial treatment.

Researchers from the Ottawa Hospital Research Institute (Canada) evaluated the prognostic value of serum NfL levels obtained shortly after MS diagnosis to identify patients likely to have a more aggressive disease course. A total of 67 MS patients were identified whose serum had been collected within 5 years of first MS symptom onset. Median follow-up was 17.4 years. Levels of serum NfL were quantified in all 67 MS patients and in 37 matched controls using a digital immunoassay (SiMoA HD-1 Analyzer, Quanterix).

The median baseline NfL level in MS patients was 10.1 pg/mL, which is 38.5% higher than in controls (7.26 pg/mL, P=0.004). Patients reaching Expanded Disability Status Scale (EDSS) ≥4 during follow-up had significantly (73.6%) higher baseline NfL levels than patients with EDSS <4 (P=0.0001). The best cut-off for predicting progression was 7.62 pg/mL. Patients with baseline NfL levels >7.62 pg/mL had a 8.9 times higher risk of developing progressive MS during follow-up (P=0.034; 95% CI 1.2-68.1). Patients in the highest tertile of NfL levels progressed most rapidly (annual EDSS rate 0.16; P=0.004). Patients with baseline NfL levels <7.62 pg/mL had a 4.3 times lower relative risk of significant disability (EDSS score ≥4; P=0.001) and a 7.1 times lower risk of reaching the progressive phase of MS (P=0.054).

1. Thebault S, et al. Abstract S10.008, AAN 2020.

Epstein-Barr virus-targeted T-cell immunotherapy for progressive MS

Off-the-shelf ATA188, an allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy, was well tolerated across all 4 dose cohorts in patients with progressive multiple sclerosis (MS) in an open-label phase 1 study. There was a possible signal of therapeutic response, with a higher proportion of patients showing sustained disability improvement with increasing dose [1].

EBV is considered a risk factor in triggering MS. Mounting evidence suggests that EBV-infected immune cells, in particular memory B cells, play an important role in propagating both relapsing and progressive forms of MS. ATA188 offers a novel treatment approach selectively targeting and eliminating EBV-infected B cells and plasma cells in the circulation and central nervous system.

A phase 1a multicentre study assessed safety and efficacy of ATA188 in patients with progressive forms of MS. Patients were treated across 4 dose-escalating cohorts, with 6 patients each in cohorts 1-3 and 7 patients in cohort 4. Across the 4 dose cohorts, ATA188 was well tolerated, with no

dose-limiting toxicities or fatal adverse events. Additionally, ATA188 infusion showed no clinically meaningful effect on cytokine levels post-infusion.

Two methods to assess clinical outcomes were used. The first scale was based on Sustained Disability Improvement (SDI), a composite of improvement in Expanded Disability Status Scale (EDSS) or Timed 25-Foot Walk at consecutive time points (3 and 6 months, 6 and 12 months). All patients in cohorts 1-3 showing SDI at 6 months maintained improvement through 12 months (see Table). Additionally, there was a dose-related increase in the number of patients with SDI. The second composite scale (designed to detect early signals of efficacy) was an *a priori* classification of patient outcomes, incorporating 7 scales for MS symptoms, function, and disability. This scale also showed a dose-related trend of a higher proportion of patients showing favourable clinical improvement. Based on these results, the cohort 3 dose was selected for the randomised, placebo-controlled phase 1b study.

1. Bar-Or A, et al. Abstract LB130, EAN 2020.

High NEDA rates after 2 years of ocrelizumab

In the CASTING open-label single-arm prospective trial of ocrelizumab, the proportion of patients with no evidence of disease activity (NEDA) at year 2 was high: 74.8%–80.4% of patients were free of clinical disease activity, while 91.5% of patients were free of MRI activity [1]. NEDA was maintained from year 1 over year 2.

CASTING is a phase 3b study evaluating the efficacy and safety of ocrelizumab in relapsing-remitting multiple sclerosis (RRMS) patients with suboptimal response to 1 or 2 prior disease-modifying treatments (DMTs). The intention-to-treat (ITT) population included 680 patients. After 2 years, 74.8% of patients had NEDA; 80.4% had no evidence of clinical activity, 91.5% had no evidence of MRI activity, and 89.8% had no relapses.

