

AAN Annual Meeting Briefing



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Hot Topic: Precision Medicine

Without a doubt, precision medicine is becoming more of a reality given recent advances in genomic sequencing and broadened access to technology such as electronic health records and smart devices. In the opening plenary session of this year's annual meeting, Dr. Francis Collins, Director of the National Institute of Health (NIH), discussed the government-sponsored All Of Us research program (<https://allofus.nih.gov/>), which aims to gather anonymized data from 1M people over the next 10 years in order to better understand the interactions between genes, lifestyle, and environment; the ultimate goal of the project is to use the information garnered to improve current approaches to disease prevention, diagnosis, and management. Over 30,000 people have already initiated enrollment and the program will officially launch this spring. The potential for outputs from All of Us to impact neurology practice is great given the high prevalence of disabling brain disorders such as migraine, dementia, and chronic pain as well as the chronicity of many neurodegenerative diseases, including those affecting the aging population such as Alzheimer's disease (AD).

The NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, aimed at delineating three-dimensional organization of diverse cell types in the brain, was also in the limelight. By studying neuronal circuitry, or the connectome, as a whole, it is hoped that new biomarkers and/or potential therapeutic targets of circumstance will be revealed. These discoveries in turn, have the potential to fuel revolution in neurotherapeutics, particularly in areas where pharmaceutical companies do not currently have strong focus. The fields of psychiatry and pain, where clinical pathologies are not always apparent, were particularly noted. Information from this initiative was also said to have potential in the opioid crisis, specifically by providing physicians with a means of distinguishing at a molecular level those patients who are truly suffering from pain, thereby supporting responsible prescribing behavior.

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Jill has 15 years of experience in healthcare communications and engages with medical affairs and market access stakeholders within the pharmaceutical industry to guide the development of sound communication strategies and tactics that address healthcare provider, payer, and patient requirements. She has recently supported a number of initiatives aimed at assessing evidence needs and gaps across these various stakeholders.

In healthcare communications, Jill has worked across a variety of therapeutic areas, with a keen interest in the areas of immunology, neurology, and oncology. She holds a BS degree in Animal Science from the University of Delaware and a PhD in Cell and Molecular Biology from the University of Pennsylvania.



Hot Topic: Big Data and the Digital Revolution

The rise of technology in healthcare was certainly evident at the meeting, with educational sessions, scientific presentations, and sponsor presence in the areas of telemedicine, patient engagement tools, and monitoring wearables and apps abound. Healint, the company behind the Migraine Buddy app, a headache diary and tracking tool designed by neurologists and data scientists, had a large presence on the meeting’s social stream. Novartis has announced they are working with Healint to raise awareness of the burden and prevalence of migraine.

A handful of presentations examined the potential for wearables to detect on/off states in Parkinson’s disease and AbbVie is undertaking a longitudinal study (PROVIDE) that will employ a wearable sensor to assess the long-term efficacy of Duopa®. Novartis and Evidation are studying the potential for data from wearables, such as number of steps and sleep, to provide insights into quality of life and well-being in patients with multiple sclerosis (MS), while Roche is conducting a formal clinical study (FLOODLIGHT) to assess the potential of sensor-based outcomes derived from preconfigured smartphones and smartwatches to measure MS progression compared with that of information collected at periodic in-clinic visits.

With more data comes discussion of data quality and utility in practice. During a discussion of the potential for digital technologies to advance MS care, participants highlighted the importance of standardizing data collection and of converting big data

into smart data through combined machine and deep learning. The Biogen-sponsored MS PATHS collaboration of 10 US and European institutions seems to have set up an infrastructure to work toward just that. Preliminary data from the collaboration demonstrated how the collected information can inform areas of unmet need for patients.