The exploratory endpoint of 2-year NEDA with MRI from screening was reached by 52.0% of patients. This lower percentage was mainly due to the lower percentage of patients with no evidence of MRI activity, which dropped to 63.8%. The percentage of no evidence of clinical activity after 2 years was 80.6%. NEDA was maintained in year 2 when analysed by epoch. In the first epoch (baseline to year 1), NEDA was 82.6%, in the second epoch (year 1 to year 2) 87%.

Safety results over 2 years were consistent with prior studies, with no newly observed signals. In the ITT population of 680 patients, 49 (7.1%) experienced a serious adverse event, leading to treatment discontinuation in 5 patients.

1. Vermersch P, et al. Abstract LBN05, EAN 2020.

Two trials comparing relapsing MS treatments

Ofatumumab markedly reduced disability progression independent of relapses versus teriflunomide [1]. In another head-to-head trial, ponesimod was superior to teriflunomide with regard to annualised relapse rate (ARR), fatigue symptoms, MRI activity, brain atrophy, and no evidence of disease activity (NEDA) in the OPTIMUM study [2,3].

In a pooled analysis of the phase 3 ASCLEPIOS I/ASCLEPIOS II trials in relapsing multiple sclerosis (RMS) patients, the effect of ofatumumab versus teriflunomide on confirmed disability progression independent of relapse activity (PIRA) was assessed. The risk of confirmed disability progression at 3/6 months (3mCDP/6mCDP) was evaluated in 3 subsets of patients:

A: without confirmed relapses during the study;
B: without confirmed relapses during the study or prior to a 3mCDP/6mCDP event;
C: with secondary progressive MS diagnosis at study entry and without confirmed relapses during the study.

Table. Clinical outcomes and composite scale of SDI in patients receiving ATA188 [1].

	Cohort 1		Cohort 2		Cohort 3		Cohort 4
Outcome	**6 m (n=6)**	**12 m (n=6)**	**6 m (n=6)**	**12 m (n=6)**	**6 m (n=6)**	**12 m (n=5)**	**6 m (n=6)**
Composite scale 1: *a priori* clinical outcome classification							
Clinical decline	4	5	1	1	2	2	2
Stable	0	0	0	0	1	0	0
Partial clinical improvement	1	0	3	2	0	0	4
Clinical improvement	1	1	2	3	3	3	0
Composite scale 2: SDI							
SDI	1	1	1	1	2	3	2

m, months; SDI, sustained disability improvement.

In all subsets, ofatumumab significantly reduced the risk of 3mCDP and 6mCDP versus teriflunomide, except for 6mCDP in the small Subset-C (see Table). An inverse probability censoring weighted estimation of PIRA confirmed a significant risk reduction for ofatumumab versus teriflunomide of 46.0% for 3mCDP (HR 0.540; 95% CI 0.396-0.738; P<0.001) and 42.5% for 6mCDP (HR 0.575; 95% CI 0.409-0.808; P=0.001).

Table. Risk of 3mCDP and 6mCDP with ofatumumab versus teriflunomide [1].

Disability-related outcomes	Ofatumumab 20mg n/N	Teriflunomide 14mg n/N	HR (95% CI)	Risk reduction	P-value
3mCDP					
Subset-A	50/793	67/661	0.587 (0.407-0.848)	41.3%	0.004
Subset-B	53/796	82/676	0.516 (0.365-0.729)	48.4%	<0.001
Subset-C	6/46	11/37	0.312 (0.114-0.859)	68.8%	0.024
6mCDP					
Subset-A	42/793	53/661	0.632 (0.421-0.947)	36.8%	0.026
Subset-B	45/796	66/674	0.551 (0.377-0.805)	44.9%	0.002
Subset-C	6/46	8/37	0.463 (0.158-1.355)	53.7%	0.160

n, number of patients with the specified event; N, total number of patients included in the analysis; 3mCDP, confirmed disability progression at 3 months; 6mCDP, confirmed disability progression at 6 months

In the superiority phase 3 OPTIMUM trial, the efficacy and safety of ponesimod and teriflunomide were compared [2,3] in 1,133 adult RMS patients (18-55 years) with an expanded disability status scale (EDSS) score of 0-5.5. They were randomised to ponesimod 20 mg or teriflunomide 14 mg once daily for 108 weeks.

The ARR for ponesimod and teriflunomide was 0.202 and 0.290, corresponding to a relative rate reduction (RRR) with ponesimod of 30.5% (P=0.0003). Respective mean change from baseline in fatigue symptom and impact questionnaire-RMS weekly symptoms score was 0.01 versus 3.57 (P=0.0019). Mean number of combined unique active lesions per year (CUALs) on MRI was 1.405 versus 3.164 (RRR 56%, P<0.0001). Time to 12- and 24-week confirmed disability accumulation risk estimates were reduced by 17% (P=0.29) and 16% (P=0.37), respectively.
In general, the safety of ponesimod and teriflunomide was comparable after 108 weeks [2]. Incidence of treatment-emergent adverse events (TEAEs) (88.8% vs 88.2%) and serious AEs (8.7% vs 8.1%) were similar. TEAEs leading to treatment discontinuation were 8.7% and 6.0%. Most common TEAEs were increased alanine aminotransferase levels (19.5% vs 9.4%), nasopharyngitis (19.3% vs 16.8%), headache (11.5% vs 12.7%), and upper respiratory tract infection (10.6% vs 10.4%).

1. Kappos L, et al. Abstract O2034, EAN 2020.
2. Kappos L, et al. Abstract S40.010, AAN 2020.
3. Sprenger T, et al. Abstract P5.021, AAN 2020.

Switching from natalizumab to moderate- versus high-efficacy DMT

Multiple sclerosis (MS) patients switching from natalizumab to another high-efficacy therapy had more favourable inflammatory and disability outcomes after 24 months than patients who deescalated to a moderate-efficacy disease-modifying therapy (DMT), which yielded greater disability progression [1].

The effect of such a treatment change was assessed after 24 months of follow-up. The 556 participants discontinued natalizumab treatment between 2005 and 2018 for various reasons, including progressive multifocal leukoencephalopathy risk (54.9%), breakthrough disease (15.3%), and adverse effects (17.3%). Of those participants, 270 (48.6%) switched to moderate-efficacy DMT (dimethyl fumarate, n=130; fingolimod, n=140), while 130 (23.4%) switched to high-efficacy therapy (ocrelizumab, n=106; rituximab, n=17; alemtuzumab, n=7).

At 24 months, there were no differences in annualised relapse rate (OR 1.44; 95% CI 0.69-1.59; P=0.334). However, a significantly lower proportion of patients in the moderate-efficacy DMT group had no disease activity compared to the high-efficacy therapy group (OR 0.41; 95% CI 0.21-0.71; P=0.004). In the moderate-efficacy DMT group, a significantly higher proportion had:

- new T2 lesions (OR 2.15; 95% CI 1.18-3.01; P=0.011);
- new gadolinium enhancing lesions (OR 1.99; 95% CI 1.12-2.73; P=0.022);
- 20% worsening of the timed 25-foot walk (OR 1.83; 95% CI 1.06-3.02; P=0.043);
- 20% worsening of the 9-hole peg test (OR 1.81; 95% CI 1.05-3.56; P=0.044).

1. Hersh CM, et al. Abstract S29.008, AAN 2020.

Results of compounds in late stages of development

MD1003 (high-dose pharmaceutical-grade biotin) did not meet any of the primary or secondary endpoints in patients with progressive multiple sclerosis (MS) in the SPI2 trial [1].

There were positive phase 2b trial results of the Bruton's tyrosine kinase (BTK) inhibitor SAR442168 [2], and positive phase 3 results of oral diroximel fumarate (DRF) [3].