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Influences of the Current Healthcare Environment on Clinical Practice and Access

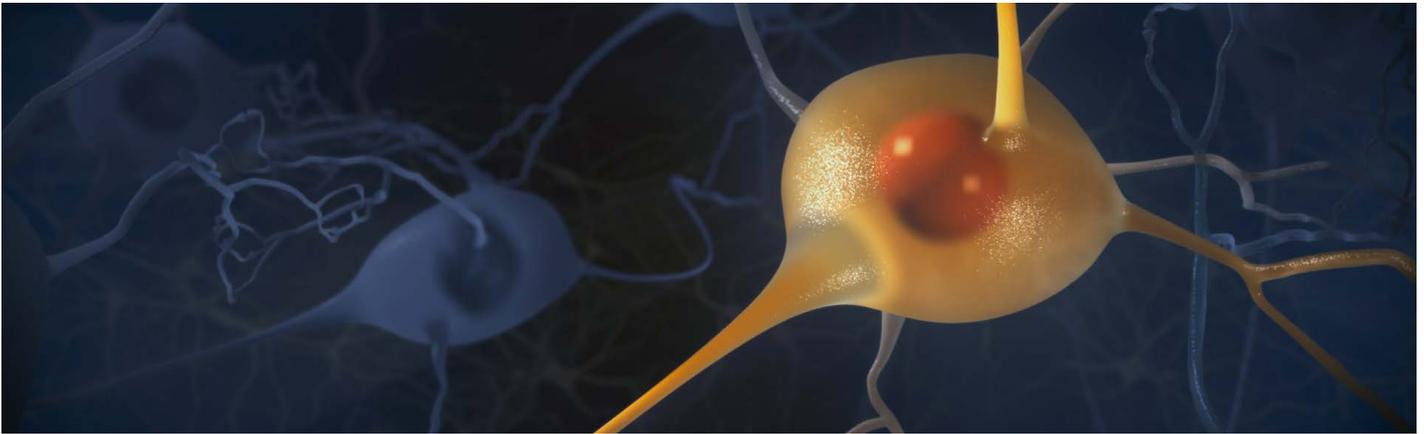
The increased focus on treatment costs and quality measures in recent years has, in turn, raised the importance of value demonstration at both the drug and practitioner level. As such, the AAN held a series of informal talks on “Maximizing Value” throughout the meeting.

Much of the AAN’s effort was focused on their quality clinical data registry, the Axon Registry®, which allows tracking and submission of various outcome measures across many neurologic disciplines. Live demonstrations of the tool and a series of discussions around its utility in improving clinician practices, quality reporting, and value occurred.

A session on high-cost neurology drugs was well attended. Practitioners discussed challenges such as provider

capacity, potential for penalties under the Centers for Medicare and Medicaid Service’s Quality Payment Program, approaches to value determination, and the potential intricacies of value-based contracting scenarios; the latter may be uniquely challenging in neurodegenerative diseases, which are often slow to progress and therefore, show clinical response to therapy.

Patient access to some of the newer therapies was also a point of concern for practitioners. They cited challenges with managing treatment switches in MS from an insurance authorization and reimbursement perspective, managing discrepancies between insurance restrictions and product labelling for treating patients with Spinraza®, and limited access to some of the newer intrathecally-administered therapies, a class that will likely grow given the meeting’s proceedings. Down the line, the calcitonin gene-related peptide (CGRP) monoclonal antibodies for migraine prevention, purified cannabidiol (Epidiolex® from GW Pharma), and the multitude of gene therapies on the horizon are expected to pose new challenges in this arena.



Spotlight on Alzheimer's Disease

The development of effective disease-modifying therapies in AD has been challenging, to say the least. Despite continued setbacks for the amyloid hypothesis, a number of companies remain committed to the development of monoclonal antibodies targeting beta amyloid (A β). Data presented at the annual meeting for aducanumab (Biogen) and gantenerumab (recently resurrected by Roche) focused on mild/prodromal patients, a population believed to have the best chance for therapeutic effect of amyloid depletion. The aducanumab analyses came from a 36-month extension of the phase 1b PRIME study and the gantenerumab analyses were from the phase 3 Marguerite and Scarlet RoAD studies, which were converted to open-label extensions after they were deemed unlikely to achieve their primary endpoints. Data presented for these compounds focused mostly on demonstration of amyloid reduction, dosing optimization, and safety assessments. Key issues with the passive A β immunotherapies as highlighted during the meeting included:

- The standardization of amyloid positron emission tomography (PET) measures, which Biogen has begun to address through application of the centiloid scale for their most recent analysis of the PRIME study data;
- The mitigation/management of amyloid-related imaging abnormalities (ARIA), an established adverse effect said to occur early in treatment and that may be addressed by the use of dose-titration strategies, being incorporated into the aducanumab and gantenerumab

phase 3 programs, or by the alteration of the antibody's A β binding properties, as is being proposed by Roche as a distinguishing feature of their other AD contender, crenezumab;

- And perhaps most critical, yet still lacking, the ability to correlate reductions in amyloid with clinical outcomes such as cognitive benefits.

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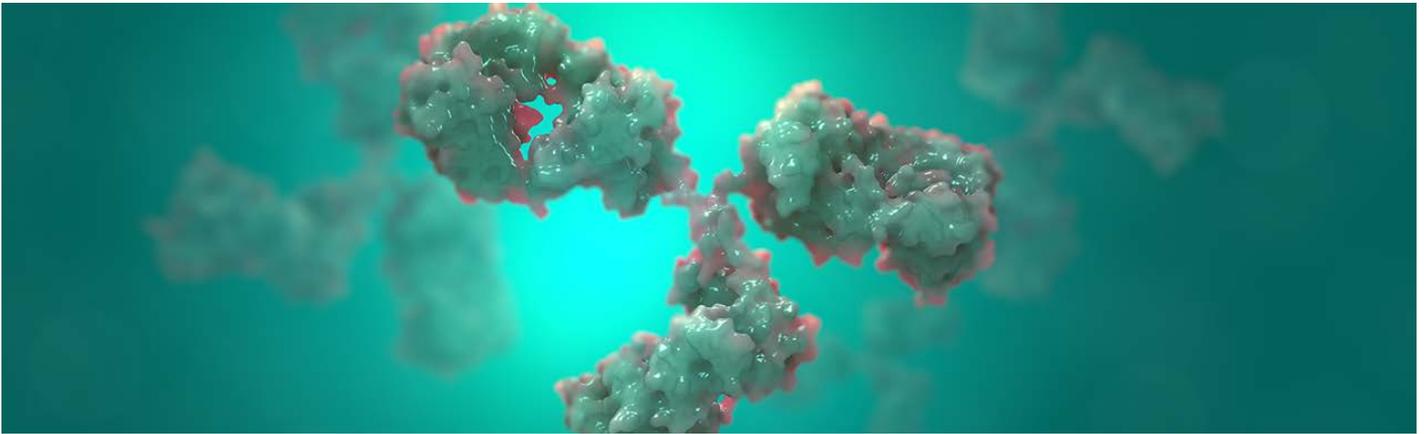
Tau, which is thought to be implicated later in the disease course but to correlate better with disease progression as compared with amyloid, is being pursued as a therapeutic target by Ionis. The design of their first-in-human study of IONIS-MAPTRx, an intrathecally-delivered tau-lowering antisense oligonucleotide (ASO), was presented. This study was recently initiated and will examine a multiple ascending dose in patients with mild AD; no data are yet available.

No data on the BACE inhibitors were presented at this year's meeting.

The National Institute on Aging and the Alzheimer's Association (NIA-AA) research framework to investigate the AD continuum was just published two weeks ago. The framework dictates

that amyloid and tau positivity qualify a patient for placement on the AD continuum. This guidance, coupled with the shift toward targeting mild/prodromal patients for treatment, fuelled various discussions of biomarkers at the meeting.