In the SPI2 trial, 642 patients were randomised to MD1003 (n=326) or placebo (n=316) [1]. Of the participants, 64.6% had secondary progressive MS; mean Expanded Disability Status Scale (EDSS) was 5.4, mean Timed 25-Foot Walk (TW25) 11.6 seconds. The double-blind period was 15-27 months. The primary endpoint, the proportion of patients with improvement in EDSS or TW25 (>20%), was not significantly different. The rate of EDSS or TW25 responders was 12.0% in the MD1003 group versus 9.2% in the placebo group (OR 1.35; 95% CI 0.81-2.26). In a subgroup analysis, there was a trend favouring MD1003, but not a single subgroup for whom MD1003 was clearly beneficial. There were no differences in times to 12-week confirmed EDSS progression, clinical global impression after 15 months, or change from baseline in TW25. MD1003 was generally well tolerated. The annualised relapse rate was very low in both groups (0.0362 vs 0.0478). These results did not confirm the beneficial effect of MD1003 on MS disability previously reported in the phase 3 MS-SPI study.

SAR442168, a central nervous system (CNS)-penetrating BTK inhibitor, was well tolerated at a dose of 60 mg and effectively lowered MRI lesions in relapsing MS patients [2]. A total of 130 relapsing MS patients were enrolled in this phase 2b study, with a median EDSS score of 2.5 at baseline. After 12 weeks, a dose-response relationship was established. Compared with placebo, the 60-mg dose resulted in an 85% relative reduction in the number of new gadolinium+ lesions, as well as an 89% relative reduction in the number of new/enlarging T2 lesions. Exploratory endpoints in terms of effects on the CNS, potentially on microglia, were still under investigation and could not yet be shared. SAR442168 was well tolerated over 12 weeks, with 129/130 patients (99%) completing the core study. There were no early safety signals, and only one serious adverse event occurred, which was hospitalisation for an MS relapse. These positive results of the DRI15928 study support further development in phase 3 studies.

The ongoing, open-label phase 3 study EVOLVE-MS-1 evaluates long-term safety, tolerability, and treatment effect of oral DRF in adults with relapsing-remitting (RR)MS. Two-year efficacy outcomes were presented of patients who: A) had newly diagnosed RRMS (≤1 year since diagnosis and treatment-naïve; n=109), or B) were most recently treated with interferon-β or glatiramer acetate (n=327) [3]. Adjusted annualised relapse rate was 0.13 (95% CI 0.07-0.23) and 0.17 (95% CI 0.12-0.23) in group A and B, respectively: a reduction of 88.6% (95% CI 79.8-93.6; P<0.0001) and 73.2% (95% CI 63.1-80.6; P<0.0001) compared to the 12 months before study entry. Mean EDSS scores remained stable at week 96 compared to baseline: 2.00 (n=60) versus 2.02 (n=108) in group A and 2.55 (n=100) versus 2.64 (n=310) in group B. More patients were free from gadolinium+ lesion at week 96 compared to baseline: 86.9% versus 54.1% (n=61) in group A; 93.9% versus 78.6% (n=98) in group B.

1. Cree BAC, et al. Abstract O2033, EAN 2020.
2. Reich DS, et al. Abstract O4010, EAN 2020.
3. Jasińska E, et al. Abstract EPR2124, EAN 2020.

Alemtuzumab efficacy and safety data of over 9 years

Alemtuzumab improved outcomes versus subcutaneous interferon (SC IFN)β-1a over 2 years in multiple sclerosis (MS) patients with highly active disease from CARE-MS and extension studies. Efficacy was maintained up to 9 years [1]. Safety data of alemtuzumab was also presented, notably acute adverse events (AEs) during infusion and in the days following, as well as AEs occurring after lymphocyte repopulation.

Alemtuzumab efficacy and safety over 9 years were reported in patients that were previously treated with disease-modifying treatment and with highly active disease at baseline of the core CARE-MS I/II trials. In the first 2 years, annualised relapse rate was decreased with alemtuzumab versus SC IFNβ-1a and remained low in years 3-9 (0.16, 0.17, and 0.25, respectively, according to definition). Through year 9, 49%-59% of patients with highly active disease achieved 6-month confirmed disability improvement and 55%-64% remained free of 6-month confirmed disability worsening. Median cumulative brain volume change ranged from -0.64% to -1.80%. Safety in patients with highly active disease was similar to that in the overall study population, including serious AEs (39.8%-47.8% vs 44.8%).

Over 9 years in pooled CARE-MS alemtuzumab treated patients (n=811), AEs occurring after lymphocyte repopulation (18-36 months post treatment) included [2]:

- thyroid disorders (47.6%);
- immune thrombocytopenia (2.7%);
- autoimmune nephropathies (0.4%);
- acute acalculous cholecystitis (0.4%).

Among 25,292 patients treated with alemtuzumab in the postmarketing setting, there were also rare cases of autoimmune hepatitis (10.7/ 10,000) and haemophagocytic lymphohistiocytosis (2.7/10,000). Notable acute AEs temporally associated with alemtuzumab in the pooled CARE-MS studies (n=811) were predominantly infusion-associated reactions and serious infections, with a respective incidence of 90% and 3% [3]. Additional postmarketing events of interest (n=25,292) included haemorrhagic stroke/pulmonary alveolar haemorrhage (7.1/10,000 patients treated), other stroke (0.8/10,000), myocardial infarction (2.0/10,000), and cervicocephalic arterial dissection (1.6/10,000). Some patients who experienced myocardial infarction were aged <40 years and had no risk factors for ischaemic heart disease; some cases had temporarily abnormal blood pressure and/ or heart rate during infusion.

1. Ziemssen T, et al. Abstract EPR3107, EAN 2020.
2. Jones J, et al. Abstract EPR2127, EAN 2020.
3. Vermersch P, et al. Abstract EPR3097, EAN 2020.

Fampridine treatment results in routine clinical practice

Long-term treatment with prolonged-release fampridine (PR-FAM) in the LIBERATE study showed clinical benefits consistent with those previously reported [1]. No new safety signals were identified in this real-world study, suggesting that routine risk minimisation measures were effective.

PR-FAM 10 mg twice-daily is indicated for the improvement of walking in adult multiple sclerosis (MS) patients with walking disability (Expanded Disability Status Scale [EDSS] 4-7). The observational LIBERATE study recruited patients newly prescribed PR-FAM at 201 sites in 13 countries.

MS Impact Scale-29 (MSIS-29) physical impact score improved significantly for patients on-treatment for 12 months versus those who discontinued (mean change from baseline to 12 months: 9.99 vs -0.34 points; P<0.001). Results were similar for MSIS-29 psychological impact. At 12 months, 61% of patients on treatment had improvement in walking ability rated by Clinical Global Impression of Improvement (CGI-I) versus 11% of those who discontinued (P<0.001).
The safety analysis included 4,646 patients. Median age was 52.6 (range 21–85), 65.7% were female; 24.9% (n=1,158) of patients discontinued treatment due to lack of efficacy. The rate of treatment-emergent adverse events (TEAEs) was 52.7%, the rate of serious TEAEs 6.0% (see Table).

Table. Overall adverse events and adverse events of special interest [1].

Treatment-emergent AE per category, n (%)	European countries (n=4,439)	Non-European countries (n=207)	Total (n=4,646)
Any	2,407 (54.2)	41 (19.8)	2,448 (52.7)
Serious	277 (6.2)	2 (1.0)	279 (6.0)
Special interest	1,767 (39.8)	32 (15.5)	1,799 (38.7)
Seizure-related	17 (0.4)	0 (0.0)	17 (0.4)
Serious hypersensitivity-related	1 (<0.1)	0 (0.0)	1 (<0.1)
Urinary tract infection-related	399 (9.0)	7 (3.4)	406 (8.7)
Severe infections other than UTI-related	148 (3.3)	0 (0.0)	148 (3.2)
Depression and suicide-related	59 (1.3)	0 (0.0)	59 (1.3)
Anxiety-related	68 (1.5)	1 (0.5)	69 (1.5)
Suggestive of CNS stimulation-related	1,382 (31.1)	26 (12.6)	1,408 (30.3)
Cardiovascular-related	80 (1.8)	1 (0.5)	81 (1.7)
Clinically significant haematological abnormality-related	26 (0.6)	0 (0.0)	26 (0.6)