- Challenges such as limited reimbursement for amyloid PET in the US and the implications for proper diagnosis were cited.
- Barriers to successful clinical trial recruitment were also highlighted. When the audience in a disease state symposium was asked how they would manage a hypothetical patient testing positive for both amyloid and tau, but with just mild cognitive impairment, only ~50% said they would recommend the patient to a clinical trial. Further, it was noted that patients with mild/prodromal disease often express reluctance to enter a trial owing to the nature of some of the required biomarker testing (eg, frequent labs, need for lumbar puncture) and the possibility of adverse events without guaranteed benefit.
- Finally, questions still remain among the general neurologist population as to whether amyloid is the "end all, be all" disease marker given the possibility for amyloid positivity in the absence of clinical symptoms. The previously discussed trials should help address this.



Spotlight on Migraine

The prevalence and underdiagnosis of migraine as well as the inadequacies of current treatment options were highlighted throughout the meeting during both scientific sessions and corporate-sponsored activities. Excitement around the likely imminent arrival of the anti-CGRP monoclonal antibodies for the prevention of migraine was also evident.

With their PDUFA date set for May 17th, Amgen/Novartis showcased distinguishing data from the phase 3b LIBERTY study of erenumab (Aimovig®) during the Emerging Science session. LIBERTY was touted as the first dedicated study to evaluate efficacy in patients with episodic migraine who had failed 2–4 prior treatments, a common scenario in clinical practice. Patients treated with erenumab had nearly 3-fold higher odds of having their migraine days cut by at least 50% compared with placebo. Both Lilly and Teva also demonstrated effectiveness of their anti-CGRP compounds (galcanezumab and fremanezumab, respectively) in previous treatment failures using pooled and subgroup analyses.

Alder, who is developing eptinezumab, a likely later-to-market entrant, was on the podium at a “Best Of” session as well as at the Clinical Trials plenary session with data from their phase 3 program in episodic (PROMISE-1) and chronic (PROMISE-2) migraine. In PROMISE-1, a cumulative increase in response with repeated dosing over the long term was noted. Long-term use came into question by attendees given the likelihood that the class will be associated with a high price tag (currently being estimated

at ~\$8500/year for erenumab). The Institute for Clinical and Economic Review (ICER) recently released a draft evidence report (<http://www.ajmc.com/newsroom/cgrp-inhibitors-yield-clinical-benefit-but-exceed-costeffectiveness-threshold-in-treatment-of-migraines>) that concluded the anti-CGRPs are “likely to exceed commonly-cited willingness-to-pay thresholds”. With cost at the forefront, remaining questions around longer-term use include: How much time on treatment will be granted by reimbursement bodies for a patient to achieve a response? Can patients eventually be transitioned to lower cost treatments? Not surprisingly, interest in head-to-head studies with other preventive treatments was voiced.

Overall, the anti-CGRPs are expected to have a relatively clean safety profile, a welcome attribute in a paradigm that includes many treatments with a range of tolerability issues. As with any new drug, attendees did raise questions about the long-term safety of the class. Questions over cardiovascular (CV) safety also arose given that CGRP is a vasodilator. Amgen/Novartis had a few data presentations that suggested this is not of concern in patients with CV risk factors or those using triptans/ergotamines; they also demonstrated a lack of effect on blood pressure.

Excitement around the likely imminent arrival of the anti-CGRP monoclonal antibodies for the prevention of migraine was also evident.

CGRP as a target for migraine treatment also received attention in the acute setting. The first results from Allergan’s phase 3 ACHIEVE-1 study of ubrogepant, an oral CGRP antagonist, for the treatment of a single attack were also showcased during the Emerging Science session. Both co-primary endpoints (pain freedom and absence of most bothersome migraine-associated symptoms at 2 hours post dose) were met. Furthermore, the safety profile was favorable with no signs of liver toxicity, which was previously raised as a potential concern. Other cellular targets with suggested ties to CGRP modulation as reported at the meeting include the 5-HT_{1F} receptor (currently the target of Lilly’s lasmiditan) and the delta opioid receptor, highlighted because of its lack of abuse potential.

Spotlight on Multiple Sclerosis

With 17 products available to treat MS and at least that many more in various stages of clinical development, presentations devoted to this therapeutic area were aplenty. With such a complex landscape of treatment options, the AAN’s release of updated practice guidelines during the meeting, the first since 2002, received much attention in the press. A main takeaway from the new guidelines is the recommendation of early treatment initiation; guidelines for switching and stopping therapy are also provided.

Not unexpectedly, the classic disease-modifying therapies (DMT) are still relying heavily on their large datasets owing to long-term patient experience.



This was reflected in themes such as Rebif®'s "Experience that keeps going" and Copaxone®'s "Past present future" exhibit booth headlines. Teva, being faced with generic competition from Mylan and Sandoz, devoted half of their scientific presentations to demonstrating differences between brand (Copaxone®) and generic glatiramer acetate (GA) with regard to composition, gene expression profiles, and function. Mylan, manufacturer of the newest generic to hit the market, presented data of their own suggesting biologic equivalence of their product to Copaxone®. Results from an open-label phase 2 clinical study of a monthly GA depot being developed by Mapi Pharma and Mylan showed that a majority of patients (87%) had no evidence of disease activity (NEDA) after up to 1 year of treatment; the companies are pursuing a 505 (b)(2) pathway for further development.

During the plenary session, Dr. Jeffrey Cohen highlighted issues of particular concern for neurologists with the arrival of the first generics to the MS landscape and the high likelihood of more to come with additional branded small molecules and biologics approaching their patent cliffs. These concerns include uncertainty around appropriate trade-offs within development programs (eg, relaxed clinical study that could jeopardize efficacy and safety vs intensive clinical study that may lead to cost disincentive), variability among generics themselves, and the inability to monitor which generic a patient is taking.

The escalating cost of DMTs remains a concern for payers, neurologists, and patients. Payers have started to manage the space more diligently, which has led to an increase in restrictions. Researchers from

Oregon State University presented results of a systematic review of Medicare Part D coverage policies and out-of-pocket spending on DMTs (excluding infusibles) in the US, which verified reduced coverage and increased access restrictions. Overall, Copaxone® and Gilenya® had the best coverage. Related to this, Novartis touted Gilenya® as the DMT with the best overall access at their exhibit booth.

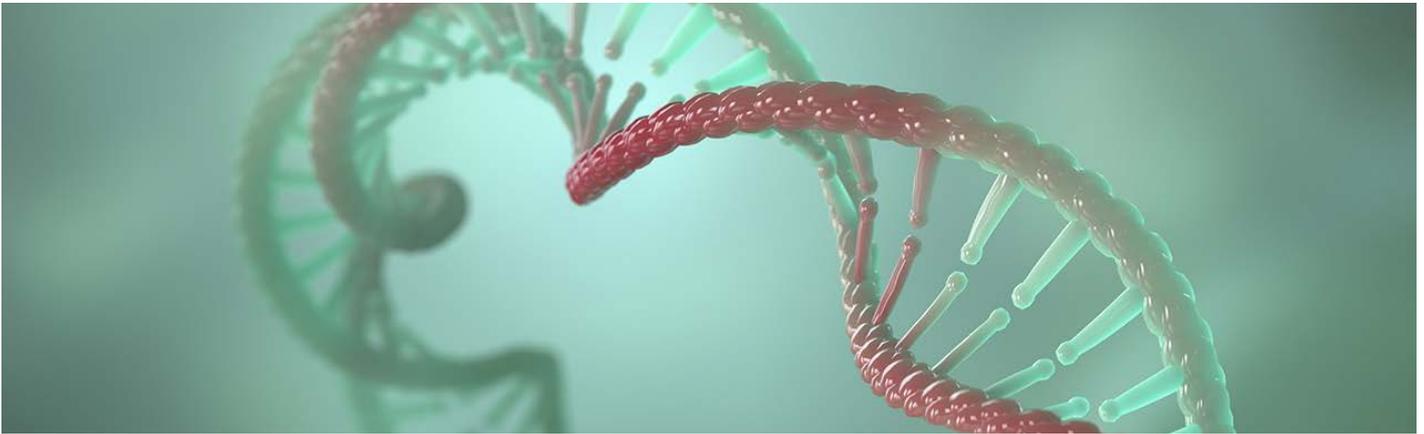
The potential for serum neurofilament light chain (NfL) as a subclinical biomarker of neuronal damage/neuroaxonal loss was a hot topic at this year's meeting. NfL has been shown to correlate with levels of disease activity and treatment response, and has prognostic relevance. Data from the Gilenya® clinical program (FREEDOMS/TRANSFORMS) as well as various Biogen product programs (ADVANCE [Plegridy®], CHAMPS [Avonex®], SENTINEL [Tysabri®])

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were shown to corroborate these relationships. Additionally, Celgene (ozanimod), Novartis (siponimod), and Roche (Ocrevus®) all presented data showing that treatment was associated with reductions in NfL. Related to this, the needs to refocus treatment goals and therapeutic development on addressing neurodegeneration and brain atrophy were also highlighted during the meeting. With that said, routine MRIs are not practical and the use of brain volume loss proved a challenge as a primary measure in the

failed ARPEGGIO study of laquinimod in primary progressive MS. Owing to its value as a marker and ease of detection, Sormani and colleagues proposed use of serum NfL in place of brain volume loss, an MRI-based assessment, as the measure of tissue destruction in the revised definition of NEDA (NEDA-4). Discussants noted a need for standardization and establishment of cut-off values for decision making prior to more widespread use of NfL.

In the progressive disease space, Novartis presented new data from a prespecified statistical analysis of the phase 3 EXPAND study of siponimod in patients with secondary progressive MS that aimed to uncouple treatment effect on relapses from that on disability. Results from this analysis showed that the reduced risk of disability conferred by siponimod was not driven by its effect on relapse activity. Novartis is expected to complete regulatory filings for siponimod in the US and Europe later this year. Results from the phase 2 SPRINT-MS study of ibudilast (Medicinova), a PDE-4/-10 inhibitor and therefore new mechanism of action in the MS space, in patients with progressive (primary and secondary) MS demonstrated a significant effect on brain atrophy progression over 96 weeks. Of note, patients in this trial were allowed concomitant interferon or GA, marking the potential of ibudilast as a combination therapy.



RNA Therapeutics on the Rise

With recent scientific advancements in genomics, gene therapy has become a reality for neurologic disease and there are now 2 RNA therapeutics on the market in the space – EXONDYS 51® (Sarepta) for Duchenne muscular dystrophy and Spinraza® (Ionis/Biogen) for spinal muscular atrophy (SMA) – and many others are in development.

Breakthroughs in the treatment of SMA were highlighted in the plenary session. Dr. Richard Finkel, who has been instrumental in the study program for Spinraza®, an SMN2 splicing modifier that addresses the underlying genetic defect in patients, showed the profound impact of the treatment in patients with infantile-onset disease (Type 1). It was an emotional moment for both Dr. Finkel and the attendees when he shared video of one of his patients, initially presenting with no head control at just a few months of age and now, after treatment, riding a tricycle and walking with the assistance of parallel bars.

Spinraza® is not curative, but its profound impact on the disease course has set the stage for others who are also developing therapies to address the genetic defect. It is clear from the volume of presentations at the meeting that the floodgates have been opened for companies to evaluate alternative gene replacement strategies for SMA. RG7916 (PTC Therapeutics), another SMN2 splicing modifier, but administered orally, was highlighted in the Emerging Science session where it was shown to increase SMN2 in a dose-dependent manner during the

first part of the phase 2/3 FIREFISH study. Initial data from the phase 3 STRIVE study of AVX-101 (Avexis, under acquisition by Novartis), an adenoviral vector that can traverse the blood-brain barrier and deliver SMN1, demonstrated a rapid increase in CHOP-INTEND score for patients with Type 1 SMA upon treatment as well as preliminary safety and tolerability.

With some real-world experience now available and ongoing evaluations in childhood-onset patients (ie, Types 2 and 3), who experience a range of clinical phenotypes depending on the amount of compensatory SMN2 they have, manufacturers will face new challenges in the coming years. Some of those discussed at the meeting included:

- The need for novel measures of disease activity and treatment effect with the emergence of new motor patterns and clinical phenotypes as patients live longer and their disease takes on a new course
- The possibility that intermediate phenotypes during the treatment course could confound the trajectory of clinical benefit
- The decision of who and when to treat, specifically with regard to the inclusion of SMN1/SMN2 in the newborn screening panel, patients who may have genetic deletions but no clinical phenotype at presentation, and childhood-onset patients who are now adults

- The determination of an adequate treatment duration – it was noted that neurologists are not observing a plateau with Spinraza®
- The establishment of reasonable treatment expectations, particularly for insurers, who expect effects in the real world to mirror those in the clinical trial setting
- The potential for future combination therapy, particularly given that the gene replacement therapies do not address deficiencies within the motor network; of note, Roche's olesoxime, a mitochondrial stabilizer that was shown to maintain motor function in patients with SMA Types 2 and 3, may have a place in this setting

The treatment landscape for hereditary ATTR (hATTR) amyloidosis, a rare protein folding disorder associated with neurologic and cardiac impairment and mortality, may soon see a major advance, with PDUFA dates for inotersen (Ionis), an ASO, and patisiran (Alnylam/Sanofi), an RNAi, set for this summer (July 6th and August 11th, respectively); both therapies are designed to treat the underlying disease pathophysiology.

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Primary data from the phase 3 Neuro-TTR study of inotersen revealed significant benefits on both coprimary endpoints, which assessed neurologic impairment and pain, and showed that patients improved over time, which is unprecedented in the disease (ie, at best, patients typically stabilize). Monitoring for the known thrombocytopenia and renal events with inotersen was said to be possible, and the events were deemed manageable.

Data from the phase 3 APOLLO study of patisiran showed decreased mortality and increased quality of life in treated patients. The ability of patisiran to address the amyloid fibril deposits in the brain, which give rise to many of the disease symptoms, was questioned by an attendee given that the compound cannot cross the blood-brain barrier. New data at the AAN meeting demonstrated quality of life improvements with both compounds. The likely high cost of these therapies (a clinical evidence review by ICER is currently underway) and variability in patient response, particularly given the range of clinical presentations seen in hATTR, will certainly pose challenges down the line.

Another RNA therapeutic receiving attention during the meeting was IONIS-HTTRx for Huntington's disease, which was correlated with dose-dependent reductions in plasma and CSF expression of the disease-causing mutant huntingtin (mHTT) in patients who participated in the first multiple ascending dose study of the compound; motor and cognitive benefits will be assessed in longer and larger trials, which are planned.

Companies such as Brainstorm Cell Therapeutics and Wave Life Sciences presented their own unique approaches to optimizing RNA therapy in diseases such as HD, amyotrophic lateral sclerosis, and frontotemporal dementia.

To speak with an ICON expert and gain further insight into these latest developments and trends, please contact us at enquiries@iconplc.com

AAN Annual Meeting Briefing Postscript

Since the writing of this briefing, Amgen received FDA approval for erenumab (Aimovig) on May 17th, making it the first CGRP inhibitor for the prevention of migraine. Subsequently, the product has been designated a lower price than originally projected and assumed in the base-case cost-effectiveness model included in the ICER draft evidence report (\$6,900/year vs \$8,500/year), which will be reviewed on June 14th. Based on this revised pricing, ICER has determined Aimovig to be cost-effective for patients who have tried and failed other preventive treatments.

In addition, the PDUFA date for inotersen has been delayed by the FDA, who cited a need for more time to review Ionis's responses to standard information requests. The new action date has been set for October 6th. Finally, Roche has announced that they are discontinuing development of their mitochondria stabilizer, olesoxime, which was previously put forth as having a potential role in the combination therapy setting for patients with SMA.

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