UTI, urinary tract infection

1. Castelnovo G, et al. Abstract EPR1160, EAN 2020.

Air pollution is a possible risk factor for MS

Air pollution could be a risk factor for the development of multiple sclerosis (MS). An Italian study in the province of Pavia –one of the most polluted areas in Europe– found a relationship between MS risk and high concentrations of the fine pollutant particulate matter PM2.5 in the air [1].

MS is associated with multiple genetic and environmental risk factors. Some environmental factors have been extensively studied, including vitamin D levels and smoking, but not air pollution. Airborne PM is a complex mixture of solids and aerosols. PM10 includes particles with a diameter of 10 µm or less, PM2.5 have a diameter of 2.5 µm or less that can penetrate even further into the lungs.

The researchers identified 927 MS patients resident in the province of Pavia (547,251 inhabitants) in Lombardy, Italy. They gathered spatial emission data for PM2.5 concentrations in winter, when PM concentrations peak. Municipalities were stratified into 3 groups by tertiles according to PM2.5 concentrations.

The overall MS prevalence in Pavia was 169.4 per 100,000 inhabitants, compared to 16 per 100,000 in 1974. In 2 of the 3 groups of municipalities, air pollution levels were above

the European Commission threshold of 25 µg/m^3. In the 2 groups with high air pollution levels, the risk of MS was 29% higher than in the third group with lower air pollution levels, which is a significant difference. The Bayesian map showed consistent high-risk clusters with an excess number of MS cases. The authors hope that this will encourage analytical studies in high-risk areas to analyse multiple environmental factors related to the uneven distribution of MS.

1. Bergamaschi RGE, et al. Abstract EPR1151, EAN 2020.

Neuromyelitis Optica Spectrum Disorder

Genetic association studies in NMOSD needed

There are differences in prevalence and phenotype of neuromyelitis optica spectrum disorder (NMOSD) in people with different genetic backgrounds. Results from a population-based comparative study suggest differences even among Caucasian populations in Europe [1].

The potential geographical variation in prevalence and phenotype of NMOSD with aquaporin-4 antibody seropositivity among the adult (age ≥16) populations of Denmark and Hungary were compared. In total, 35 Danish and 99 Hungarian cases could be identified. The prevalence in Hungary compared to Denmark on 1 January 2014 was significantly higher: 1.39/100,000 (95% CI 1.11-1.71) versus 0.71/100,000 (95% CI 0.48-1.01) (P=0.0019). The most frequent onset attack in the Hungarian cohort was optic neuritis (n=41, 41% vs n=6, 17%; P=0.013), while transverse myelitis was the most common in the Danish cohort (n=21, 60% vs n=35, 35%; P=0.009). The Danish cohort was more affected by spinal cord damages. The authors concluded that their results substantiate the need for genetic association studies in NMOSD.

1. Papp V, et al. Abstract EPR3076, EAN 2020.

Eculizumab in NMOSD: the PREVENT study

In the phase 3, randomised, double-blind PREVENT study, eculizumab was effective in aquaporin-4 immunoglobulin (Ig)G-positive neuromyelitis optica spectrum disorder (NMOSD) in different regions of the world, despite significant differences in standard of care [1]. Long-term results from the PREVENT study's open-label extension (OLE) supported the efficacy of eculizumab monotherapy in reducing relapse risk [2].

The PREVENT study assessed the efficacy and safety of eculizumab in adult patient populations in Europe, the Americas, and Asia-Pacific. Patients were randomised to eculizumab or placebo. Stable doses of concomitant immunosuppressive therapy (IST) were allowed. IST use at baseline was much lower in Europe than in the other 2 regions, so that a large proportion of European participants in the placebo group had no medication at all. Compared with placebo, eculizumab significantly reduced relapse risk, relapse-related hospitalisation, and rates of acute relapse treatment with intravenous methylprednisolone across regions [1].

These results suggested a treatment effect of eculizumab monotherapy that is consistent with the overall population. A post-hoc analysis of long-term results from the OLE of the PREVENT study confirmed the efficacy of eculizumab monotherapy in reducing relapse risk [2]. Relapse-related disability outcomes and healthcare resource utilisation were reported in a subgroup of 34 patients (24%) who received eculizumab monotherapy or placebo without concomitant IST use. The majority (95%) experienced stability or improvement in measures of disability. In the prespecified subgroup analysis, adjudicated relapses occurred in 0/21 patients receiving eculizumab monotherapy and 7/13 (53.8%) receiving placebo (P<0.0001). Fewer patients in the eculizumab group had disability progression. In the placebo group, 6/13 patients (46.2%) were hospitalised for adjudicated relapses and received treatment. In the eculizumab and in the placebo group, Expanded Disability Status Scale (EDSS) scores worsened in 5/13 (38.5%) patients, respectively (P=0.151). Hauser Ambulation Index score worsened in 1/21 (4.8%) and 4/13 (30.8%), respectively (P=0.205).

1. Oreja-Guevara C, et al. Abstract O4009, EAN 2020.
2. Pittock SJ, et al. Abstract LB90, EAN 2020.

Long-term safety of satralizumab consistent with double-blind periods

In patients with neuromyelitis optica spectrum disorder (NMOSD), satralizumab continued to be well tolerated and to have a favourable safety profile when open-label extension period data were included in the analysis [1]. The overall satralizumab treatment data were consistent with the double-blind periods.

Satralizumab is a humanised monoclonal antibody that binds to and blocks the IL-6 receptor and was shown to reduce NMOSD relapse risk in both the SAkuraSky (satralizumab in combination with baseline immunosuppressants), and the SAkuraStar (satralizumab monotherapy) phase 3 trials. The pooled double-blind population included 178 patients (satralizumab, n=104; placebo, n=74); 166 patients received satralizumab in the open-label extension period. The combined double-blind/extension period was defined as the overall satralizumab treatment period, in which mean exposure was around 130 weeks.

In the double-blind period, rates of adverse events (AEs) and serious AEs in the satralizumab arms were comparable to those with placebo. Infection rates were lower with satralizumab. In the double-blind and overall treatment periods, AE, serious AE, and infection rates were comparable (see Table). An AE led 4 patients (3.8%) on satralizumab and 6 (8.1%) on placebo to withdraw from the double-blind period. The injection-related reaction (IRR) rate was higher with satralizumab. IRRs were mostly mild-to-moderate and did not lead to treatment discontinuation.

Table. Pooled adverse event rates across the SAkuraSky and SAkuraStar trials [1].

Events/100 PY (95% CI)	Double-blind period		OST period
	Satralizumab (n=104)	Placebo (n=74)	Satralizumab (n=166)
AEs	478.49 (448.18-510.31)	506.51 (463.38-552.59)	418.79 (399.83-438.41)
Serious AEs	14.97 (10.02-21.50)	17.98 (10.66-28.42)	12.57 (9.47-16.36)
Infections	113.04 (98.56-129.04)	154.85 (131.43-181.24)	112.41 (102.69-122.79)
Serious infections	4.13 (1.78-8.14)	6.99 (2.81-14.41)	3.88 (2.26-6.22)
Injection-related reactions	17.03 (11.73-23.92)	8.99 (4.11-17.07)	12.11 (9.07-15.84)

AE, adverse event; OST period, overall satralizumab treatment period; PY, patient year.

1. Greenberg BG, et al. Abstract EPR2140, EAN 2020.

Neuromuscular Disorders

Biomarkers predicting motor function in SMA

Cerebrospinal fluid (CSF) and plasma phosphorylated neurofilament heavy chain (pNfH) levels following nusinersen loading may predict future motor function in participants of the phase 2 study NURTURE [1]. This ongoing open-label study is examining the efficacy and safety of intrathecal nusinersen in presymptomatic infants with 2 or 3 copies of the *SMN2* gene.

The study enrolled 25 clinically presymptomatic infants that were genetically diagnosed with spinal muscular atrophy (SMA) (15 had 2 copies of *SMN2*, 10 had 3 copies). All were ≤6 weeks old when treatment was initiated. CSF samples were collected at baseline, on days 1, 15, 29, 64, and 183, and every subsequent 119 days. The samples were used to measure levels of pNfH, which were correlated with Hammersmith Infant Neurological Examination (HINE)-2 motor milestone total score and WHO motor milestone walking alone. The ongoing study's primary endpoint is time to death or respiratory intervention (invasive/non-invasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy).

The median age at last visit was 34.8 months (range 25.7-45.4). All the infants were alive and none required permanent ventilation. CSF pNfH levels rapidly declined during the nusinersen loading period and then stabilised at lower plateau levels. CSF pNfH levels at baseline and day 64 significantly correlated with the ability to walk alone earlier (a WHO motor milestone), and with total HINE-2 score at day 302. In participants with 2 *SMN2* copies, day 64 weight for age and compound muscle action potential amplitude also correlated with these outcome measures. The rate of infants achieving WHO motor milestones was unusually high for SMA types 1 and 2 (which is what they will most likely develop), many of them doing so in the normal time frame for a toddler.

1. Sansone VA, et al. Abstract O1012, EAN 2020.

Sustained benefits of avalglucosidase alfa in late-onset Pompe disease

The novel investigational enzyme replacement therapy (ERT) avalglucosidase alfa (neoGAA) continued to show clinically meaningful improvement of pulmonary and motor function in patients with late-onset Pompe disease (LOPD) after up to 5.5 years in the NEO1/NEO-EXT studies [1].

NEO-EXT, an ongoing NEO1 extension, assesses efficacy trends of long-term neoGAA use in LOPD patients. In the open-label ascending dose study NEO1, 24 patients enrolled who were either naïve to enzyme replacement therapy (Naïve; n=10) or had received ≥9 months' standard-of-care alglucosidase alfa (Switch; n=14). They received neoGAA 5, 10, or 20 mg/kg every other week for 6 months. In NEO-EXT, patients continued their NEO1 dose until, in 2016, they all transitioned to 20 mg/kg.

Of the 24 NEO1 participants, 19 continued to NEO-EXT (8 Naïve, 11 Switch), and 17 remained on treatment (7 Naïve, 10 Switch) at the cut-off in July 2019. Upright predicted percentage for forced vital capacity remained stable at group level and mostly at an individual level (see Table). Upright predicted percentage for maximum inspiratory pressure and maximum expiratory pressure also generally remained stable, but varied more among individual patients. Predicted percentage for 6-minute walk test (6MWT) distance remained stable among most patients in both groups. Improvement in 6MWT was observed in patients aged ≤50 years at NEO1 enrolment. NeoGAA was generally well tolerated; the safety profile in NEO1 and NEO-EXT was consistent.

1. Schoser B, et al. Abstract EPR3110, EAN 2020.

Table. Estimates of linear mixed effect model – efficacy analysis set (patients who ever received 20 mg/kg avalglucosidase alfa for up to 5.5 years) [1].

	Slope (years)	
	Naïve patients (n=7)	Switch patients (n=12)
	Estimate (95% CI)	Estimate (95% CI)
FVC, % predicted	0.396 (-0.351, 1.144)	-0.331 (-0.778, 0.115)
MIP, % predicted	0.743 (-0.613, 2.100)	-0.946 (-2.001, 0.110)
MEP, % predicted	0.698 (-0.692, 2.088)	1.192 (-0.148, 2.531)
6MWT, distance walked, % predicted	-0.965 (-1.891, -0.038)	-1.216 (-2.027, -0.405)

6MWT, 6-minute walk test; CI, confidence interval; FVC, forced vital capacity; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure