AMERICAN ACADEMY OF NEUROLOGY ANNUAL MEETING
LOS ANGELES, CALIFORNIA • APRIL 21-27, 2018

2018 Post-AAN Report

Biomedtracker
Pharma intelligence | informa

Datamonitor Healthcare
Pharma intelligence | informa

Summary

The American Academy of Neurology (AAN) 2018 Annual Meeting was held in Los Angeles, California, from April 21–27, 2018.

The highlight of this year's AAN meeting was Phase III data from Amgen's LIBERTY trial and a sub-group analysis of Eli Lilly's EVOLVE1&2 trials studying Aimovig and galcanezumab respectively in prophylactic treatment-refractory migraine patients. While it is difficult to compare across trials, interestingly, galcanezumab's efficacy in episodic migraine patients appeared stronger than Aimovig's. Aimovig, however, was approved shortly after the conference, making it first to market. In the multiple sclerosis space, first evidence for BIIB098's (BIIB) clinical efficacy was provided by analysis of interim data from the Phase III EVOLVE-MS-1 trial. Another notable highlight was topline results for the pivotal STR1VE trial evaluating AVXS gene replacement therapy for spinal muscular atrophy type 1, which were encouraging.

We highlight these and other presentations below.

The spinal muscular atrophy KOL interview will be available in BMT's special reports section in the future, available free of charge to KOL Insight subscribers.

Like our report? Have any questions or feedback? Please let us know at askanalyst@sagientresearch.com

Migraine

- Amgen's first conference details from the LIBERTY trial and Eli Lilly's sub-group analysis of galcanezumab's EVOLVE1&2 trials demonstrated efficacy for these anti-calcitonin gene-related peptides (CGRPs) for migraine patients who had previously failed at least two preventive therapies. While it is difficult to compare across trials, Aimovig's efficacy in episodic migraine patients was weaker than galcanezumab in terms of the mean change in monthly migraine days (MMDs) over placebo and proportion of patients with ≥50% reduction in MMDs over placebo.
    - Furthermore, galcanezumab advantageously showed efficacy in preventive-refractory patients with chronic migraine, which Aimovig did not produce data for.
    - Nevertheless, Aimovig holds a strong position in the anti-CGRP race to market as it has obtained the first approval for its class, shortly after the conference, and it will benefit from the extensive commercial resources of Novartis and Amgen, thus galcanezumab is unlikely to outperform Aimovig overall. Fremanezumab is also being studied in the Phase III FOCUS trial targeting this population for episodic and chronic migraine, however data are yet to be released.
        - It is also important to note that competition between the anti-CGRP prophylactics will be impacted by reimbursement negotiations. Interestingly, Aimovig's list price, $6,900, is actually lower than $8,500 placeholder price used in a recent ICER evaluation of cost effectiveness.
- Eli Lilly presented updated data from lasmiditan's Phase III development program, including pivotal SAMURAI and SPARTAN trials. Lasmiditan is a first-in-class oral drug being positioned as an alternative therapy for those who cannot take triptans or are unresponsive to them, thus competing with the emerging anti-CGRP class of novel migraine treatments. Presented data suggest that lasmiditan may hold the upper hand over oral anti-CGRPs rimegepant and

ubrogepant in terms of efficacy, however, it appears less attractive on the tolerability front. Eli Lilly plans to submit a New Drug Application for lasmiditan in the acute treatment of migraine to the FDA in the second half of 2018.

Multiple Sclerosis (MS)

- The first evidence for BIIB098's (BIIB) clinical efficacy was provided by analysis of interim data from the Phase III EVOLVE-MS-1 study.
    - Indirect comparisons of both efficacy and tolerability versus Tecfidera's pivotal trials were favorable for BIIB098, raising expectations for the head-to-head EVOLVE-MS-2 trial.
    - Biogen's decision to acquire rights to BIIB098 (formerly ALKS 8700) is vindicated as it is bringing a competitor to Tecfidera in-house, while gaining the potential to increase upon its already impressive market penetration owing to clinical superiorities. The company also gains another line of defense against would-be generic Tecfidera competitors.
- Interim data from the international Phase III MIST trial evaluating autologous hematopoietic stem cell therapy (aHSCT) for highly active relapsing-remitting multiple sclerosis (RRMS) patients who failed conventional approved therapies proved promising. The impressive efficacy of aHSCT in terms of expanded disability status scale (EDSS) reduction was unprecedented and positions the treatment to address crucial unmet need in the MS market.
    - Current treatments have been limited to slowing disability progression, as opposed to demonstrating improvements that were remarkably evident with aHSCT. Treatment benefits were tangible relatively soon after aHSCT and positive effects persisted years later. Thus far, aHSCT has appeared safe with no deaths, grade IV toxicity, or opportunistic infections. Since aHSCT is only suitable for a specific population of MS patients with aggressive RRMS that is treatment-refractory, it will likely pose a threat to disease-modifying therapies (DMTs) reserved for highly active RRMS.

Spinal Muscular Atrophy (SMA)

- Initial CHOP-INTEND scores from the AVXS-101 (NVS) pivotal Phase III trial were encouraging and similar to those seen in the high-dose cohort of Phase I.
    - Event-free survival from the Phase III trial was premature, but updated data from the Phase I study continued to be promising, with all patients still without an event after 24 months of therapy.
    - Shortly before the conference, AVXS-101's study in pre-symptomatic patients began recruiting.
- RG7916 (RHHBY, PTCT) had new positive data on SMN protein increases from the FIREFISH study in type 1 SMA, though without a control for the natural increase infants may have.
    - Updated event-free survival data were also encouraging, with no further deaths or permanent ventilation beyond the two already reported, though this was still quite preliminary. There were no other clinical efficacy data presented, except that no patients lost the ability to swallow, though with only limited follow-up.
    - Data in older children has also been supportive.

Myasthenia Gravis (MG)

- The first conference presentation of efgartigimod's (ARGX) Phase II myasthenia gravis trial showed a clinical improvement versus placebo and a very favorable tolerability profile. In addition to its positive safety and efficacy data, this proof-of-concept trial showed a strong correlation between a reduction in IgG and an improvement in the MG-quality of life score (QoL), helping to

affirm argenx's approach to MG treatment. The company is expected to initiate a pivotal Phase III trial by the end of 2018.

Transthyretin (TTR)-related Hereditary Amyloidosis

- Post-hoc analysis of patisiran's (ALNY, SNY, IONS, ABUS) Phase III APOLLO trial showed intriguing reduction in all-cause hospitalization/mortality, though the study was small and the analysis for cumulative events.
    - The findings could help in competition against inotersen (IONS), which has a safety risk of thrombocytopenia. In a recent FDA advisory committee meeting, the agency expressed serious concerns about the issue for another IONS second-generation drug, volanesorsen, though a different division is responsible for that drug.

Seizure Disorders (Epilepsy)

- Updated Phase II trial data from SK Biopharmaceuticals' cenobamate highlighted its attractive efficacy and tolerability profiles, but also revealed safety issues with cases of allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS) and morbilliform rashes. Cenobamate's favorable efficacy for partial-onset seizures (POS) was demonstrated to be comparable to gold-standard therapy, Keppra (levetiracetam).
    - While cenobamate may be associated with DRESS, this may not completely deter its use. Lamictal (lamotrigine) possesses a warning in its label for DRESS, nevertheless, it remains a widely-prescribed product. However, cenobamate's undifferentiated mechanism and potential late market entry would hinder its penetration of the saturated POS segment.

Amyotrophic Lateral Sclerosis (ALS)

- NP001 (Neuraltus) failed a Phase II trial, failing to confirm earlier Phase IIa findings. While the company is still investigating details, the drug is likely ineffective, or at best only marginally effective in this population.

Alzheimer's Disease (AD)

- Following a failed futility analysis of gantenerumab's SCarlet RoAD study in prodromal AD, Roche converted Marguerite RoAD in mild AD to an open-label extension, and conducted an open-label extension PET substudy using a higher dose. A review of the substudy data presented at the AAN demonstrated up to a three-fold increase in mean change in PET SUVR in a shorter amount of time than SCarlet RoAD (6–9 months versus 2 years), though the larger drops were mainly seen in patients from the prior Marguerite RoAD study. Additionally, after a year, a third of patients were experiencing reductions in amyloid below the positivity threshold via PET SUVR (standard uptake value ratio methodology) signals, suggesting a dose-response relationship.
    - Despite data resembling Biogen's aducanumab, results were confined to surrogate outcomes without detecting improvements in cognition. Questions have been raised as to whether or not the improvements are meaningful without any demonstration that cognition is improved. As a result, and given previous failures within this class of drugs (solanezumab and bapineuzumab), additional data are required to have much confidence in efficacy. A new Phase III trial is slated to start in July.

This report also has information on eptinezumab's (ALDR) PROMISE-1 and ubrogepant's (AGN) ACHIEVE I trials in migraine, olesoxime's (RHHBY) open-label extension in SMA, and the first supportive clinical evidence for Abide Therapeutics's endocannabinoid ABX-1431 in Tourette's syndrome.

About the Author

Biomedtracker is an independent research service that offers proprietary clinical assessments of developmental drugs within a comprehensive and intuitive drug information database. Clients from the pharmaceutical, biotech, and investment industries rely on Biomedtracker for its insight on the likelihood of approval, commercial potential, and future data and regulatory catalysts for drugs within the competitive landscape of every important disease and indication. Over recent years, Biomedtracker has become the leader in providing objective information alongside evidence-based clinical assessments and investment research on pipeline drugs worldwide. For more information on getting direct access to Biomedtracker, please email BioMedSupport@sagientresearch.com.

Datamonitor Healthcare provides a total business information solution to the pharmaceutical and healthcare industries. We provide expertise in therapeutic, strategic, and company market analysis, and competitive intelligence to the global pharmaceutical and healthcare markets, enabling them to ultimately make valuable and profitable decisions. For more information about our products or to arrange a demo of our online service, please contact: getcloser@datamonitorhealthcare.com.

Disclaimer

Contents

Selected Abstracts Featured at AAN

Migraine

Aimovig (AMGN/NVS, Approved)

Phase IIIb – LIBERTY
Trial Data – Final Results

Change to Likelihood of Approval: +2%

	Placebo	Treatment	Difference Between Treatment and Placebo
Treatment Description	Placebo	Aimovig 140mg	Aimovig 140mg vs Placebo
Patients with ≥50% Reduction of Monthly Migraine Days From Baseline on Weeks 9-12 *(Endpoint=Primary)*	13.7%	30.3%	Odds Ratio 2.73 (p<0.002)
Mean Monthly Migraine Days	-	-	-1.61 (p=0.004)
Mean Migraine-specific Medication Days	-	-	-1.73 (p<0.001)

Context

The US Food and Drug Administration (FDA) has set a Prescription Drug User Fee Act (PDUFA) target action date of May 17, 2018, for Aimovig and the European Medicines Agency has validated the Marketing Authorization Application (MAA) for Aimovig. If approved, it will be administered once-monthly using a self-injection device. If approved, Amgen and Novartis will co-commercialize Aimovig in the US Amgen has exclusive commercialization rights to the drug in Japan, and Novartis has exclusive rights to commercialize in rest of world.

Design

LIBERTY is a Phase IIIb, multicenter, randomized 12-week, double-blind, placebo-controlled study evaluating the safety and efficacy of Aimovig in patients with episodic migraine (defined in the trial as four to 14 migraine days per month at baseline) who have failed up to four prior preventive treatments for migraine. In the study, 246 participants with episodic migraine who had two to four previous treatment failures were randomized to receive Aimovig 140mg or placebo during the 12-week double-blind treatment phase. The study includes an ongoing 52-week open-label extension study. Over 97% of Aimovig patients completed the double-blind phase of the LIBERTY study.

Endpoints

The primary endpoint was the percentage of patients with at least a 50% reduction of monthly migraine days from baseline over the last four weeks of the double-blind treatment phase of the study (weeks 9–12). Secondary endpoints assessed during the same time period included: change from baseline in monthly migraine days, change from baseline in the number of monthly acute migraine-specific medication treatment days, and change from baseline in the Migraine Physical Function Impact Diary (MPFID) physical impairment and impact on everyday activities domain scores. The MPFID is a scale developed to measure these two domains. The scale has been validated in line with FDA Patient Reported

Outcomes Guidance. Percentages of patients with a 75% response rate and 100% response rate to Aimovig were also assessed as secondary endpoints.

Results

Patients taking Aimovig had nearly three-fold higher odds of having their migraine days cut by at least 50%, with more than twice as many patients taking Aimovig achieving this reduction compared to placebo (weeks 9–12: 30.3% with Aimovig, 13.7% with placebo, p<0.002, odds ratio 2.73). In the study, patients taking Aimovig also had statistically significant and clinically meaningful improvements from baseline compared to placebo across all secondary endpoints:

- reduction in monthly migraine days
- decrease in monthly acute migraine-specific drug use
- 75% or greater reduction in monthly migraine days
- 100% reduction in monthly migraine days
- Improved physical functioning and ability to complete everyday activities as measured by the Migraine Physical Function Impact Diary (MPFID).

Most Common Adverse Events

There were no adverse events leading to discontinuation of treatment in the Aimovig group, while 0.8% of those in the placebo group experienced adverse events leading to discontinuation of treatment.

Conclusion

The data show the potential of Aimovig as an effective preventive treatment option for these patients, who have tried several treatment options without gaining relief.

Comment

In light of the positive full data from the pivotal LIBERTY trial we are increasing its LOA by 2%.

Aimovig patients who failed up to four previous prophylactic treatments were twice as likely to experience a ≥50% reduction in monthly migraine days compared to the placebo arm. In fact, the drug encouragingly demonstrated statistically significant efficacy across all secondary endpoints as well. Furthermore, in line with available anti-calcitonin gene-related peptide (CGRP) trial data, these Aimovig-specific data on adverse events reaffirmed the favorable tolerability profile of the overall anti-CGRP class as no Aimovig patients discontinued treatment. These data further corroborate Aimovig's attractive clinical profile evident in other pivotal trials.

Conversely, while it is difficult to compare across trials, Aimovig's efficacy in this population of episodic migraine patients seemed weaker than data from a sub-group analysis of the EVOLVE 1&2 trials (please see comment under galcanezumab). In the sub-group analysis, galcanezumab patients experienced a ~3.04 mean reduction in monthly migraine days (MMDs) over placebo compared to ~1.61 for Aimovig patients. In terms of the proportion of patients with ≥50% reduction in MMDs from baseline, galcanezumab had an OR of 4.44 versus Aimovig's 2.73. Furthermore, galcanezumab advantageously showed efficacy in preventive-refractory patients with chronic migraine, which Aimovig did not produce data for.

Nevertheless, Aimovig holds a strong position in the anti-CGRP race to market as it has obtained the first approval for this class, shortly after the AAN conference, and it will benefit from the extensive commercial resources of Novartis and Amgen, thus galcanezumab is unlikely to outperform Aimovig overall. Fremanezumab, which has a quarterly dosing option, is also being studied in the Phase III FOCUS

trial targeting this population for episodic and chronic migraine, however data are yet to be released. It is also important to note that competition between the anti-CGRP prophylactics will be impacted by reimbursement negotiations. Datamonitor Healthcare's Pharma Vitae forecasts of these products will be updated in the coming weeks.

Source:
Press Release 04/17/2018 (AMGN)
Press Release 04/17/2018 (NVS)
American Academy of Neurology (AAN)
Sagient Analysis

Lasmiditan (LLY, Phase III)

Phase III – SAMURAI, SPARTAN
Trial Data – Updated Results

Plenary session: Phase 3 Studies (SAMURAI, SPARTAN) of Lasmiditan Compared to Placebo for Acute Treatment of Migraine

Change to Likelihood of Approval: 0%

	Placebo	Treatment	Placebo	Treatment
Treatment Description	Placebo **SAMURAI**	Lasmiditan 200mg **SAMURAI** *P-value vs. Placebo*	Placebo **SPARTAN**	Lasmiditan 200mg **SPARTAN** *P-value vs. Placebo*
Headache Pain-free 2 Hours Post Dose *(Endpoint=Primary)*	15.3%	32.2% (p<0.001)	21.3%	38.8% (p<0.001)
Most Bothersome Symptom (MBS) Free 2 Hours Post Dose	29.5%	40.7% (p<0.001)	33.5%	48.7% (p<0.001)

Design

SAMURAI and SPARTAN were Phase III, randomized, double-blind, placebo-controlled studies. Inclusion criteria included Migraine Disability Assessment Score ≥11 (moderate disability) and 3–8 migraine attacks per month. Patients were randomized to a first dose of treatment (SAMURAI, 1:1:1 ratio of lasmiditan 200/100mg or placebo; SPARTAN, 1:1:1:1 ratio of lasmiditan 200/100/50mg or placebo) which was taken within four hours of migraine onset (moderate severity or worse and not improving). For rescue or recurrence, patients took a randomly assigned second dose of the previously assigned lasmiditan dose or placebo. Treatment-emergent adverse events (TEAEs) were used to assess safety. Logistic regression was used for comparisons.

Endpoints

The primary and key secondary analyses compared the proportions of patients in the lasmiditan 200mg group with the placebo group who were headache pain-free and who were most bothersome symptom (MBS)-free at two hours post-first dose, respectively.

Results

At two hours post-first dose, significantly greater proportions of patients (p<0.001) were headache pain free (lasmiditan 200mg: SAMURAI 32.2%, SPARTAN 38.8%; placebo: SAMURAI 15.3%, SPARTAN 21.3%) and MBS-free (lasmiditan 200mg: SAMURAI 40.7%, SPARTAN 48.7%; placebo: SAMURAI 29.5%, SPARTAN 33.5%) with lasmiditan 200mg compared with placebo. For both endpoints, significance was also noted for other lasmiditan dose groups (100mg, 50mg) compared to placebo.

Most Common Adverse Events

The most frequently reported TEAEs with lasmiditan (≥2% and greater than placebo) after the first dose were dizziness, paresthesia, somnolence, fatigue, nausea, and lethargy, and most events were mild-to-moderate in severity.

Treatment-Emergent Adverse Events After 1st Dose (≥ 2% and > Placebo)

	SAMURAI (First Dose)			SPARTAN (First Dose)			
TEAEs	L 200mg (n=609)	L 100mg (n=630)	PBO (n=617)	L 200mg (n=649)	L 100mg (n=635)	L 50mg (n=654)	PBO (n=645)
≥1 TEAEs	42.2%	36.3%	16.0%	39.0%	36.1	25.4	11.6
Dizziness	16.3%	12.5%	3.4%	18.0%	18.1	8.6	2.5
Paresthesia	7.9%	5.7%	2.1%	6.6%	5.8	2.4	0.9
Somnolence	5.4%	5.7%	2.3%	6.5%	4.6	5.4	2.0
Fatigue	3.1%	4.1%	0.3%	4.8%	4.1	2.8	0.9
Nausea	5.3%	3.0%	1.9%	2.6%	3.3	2.8	1.2
Lethargy	2.5%	1.9%	0.3%	2.2%	1.3	1.2	0.2

Treatment-Emergent Cardiovascular Adverse Events

	SAMURAI			SPARTAN			
System Organ Class Preferred Term, n (%)	L 200mg (n=609)	L 100mg (n=630)	PBO (n=617)	L 200mg (n=649)	L 100mg (n=635)	L 50mg (n=654)	PBO (n=645)
Cardiac Disorders	0.8%	0.6%	0.3%	0.6%	0.6%	0.5%	0.2%
Palpitations	0.7%	0.3%	0	0.3%	0.3%	0.3%	0.2%
Bradycardia	0	0.2%	0.2%	-	-	-	-
LV hypertrophy	0	0	0.2%	-	-	-	-
Sinus bradycardia	0.2%	0	0	-	-	-	-
Tachycardia	0	0.2%	0	0.3%	0.3%	0.2%	0

Conclusion

The primary and key secondary endpoints were met and safety outcomes were consistent across the two Phase III studies.

Comment

Lasmiditan is a first-in-class neurally acting anti-migraine agent, targeting 5HT1F, designed to deliver acute efficacy in migraine without the vasoconstrictor activity associated with standard-of-care triptans. As the drug is being positioned as an alternative therapy for those who cannot take triptans or are unresponsive to them, lasmiditan competes with the emerging anti-CGRP (calcitonin gene-related peptide) class of novel migraine treatments.

In pivotal SAMURAI and SPARTAN trials, lasmiditan's efficacy data regarding the primary endpoint of the percentage of patients with pain freedom at two hours (~16.9–17.5% over placebo) appear to edge out the oral anti-CGRPs rimegepant (~5.0–7.6% over placebo) and ubrogepant (~7.5–9.3% over placebo).

In both pivotal trials, treatment-emergent cardiovascular adverse events arose, which were deemed possibly related to lasmiditan. While the incidences of mild to moderate palpitations, bradycardia and tachycardia with treatment exceeded those with placebo, the overall risk seems low (~<1%). Nevertheless, with dizziness, paresthesia, and somnolence manifesting as the most frequent treatment-emergent adverse events (eg dizziness ranged from 12.5–18.1% versus 2.5–3.4% for placebo), lasmiditan's tolerability profile does not compete with the placebo-like tolerability evident from pivotal trials evaluating anti-CGRPs. Conversely, since efficacy will likely be most highly valued, lasmiditan may prove to become the oral therapy of choice as an alternative to triptans and oral anti-CGRPs may be relied on for those who do not tolerate lasmiditan well. Datamonitor Healthcare's Pharma Vitae currently projects lasmiditan to achieve overall worldwide sales of $2.7bn in 2027.

Source:
American Academy of Neurology (AAN) 04/27/2018 (Abstract S50.008)
Sagient Analysis

Galcanezumab (LLY, BLA)

Phase III - EVOLVE-1 (Episodic Migraine), Phase III - EVOLVE-2 (Episodic Migraine), Phase III - REGAIN (Chronic Migraine)
Trial Data – Subgroup Analysis

Abstract S20.004: Efficacy of Galcanezumab in Patients Who Failed to Respond to Preventives Previously: Results from EVOLVE-1, EVOLVE-2 and REGAIN Studies

Change to Likelihood of Approval: +2%

	Placebo	Treatment	Treatment	Placebo	Treatment	Treatment
Treatment Description	Placebo **Patients Who Failed ≥2 Prior Preventives**	Galcanezumab 120mg **Patients Who Failed ≥2 Prior Preventives** *P-value vs. Placebo*	Galcanezumab 240mg **Patients Who Failed ≥2 Prior Preventives** *P-value vs. Placebo*	Placebo **Patients Who Did Not Failed ≥2 Prior Preventives**	Galcanezumab 120mg **Patients Who Did Not Failed ≥2 Prior Preventives** *P-value vs. Placebo*	Galcanezumab 240mg **Patients Who Did Not Failed ≥2 Prior Preventives** *P-value vs. Placebo*
Overall Mean Change in Monthly Migraine Headache Days *EVOLVE-1 and EVOLVE-2 Studies*	-0.81 Days	-3.45 Days (p<0.001)	-3.85 Days (p<0.001)	-2.68 Days	-4.61 Days (p<0.001)	-4.36 Days (p<0.001)
Overall Mean Change in Monthly Migraine Headache Days *REGAIN Study*	-1.44 Days	-5.91 Days (p<0.001)	-3.30 Days (p<0.01)	-3.69 Days	-4.82 Days (p<0.05)	-5.77 Days (p<0.001)
Proportion of People with ≥50% Reduction in Monthly MHDs *EVOLVE-1 and EVOLVE-2 Studies*	26.2%	54.6% (p<0.001)	61.2% (p<0.001)	38.4%	61.6% (p<0.001)	58.4% (p<0.001)
Proportion of People with ≥50% Reduction in Monthly MHDs *REGAIN Study*	9.7%	30.4% (p<0.001)	18.3% (p<0.05)	18.0%	26.6% (p<0.01)	32.4% (p<0.001)
Mean Change in Monthly MHD with Medication Use *EVOLVE-1 and EVOLVE-2 Studies*	-1.57 Days	-3.59 Days (p<0.01)	-3.96 Days (p<0.001)	-2.08 Days	-3.90 Days (p<0.001)	-3.70 Days (p<0.001)
Mean Change in Monthly MHD with Medication Use *REGAIN Study*	-1.35 Days	-5.87 Days (p<0.001)	-3.24 Days (p<0.01)	-3.09 Days	-4.79 Days (p<0.001)	-5.32 Days (p<0.001)
Mean Change from Baseline in MSQ Role Function-Restrictive *EVOLVE-1 and EVOLVE-2 Studies*	13.32	23.07 (p<0.001)	24.39 (p<0.001)	22.78	31.10 (p<0.001)	29.70 (p<0.001)
Mean Change from Baseline in MSQ Role Function-Restrictive *REGAIN Study*	11.40	18.94 (p<0.05)	18.38 (p<0.05)	19.72	23.06	26.09 (p<0.01)

Context

The US Food and Drug Administration (FDA) is reviewing galcanezumab for the prevention of migraine in adults. A decision is expected in the third quarter of 2018. Lilly also is evaluating galcanezumab for the treatment of cluster headache with Phase III trial results expected in the second quarter of 2018.

Design

EVOLVE-1, EVOLVE-2, and REGAIN were Phase III, randomized, double-blind, placebo-controlled studies that evaluated the efficacy of two doses of galcanezumab (120mg and 240mg) in patients with episodic or chronic migraine. This subgroup analysis evaluated patients treated in the EVOLVE-1 and EVOLVE-2 studies for six months and the REGAIN study for three months. The subgroup analysis reviewed the mean change from baseline in the number of monthly migraine headache days and the proportion of patients with at least a 50% reduction in number of monthly migraine headache days in patients who previously failed two or more preventive therapies, using integrated EVOLVE-1 and EVOLVE-2 results and REGAIN results. Subgroup-by-treatment interactions were calculated using linear or generalized linear mixed models.

Results

In this subgroup analysis, patients treated with both doses of galcanezumab who previously failed two or more preventive therapies experienced a statistically significant reduction in the average number of monthly migraine headache days, and at least a 50% reduction in the number of migraine headache days, compared to patients treated with placebo.

- EVOLVE-1/ EVOLVE-2 (as evaluated over six months) for patients who failed at least two prior preventive medications (n=172):
  - Average reduction in monthly migraine headache days: 3.45 days for 120mg and 3.85 days for 240mg compared to 0.81 days for placebo, p<0.001 for both dosing groups compared with placebo.
  - Mean percentages of patients with at least 50% reduction in monthly migraine headache days: 54.6% for 120mg and 61.2% for 240mg compared to 26.2% for placebo, p<0.001 for both dosing groups compared with placebo.
- REGAIN (as evaluated over three months) for patients who failed at least two prior preventive medications (n=323):
  - Average reduction in monthly migraine headache days: 5.91 days for 120mg and 3.30 days for 240mg compared to 1.44 days for placebo, p<0.01 for both dosing groups compared with placebo.
  - Mean percentages of patients with at least 50% reduction in monthly migraine headache days: 30.4% for 120mg and 18.3% for 240mg compared to 9.7% for placebo, p<0.05 for both dosing groups compared with placebo.

Most Common Adverse Events

As previously reported, in these Phase III studies, the most commonly reported adverse events were injection site reactions.

Conclusion

Galcanezumab 120mg/240mg is efficacious compared with placebo in reducing monthly MHDs in both patients who failed and did not fail ≥2 prior preventives. Treatment-by-subgroup interactions may be driven by lower placebo response in patients who failed preventives previously as magnitude of change for GMB-treated patients were similar in both subgroups.

Comment

We are raising galcanezumab's LOA by 2% considering its efficacy for patients who failed ≥2 preventives.

In this sub-group analysis, galcanezumab elicited significant efficacy in episodic migraine. While it is difficult to compare across trials, these data seem superior to that demonstrated by Aimovig in the LIBERTY trial (please see comment under Aimovig). Galcanezumab patients experienced a ~3.04 mean reduction in monthly migraine days (MMDs) over placebo compared to ~1.61 for Aimovig patients. In terms of the proportion of patients with ≥50% reduction in MMDs from baseline, galcanezumab had an OR of 4.44 versus Aimovig's 2.73. Furthermore, galcanezumab advantageously showed efficacy in preventive-refractory patients with chronic migraine, which Aimovig did not produce data for.

Galcanezumab has successfully established that it is amenable to treating refractory patients, which bolsters its clinical attractiveness and will help it to better compete with Aimovig. Conversely, Aimovig will launch ahead of galcanezumab, as it gained approval shortly after the conference, and will benefit from the extensive commercial resources of Novartis and Amgen, thus galcanezumab is unlikely to outperform

Aimovig overall. Fremanezumab, which as a quarterly dosing option, is also being studied in the Phase III FOCUS trial targeting this population for episodic and chronic migraine, however data are yet to be released. It is also important to note that competition between the anti-CGRP prophylactics will be impacted by reimbursement negotiations. Datamonitor Healthcare's Pharma Vitae forecasts of these products will be updated in the coming weeks.

Source:
Press Release 04/24/2018 (LLY)
American Academy of Neurology (AAN) 04/24/2018 (Abstract S20.004)
Sagient Analysis

Eptinezumab (ALDR, Phase III)

Phase III - PROMISE 1 (High Frequency; IV)

Trial Data – Updated Results

Abstract S20.001: Primary Results of PROMISE-1 (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy–1) Trial: a Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eptinezumab for Prevention of Frequent Episodic Migraines

Change to Likelihood of Approval: 0%

	Placebo	All Treatment	Treatment	Treatment	Treatment
Treatment Description	Placebo	Eptinezumab	Eptinezumab 30mg *P-value vs. Placebo*	Eptinezumab 100mg *P-value vs. Placebo*	Eptinezumab 300mg *P-value vs. Placebo*
Number of Evaluable Patients	222	-	223	221	222
≥50% Reduction in Monthly Migraine Days From Baseline For Month 6 Through 12	58.7%	70.7%	-	-	-
≥75% Reduction in Monthly Migraine Days From Baseline For Month 6 Through 12	38.7%	51.5%	-	-	-
Mean Change in Migraine Days From Weeks 1-12 (Endpoint=Primary)	-3.2 Days	-	-4.0 Days (p=0.0046)	-3.9 Days (p=0.0182)	-4.3 Days (p<0.0001)
≥75% Migraine Responder Rate: Weeks 1–4	20.3%	-	-	30.8% (p=0.012)	31.5% (p=0.0066)
≥75% Migraine Responder Rates: Weeks 1–12	16.2%	-	-	22.2% (p>0.05)	29.7% (p=0.0007)
≥50% Migraine Responder Rates: Weeks 1–12	37.4%	-	-	49.8% (p=0.0085)	56.3% (p<0.0001)
Day 1 Reductions From Baseline in % of Subjects With a Migraine	21%	-	-	52% (p=0.0167)	54% (p=0.0087)

Context

In June 2017, Alder announced that eptinezumab met the primary endpoint and key secondary endpoints in PROMISE 1 with very high statistical significance. In January 2018, Alder announced that eptinezumab

met the primary endpoint and key secondary endpoints in PROMISE 2 with very high statistical significance.

Design

PROMISE 1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) was a Phase III randomized, double-blind, placebo-controlled global trial evaluating the safety and efficacy of eptinezumab for episodic migraine prevention. In the study, 888 patients were randomized to receive eptinezumab (300mg, 100mg, or 30mg) or placebo administered by infusion once every 12 weeks. To be eligible for the trial, patients must have experienced ≤14 headache days per month, of which at least four met the criteria for migraine.

Endpoints

The primary endpoint was the mean change from baseline in monthly migraine days over the 12-week, double-blind treatment period.

Results

The data demonstrated that patients experienced even further reductions in migraine following the third and fourth quarterly infusions at both dose levels (100mg and 300mg) of eptinezumab, Alder's lead investigational product candidate for migraine prevention targeting calcitonin gene-related peptide (CGRP).

PROMISE 1 Results Following Third and Fourth Eptinezumab Infusions

Responder rates for month six through month 12:

- 70.7% of patients achieved on average a 50% reduction or greater of monthly migraine days from baseline compared to 58.7% for placebo. This represents an 8.9% improvement from the reductions experienced during the first two quarterly doses of eptinezumab;
- 51.5% of patients achieved on average a 75% reduction or greater of monthly migraine days from baseline compared to 38.7% for placebo. This represents a 12.8% improvement from the reductions experienced during the first two quarterly doses of eptinezumab

Most Common Adverse Events

The observed safety profile for PROMISE 1, to date, is consistent with previously reported eptinezumab studies. The most commonly reported adverse events occurring at an incidence of 5% or greater across all eptinezumab treatment groups were upper respiratory infection (10.5%), nasopharyngitis (common cold) (6.8%) and sinusitis (3.6%).

Conclusion

All doses of eptinezumab significantly reduced migraine activity through three months after first infusion in patients with frequent episodic migraine. The probability of migraine was significantly reduced on day 1 posttreatment and benefits were maintained for three months with a single infusion. Adverse event rates were similar to placebo.

Comment

These additional data from eptinezumab's PROMISE-1 trial confirm its long-term efficacy showing further benefits in responder rates from month 6 through to month 12. ~12% of eptinezumab patients experienced ≥50% reduction in monthly migraine days from baseline for month 6 through 12 over placebo, while ~12.8% experienced ≥75% over placebo. Eptinezumab's efficacy appears on par with the other anti-calcitonin gene-related peptide (CRGP) prophylactics, however a direct comparison cannot be definitively made as we lack head-to-head trials. Additionally, while eptinezumab is dosed quarterly, eptinezumab is not as clinically attractive as other anti-CGRP preventives as it is administered by intravenous infusion, whereas other products have the option of subcutaneous injection.

Source:
Press Release 04/24/2018 (ALDR)
American Academy of Neurology (AAN) 04/24/2018 (Abstract S20.001)
American Academy of Neurology (AAN) 04/24/2018 (Slides)
Sagient Analysis

Eptinezumab (ALDR, Phase III)

Phase III – PROMISE 1 (High Frequency; IV)

Trial Data – Updated Results

Abstract P4.108: Repeat Infusions of Eptinezumab Associated With Greater Migraine Reductions and Longer Migraine-Free Intervals: Results From the Phase 3 PROMISE-1 Trial

Design

PROMISE 1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) was a Phase III randomized, double-blind, placebo-controlled global trial evaluating the safety and efficacy of eptinezumab for episodic migraine prevention. In the study, 888 patients were randomized to receive eptinezumab (300mg, 100mg, or 30mg) or placebo administered by infusion once every 12 weeks. To be eligible for the trial, patients must have experienced ≤14 headache days per month, of which at least four met the criteria for migraine.

Endpoints

The primary endpoint was the mean change from baseline in monthly migraine days over the 12-week, double-blind treatment period.

Results

Patients with episodic migraine who on average had 8.6 days of migraine per month demonstrated significant reductions in migraine frequency over weeks 1–12, associated with the 300mg dose group. 29.7% of patients were found to achieved a 75% or greater reduction in migraine days from baseline, compared to 16.2% for placebo, p<0.0007.

Per the abstract, up to 30% of patients in the 30-, 100-, and 300mg groups had ≥75% reduction in migraine days over weeks 1–12 (24.7%, p=0.027; 22.2%, p=NS; 29.7%, p=0.001, respectively) versus 16.2%, placebo. After two quarterly infusions of eptinezumab 300mg, the percentage of patients with ≥50% RR increased from 56.3% in weeks 1–4 to 63.1% in weeks 21–24. Placebo rates were 40.5% to 52.3% in the same time intervals. Similarly, the percentage of patients with ≥75% RR increased from 31.5% to 40.5% (300mg) versus 20.3% to 32.4% (placebo). The percentage of patients with 100% RR

increased from 14.9% to 23.4% (300mg) versus 5.9% to 14.4% (placebo) in the same time frames. In the 300mg group, the median duration of migraine-free intervals in patients with ≥75%, <75% to 50%, <50% to 25%, and <25% RR were 40, 13.5, 9.3, and 9.5 days, respectively, over weeks 1–12.

Most Common Adverse Events

The observed safety profile for PROMISE 1, to date, is consistent with previously reported eptinezumab studies. The most commonly reported adverse events occurring at an incidence of 5% or greater across all eptinezumab treatment groups were upper respiratory infection (10.5%), nasopharyngitis (common cold) (6.8%) and sinusitis (3.6%).

Conclusion

Repeated quarterly infusions of eptinezumab were associated with incremental reductions in migraine frequency and increasing migraine RR up to six months. Greater migraine RR were associated with meaningful longer migraine-free intervals.

Comment

Please see comment above under the Primary Results of PROMISE-1.

Source:
Press Release 04/25/2018 (ALDR)
American Academy of Neurology (AAN) 04/25/2018 (Abstract P4.108)
American Academy of Neurology (AAN) 04/25/2018 (Poster P4.108)

Eptinezumab (ALDR, Phase III)

Phase III – PROMISE 1 (High Frequency; IV)

Trial Data – Updated Results

Abstract 32.002: Increased Migraine-Free Intervals With Eptinezumab Were Associated With Improved Health-Related Quality-of-Life Outcomes Through Week 12: Results From the Phase 3 PROMISE-1 Trial

Design

PROMISE 1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) was a Phase III randomized, double-blind, placebo-controlled global trial evaluating the safety and efficacy of eptinezumab for episodic migraine prevention. In the study, 888 patients were randomized to receive eptinezumab (300mg, 100mg, or 30mg) or placebo administered by infusion once every 12 weeks. To be eligible for the trial, patients must have experienced ≤14 headache days per month, of which at least four met the criteria for migraine.

Endpoints

The primary endpoint was the mean change from baseline in monthly migraine days over the 12-week, double-blind treatment period.

Results

In a post-hoc analysis, patients achieving a 75% or greater response rate had over an eight-fold increase in days between migraines. During weeks 1–12, the median migraine-free interval between migraine days increased from 3.9 days at baseline to 32.5 days. Achieving a 75% or greater response rate was associated

with more meaningful improvements in bodily pain and physical function at week 12, as measured by a quality-of-life patient-reported survey (SF-36).

Per the abstract, the largest eptinezumab effect was observed with the 300mg dose, with 29.7% (p=0.001) of patients with a ≥75% reduction in migraine days over weeks 1–12 versus 16.2% for placebo. In the 300mg group, percentages of patients with a response rate (RR) <75% to 50%, <50% to 25%, and <25% were 26.6%, 23.4%, and 8.1%, respectively. For the 300mg group, in patients with RR ≥75%, <75% to 50%, <50% to 25%, and <25%, the median duration of MFI at baseline was 4.1, 3.8, 4.4, and 4.4 days, respectively, versus 40, 13.5, 9.3, and 9.5 days, respectively, at week 12. Baseline SF-36 scores were lowest in bodily pain (BP), role physical (RP), and social functioning (SF) domains. The greatest SF-36 score improvements at week 12 were in BP (+5.2, +6.0, +4.0, +2.5), RP (+3.7, +2.6, +2.6, +2.6), and SF (+2.2, +2.3, +0.1, +2.2) domains according to above RR.

Conclusion

After a single infusion of eptinezumab 300mg, approximately 30% of patients achieved a ≥75% RR over three months, which was associated with an approximately 10-fold increase in MFI and greater improvements in SF-36 domains most affected by migraine in this FEM population.

Comment

Please see comment above under the Primary Results of PROMISE-1.

Source:

Press Release 04/25/2018 (ALDR)
American Academy of Neurology (AAN) 04/25/2018 (Abstract S32.002)
American Academy of Neurology (AAN) 04/25/2018 (Presentation S32.002)

Ubrogepant (AGN, Phase III)

Phase III - ACHIEVE I (UBR-MD-01)

Trial Data – Updated Results

Abstract ES.008: Efficacy, Safety, and Tolerability of Ubrogepant for the Acute Treatment of Migraine: Results from a Single Attack Phase II Study, ACHIEVE I

Change to Likelihood of Approval: 0%

	Placebo	Treatment	Treatment	Difference Between Treatment and Placebo
Treatment Description	Placebo	Ubrogepant 50mg	Ubrogepant 100mg	Ubrogepant vs. Placebo
Pain Freedom 2 Hours After Initial Treatment *(Endpoint=Primary)*	12%	19%	21%	(p=0.0003)
Absence of MBS 2 Hours After Initial Treatment *(Endpoint=Primary)*	28%	39%	38%	(p=0.002)
Pain Relief at 2 Hours	49%	61%	61%	(p=0.002)
Pain Relief at 2 to 24 Hours	21%	36%	38%	(p=0.002)
Pain Freedom at 2 to 24 Hours	8.6%	-	15.4%	(p=0.002)
Absence of Photophobia at 2 Hours	31.4%	-	45.8%	(p<0.0001)

Context

Results from ACHIEVE II are expected to be released before July 1 of this year. The manufacturer hopes to submit a new drug application to the US Food and Drug Administration during the first part of 2019.

Design

The Phase III ACHIEVE I trial is a randomized controlled study comparing the novel oral calcitonin gene-related peptide (CGRP) receptor antagonist ubrogepant (Allergan) vs placebo for acute treatment of a single attack of migraine, report researchers.

Results

Both primary efficacy endpoints were met in the trial. Findings from ACHIEVE I, which included more than 1,300 patients in the intent-to-treat analysis, showed that significantly more of those who received 50mg or 100mg of the study drug achieved "pain freedom" two hours after treatment (in 19% and 21%, respectively) than those who received matching placebo (12%). Greater percentages of both dosing groups also achieved absence of migraine-related most bothersome symptoms (MBS), including photophobia, phonophobia, and nausea versus placebo (in 39% and 38% versus 28%, respectively).

In ACHIEVE I, the 1,672 participants (87.5% women; 82.4% white; mean age, 40.7 years) were randomly assigned to receive placebo (n=559) or ubrogepant at the lower (n=556) or higher (n=557) dosages. All of the patients had a history of migraine, with and without aura. They had up to 60 days to treat a single migraine attack with moderate-to-severe headache pain intensity with their assigned therapy. At baseline, 63% reported moderate pain and 37% reported severe pain. In addition, 11% had moderate-to-high cardiovascular risk at baseline. A total of 1,436 of the participants were included in the safety-assessing analysis, while 1,327 were included in the modified intent-to-treat efficacy analysis.

Photophobia was the MBS reported at time of treatment (by 56.4%), followed by phonophobia (22.3%)

and nausea (20.9%). Both co-primary endpoints, evaluated two hours after initial treatment, were greater in both ubrogepant groups compared with the placebo group: achieving pain freedom (p=0.0003) and achieving absence of MBS (p=0.002). Secondary endpoints showed that 61% of each dosing group achieved pain relief at two hours vs 49% of the placebo group (adjusted p=0.002 for both comparisons); 36% and 38%, respectively had sustained pain relief between hours two and 24 vs 21% (p=0.002). Significantly more members of the 100mg group also had sustained pain freedom at two to 24 hours (15.4% vs 8.6%, p=0.002) and absence of photophobia at two hours (45.8% vs 31.4%, p<0.0001).

Most Common Adverse Events

The study drug was well-tolerated with no identified safety concerns. Although the most common adverse events (AEs) were nausea, somnolence, and dry mouth, all were reported by fewer than 5% of the participants receiving ubrogepant.

In the ubrogepant 50mg and 100mg and placebo groups, 9.4%, 16.3%, and 12.8%, respectively, reported an AE. Also, 5.8%, 12.0%, and 8.5% reported a treatment-related AE. Nausea was reported by 1.7%, 4.1%, and 1.6% of the groups, respectively; somnolence by 0.6%, 2.5%, and 0.8%; and dry mouth by 0.6%, 2.1%, and 0.4%. Among the five serious AEs reported within 30 days were two reports of appendicitis and one report each of pericardial effusion, spontaneous abortion, and seizure. Only the seizure was considered to be treatment related. A generalized seizure occurred six hours after a 44-year-old woman took ubrogepant at the 100mg dose. Alprazolam (benzodiazepine) withdrawal was considered a possible etiology.

Regarding liver safety, there were six instances of having at least three times the upper limit of normal alanine aminotransferase or aspartate aminotransferase elevation: one within seven days of treatment exposure and the others at the one-month safety follow-up. Of these, four instances occurred while the patients were receiving ubrogepant but were adjudicated as "unlikely" to be related to study medication. The remaining two cases, one during receipt of the study drug and one during receipt of placebo, were adjudicated as "possibly related" to treatment. None were found to be "probably related" to treatment. The liver safety data from this study do not suggest any signal of hepatoxicity for ubrogepant.

Comment

These updated data relating to secondary endpoints are encouraging as they confirm that ubrogepant's efficacy as an acute migraine therapy lasts beyond two hours following initial treatment. Notably pain relief with ubrogepant at 2 hours was ~12% over placebo, while at 2 to 24 hours it was ~17%, and pain freedom with ubrogepant at 2 to 24 hours was ~6.8% over placebo. It was also promising that the absence of photophobia at 2 hours with ubrogepant was ~14.4% over placebo.

Overall, from pivotal trials, ubrogepant appears superior to its direct competitor oral anti-calcitonin related-gene peptide (CGRP) rimegepant with regards to its efficacy. However, it is not as efficacious as novel, oral acute treatment, lasmiditan. In terms of tolerability, ubrogepant has been well-tolerated in trials, although there may be questions over its safety due to the manifestation of liver-related side effects (see previous comment). Lasmiditan's tolerability profile does not compete with the placebo-like tolerability evident from pivotal trials evaluating anti-CGRPs. Conversely, since efficacy will likely be most highly valued, lasmiditan may prove to become the oral therapy of choice as an alternative to triptans and oral anti-CGRPs may be relied on for those who do not tolerate lasmiditan well.

Source:
Medscape 04/23/2018
American Academy of Neurology (AAN) 04/24/2018 (Abstract ES.008)
Sagient Analysis

Multiple Sclerosis

BIIB098 (BIIB, Phase III)

Phase III – EVOLVE-MS
Trial Data – Updated Results

Abstract 006: MRI and Relapse Results for ALKS 8700 in Patients With Relapsing Remitting Multiple Sclerosis: 1-year Interim Results From the Phase 3 EVOLVE-MS-1 Study
Abstract 360: EVOLVE-MS-1: A Phase 3, Open-Label, Long-Term Safety Study of ALKS 8700 in Relapsing-Remitting Multiple Sclerosis

Change to Likelihood of Approval: +5%

	Treatment	Baseline	Treatment	Difference between Treatment and Baseline
Treatment Description	ALKS 8700 De novo patients	ALKS 8700 De novo patients with 1-year MRI assessments		
Number of Patients	528	374		
Annualized relapse rate (ARR)	0.16 (total follow up of 497.1 patient-years)	-	-	-
New/enlarging T2 lesions Mean number of lesions (SD)	-	-	3.1 (8.6)	-
New T1 hypointense lesions Mean number of lesions (SD)	-	-	2.2 (5.6)	-
Number of Gd+ lesions (% of patients) 0 1-4 5-8 ≥9	-	 65.8% 26.2% 4.8% 3.2%	 89.3% 9.6% 0.3% 0.8%	-
Mean (SD) number of Gd+ lesions	-	1.5 (4.9)	0.3 (1.8)	-80% (p<0.001)

Design
ALKS 8700 (also known as BIIB098) is an investigational oral treatment for relapsing forms of MS. The ongoing EVOLVE-MS-1 study evaluates long-term safety and efficacy of ALKS 8700 in relapsing-remitting MS (RRMS) patients. EVOLVE-MS-1 evaluates ALKS 8700 (462mg twice daily) for up to 96 weeks in RRMS patients. Main inclusion criteria: 18–65 years, RRMS (2010 revised McDonald criteria), EDSS ≤6.0, no evidence of relapse ≤30 days of study start. Enrollment of approximately 900 patients from 100 sites in the United States, Canada, Eastern Europe, and Western Europe is planned. De novo patient enrollment, which began in December, 2015, is complete.

Endpoints

Efficacy analyses include brain MRI endpoints, clinical endpoints (annualized relapse rate, proportion of subjects with relapses, EDSS score, timed 25-foot walk, and proportion of patients with no evidence of disease activity at week 96), and quality of life.

Results

As of March 30, 2018, 757 patients have enrolled in EVOLVE-MS-1, including 593 de novo patients and 164 rollover patients. The present analysis is based on a data cutoff of January 12, 2018 to allow inclusion of fully cleaned data. As of this data cutoff, the study included 617 patients with fully clean data (528 de novo and 89 rollover). Of the 528 de novo patients, 374 have completed a 1-year MRI assessment.

Median follow-up time was 0.93 patient-years for the 528 de novo patients and ARR was 0.16 (total follow-up time of 497.1 patient-years).

With ALKS 8700 treatment, there was a significant reduction ($p<0.0001$) in the number of gadolinium-enhancing lesions from baseline (mean 1.5 [SD 4.9]) to 1 year (0.3 [1.8]) among de novo patients with a 1-year MRI assessment.

Most Common Adverse Events

During the first month of treatment, three patients (0.5%) discontinued due to GI AEs; there were no serious GI AEs. Serious AE and AE-related discontinuation rates were 2.3% and 3.7% for months 0–3.

	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Treatment Description	ALKS 8700 De Novo, Months 0-1	ALKS 8700 Rollover, Months 0-1	ALKS 8700 De novo, Months 0-3	ALKS 8700 Rollover, Months 0-3	ALKS 8700 De novo, Months 0-24	ALKS 8700 Rollover, Months 0-24
Number of Patients	525	66	525	32	528	89
Discontinuations due to AEs	2.3%	0%	3.6%	0%	7.0%	2.2%
Discontinuations due to GI AEs	0.6%	0%	0.8%	0%	0.9%	0%
Any AEs	61.7%	53.0%	71.4%	65.6%	82.4%	77.5%
Any GI AEs	19.0%	10.6%	22.7%	9.4%	29.5%	22.5%
Serious GI AEs	0%	0%	0.4%	0%	0.4%	0%
Deaths	0%	0%	0%	0%	0.4%	0%

Conclusion

This is the first study reporting clinical efficacy results in patients with RRMS treated with ALKS 8700. In this single-arm, open-label study, preliminary results for ARR and MRI parameters support ALKS 8700 as an oral treatment for patients with RRMS.

Safety data from the first three months of the EVOLVE-MS-1 study showed that treatment with ALKS 8700 was associated with low rates of GI AEs leading to discontinuation. Serious AE and AE-related discontinuation rates in months 0–3 were also low. Although the study is still ongoing, preliminary data indicate that ALKS 8700 is associated with a promising tolerability profile, with low rates of discontinuations due to GI AEs, and thereby demonstrates the potential to be an oral therapeutic option for patients with RRMS.

Comment

The first detailed look at these data is promising for BIIB098 and will enable Biogen to position the drug as a potential improvement upon Tecfidera. In terms of efficacy, the reported 0.16 ARR for BIIB098 beats out the corresponding 0.17-0.22 ARRs for twice daily Tecfidera in the pivotal DEFINE and CONFIRM studies. The initial tolerability of BIIB098 also looks favorable, with fewer patients discontinuing treatment due to GI AEs. The important number to note for Tecfidera is 4% in its prescribing information document, while just 0.5% of BIIB098 patients withdrew from the trial protocol within 3 months for such GI side effects. As these AEs are typically present early in the course of treatment and dissipate with time, we expect the direct comparison with Tecfidera in the EVOLVE-MS-2 trial to be positive.

With Biogen acting defensively to acquire rights to BIIB098 since the initiation of these trials, the commercial context of the comparison with Tecfidera is less important. Nevertheless, this product will provide Biogen with another line of defense against potential generic threats for Tecfidera, which has been an attractive target for would-be competitors. Furthermore, with this positive trial and a potential positive direct comparison to Tecfidera in EVOLVE-MS-2, Biogen may be able to grow upon its already-impressive market penetration. We are raising the LOA for BIIB098 by 5% accordingly.

Source:
American Academy of Neurology (AAN) (Poster 006)
American Academy of Neurology (AAN) (Abstract P6.360)
American Academy of Neurology (AAN) (Poster 360)
Sagient Analysis

Autologous Hematopoietic Stem Cell Therapy (Phase III investigator initiated)

Phase III – MIST

Trial Data – Interim Results

Plenary Session: Non-myeloablative hematopoietic stem cell transplantation (HSCT) is superior to disease-modifying drug (DMD) treatment in highly active Relapsing Remitting Multiple Sclerosis (RRMS): interim results of the Multiple Sclerosis International Stem cell Transplant (MIST)

Change to Likelihood of Approval: N/A

	Control	Treatment	Difference Between Treatment and Control
Number of Patients	55	55	110
Number of Evaluable Patients	51	52	103
Percentage treatment failure with mean follow up of three years (range 1-5 years) (%) *(Endpoint=Primary)*	60	6	-54
Mean change in EDSS score from baseline to one year	0.6	-1.1	-1.7 (p<0.001)
Percentage NEDA at four years (%)	0-5	80	~75-80 (p<0.001)
Percentage EDSS failure-free survival at five years (%)	~25	~90	~65 (p=0.001)
Percentage change in T2 lesion volume (%)	34.5	-26.6	-61.1

Design

MIST is a Phase III, multicenter, randomized, comparator study evaluating the safety and efficacy of aHSCT in highly active RRMS patients, which was conducted in sites across the US, UK, Sweden, and Mexico. In the study, 110 patients on stable DMDs with >2 relapses within the prior 12 months were randomized (1:1) to treatment with cyclophosphamide and rabbit anti-thymocyte globulin followed by hematopoietic stem cell infusion or to a control arm with continued treatment with the most appropriate DMD as judged by their treating neurologist.

Endpoints

The primary endpoint was treatment failure defined as an increase in EDSS, assessed by a blinded evaluating neurologist, by at least 1.0 point sustained for at least six months. Patients on DMDs who failed after at least one year of treatment were allowed to crossover to HSCT.

Results

110 patients were randomized, 55 to each arm. Three HSCT patients were withdrawn: two for failing enrollment criteria, one for recurrent infections occurring before transplant. Five control patients were withdrawn after soliciting transplants at other centers. DMDs (number of patients) used in the control arm were: natalizumab (22), dimethyl fumarate (18), fingolimod (13), interferons (10), glatiramer acetate (8), and mitoxantrone (5). Other immune drugs used in the control arm were corticosteroids (39), cyclophosphamide (2), and rituximab (2). With a mean follow-up of three years (range one to five years), treatment failure was 60% (30 of 50) for control arm and 6% (3 of 52) for HSCT ($p< 0.001$). During the first year after HSCT, mean EDSS improved from 3.5 to 2.4, while it worsened from 3.3 to 3.9 in the control arm ($p<0.001$).

Most Common Adverse Events

No deaths occurred and no CTC grade 4 non-hematopoietic toxicities occurred in the transplant arm.

Conclusion

HSCT for RRMS with > 2 relapses a year was superior to continued DMDs.

Comment

Data from the international Phase III MIST trial evaluating autologous hematopoietic stem cell therapy (aHSCT) for highly active relapsing-remitting multiple sclerosis (RRMS) patients who failed conventional approved therapies proved promising.

The impressive efficacy of aHSCT in terms of Expanded Disability Status Scale (EDSS) reduction was unprecedented and positions the treatment to address crucial unmet need in the MS market. Current treatments have been limited to slowing disability progression, as opposed to demonstrating improvements that were remarkably evident with aHSCT. Moreover, at four years, the stark contrast in terms of no evidence of disease activity (NEDA) between the two arms drives home the sustained impact of aHSCT as a potentially curative treatment.

It is encouraging that aHSCT's efficacy in terms of EDSS was evident over the comparator arm during the first year after enrollment and efficacy remained apparent up to five years with a low rate of treatment failure during follow-up at 6% (three patients). Hence, treatment benefits were tangible relatively soon after aHSCT and positive effects persisted years later. Additionally, incorporating numerous standard disease-modifying therapies in the active comparator arm only strengthens the data.

Thus far, aHSCT has appeared to be safe, with no deaths, no grade IV toxicity, and no early or late opportunistic infections including fatal progressive multifocal leukoencephalopathy (PML) that is associated with some approved MS therapies like Tysabri (natalizumab; Biogen). While there was one case of bacteremia during the vulnerable stage of neutropenia with aHSCT, there was no sepsis or hypotension.

No pharmaceutical companies were involved in the MIST trial. Drug companies will not hold a license to perform aHSCT, nor will they receive royalties. In the future, university centers would carry out this treatment. Since aHSCT is only suitable for a specific population of MS patients with aggressive RRMS that is treatment-refractory, it will likely pose a threat to DMTs reserved for highly active RRMS, including Gilenya, Lemtrada, Mavenclad, and Tysabri.

Source:
American Academy of Neurology (AAN) 04/25/2018 (Abstract S36.004)
Sagient Analysis

Spinal Muscular Atrophy

AVXS-101 (NVS, Phase III)

Phase III – STR1VE
Trial Data – Top-Line Results

Abstract ES.466: AVXS-101 Gene Replacement Therapy for SMA Type 1: Pivotal Study (STR1VE) Update

Change to Likelihood of Approval: +1%

	Treatment
Treatment Description	AVXS-101
Number of Evaluable Patients	6
Event Free Survival **As of April 11, 2018**	100%
Mean Change in Average CHOP-INTEND Scores at 1 Month	7.8 points
Mean Change in Average CHOP-INTEND Scores at 3 Month **In Three Patients**	17.3 points

Context
AveXis also announced 24-month follow-up data from the Phase I trial of AVXS-101 for the treatment of spinal muscular atrophy (SMA) type 1 at AAN 2018.

Design
The open-label, single-arm, single-dose, multi-center trial – known as STR1VE – is designed to evaluate the efficacy and safety of a one-time IV infusion of AVXS-101 of 1.1 x 10^{14} vector genomes/kg in patients with SMA type 1 who are under six months of age at the time of gene therapy, have one or two copies of

the SMN2 backup gene as determined by genetic testing, and have bi-allelic SMN1 gene deletion or point mutations. The intent-to-treat population is defined as patients who are under six months of age and symptomatic at the time of gene therapy, with two copies of the SMN2 gene as determined by genetic testing, bi-allelic SMN1 gene deletion and no c.859G>C mutation in SMN2.

As of April 11, 2018, 11 patients were enrolled in the trial, and six patients were symptomatic and at least one month post-gene therapy treatment. All patients had homozygous deletion of SMN1 and two copies of SMN2; no patient had the known SMN2 gene modifier mutation (c.859G>C). The patient population and baseline characteristics are closely matched to the Phase I trial.

Endpoints

The co-primary efficacy outcome measures include the achievement of the developmental milestone of independent sitting for at least 30 seconds at 18 months of age and event-free survival at 14 months of age, with an event defined as either death or at least 16 hours per day of required ventilation support for breathing for 14 consecutive days in the absence of acute reversible illness or perioperative change. Co-secondary outcome measures include the ability to thrive and the ability to remain independent of ventilatory support at 18 months of age.

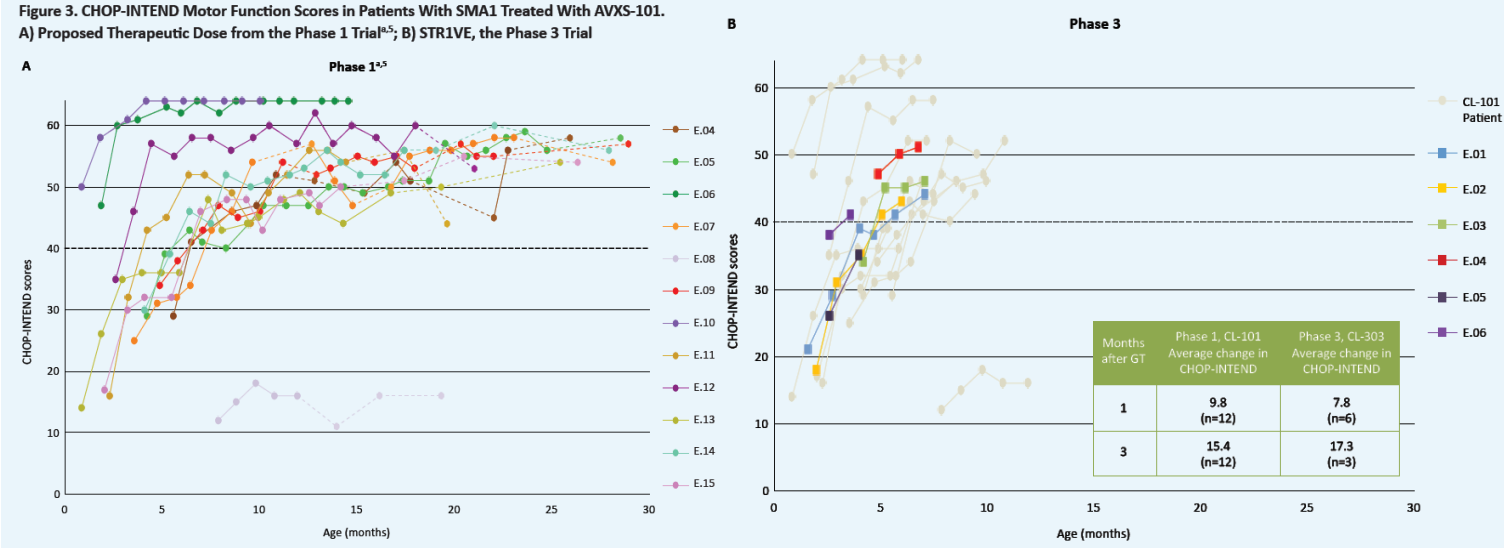
Results

All patients (6/6) were alive and event-free as of April 11, 2018.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores increased by an average of 7.8 at one month after gene transfer (in six patients) and 17.3 at three months after gene transfer (in three patients), reflecting improvement in motor function. These data correlate to CHOP-INTEND achievement by the proposed therapeutic dose cohort (Cohort 2) in the Phase I trial, which experienced mean increases of 9.8 points at one month and 15.4 points at three months. Early CHOP-INTEND increases have been observed to be associated with eventual milestone achievement.

AVXS-101, CHOP-INTEND Phase I (left) compared to Phase III (right)

Figure 3. CHOP-INTEND Motor Function Scores in Patients With SMA1 Treated With AVXS-101. A) Proposed Therapeutic Dose from the Phase 1 Trial[a,5]; B) STR1VE, the Phase 3 Trial



Source: company poster

Most Common Adverse Events

AVXS-101 appeared to have a favorable safety profile and to be generally well tolerated. At the time of gene transfer, the mean age was 3.2 months, with the oldest patient being 5.0 months of age.

In the six patients who were at least one month post-gene transfer, a cumulative total of 25 adverse events (AEs) were reported. Two patients experienced transient elevations in transaminases greater than 3x ULN that were not clinically significant and all resolved with prednisolone treatment without any clinical manifestations or sequelae. There were no serious adverse events (SAEs) reported.

Comment

The initial data released for AVXS-101 from the STR1VE pivotal study are promising, with patients showing improvement in motor function measured by the CHOP-INTEND score and with none of the patients experiencing events such as requiring ventilation support for more than 16 hours a day for 14 consecutive days or death. The increases in CHOP-INTEND scores in this trial are comparable to those observed in Cohort 2 of the Phase I study (7.8 after 1 month of gene transfer compared to 9.8 in cohort 2 of the Phase I study, and 17.3 compared to 15.4 at 3 months, though only in a limited number of patients), and the ability to achieve consistent results is also a positive aspect for AveXis. However, longer follow-up is needed to evaluate the benefits and persistence of the gene therapy for patients, since it may only be able to be given once.

Only six patients have been followed over a month so far, and while it was positive that they were alive and event free, they appeared per a graph to have been followed less than five months so far and be under seven months of age. However, updated data from the Phase I study were also presented at the conference, showing that all 15 patients were alive without the need for permanent ventilation, after 24 months following gene therapy (with median ages of 27.8 and 30.7 in the high dose cohort [cohort 2, 12 patients] and low-dose cohort [cohort 1, 3 patients], respectively). The release noted that per natural history, only 8% of untreated patients would be expected to survive event-free at 20 months.

The event-free survival from the Phase I study is also fairly impressive, given that for Spinraza, the figure is only around 60% at a year (in the publication). Extension data (SHINE) from that study was also presented at the conference, with infants in the treatment arm who continued in the extension having a median time to death or permanent ventilation of only 73 weeks (close to 17 months), though it will be interesting to see how the remaining patients continue to fare longer term.

However, as we have noted before for the Phase I trial, which enrolled patients at a similar age to the pivotal trial (average 3.2 months at gene transfer compared to 3.4 months in cohort 2 of Phase I), the data are difficult to compare, since the average age when drug was started was younger for AVXS-101, and earlier treatment may confer advantages. AveXis has pointed out, though, that the CHOP-INTEND scores at baseline for cohort 2, which comprised the bulk of the study, were similar to those in Spinraza's study. A KOL we spoke with also felt it was difficult to say if AVXS-101 was more effective, given the age difference, but noted it could be, since the gene therapy may more widely distribute the treatment (Spinraza is given into the CSF and so limited by CSF flow) and there could be a benefit from actions in non-neural tissue, though the latter may diminish as patients grow.

The mean change for Spinraza in CHOP-INTEND has also not been reported, but from a graph in the FDA review, at around three months, it appears to be about a 6.5-point improvement, so not as strong as for AVXS-101, though again, the caveat about a difference in age may apply.

Of course, the improved dosing schedule and route of administration (single IV dose of AVXS-101 compared to the repetitive intrathecal dosing with Spinraza) would definitely be an advantage that would help AVXS gain market share. The KOL we spoke with said 80% of his patient families would likely want to start with the gene therapy, and they were asking about it already. Interestingly, though, in Biogen's Q1 earnings call, officials mentioned that seven of 15 patients in AVXS-101's study subsequently received Spinraza. Details on the cases are not available, though an AveXis official told us that they believe the addition of Spinraza was due to parents wanting to assure themselves that they have done all they can for their children, and not because the patient deteriorated. In the long-term follow-up portion of the Phase I study, patients could receive Spinraza, but only four patients achieved new milestones so far, and three of these were on AVXS-101 alone. Hence, it is not clear how much added benefit Spinraza would have. However, the KOL noted they could well be complementary, though there are questions as to whether payors would be willing to reimburse two such expensive treatments, especially since sequential use has not been studied.

From the conference update of AVXS-101's Phase I study, only 4/12 patients in cohort 2 could stand with assistance and only two could walk independently (also mentioned in the past NEJM publication). Hence, while it will be interesting to see longer-term data from the pivotal study, the Phase I study suggests that when started after patients are a few months old and have findings, the gene therapy does not appear curative. In light of this, AveXis announced a couple days earlier the initiation of a trial in pre-symptomatic infants less than 6 weeks of age (with 2–4 copies of SMN2, so it includes later-onset forms of SMA as well). This will be interesting to compare to Spinraza's NURTURE study in presymptomatic infants enrolled less than six weeks of age (with 2–3 SMN2 copies), which found much improved milestone achievement, with half of those with two SMN2 copies (so probably the infant onset form of the disease) able to walk independently at the last data presentation (this could improve still).

The safety profile of AVXS-101 in the newly reported pivotal study did not reveal any new issues, with no patients reporting serious adverse events at least one month post-gene transfer. There were two patients with transient liver enzyme elevations, a known complication from the AAV vector, but these resolved with prednisolone.

Given the positive though preliminary results from the new pivotal study, we are increasing our likelihood of approval another 1%, as we await results from more patients over a longer follow-up period. Competition could also come from oral agents in development.

Source:
Press Release 04/24/2018 (AVXS)
American Academy of Neurology (AAN) (ES.466)
Sagient Analysis

AVXS-101 (NVS, Phase III)

Phase I/II - IRB13-00627 (SMA Type 1)

Trial Data – Updated Results

Abstract S29.001: AVXS-101 Phase 1 Gene Replacement Therapy Clinical Trial in SMA Type 1: Continued Event Free Survival and Achievement of Developmental Milestones

Abstract S29.003: AVXS-101 Phase 1 Gene Replacement Therapy Clinical Trial in SMA Type 1: Continued Independence from Nutritional and Ventilatory Support in Patients Dosed Early in Disease Progression
Abstract S29.004: AVXS-101 Trial Experience: CHOP-INTEND Detects Early Improvements in Infants with SMA Type 1 but is not Sensitive to Continued Advances in Motor Function

Design

The Phase I, open-label, dose-escalation trial was designed to evaluate the safety and tolerability of AVXS-101 in patients with SMA type 1. After the 24-month follow-up, to date, 11 patients have enrolled in the Long-Term Follow-Up (LTFU) trial for ongoing evaluation.

Endpoints

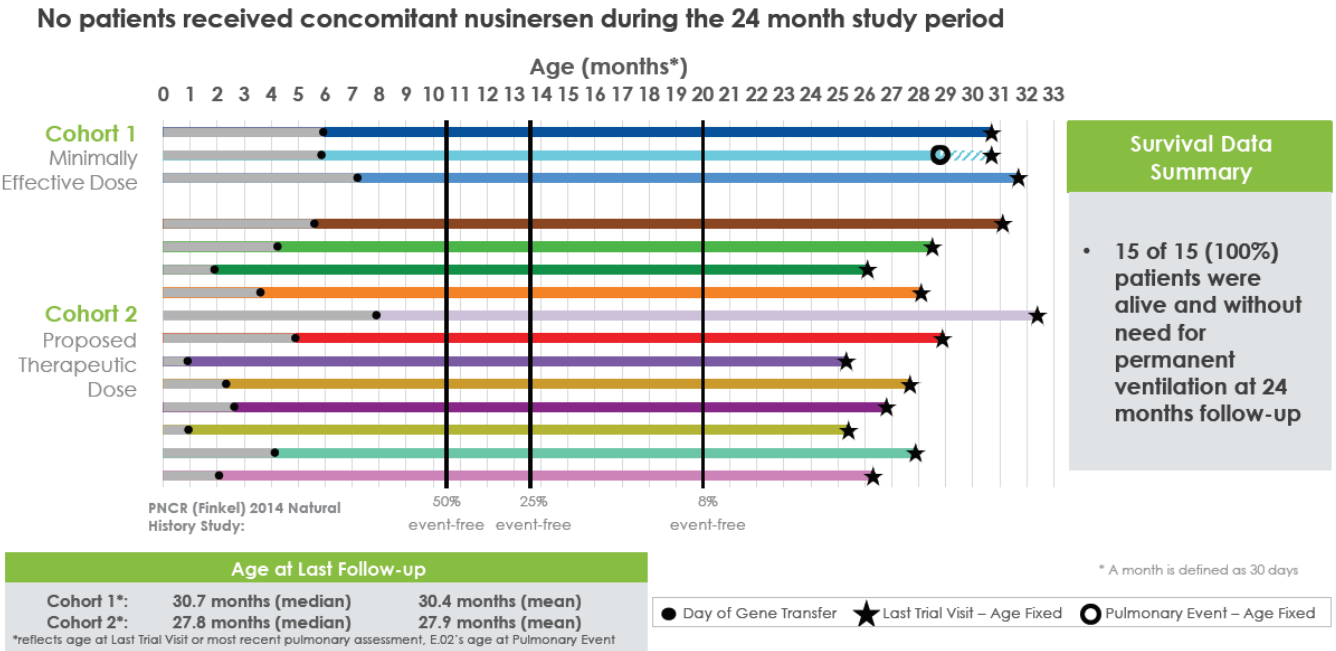
The key measures of efficacy were the time from birth to an event and video confirmed achievement of ability to sit unassisted. Additionally, several exploratory objective measures were assessed, including a standard motor milestone development survey and CHOP INTEND.

Results

Event-free Survival

24 months following gene transfer, 15 of 15 (100%) patients were alive and without need for permanent ventilation. The median age at last follow-up was 27.8 months and 30.7 months for patients in the Cohort 2 and low-dose cohort (Cohort 1), respectively. Natural history indicates only 8% of untreated patients with SMA type 1 survive event-free at 20 months of age.

AVXS-101 Phase I/II Updated Event-free Survival



Source: presentation slides from company

Treatment Durability and Motor Milestone Achievement from Long-Term Follow-Up Study

- Two additional patients achieved the ability to sit unassisted for 30 seconds or more. 11 of 12 (92%) patients could sit unassisted.

- Two additional patients achieved the ability to stand with assistance. Four of 12 (33%) could stand with assistance.
- Three of four patients achieving these new milestones were on AVXS-101 alone (one sitting and two standing with assistance).
- The oldest child from Cohort 2 at the time of last visit in the LTFU study was 46.2 months and 40.6 months post-gene therapy.

Nutritional and Respiratory Support

Patients in Cohort 2 showed a reduced need for nutritional and ventilatory support and improvement in swallowing function. According to natural history, nearly all patients with SMA type 1 require nutritional and respiratory support by 12 months of age, and most patients are not able to swallow or speak effectively.

- Six of seven (86%) patients in Cohort 2 that did not require feeding support before treatment continued without feeding support after treatment; seven of 10 (70%) patients that did not require BiPAP support before treatment continued without any BiPAP after treatment.
- 11 of 12 (92%) patients in Cohort 2 were fed orally, and six of 12 (50%) patients were exclusively fed orally; and 11 of 12 (92%) patients were able to speak.

AVXS-101 Phase I/II and Milestones

Continued Motor Milestone Achievement Demonstrates Durability in Long Term Follow up Study (post 24 months)

Cohort 2 Proposed Therapeutic Dose	Age at GT (mos)	Motor Milestone Achievement							
		Brings hand to mouth	Head control	Roll[a]	Sitting with assistance	Sitting Unassisted ≥ 5 seconds[b]	Sitting Unassisted ≥ 10 seconds[c]	Sitting Unassisted ≥ 30 seconds[d]	Standing Assisted
E.04	6	✔	✔	✔	✔	✔	✔	✔	
E.05	4	✔	✔	✔	✔	✔	✔	✔	
E.06	2	✔	✔	✔	✔	✔	✔	✔	✔
E.07	4	✔	✔	✔	✔	✔	✔	✔	
E.08	8	✔							
E.09	5	✔	✔	✔	✔	✔	✔	✔	
E.10	1	✔	✔	✔	✔	✔	✔	✔	✔
E.11	2	✔	✔	✔	✔	✔	✔	✔	✔
E.12	3	✔	✔	✔	✔	✔	✔	✔	
E.13	1	✔	✔		✔	✔	✔	✔	
E.14	4	✔	✔	✔	✔	✔	✔	✔	✔
E.15	2	✔	✔		✔	✔	✔	✔	
Total (%)	N/A	100	92	75	92	92	92	92	33

- Two children crawl, pull to a stand, and stand and walk independently
- 4 Patients attained new milestones during the LTFU Study*
  - Subjects E.04 and E.07 gained the ability to sit for ≥30 seconds during LTFU Study
  - Subject E.11 and E.14 gained ability to stand with support during LTFU Study
  - 3 of 4 children who achieved new milestones were treated with AVXS-101 alone (1 sitting ≥ 30 seconds and 2 standing with assistance)

■ = 24 months of age cut-off
■ = Long-Term Follow-Up Study(LTFU)*

* Video documentation not assessed and adjudicated by external reviewer

Source: company poster

Most Common Adverse Events

AVXS-101 appeared to have a favorable safety profile and to be generally well tolerated, with no new treatment-related safety or tolerability concerns identified at the 24-month follow-up.

- A cumulative total of 319 AEs (five treatment-related AEs and 314 non-treatment related AEs) were reported following monitoring and source verification. Of these, 60 were determined to be SAEs and 259 were non-serious AEs.
- As reported in 2016, one patient in Cohort 1 had a pulmonary event that required increased use of bi-level positive airway pressure (BiPAP) in advance of surgery related to hypersalivation, a condition experienced by some SMA patients; the event was determined by independent review to represent progression of disease and not to be related to the use of AVXS-101. Following surgery, the respiratory support needs decreased below event definition threshold.
- As has been previously reported, a total of five AEs in four patients were deemed treatment-related. Of these, two were SAEs experienced by two patients, and three were non-serious AEs experienced by two patients. All consisted of clinically asymptomatic liver enzyme elevations and were resolved with prednisolone treatment. There were no clinically significant elevations of gamma-glutamyl transferase, alkaline phosphatase or bilirubin and, as such, Hy's law was not met. Other non-treatment-related AEs were expected and were associated with SMA.

Comment
Please see the comment above on the pivotal trial results.

Source:
Press Release 04/24/2018 (AVXS)
American Academy of Neurology (AAN) (Abstract S29.001)
American Academy of Neurology (AAN) (Abstract S29.003)
American Academy of Neurology (AAN) (Abstract S29.004)
Sagient Analysis

RG7916 (RHHBY, PTCT, Phase II)

Phase II - FIREFISH

Trial Data – Updated Results

Abstract ES.004: RG7916 significantly increases SMN Protein in SMA type 1 Babies

Change to Likelihood of Approval: +2%

Context
Recruitment is ongoing globally for the pivotal second part of the FIREFISH study.

The SMA program was initially developed by PTC Therapeutics in partnership with the SMA Foundation in 2006 to accelerate the development of a treatment for SMA. In November 2011, Roche gained an exclusive worldwide license to the PTC/SMA Foundation SMN2 alternative splicing program. The development of these compounds is being executed by Roche and overseen by a joint steering committee with members from PTC, Roche, and the SMA Foundation.

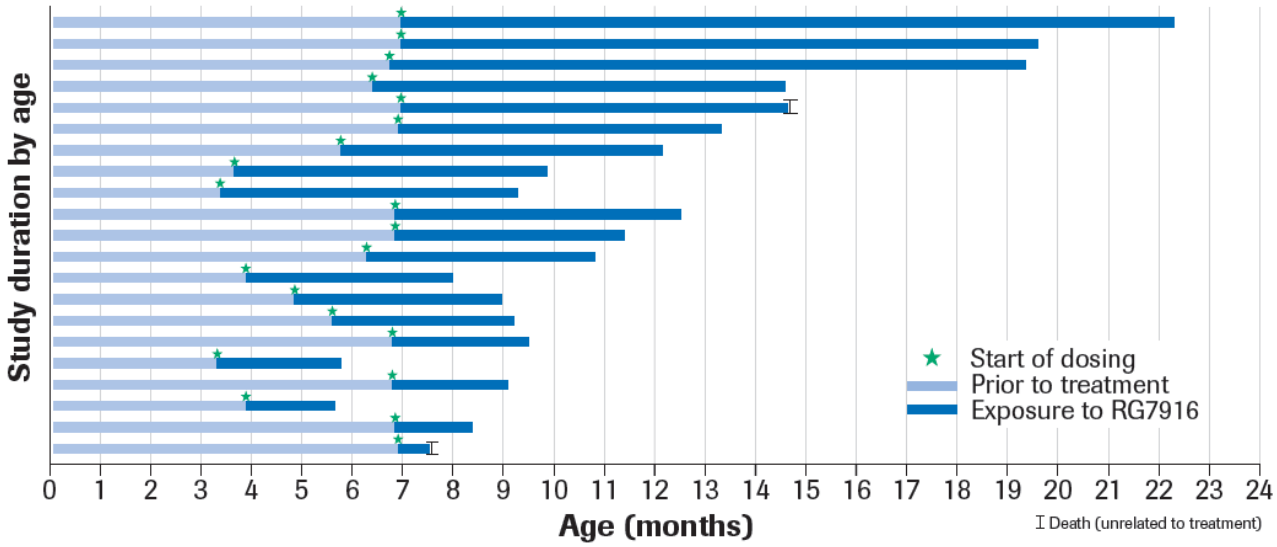
Design
The open-label trial is evaluating RG7916, an oral survival motor neuron 2 (SMN2) splicing modifier, in type 1 SMA patients.

The exploratory Part 1 (n=21) of the FIREFISH study assesses safety, tolerability, pharmacokinetics, and pharmacodynamics of RG7916 at different dose levels. The confirmatory Part 2 (n=40) will assess safety and efficacy of RG7916.

Results

No babies have required a tracheostomy or permanent ventilation since study initiation and no baby has lost the ability to swallow (figures below). Two babies died (see Most Common Adverse Events below). The median age of first dose was 6.7 months and babies have received RG7916 for a duration of up to 14.8 months.

RG7916 FIREFISH - age of babies and duration of exposure to treatment



Study duration is measured from the start date of the first dose to the date of data extraction. Deaths were not related to study treatment, one death was due to aspiration and one death was due to pneumonia.
Data cut: 11th April 2018.

Source: company poster

FIREFISH - summary of swallowing ability

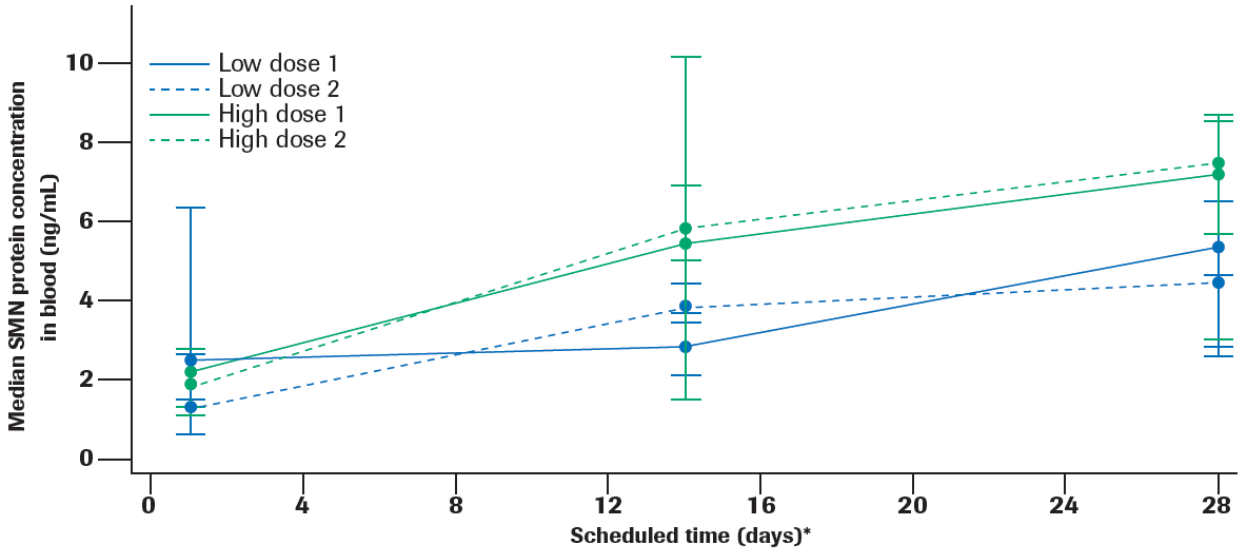
Visit	All treatments
Baseline	**N=21**
Able to swallow, n	20
Unable to swallow, n	1
Week 8	**N=18**
Able to swallow, n	17
Unable to swallow, n	1
Week 17	**N=12**
Able to swallow, n	11
Unable to swallow, n	1
Week 26	**N=8**
Able to swallow, n	8
Unable to swallow, n	0
Week 35	**N=3**
Able to swallow, n	3
Unable to swallow, n	0
Week 43	**N=3**
Able to swallow, n	3
Unable to swallow, n	0

Data cut: 11th April 2018.

Source: company poster

Data from 21 patients from the completed Part 1 portion of this study suggested that RG7916 produced a dose-dependent increase in SMN protein levels in babies with type 1 SMA.

FIREFISH - Median SMN protein level in blood over time



SMN protein	$AUC_{0-24h} \leq 1000$ ng.h/mL (N=7)†	$AUC_{0-24h} > 1000$ ng.h/mL (N=7)†
Absolute (ng/mL)	4.62 [2.61–6.63]	7.57 [2.97–8.76]
Fold-change from baseline	1.95 [1.04–5.35]	3.19 [1.57–6.79]

*Data from 16 babies. Error bars show minimum and maximum values. The first baby enrolled into the study and unscheduled visits have not been included in this summary plot.
Median [range] †SMN protein level data from 14 babies on Day 28. Data unavailable for two babies.

Source: company poster

Most Common Adverse Events

Data from Part 1 demonstrated that RG7916 has been well tolerated at all dose levels and to date there have been no drug-related safety findings leading to withdrawal.

Fatal events were reported in two babies:

- respiratory tract viral infection in a female baby aged seven months at enrollment. First symptoms started on study Day 4 with fatal outcome on study Day 21. The event was complicated by bilateral atelectasis.
- fatal cardiac arrest and respiratory arrest on study Day 236 in female baby aged seven months at enrollment on concurrent night ventilation (bilevel positive airway pressure for less than 16 hours per day) in the context of suspected aspiration.

Ophthalmologic monitoring in babies exposed to RG7916 did not show any evidence of the retinal findings seen in preclinical monkey studies.

Conclusion

The observed SMN protein level increase in the blood (median 3.2, up to 6.5-fold) is expected to lead to clinically relevant efficacy in babies with SMA, and per the abstract, the up to 6.5-fold increase in SMN

protein observed in FIREFISH Part 1 compares favorably with the approximately two-fold difference in SMN protein levels between SMA severity types (eg type 2 versus type 1).

To date, RG7916 has been well tolerated at all dose levels and there have been no drug-related safety findings leading to withdrawal in any SMA babies exposed to RG7916.

FIREFISH Part 2 has started and will assess the efficacy and safety of RG7916. Recruitment is ongoing globally.

Comment

In the FIREFISH study of type 1 SMA (onset in early infancy), while there was no control group to compare the increase in SMN protein in the blood, it was interesting that those who had a higher concentration of the drug had higher SMN protein levels, showing a median 3.19-fold increase compared to a 1.95-fold increase for those with lower levels. Overall, the median increase was 3.2-fold. While these are blood levels and the main area of interest would be in nervous tissue, preclinical work has noted a correlation.

There have been limited data to compare this to other drugs. There have been no data from gene therapy AVXS-101; a company spokesperson said it does not impact the tissue used in blood assays and they have not had any infants pass away in order to do biopsies. Spinraza had limited spinal cord biopsy data from SMA infants who died, showing a 2.6-fold increase in full-length SMN2 transcripts compared with untreated infants and 63.7% increase in staining intensity for SMN protein. However, there were only three Spinraza-treated patients, and officials from Ionis have also noted that without more natural history data, such data in infants are difficult to interpret. Still, the increase for RG7916 was over 28 days, so not too long a time frame, and the difference between groups with higher or lower drug concentration suggests at least some effect.

On survival and need for permanent ventilation, the data are fairly preliminary and difficult to draw conclusions from, though they appear encouraging. There have been two deaths, but no infants have required permanent ventilation. If one does an informal Kaplan-Meier type analysis, it would correlate with an event-free survival of around 76% out to 8–12 months of treatment, but only 3–4 infants have had data out that long. In Spinraza's pivotal study, event-free survival at eight and 12 months was around 65% and 55% (per the publication graph) compared to around 30% and 27% for controls. Hence the data are suggestive, but it is difficult to draw conclusions with so few patients.

There were little data on milestones or other clinical endpoints, other than no infants lost their ability to swallow (one already could not swallow at baseline, which may not have changed), but only eight had been followed to 26 weeks and three for 35 weeks or more. There are limited published data on what to expect. One natural history study noted that nutritional support was initiated about three months before ventilation support. Using the control event-free survival curve in Spinraza's Phase III study as a proxy, this might mean that by 26 weeks of treatment (there was only a slight difference in age at first dosing between the Spinraza and RG7916 studies), about 70% might be expected to need nutritional support. However, such comparisons are quite tentative. For example, at the median age of 6.74 months at first dose in FIREFISH, using the event-free curve according to age in the natural history study, about 30% may already be expected to require nutritional support, so infants in the FIREFISH study may not have been as severe, and patients will have to be followed longer with more milestones reported to get a better idea of the drug's effects.

Subsequent RG7916 data from the conference in older children showed a dose-dependent increase in

SMN protein in blood up to a median 2.5-fold in Part 1 of SUNFISH, though we should note that per other recently presented data, that increase was only seen in patients over age 12; younger patients only had an increase up to 1.96 at a high dose (dose 4), and tolerability for that dose was not released (note: BMT did not have access to the AAN poster for this study). More clarity is needed on why there may be a difference in the age groups. Similarly, in data from JEWELFISH presented at the AAN, which involved older patients age 16–52 who had previously been in a study with a therapy targeting SMN2 mRNA splicing, there was a median increase around 2 in SMN protein (per the graph), though there was a wide range with increases up to 4-fold. The dose involved in JEWELFISH was the first dose given in SUNFISH (in the prior SUNFISH data, there was only a slightly higher increase in SMN protein with dose 2 compared to dose 1 for those aged 12–25). The presenter for JEWELFISH also showed a slide with data from both JEWELFISH and SUNFISH, showing an increase of SMN protein levels in the blood with increasing concentration of the drug, and consistent findings between the two studies.

A KOL we spoke with felt that the ~3-fold increase in infants was encouraging, but so was the ~2-fold increase in older children, since most of the latter have at least three copies of SMN2 at baseline, and each copy makes about 10% full length SMN protein. Hence doubling could increase that to 60% full length SMN protein (similar to a 3-fold increase in those type 1 patients with 2 SMN2 copies), which is more than the 50% that some carriers have. There is not an absolute correlation, though, between symptoms and copy number. For Spinraza, one study in type 2 and 3 SMA children, age 2–14, found that a 6mg dose increased CSF SMN protein by 118% (so a 2-fold increase) and 9mg by 161%, but 12mg was used in Phase III, so the increase may be higher than that. Nevertheless, in the Phase III trial in this age group (age 2–12), Spinraza only had relatively modest benefits. However, there are questions on how accurate the CSF SMN protein measurements were. The KOL we spoke with also noted that as an oral drug, RG7916 may have better distribution throughout the spinal nerves, as well as muscle and other tissue, whereas Spinraza, delivered into the CSF, is limited by flow of spinal fluid. On the other hand, the wider distribution of an oral drug also opens the door to more safety issues.

On safety, retinal toxicity had been seen with RG7916 in preclinical monkey studies, but no obvious findings have been reported in the clinical data released.

Overall, the data from this and subsequent presentation abstracts are suggestive that the drug could be efficacious, particularly for the infants, but quite preliminary, so we are increasing our likelihood but limiting that to 2%.

Source:
American Academy of Neurology (AAN) 04/24/2018 (Abstract ES.004)
American Academy of Neurology (AAN) 04/24/2018 (Poster)
Press Release 04/24/2018 (PTCT)
Sagient Analysis

RG7916 (RHHBY, PTCT, Phase II)

Phase II - SUNFISH

Trial Data – Updated Results

Abstract P4.453: Updated pharmacodynamic and safety data from SUNFISH Part 1, a study evaluating the oral SMN2 splicing modifier RG7916 in patients with Type 2 or 3 spinal muscular atrophy

Context
Researchers have previously presented an early analysis of SUNFISH Part 1, which showed that RG7916 administration results in a dose-dependent increase in full-length SMN2 mRNA and a concomitant decrease in SMN2Δ7 mRNA.

Design
SUNFISH is a multicenter, double-blind, placebo-controlled trial (randomized 2:1, RG7916:placebo) in patients with type 2 or 3 SMA aged 2–25 years. SUNFISH comprises two parts: Part 1 is evaluating the safety, tolerability, and PK/PD of several RG7916 dose levels (n=51); the pivotal Part 2 is assessing the safety and efficacy of the RG7916 dose level selected from Part 1 (n=168).

Results
Recent analysis of SMN protein levels in whole blood showed that in patients with SMA, SMN protein increased in a dose-dependent manner up to median 2.5-fold. The safety, tolerability, and PK/PD data from Part 1 informed the selection of a RG7916 dose level for SUNFISH Part 2 predicted to lead to clinically efficacious increases in SMN protein.

Most Common Adverse Events
To date, no drug-related adverse events leading to withdrawal have been observed.

Conclusion
In SUNFISH Part 1, RG7916 treatment modulated SMN2 mRNA and increased SMN protein dose dependently. The clinical benefit of the selected dose level is being assessed in SUNFISH Part 2, which is currently recruiting globally.

Comment
Please see comment above under the FIREFISH.

Source:
American Academy of Neurology (AAN) 04/25/2018 (Abstract P4.453)
Sagient Analysis

RG7916 (RHHBY, PTCT, Phase II)

Phase II - JEWELFISH
Trial Data – Updated Results

Abstract S46.003: Preliminary Evidence for Pharmacodynamics Effects of RG7916 in JEWELFISH, a Study in Patients with Spinal Muscular Atrophy who Previously Participated in a Study with Another SMN2-Splicing Targeting Therapy

Design
JEWELFISH is a multicenter, open-label, exploratory study evaluating the safety, tolerability, and PK of daily oral RG7916 in patients with SMA type 2 or 3, age 12–60 years, who previously participated in a study with therapies targeting SMN2 splicing. The pharmacodynamic (PD) effects on SMN2 mRNA and SMN protein are also assessed.

Results

At the time of abstract submission, eight patients had received RG7916 for up to 32 weeks. Preliminary PD data following RG7916 treatment showed a rapid increase in the full-length SMN2 (SMN2FL)/SMNΔ7 mRNA ratio after treatment onset, and an up to four-fold increase from baseline over four weeks. This SMN2FL/SMNΔ7 mRNA ratio increase resulted in an up to four-fold SMN protein increase over four weeks.

Most Common Adverse Events

To date, RG7916 has been safe and well tolerated, with no drug-related safety findings leading to withdrawal in any SMA patient exposed to RG7916.

Conclusion

JEWELFISH is currently recruiting in sites across Europe and the US. Together with the ongoing SUNFISH (SMA type 2 and 3) and FIREFISH (SMA type 1) studies, JEWELFISH will provide insights into the safety, tolerability, PK and PD of daily oral RG7916.

Comment

Please see comment above under the FIREFISH results.

Source:
American Academy of Neurology (AAN) 04/26/2018 (Abstract S46.003)

Olesoxime (RHHBY, Phase II)

Phase II – OLEOS

Trial Data – Top-Line Results

Abstract S46.002: A Long-Term, Open-Label Follow-Up Study of Olesoxime in Patients with Type 2 or Non-Ambulatory Type 3 Spinal Muscular Atrophy who Participated in a Placebo-Controlled Phase 2 Trial

Change to Likelihood of Approval: -4%

	Placebo	Treatment	Difference Between Treatment and Placebo	Untreated	Untreated	Treatment	Treatment	Treatment
	Original double-blind study (2 years)			Change from start of Ph II to OLEOS baseline (median 3 years untreated)		OLEOS Open-label extension		
	Placebo	Olesoxime	Olesoxime vs Placebo	Placebo in Phase II	Olesoxime in Phase II	Olesoxime Week 26	Olesoxime Week 52	Olesoxime Week 78
Number of Patients	57	108		39	89	125	109	107
MFM D1+D2	-1.82	0.18	2 (p=0.0676)	-11.04	-7.94	-0.05	-0.3	-1.1
MFM D1+D2 (sensitivity analysis*)	-1.96	0.24	2.2 (p=0.0379)	-	-	-	-	-
MFM D1+D2 (6-15 years old)	-2.91	0.71	3.61 (p=0.0362)	-	-	-	-	-

*Data from whichever form of the MFM that was used

Context
In a previous randomized, double-blind Phase II trial in patients aged three–25 years with type 2 or nonambulatory type 3 SMA, olesoxime maintained motor function over 24 months, whilst the placebo group declined.

Design
OLEOS is an open-label extension study assessing the long-term safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy (SMA).

One hundred and twenty-nine patients with type 2 or non-ambulatory type 3 SMA from the previous Phase II study were enrolled and treated with olesoxime (10 mg/kg); the majority have been followed for 12 months (n=104). OLEOS baseline visit occurred 2.4–5.1 years (median three years) after study drug discontinuation in Phase II.

Endpoints
The primary endpoint is safety and the secondary endpoints include change in Motor Function Measure (MFM) D1+D2 from baseline up to five years.

Results
Maintenance of motor function observed over two years in the Phase II study was followed by a substantial decline in MFM D1+D2 (>2 points/year) after drug discontinuation. However, the ~two-point MFM treatment difference between olesoxime and placebo at the end of Phase 2 was maintained at OLEOS baseline. Furthermore, olesoxime open-label treatment stabilized motor function (mean change in MFM D1 + D2 from baseline:six months, -0.03 [SD, 4.79; n=124]; 12 months, -0.22 [SD, 4.74, n=104]).

Most Common Adverse Events
Consistent with previous studies, olesoxime was generally safe and well tolerated at the dose assessed.

Conclusion
These data support the long-term stabilization of motor function observed in the Phase II study.

Comment
On the face of it, the data looked suggestive. There was some separation from placebo during the double-blind portion, then when patients were off drug for a few years they declined, though maintaining a separation. Finally, when started back on open-label treatment, there was some stability for a year before they started declining again.

However, a KOL we interviewed was skeptical of the results. For one thing, the primary analysis was not statistically significant. Also, he said the two-point difference on the MFM was not that meaningful. Finally, while there was some stability in the extension over a year, he said one can see that in patients in a natural history study, that they stabilize for a time on study entry then start to decline again, and the 1.1 decline through week 78 was not out of what might be expected.

So while it is possible the drug confers some stability, there are reasons to question the results, and we are lowering our likelihood of approval by 4%.

Of note, the conference presenter said that some patients discontinuing the study left to start Spinraza, which is changing the treatment landscape. He said they will need to consider whether olesoxime can be effective as add-on therapy, but also they do not know yet how much Spinraza will change the scenario for SMA type 2 and non-ambulatory type 3 patients.

Myasthenia Gravis (MG)

Efgartigimod (ARGX, Phase II)

Phase II - Generalized Muscle Weakness
Trial Data – Final Results

Plenary Session: A Double-blind Placebo-controlled Study to Evaluate the Safety and Efficacy of FcRn-antagonist ARGX-113 (efgartigimod) in Generalized Myasthenia Gravis

Change to Likelihood of Approval: +1%

	Placebo	Treatment
	Placebo	Efgartigimod *P-value vs. Placebo*
Number of Patients	12	12
Percent of Patients with at Least a 2-Point Reduction MG-ADL from Baseline for 6 Consecutive Weeks	25%	75% (p=0.0391)
Percent of Patients with at Least a 2-Point Reduction MG-ADL from Baseline	-	83%

Context
argenx is conducting two additional ongoing Phase II clinical trials of efgartigimod in immune thrombocytopenia (ITP) and pemphigus vulgaris (PV). Topline data from the ITP trial and interim data from the PV trial are both expected in the second half of 2018.

Design
The Phase II trial evaluated 24 MG patients with generalized muscle weakness, and a total MG-ADL score ≥5, with more than 50% of the score consisting of non-ocular items. Patients were randomized to receive four weekly doses of either standard of care plus 10mg/kg of ARGX-113, or standard of care plus placebo. Standard of care therapies included acetylcholinesterase inhibitors, corticosteroids, and/or immunomodulatory agents.

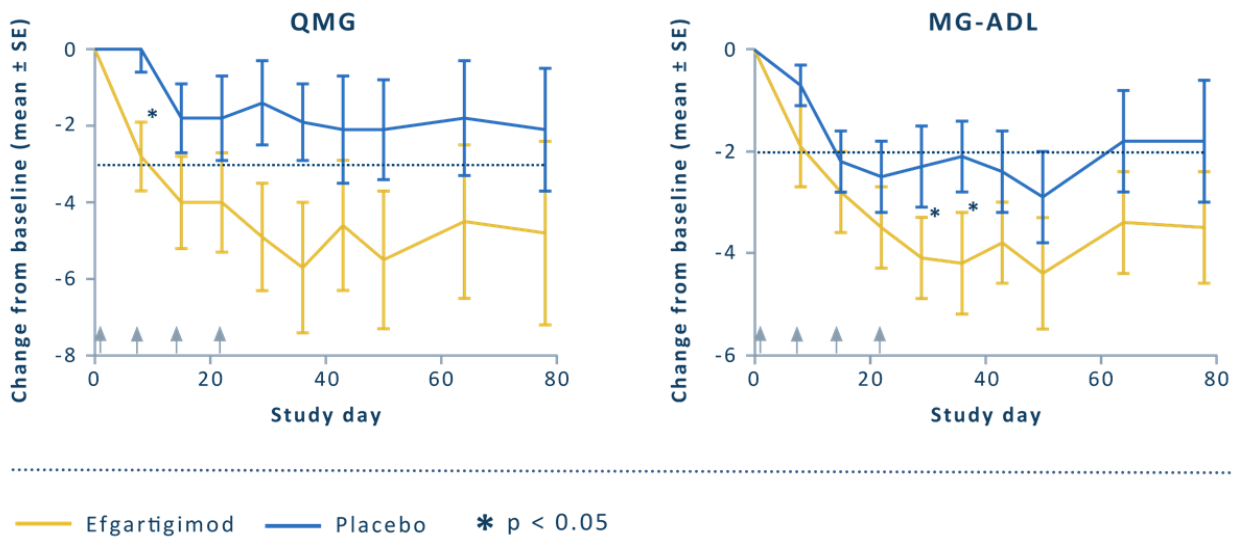
Endpoints
The primary endpoints of the trial were safety and tolerability. Secondary endpoints included efficacy as measured by the change from baseline of the MG-ADL, QMG, and MGC disease severity scores; impact on quality of life as measured by the MGQoL score; and an assessment of pharmacokinetics (PK) and pharmacodynamic (PD) markers and immunogenicity.

Results

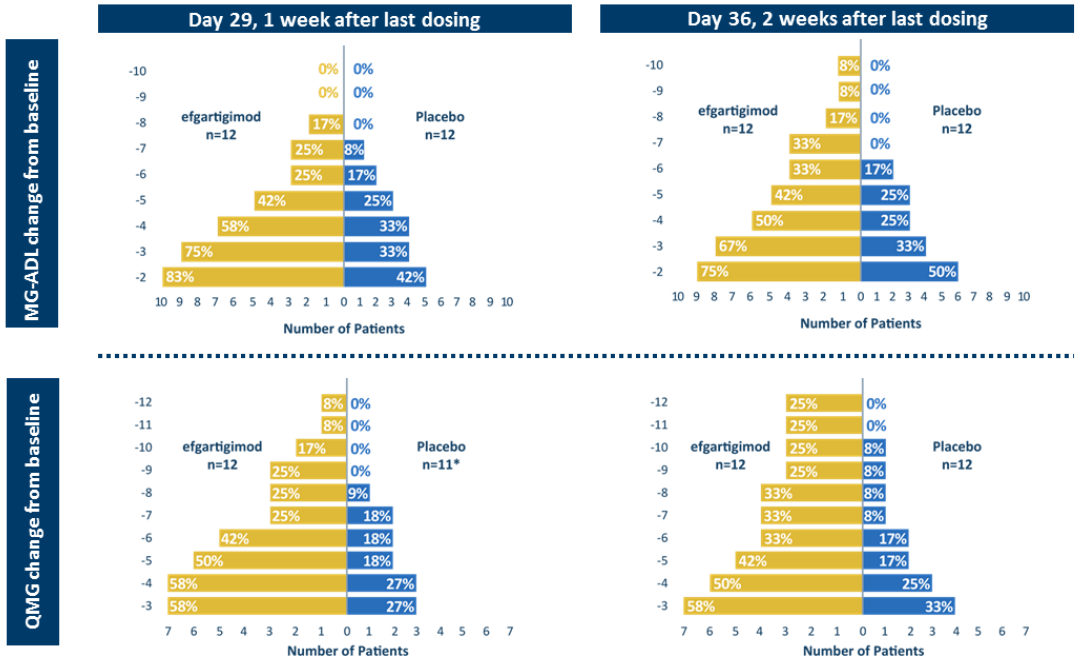
Key Highlights from Full Phase II Dataset:

- Full efficacy data through the eight-week follow-up phase show that administration of efgartigimod resulted in clinical improvement over the placebo through the entire duration of study (11 weeks). Clinical benefit in the efgartigimod treatment group maximized as of one week after the administration of the last dose, achieving statistical significance over the placebo group (p=0.0356) on the Myasthenia Gravis Activity-of-Daily-Living (MG-ADL) score.
    - 75% of patients treated with efgartigimod had a clinically meaningful and statistically significant improvement in MG-ADL scores (at least a two-point reduction from baseline) for a period of at least six consecutive weeks, versus 25% of patients on the placebo (p=0.0391).
    - Increasing differentiation was observed between the efgartigimod treatment group versus the placebo group, with increasing MG-ADL thresholds. Updated results will include the differentiation between the treatment and placebo groups for both the MG-ADL and Quantitative Myasthenia Gravis (QMG) thresholds at the 29-day point and the 36-day point.
    - Patients in the treatment arm showed disease improvement, with separation from the patients in the placebo group one week after the first infusion that persisted after the last dose.
    - Efgartigimod treatment resulted in clinical improvement over the placebo, as measured by all four predefined clinical efficacy scales–MG-ADL, QMG, Myasthenia Gravis Composite (MGC), and Myasthenia Gravis Quality of Life (MG-QoL).

Efgartigimod Phase II: QMG and MG-ADL scores, average (top) and categorical (bottom) changes



- Clinically meaningful and statistically significant improvement reached in small patient population (N=24)
- Clear consistency between QMG and MG-ADL scores

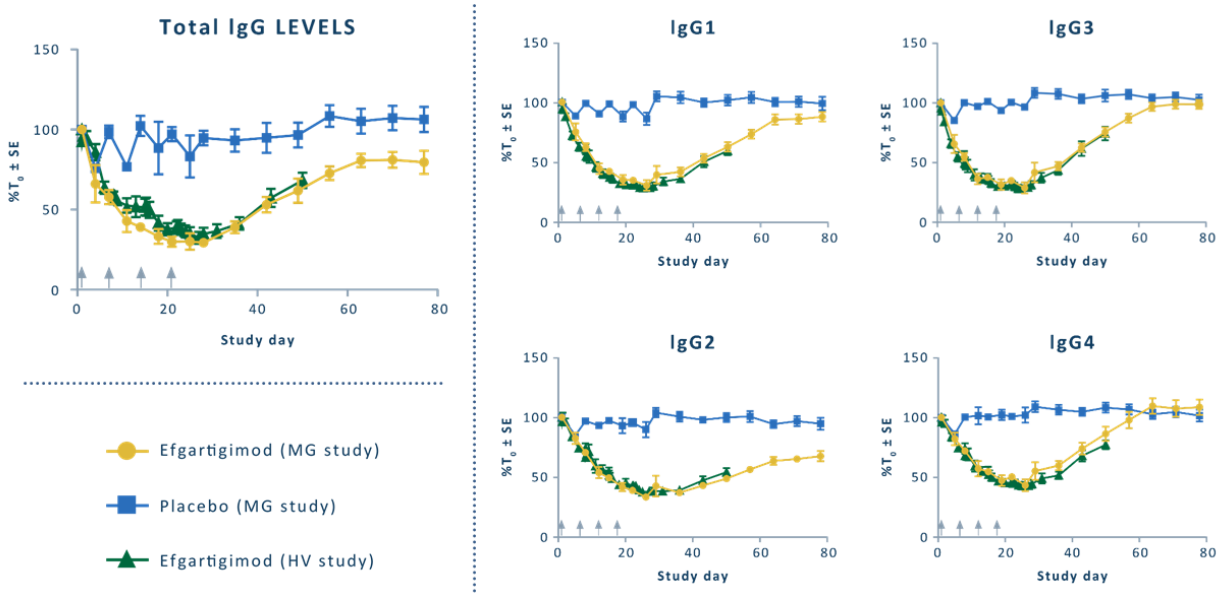


- Efgartigimod *vs.* placebo: increasing differentiation observed with increasing MG-ADL/QMG thresholds

Source: Company webcast

- All patients in the treatment arm showed a reduction of total IgG levels. Clinically meaningful disease improvement was found to correlate with reduction in pathogenic IgG levels.
    - Total IgG reduction in patients was consistent with the Phase I healthy volunteer trial.
    - Reduction of IgG levels was consistent across IgG subtypes, including AChR autoantibodies (IgG1 and IgG3).
    - Updated results show mean maximum IgG reduction of up to 70.7% among treated patients.

Efgartigimod Phase II: IgG reductions, across IgG isotypes

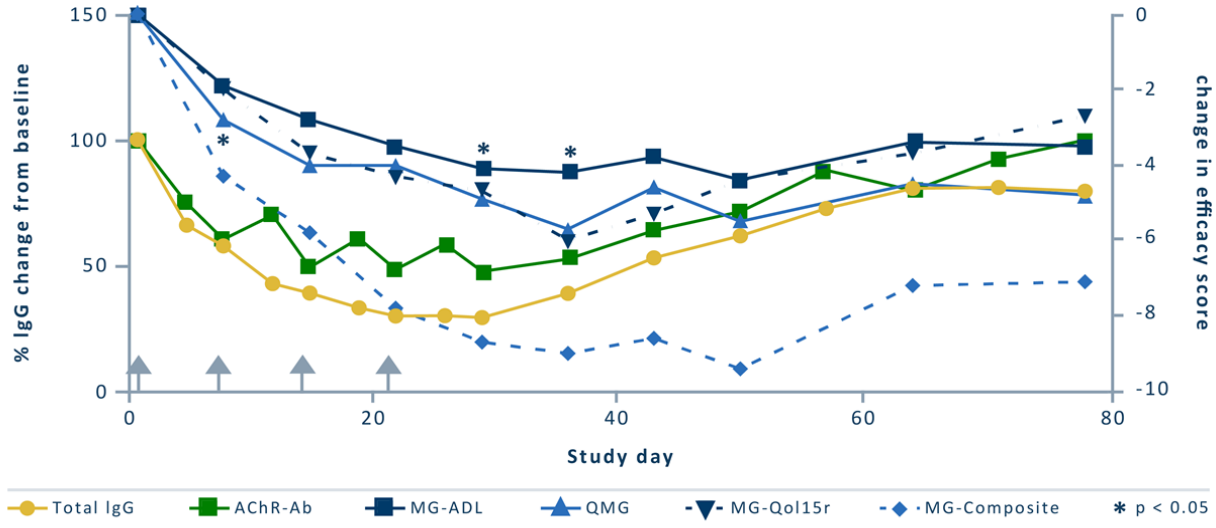


- PD effect of efgartigimod in the Phase 2 clinical trial very similar to the Phase 1 trial in healthy volunteers
- Significant IgG reduction across IgG subtypes (AChR autoantibodies are IgG1/3; MuSK autoantibodies are IgG4)
- IgM, IgA and albumin levels not affected (data not shown)

Source: Company webcast

- Strong correlation between IgG level reduction and disease improvement, validating focus on IgG-mediated diseases.

Efgartigimod Phase II: correlation between IgG levels and disease scores



- Clinical improvement persists despite return of IgG levels
- Potential differentiation from PLEX, where clinical benefit was reported to be lost 2-4 weeks after end of treatment [1]

Source: Company webcast

Most Common Adverse Events

The tolerability of efgartigimod remained consistent with findings from the Phase I trial in healthy volunteers. The study drug candidate was well-tolerated in all patients with no serious or severe adverse events reported, and most adverse events were characterized as mild and deemed unrelated to the drug candidate.

Efgartigimod Phase II Safety and Tolerability Profile

- Efgartigimod was well-tolerated in patients confirmed findings from Phase 1 healthy volunteer trial
- The TEAEs profile was balanced between efgartigimod and placebo
- TEAEs were mostly mild (grade 1) in severity; no severe AEs were reported
- No deaths, serious AEs or TEAEs leading to discontinuation of treatment were reported during the trial

Treatment Emergent Adverse Events (TEAEs) Reported in ≥ 2 patients	Placebo (N = 12)	Efgartigimod (N = 12)
TEAEs (Total)	**10 (83.3%)**	**10 (83.3%)**
• Headache	3 (25.0%)	4 (33.3%)
• Nausea	1 (8.3%)	1 (8.3%)
• Diarrhea	1 (8.3%)	1 (8.3%)
• Abdominal pain upper	1 (8.3%)	1 (8.3%)
• Arthralgia	2 (16.7%)	-
• B-lymphocyte decrease	-	2 (16.7%)
• Lymphocyte count decrease	-	2 (16.7%)
• Monocyte count decrease	-	2 (16.7%)
• Neutrophil count increase	-	2 (16.7%)
• Myalgia	-	2 (16.7%)
• Pruritus	2 (16.7%)	1 (8.3%)
• Rhinorrhea	1 (8.3%)	1 (8.3%)
• Tooth abscess	2 (16.7%)	-
• Toothache	2 (16.7%)	-
Efgartigimod deemed related TEAEs	**3 (25.0%)**	**8 (66.7%)**
• Headache	1 (8.3%)	3 (25.0%)
• Monocyte count decrease	0 (0.0%)	2 (16.7%)
• Rhinorrhea	1 (8.3%)	1 (8.3%)

- Efgartigimod was well-tolerated in patients confirmed findings from Phase 1 healthy volunteer trial
- The TEAEs profile was balanced between efgartigimod and placebo
- TEAEs were mostly mild (grade 1) in severity; no severe AEs were reported
- No deaths, serious AEs or TEAEs leading to discontinuation of treatment were reported during the trial

Treatment Emergent Adverse Events (TEAEs) Reported in ≥ 2 patients	Placebo (N = 12)	Efgartigimod (N = 12)
TEAEs (Total)	**10 (83.3%)**	**10 (83.3%)**
• Headache	3 (25.0%)	4 (33.3%)
• Nausea	1 (8.3%)	1 (8.3%)
• Diarrhea	1 (8.3%)	1 (8.3%)
• Abdominal pain upper	1 (8.3%)	1 (8.3%)
• Arthralgia	2 (16.7%)	-
• B-lymphocyte decrease	-	2 (16.7%)
• Lymphocyte count decrease	-	2 (16.7%)
• Monocyte count decrease	-	2 (16.7%)
• Neutrophil count increase	-	2 (16.7%)
• Myalgia	-	2 (16.7%)
• Pruritus	2 (16.7%)	1 (8.3%)
• Rhinorrhea	1 (8.3%)	1 (8.3%)
• Tooth abscess	2 (16.7%)	-
• Toothache	2 (16.7%)	-
Efgartigimod deemed related TEAEs	**3 (25.0%)**	**8 (66.7%)**
• Headache	1 (8.3%)	3 (25.0%)
• Monocyte count decrease	0 (0.0%)	2 (16.7%)
• Rhinorrhea	1 (8.3%)	1 (8.3%)

Source: Company webcast

Comment

Adverse effects associated with the standard of care for Myasthenia Gravis (MG) are a key concern; indeed, the only FDA-approved therapy for MG, Soliris, carries a black box warning for the risk of meningococcal infection. This makes ARGX-113's tolerability and lack of adverse effects notable. There was a transient reduction in monocytes in those who already had low levels, but this rapidly reversed in the study and the investigators did not consider it significant. Other drug-related TEAEs included headaches and rhinorrhea. If the drug's impressive safety profile can be proven in larger Phase III trials it may provide the drug with a significant advantage.

In addition to its positive safety and efficacy data, this proof-of-concept trial showed a strong correlation between a reduction in IgG and an improvement in the MG-quality of life score (QoL), helping to affirm argenx's approach to MG treatment. Additionally, changes in IgG matched those observed in human volunteer trials, indicating that the drug acts similarly in healthy and diseased populations. IgM, IgA and albumin levels were not affected. The reduction in IgG brought about by the drug reversed over the eight-week post-dose monitoring period which was accompanied by a comparable reduction in MG-QoL score. It should be noted that a strong placebo effect was reported, something that will need to be carefully considered in the design of Phase III trials, though the presenter noted this is seen in all MG trials.

We should also note, there was a baseline imbalance with more treated patients on immunosuppressants, but the investigators felt the duration of the study was short enough that they did not think this had an impact.

The majority of patients in this trial had mild to moderate MG, with one patient having severe MG; no severity-specific data were given. If approved, the breadth of ARGX-113's label and the reimbursement considerations will be interesting, given that the drug will likely be expensive. The presenter said he felt the drug could be a replacement for IVIG and plasma exchange.

A subcutaneous (SQ) formulation is currently under development. A Phase I study in healthy volunteers is comparing a single dose of the SQ formulation to a single dose of the IV formulation. A third arm will test induction with two doses of the IV formulation (D1 and D4) followed by eight weekly doses of the SQ formulation. Data are expected in mid-2018.

As we await the start of pivotal Phase III trial by the end of 2018, we are increasing the LOA by 1%.

Source:
Press Release 04/24/2018 (ARGX)
American Academy of Neurology (AAN) 04/24/2018
Company Conference Call 04/24/2018 (ARGX)
Sagient Analysis

Transthyretin (TTR)-related Hereditary Amyloidosis (Familial Amyloid Polyneuropathy)

Patisiran (SNY, NDA)

Phase III - APOLLO
Trial Data – Retrospective Analysis

Abstract CT.001: Patisiran, an Investigational RNAi Therapeutic for Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: Results from the Phase 3 APOLLO Study

Change to Likelihood of Approval: 0%

	Placebo	Treatment	Difference Between Treatment and Comparator
Treatment Description	Placebo	Patisiran	Patisiran vs. Placebo
Number of Evaluable Patients	77	148	225
Any Hospitalization/Death Analysis: Negative Binomial Regression Rate Ratio	-	-	0.49 (p<0.05)
Any Hospitalization/Death Analysis: Anderson-Gill Hazard Ratio	-	-	0.48 (p<0.05)
Cardiac Hospitalization/Death Analysis: Negative Binomial Regression Rate Ratio	-	-	0.54 (p>0.05)
Cardiac Hospitalization/Death Analysis: Anderson-Gill Hazard Ratio	-	-	0.54 (p>0.05)
Rate of Death	7.8%	4.7%	-

Context
Detailed results regarding patisiran's effect on quality of life will also be presented in a separate oral presentation on April 25, 2018.

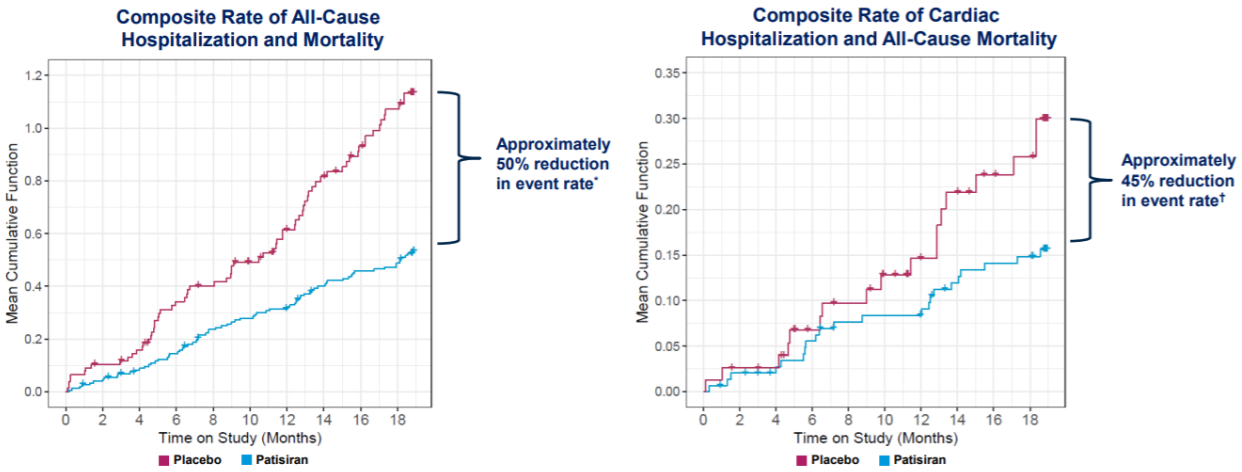
Design
The APOLLO Phase III trial was a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in hATTR amyloidosis patients with polyneuropathy. In addition, exploratory cardiac assessments included measurement of N-terminal pro-brain natriuretic peptide (NT-ProBNP) levels and echocardiography. The trial enrolled 225 hATTR amyloidosis patients from 19 countries with 39 genotypes who were randomized 2:1, patisiran:placebo, with patisiran administered at 0.3mg/kg once every three weeks for 18 months. All patients who completed the APOLLO Phase III study were eligible to screen for the Global OLE study, in which they have the opportunity to receive patisiran on an ongoing basis.

Endpoints
The primary endpoint of the study was the change from baseline in modified Neurologic Impairment Score +7 (mNIS+7) relative to placebo at 18 months. Secondary endpoints included: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; NIS-weakness (NIS-W); Rasch-built Overall Disability Scale (R-ODS); timed 10-meter walk (10-MWT); modified BMI (mBMI); and the composite autonomic symptom score-31 (COMPASS-31).

Results

A new post-hoc, exploratory recurrent event analysis revealed an approximately 50% decrease in the composite rate of all-cause hospitalization and mortality over 18 months in patisiran-treated patients, relative to placebo, based upon hospitalizations and deaths designated as serious adverse events (SAEs) within 28 days after last dose of study drug (figure below). A similar finding was observed with the composite rate of cardiac hospitalization and all-cause mortality, showing an approximately 45% decrease with patisiran, relative to placebo; cardiac hospitalization events were defined as any hospitalizations designated as SAEs within the system organ class designation of cardiac disorder.

Patisiran APOLLO: mortality/hospitalization composites



Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization

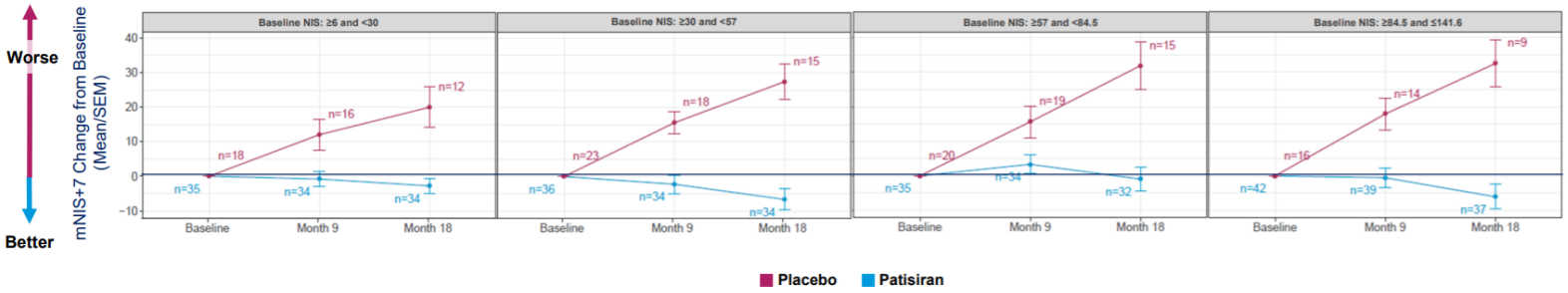
*For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]

†For cardiac hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.54 [0.25, 1.16]; Anderson-Gill hazard ratio (HR) 0.54 [0.28, 1.01]

Source: company presentation

Furthermore, based on a quartile analysis of baseline Neurologic Impairment Score (NIS), patisiran demonstrated halting or improvement in the modified NIS+7 (mNIS+7) primary endpoint in patients regardless of baseline neuropathy severity, in contrast to the progression in mNIS+7 seen in placebo-treated patients (figure below). While treatment benefit is observed across all stages of disease, these results support the rationale for early treatment with patisiran to potentially halt or improve neuropathy progression or impairment, respectively.

Patisiran APOLLO: consistent change in mNIS+7 across baseline NIS scores



Source: company presentation

Specifically, patisiran treatment was associated with improvement across all domains of the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire at nine and 18 months, relative to placebo. Significant improvements in disability, gait speed, autonomic neuropathy symptoms, and overall quality of life, as reported by the patient, were also noted at 18 months upon treatment with patisiran compared to placebo, with improvements in disability, gait speed, and overall quality of life observed as early as nine months.

Finally, results of an analysis of the utilization of genetic testing through Alnylam Act were also presented, with evidence underscoring the heterogeneous presentation of hATTR amyloidosis symptoms. As of March 2018, Alnylam Act has facilitated testing of approximately 4,600 individuals who may carry gene mutations known to be associated with hATTR amyloidosis. Among these, approximately 350 patients were identified with positive pathogenic TTR mutations, representing approximately 7.5% of the patients tested since the Alnylam Act program was initiated in 2014.

Most Common Adverse Events

Overall, there were 13 deaths in the APOLLO study; none were considered related to study drug and the frequency of deaths was lower in the patisiran group (4.7%) as compared with placebo (7.8%). The most commonly reported adverse events (AEs) that occurred more frequently in patisiran-treated patients were peripheral edema and infusion-related reactions (IRRs), and were generally mild to moderate in severity. AEs leading to treatment discontinuation were lower in patisiran-treated patients (4.7%) compared with placebo-treated patients (14.3%).

Conclusion

APOLLO is the largest, controlled study in hATTR amyloidosis and included a wide range of TTR genotypes and neuropathy severity and a majority with cardiac involvement. Use of patisiran resulted in significant improvement in motor, sensory, and autonomic neuropathy, a significant reduction in disease symptoms, and a favorable safety profile compared to placebo.

Comment

While only a post-hoc analysis, the apparent reduction in composite endpoints of hospitalization/mortality are intriguing, showing a 45–50% reduction depending on whether one includes cardiac or all-cause hospitalization, though only the results including all-cause hospitalization were statistically significant, possibly due to the somewhat larger number of events.

One caveat is that the analysis apparently involved cumulative events, not just the first event, so if there were more patients prone to events due to their underlying disease in the placebo group (eg if randomization was not successful due to the modest patient numbers), they may exaggerate the effects. However, when just looking at the rate of death in the safety data, it was also about 40% lower for patisiran, though numbers were not large enough to be statistically significant. The findings are encouraging, because as the presenter noted, median survival is 4.7 years after diagnosis in neurologic phenotypes and 3.4 years for those presenting with cardiomyopathy.

In addition, the study was relatively small, so the data are not that robust. It would be useful to know more details on the all-cause hospitalization, and why that data had a clearer separation.

Alnylam is hoping to get a broad label for patisiran in the US and EU, not just an indication to treat polyneuropathy, the main focus of the APOLLO trial. While the current data are supportive of that, they may not be robust enough to tip a decision, unless regulators are already quite open to that.

The data could also help in competition against Ionis's inotersen, which while it has the advantage of subQ administration versus IV, also has safety issues that require more monitoring. Inotersen had more deaths in its study than placebo, though most were not considered drug-related (5 [4.5%] versus 0; one death was associated with thrombocytopenia that was likely from the drug). The company has not yet reported on hospitalizations, so that will be interesting to see, but it could well be they have not reported it as there was not much benefit. Please see our prior comment for additional comparisons of the two drugs.

The presentation also showed the impact on mNIS+7 was similar regardless of baseline scores, so the presenter said one should start as early as possible.

In terms of likelihood of approval (LOA), while the data are supportive, we cannot make further adjustments, as the LOA is at 99% already.

Source:
Press Release 04/24/2018 (ALNY)
American Academy of Neurology (AAN) (Slides)
American Academy of Neurology (AAN) (Abstract CT.001)
Sagient Analysis

Seizure Disorders (Epilepsy)

Cenobamate (SK Biopharmaceuticals, Phase III)

Phase II - Adjunctive Therapy
Trial Data – Updated Results

Abstract S19.005: Efficacy and Tolerability of Adjunctive Cenobamate Therapy in Different Types of Partial-Onset Seizures

Change to Likelihood of Approval: +2%

	Placebo	Treatment	Treatment	Treatment
Treatment Description	Placebo	Cenobamate 100mg/day *P-value vs. Placebo*	Cenobamate 200mg/day *P-value vs. Placebo*	Cenobamate 400mg/day *P-value vs. Placebo*
Number of Patients	108	108	110	111
Number of Evaluable Patients	108	108	110	111
Reduction in median seizure frequencies from baseline	24.0%	35.5% (p=0.007)	55.0% (p<0.001)	55.0% (p<0.001)
Reduction in median frequencies for SPS from baseline	-7.0%	48.0%	63.0%	58.5%
Reduction in median frequencies for CPS from baseline	28.5%	-	55.0%	60.0%
Reduction in median frequencies for SGTC from baseline	33.0%	-	91.0%	78.0%

Design
This 18-week (six-week titration, 12-week maintenance phase), randomized, double-blind, placebo-

controlled, dose-response study assessed the safety and efficacy of cenobamate 100mg/day, 200mg/day, and 400mg/day in the treatment of partial-onset seizures.

Endpoints

Outcomes included median percent reduction from baseline in both seizure frequency for the complete cohort (primary endpoint) and seizure frequency for each seizure type (SPS, CPS, and SGTC), when these seizures were present at baseline. Safety was assessed by reported adverse events (AEs).

Results

437 subjects were randomized to 100mg/day (n=108), 200mg/day (n=110), 400mg/day (n=111), and placebo (n=108). Most patients had a history of CPS (78.9%) or SGTC (60.0%), and were receiving two or three concomitant AEDs. Median seizure frequencies decreased for all doses of cenobamate (100mg/day: 35.5%, p=0.007; 200mg/day: 55.0%, p<0.001; and 400mg/day: 55.0%, p<0.001) compared with placebo (24.0%). Median frequencies for SPS were decreased with all doses of cenobamate (100mg/day: 48.0%; 200mg/day: 63.0%; and 400mg/day: 58.5%) compared with placebo (–7.0%). Median frequencies for CPS and SGTC were decreased with 200mg (55.0% and 91.0%) and 400mg (60.0% and 78.0%) cenobamate compared with placebo (28.5% and 33.0%).

Most Common Adverse Events

The most common AEs were somnolence and dizziness.

Conclusion

Compared with placebo, cenobamate reduced the frequency of different types of partial-onset seizures, including some that are particularly difficult to treat.

Comment

In light of cenobamate's positive Phase II data, with significant efficacy and favorable tolerability demonstrated on one hand but also potential safety concerns, we are increasing its LOA by 2%.

At the highest dose, cenobamate elicited a reduction in median seizure frequency from baseline of 31% over placebo, which is comparable to gold-standard therapy Keppra (levetiracetam). While the drug's tolerability was favorable, there were three cases of allergic reactions including DRESS (drug rash with eosinophilia and systemic symptoms) and morbilliform rashes. The single case of DRESS and one case of morbilliform rash occurred during fast titration, whereas the other case of morbilliform rash presented during slower titration. These reactions, especially the serious case of DRESS, raise questions over cenobamate's potential safety profile. It will be important to track the drug's safety in subsequent Phase III trials as this could result in a future black box for the drug's label if it is eventually approved. While cenobamate may be associated with DRESS, this may not completely deter its use. Lamictal (lamotrigine) possesses a warning in its label for DRESS, nevertheless it remains a widely prescribed product.

Cenobamate's mechanism of action has not been clearly characterized, however, it is thought to involve atypical sodium channel modulation. In this way, the drug is not substantially differentiated from the majority of anti-epileptic drugs on the market. If development is successful, the drug may struggle to penetrate the epilepsy market as it is targeting the competitive partial-onset seizures segment. While this is the largest segment, it is also the most saturated. Cenobamate's efficacy and tolerability may be insufficient to drive its sales as it would enter as a me-too drug at a higher price than widely available generics of many standard-of-care therapies.

Source:
Press Release 04/23/2018
American Academy of Neurology (AAN) 04/23/2018 (Abstract S19.005)
Sagient Analysis

Tourette's Syndrome

ABX-1431 (Abide Therapeutics, Phase I)

Phase Ib – PN015
Trial Data – Updated Results

Abstract 002: ABX-1431, A First-in-Class Endocannabinoid Modulator, Improves Tics and the Urge to Tic in Adult Patients with Tourette Syndrome

Change to Likelihood of Approval: +3%

	Placebo	Treatment
Treatment Description	Placebo	AX-1431
Number of Patients	19	19
Number of Evaluable Patients	N/A	N/A
> 25% Decrease on the TTS	1 Patient	4 Patients
Change in Motor Tics at 4 and 8 Hours	-	(p<0.05)
>50% Decrease on the ATQ Intensity at 8 Hours	0 Patients	8 Patients
>25% Decrease on the ATQ Intensity at 8 Hours	2 Patients	6 Patients

Design
This study was a single-dose (40mg), double-blind, placebo-controlled crossover study in 20 adults with Tourette Syndrome. Adults with a Yale Global Tourette Severity Scale (YGTSS) -Total Tic Score (TTS) >18 at screening, stable comorbidities, without a history of psychosis or suicide attempts, and with stable organ function participated. Patients continued all medications except medicinal cannabis / cannabinoids, which were eliminated for four days to avoid mechanistic overlap with ABX-1431. A second two-period crossover was run in eight of these patients with a 20mg dose to explore effect of food on pharmacodynamics. Efficacy endpoints were collected pre-dose, four hours post-dose, and eight hours post-dose. Questionnaire reference periods were shortened to four hours.

Endpoints
Efficacy endpoints included Total Tic Score (TTS), a subscale of the YGTSS used for treatment trials of pharmacotherapy, Adult Tic Questionnaire (ATQ), Premonitory Urge to Tics Scale (PUTS), Modified Video Rush Scale (MRVS), and Clinician Global Impression of Improvement (CGI-I).

Results
4/19 patients had > 25% decrease on the TTS vs 1/19 on placebo. These patients had a statistically significant change in motor tics at four and eight hours. 8/19 patients had >50% decrease on the ATQ Intensity at eight hours vs 0/19 on placebo. 6/19 patients had >25% decrease on ABX-1431 vs 2/19 patients on placebo.

Most Common Adverse Events

ABX-1431 well tolerated safety profile. No SAE; most commonly observed AE are headache, somnolence, fatigue.

Conclusion

In adults with moderately severe Tourette Syndrome on standard of care medications, ABX-1431 shows a statistically significant positive impact on key measures of Tourette Syndrome:

- reduction of Total Tic Score (TTS) of Yale Global Tic Severity Scale (YGTSS)
- reduction in number and intensity of tics by patient self-assessment
- reduction in premonitory urge
- improvement in Clinician Global Impression

The study showed strong target engagement of MGLL with 40mg dose, inconclusive data in smaller extension arm with lower drug exposure, and the first clinical evidence of a positive effect for ABX-1431, a first-in-class MGLL inhibitor with potential in multiple central nervous system diseases.

Comment

The nature of the trial design, using a placebo control arm, and the reporting of endpoints with response rates means that like-for-like comparisons with other pipeline agents for Tourette's syndrome such as Austedo and THX-110 are not yet possible. That said, it is impressive for ABX-1431 to demonstrate significant improvements over placebo over a range of endpoints in such a small trial. Taken in isolation, this trial shows the potential of ABX-1431 as an endocannabinoid modulator to improve patient outcomes above that currently achieved with standard-of-care treatments such as behavioral therapy, antipsychotics and alpha-2 agonists alone. On this basis, we are raising ABX-1431's LOA by 3% - a greater increase than for THX-110's open-label Phase IIa success.

Source:
American Academy of Neurology (AAN) 04/24/2018 (Poster)
Sagient Analysis

Amyotrophic Lateral Sclerosis (ALS)

NP001 (Neuraltus Pharmaceuticals, Phase II)

Phase II - North America
Trial Data – Top-Line Results

Abstract S38.004: Randomized Phase 2B trial of NP001, a Novel Immune Regulator, in ALS

Change to Likelihood of Approval: -7%

	Placebo	Treatment	Difference Between Treatment and Placebo
Treatment Description	Placebo	NP001	NP001 2mg/kg vs. Placebo
Number of Patients	68	68	138
Mean change in ALSFRS-R from baseline *(Endpoint=Primary)*	-	-	(p=0.79)
Mean change in pulmonary function	-	-	(p=0.65)
ALSFRS-R Slope	0.80	0.84	-
Patients w/no decline in ALSFRS-R over six months	21%	23%	-

Context

Neuraltus is conducting additional analyses of the trial results to determine if and how the company will proceed in developing the compound.

In the first Phase II study of NP001, Neuraltus assessed the safety, tolerability, and preliminary efficacy of two dose levels of NP001 versus placebo using the ALSFRS-R. A secondary analysis of the study results suggested that increased levels of a biomarker for systemic inflammation, C-reactive protein (CRP), may indicate which patients are more likely to respond to NP001.

Design

The confirmatory Phase II study was a randomized, double-blind, placebo-controlled, multicenter study that enrolled 138 subjects in North America with ALS and evidence of systemic inflammation. Patients received either NP001 2mg/kg or placebo over a period of six months.

Endpoints

The study was designed to evaluate the change from baseline in ALSFRS-R during the study period. Secondary objectives include a change in pulmonary function as measured by vital capacity readings and inflammatory biomarkers.

Results

The study, which enrolled 138 patients, did not meet its primary or secondary endpoints, a change from baseline in the ALS Functional Rating Scale-Revised (ALSFRS-R) score and in pulmonary function as measured by vital capacity readings.

Most Common Adverse Events

NP001 was generally safe and well-tolerated. Five patients died from disease progression. The incidence of infusion-related adverse events was low.

Number (%) of Subjects Reporting at Least One	Placebo (n=68)	NP001 (n=69)
Treatment-Emergent Adverse Event (TEAE)	61 (89.7%)	64 (92.8%)
TESAE	7 (10.3%)	8 (11.6%)
TEAE Leading to Discontinuation of Study Drug	2 (2.9%)	5 (7.2%)
TEAE Requiring Dose Interruption of Study Drug	5 (7.4%)	5 (13.0%)

Conclusion

NP001 did not slow ALS progression but was generally safe and well-tolerated. NP001 did not differentiate from placebo in slowing disease progression. Overall, both groups progressed less than

expected. More systematic investigation of biomarkers needed. Ongoing inflammatory biomarker analysis will inform modulation if inflammation by NP001 and the role of neuroinflammation in ALS progression.

Comment

This trial was designed to be confirmatory for the prior positive findings in an earlier Phase IIa study in which drug treatment slowed disease progression and reduced inflammatory cytokine biomarkers. However, with the clearly negative data presented at the AAN annual meeting, with no separation whatsoever from placebo on a range of endpoints, the strong likelihood is that NP001 is ineffective, or at best only marginally effective among this population. As such, we assign a low probability for NP001 as a disease-modifying ALS treatment and are lowering its LOA by 7%.

Source:
Press Release 04/26/2018
American Academy of Neurology (AAN) 04/26/2018 (Abstract S38.004)
Sagient Analysis

Alzheimer's Disease (AD)

Gantenerumab (RHHBY, Phase III)

Phase II/III - SCarlet RoAD and Marguerite RoAD OLEs
Trial Data – Updated Results

Abstract S2.005: Higher Dose Gantenerumab leads to Significant Reduction in Amyloid Plaque Burden - Results for the Marguerite and Scarlet Road Open Label Extension Studies

Change to Likelihood of Approval: +5%

	Placebo	Treatment	Treatment	Treatment	Treatment	Treatment
	SCarlet RoAD double-blind Year 2 results			Open-label extension 6-9 months at high dose		
Treatment Description	Placebo	Gantenerumab 105mg Q4W	Gantenerumab 225mg Q4W	MR-NP	MR-P	SR
Number of Patients	-	-	-	14	17	9
Mean (SD) change in PET SUVR	0.02 (0.12)	-0.03 (0.13)	-0.11 (0.16)	-0.24 (0.21)	-0.27 (0.14)	-0.13 (0.16)

MR-NP = Marguerite RoAD, non-pretreated; MR-P = Marguerite RoAD, pre-treated, SR = SCarlet RoAD

Context

The SCarlet RoAD placebo controlled trial in prodromal AD patients had been discontinued due to a negative futility analysis, with patients followed in an extension study, and as a result, the Marguerite RoAD placebo-controlled trial in mild AD was converted to an open-label extension study. The extension studies evaluated several titration schemes aiming at a higher dose of 1,200mg SC Q4W (as opposed to 105mg and 225mg Q4W). A new Phase III trial is slated to start in July 2018.

Design

Patients enrolled in SR and MR double-blind (DB) trials were eligible to enter OLE studies. Patients were

assigned to one of six titration schedules (ranging from 2 to 6 months), all with a target dose of 1,200mg SC monthly. Change in amyloid burden was assessed by comparing florbetapir PET at OLE baseline and week 52.

Results

Among 81 patients enrolled in the OLE PET substudies, 40 (14 in MR-Placebo, 17 in MR-Gantenerumab, 9 in SR) met the criteria for high dose analysis (cutoff date: August 31, 2017). Mean (SD) change in absolute SUVR units seen in the three groups were -0.24 (0.21), -0.27 (0.14), -0.13 (0.16); up to three times the two-year change seen at 225mg dose in the DB SR study. Overall, approximately one third of patients had amyloid levels below the cut point for amyloid positivity at week 52.

Conclusion

This study showed significantly higher reductions of amyloid plaque with 1,200mg gantenerumab dosing regimen compared to 105 or 225mg dosing. Results in this ongoing study confirmed the amyloid plaque removal component of the gantenerumab mechanisms of action, and showed that within a 6–9 month higher-dose treatment period, approximately one third of subjects achieved below threshold PET SUVR signals based on quantitative measures.

Comment

The data provided from higher-dose gantenerumab are promising, with one-third of patients exhibiting amyloid plaque levels below the amyloid positivity threshold. The results came from the open-label extension PET substudy of the SCarletRoAD trial in prodromal AD and Marguerite RoAD in mild AD. There was up to a three-fold decrease in mean PET SUVR in a shorter amount of time than in the prior SCarlet RoAD study (6–9 months versus two years), though the larger drops were mainly seen in patients from the prior Marguerite RoAD study. The speaker noted that the data were consistent with their amyloid models showing that after two years on a dose-titration, a 24% PET SUVR reduction should be seen.

Nevertheless, despite data resembling that of Biogen's aducanumab, gantenerumab's history of trial suspension and previous failures from anti-amyloid monoclonal antibodies (solanezumab and bapineuzumab) mean additional data are required to determine efficacy and have much confidence. The extension studies tested a higher dose than in the initial placebo-controlled portions (see Context section above). The audience did attempt to glean an answer from the presenter on whether patients in the extension showed a cognitive benefit, however it was suggested that "lack of placebo and small sample size" made that difficult to demonstrate, which is also somewhat concerning.

On account of the data, we are raising the LOA by 5%, though still leaving it far below average. A new Phase III trial is slated to start in July 2018.

Source:
American Academy of Neurology (AAN) 04/22/2018 (Abstract S2.005)
American Academy of Neurology (AAN) 04/27/2018 (Conference presentation)
Sagient Analysis

Biomedtracker
Pharma intelligence | informa

Biomedtracker 2018 AAN Events

Drug	Indication	Lead Company	Ticker	Event Type	Trial Name	Link
Aducanumab	Alzheimer's Disease (AD)	Biogen, Inc.	BIIB	Trial Data - Updated Results	Phase Ib - PRIME	302002
Crenezumab	Alzheimer's Disease (AD)	Roche Holding AG	RHHBY	Trial Data - Top-Line Results	Phase Ib - GN29632	302601
Gantenerumab	Alzheimer's Disease (AD)	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase II/III - SCarlet RoAD (Prodromal AD, OLE), Phase III - Marguerite RoAD OLE (WN28745; Mild AD)	302031
MN-166	Amyotrophic Lateral Sclerosis (ALS)	MediciNova, Inc.	MNOV	Trial Data - Updated Results	Phase II - 1201	302580
NP001	Amyotrophic Lateral Sclerosis (ALS)	Neuraltus Pharmaceuticals, Inc.		Trial Data - Top-Line Results	Phase II - North America	302370
NurOwn	Amyotrophic Lateral Sclerosis (ALS)	BrainStorm Cell Therapeutics Inc.	BCLI	Trial Data - Updated Results	Phase II - BCT-001-US	302443
Toca 511	Brain Cancer (Malignant Glioma; AA and glioblastoma (GBM))	Tocagen, Inc.	TOCA	Trial Data - Updated Results	Phase I - Recurrent Malignant Brain Tumor	302169
CX-8998	Chemotherapy Induced Peripheral Neuropathy (CIPN)	Cavion LLC		Trial Data - Preclinical Results	Preclinical Studies	302058
Quell	Chronic Pain	NeuroMetrix, Inc.	NURO	Trial Data - Top-Line Results	Sleep/Wake Classification Pilot Study (US)	301948
Epidiolex	Dravet Syndrome (Epilepsy)	GW Pharmaceuticals plc	GWPH	Trial Data - Top-Line Results	Phase III - GWPCARE5 (OLE Study)	302067
ZX008	Dravet Syndrome (Epilepsy)	Zogenix, Inc.	ZGNX	Trial Data - Updated Results	Phase III - Study 1501 (Study 1 - US/Canada), Phase III - Study 1502 (Study 1 - EU/Australia)	302203
ZX008	Dravet Syndrome (Epilepsy)	Zogenix, Inc.	ZGNX	Trial Data	Phase III - Study 1501 (Study 1 - US/Canada), Phase III - Study 1502 (Study 1 - EU/Australia)	302566
Edasalonexent	Duchenne Muscular Dystrophy (DMD)	Catabasis Pharmaceuticals, Inc.	CATB	Trial Data - Updated Results	Phase I/II - MoveDMD	302322
Ezutromid	Duchenne Muscular Dystrophy (DMD)	Summit Therapeutics plc	SMMT	Trial Data - Updated Results	Phase II - PhaseOut DMD (US and EU)	301845
RG6206	Duchenne Muscular Dystrophy (DMD)	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase I/II - Ambulatory Boys	302468
Cala ONE	Essential Tremor	Cala Health, Inc.		Trial Data - Top-Line Results	At-Home Study (US), In-Clinic Study (US)	303103
Omaveloxolone	Friedreich's Ataxia	Reata Pharmaceuticals, Inc.	RETA	Trial Data - Preclinical Results	Preclinical Studies	302242
IONIS-HTTRx	Huntington's Disease	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase I/IIa - Dose Escalation	302162
Banzel	Lennox-Gastaut Syndrome (LGS; Epilepsy)	Eisai Co., Ltd.	ESALY	Trial Data - Retrospective Analysis	Phase III - Japan, Phase III - Pediatric (303), Phase III - w/Ongoing Therapy	302015
Epidiolex	Lennox-Gastaut Syndrome (LGS; Epilepsy)	GW Pharmaceuticals plc	GWPH	Trial Data - Top-Line Results	Phase III - GWPCARE5 (OLE Study)	302017
Epidiolex	Lennox-Gastaut Syndrome (LGS; Epilepsy)	GW Pharmaceuticals plc	GWPH	Trial Data - Retrospective Analysis	Phase III - GWPCARE3, Phase III - GWPCARE4	302069
Gocovri	Levodopa-Induced Dyskinesia	Adamas Pharmaceuticals, Inc.	ADMS	Trial Data - Retrospective Analysis	Phase III - EASE LID, Phase III - EASE LID 3	302004
Aimovig	Migraine and Other Headaches	Amgen, Inc.	AMGN	Trial Data - Final Results	Phase IIIb - LIBERTY	301571
Eptinezumab	Migraine and Other Headaches	Alder Biopharmaceuticals, Inc.	ALDR	Trial Data - Updated Results	Phase III - PROMISE 1 (High Frequency; IV)	302114
Eptinezumab	Migraine and Other Headaches	Alder Biopharmaceuticals, Inc.	ALDR	Trial Data - Updated Results	Phase III - PROMISE 1 (High Frequency; IV)	302210
Fremanezumab	Migraine and Other Headaches	Teva Pharmaceutical Industries Ltd.	TEVA	Trial Data - Updated Results	Phase III - HALO EM	302302
Fremanezumab	Migraine and Other Headaches	Teva Pharmaceutical Industries Ltd.	TEVA	Trial Data - Updated Results	Phase III - HALO CM	302309
Galcanezumab	Migraine and Other Headaches	Eli Lilly & Company	LLY	Trial Data - Subgroup Analysis	Phase III - EVOLVE-1 (Episodic Migraine), Phase III - EVOLVE-2 (Episodic Migraine), Phase III - REGAIN (Chronic Migraine)	302085
Lasmiditan (Oral)	Migraine and Other Headaches	Eli Lilly & Company	LLY	Trial Data - Updated Results	Phase III - COL MIG-301 (SAMURAI), Phase III - COL MIG-302 (SPARTAN)	302593
Ubrogepant	Migraine and Other Headaches	Allergan plc	AGN	Trial Data - Updated Results	Phase III - ACHIEVE I (UBR-MD-01)	305176
Aubagio	Multiple Sclerosis (MS)	Sanofi	SNY	Trial Data - Updated Results	Phase III - TENERE - EFC10891 (RMS), Phase IV - TERI-PRO	302056
BAF312	Multiple Sclerosis (MS)	Novartis AG	NVS	Trial Data - Subgroup Analysis	Phase III - EXPAND (Secondary Progressive)	301830
BIIB098	Multiple Sclerosis (MS)	Biogen, Inc.	BIIB	Trial Data - Updated Results	Phase III - EVOLVE-MS	305120

Biomedtracker
Pharma intelligence | informa

Biomedtracker 2018 AAN Events

Drug	Indication	Lead Company	Ticker	Event Type	Trial Name	Link
Copaxone	Multiple Sclerosis (MS)	Teva Pharmaceutical Industries Ltd.	TEVA	Trial Data - Updated Results	Phase III - GALA (TIW)	302591
Lemtrada	Multiple Sclerosis (MS)	Sanofi	SNY	Trial Data - Updated Results	Phase III - CARE-MS I, Phase III - CARE-MS II	302003
Mavenclad	Multiple Sclerosis (MS)	Merck KGaA	MKGAY	Trial Data - Updated Results	Phase III - CLARITY (RRMS)	302456
Mavenclad	Multiple Sclerosis (MS)	Merck KGaA	MKGAY	Trial Data - Updated Results	Phase III - CLARITY (RRMS), Phase III - ORACLE MS (Early MS), Phase IIIb - CLARITY Extension	302459
MN-166	Multiple Sclerosis (MS)	MediciNova, Inc.	MNOV	Trial Data - Updated Results	Phase IIb - SPRINT-MS (RG 4778-A-6)	302127
Ocrevus	Multiple Sclerosis (MS)	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase III - Biomarker MOA, Phase III - OPERA I (RRMS), Phase III - OPERA II (RRMS), Phase III - ORATORIO (PPMS)	301909
Ozanimod	Multiple Sclerosis (MS)	Celgene Corporation	CELG	Trial Data - Updated Results	Phase III - RADIANCE (Phase II/III Part B), Phase III - SUNBEAM	302087
Rebif (serum-free)	Multiple Sclerosis (MS)	Merck KGaA	MKGAY	Trial Data - Retrospective Analysis	Phase III - REFLEXION	302598
Ublituximab	Multiple Sclerosis (MS)	TG Therapeutics, Inc.	TGTX	Trial Data - Updated Results	Phase IIa - RMS-201	302113
ACE-083	Muscular Dystrophy	Acceleron Pharma, Inc.	XLRN	Trial Data - Updated Results	Phase II - A083-02	302366
Efgartigimod	Myasthenia Gravis (MG)	argenx N.V.	ARGX	Trial Data - Final Results	Phase II - Generalized Muscle Weakness	302126
RA101495	Myasthenia Gravis (MG)	Ra Pharmaceuticals, Inc.	RARX	Trial Data - Updated Results	Phase I - Healthy Volunteers	302231
AGIL-AADC	Neurology - Other	Agilis Biotherapeutics, Inc.		Trial Data - Updated Results	Phase IIb - Multiple Dose (Taiwan)	302154
RT001 (Retrotope)	Neurology - Other	Retrotope, Inc.		Trial Data - Top-Line Results	Expanded Access Program	303455
Botox - Therapeutic	Neuromuscular Spasm and Spasticity	Allergan plc	AGN	Trial Data - Top-Line Results	Phase III - Pediatric Lower Limb Spasticity	302308
Brineura	Neuronal Ceroid Lipofuscinosis (NCL)	BioMarin Pharmaceutical Inc.	BMRN	Trial Data - Published Results	Phase I/II - 202 (Ext.), Phase I/II - UK (CLN2/Batten)	302151
AP-CD/LD	Parkinson's Disease (PD)	Intec Pharma Ltd.	NTEC	Trial Data - Top-Line Results	Phase I - IN11005 (Healthy Adults) , Phase I - IN14001 (Healthy Adults)	302131
BIIB054	Parkinson's Disease (PD)	Biogen, Inc.	BIIB	Trial Data - Top-Line Results	Phase I - Healthy Subjects	302175
Human Parthenogenetic Stem Cells	Parkinson's Disease (PD)	International Stem Cell Corporation	ISCO	Trial Data - Updated Results	Phase I - Australia	302179
ITI-214	Parkinson's Disease (PD)	Intra-Cellular Therapies, Inc.	ITCI	Trial Data - Preclinical Results	Preclinical Studies	302390
Nuplazid	Parkinson's Disease (PD)	Acadia Pharmaceuticals, Inc.	ACAD	Trial Data - Retrospective Analysis		302778
Nuplazid	Parkinson's Disease (PD)	Acadia Pharmaceuticals, Inc.	ACAD	Trial Data - Retrospective Analysis		302781
Vercise DBS System	Parkinson's Disease (PD)	Boston Scientific Corporation	BSX	Trial Data - Top-Line Results	IDE - INTREPID (US)	302088
ADS-4101	Partial Seizures (Epilepsy)	Adamas Pharmaceuticals, Inc.	ADMS	Trial Data - Updated Results	Phase I - Safety/PK (Healthy Volunteers), Phase Ib - Tolerability/PK (Healthy)	302000
Fycompa	Partial Seizures (Epilepsy)	Eisai Co., Ltd.	ESALY	Trial Data - Retrospective Analysis	Phase III - Study 332	302026
Fycompa	Partial Seizures (Epilepsy)	Eisai Co., Ltd.	ESALY	Trial Data - Retrospective Analysis	Phase II - Study 235 (Adolescents), Phase III - Study 307 (Extension), Phase III - Study 332, Phase III - Study 335 (Japan/Korea)	302023
BIIB092	Progressive Supranuclear Palsy	Biogen, Inc.	BIIB	Trial Data - Top-Line Results	Phase I - CN002-003	302318
TV-7820	Rett Syndrome	Teva Pharmaceutical Industries Ltd.	TEVA	Trial Data - Preclinical Results	Preclinical Studies	302176
Cenobamate	Seizure Disorders (Epilepsy)	SK Biopharmaceuticals Co., Ltd.		Trial Data - Updated Results	Phase II - Adjunctive Therapy	301906
CX-8998	Seizure Disorders (Epilepsy)	Cavion LLC		Trial Data - Top-Line Results	Phase I - PK/PD Study	302324
ZYN-002	Seizure Disorders (Epilepsy)	Zynerba Pharmaceuticals, Inc.	ZYNE	Trial Data - Updated Results	Phase II - STAR 2 (STAR 1 ext.)	302193
AVXS-101	Spinal Muscular Atrophy	Novartis AG	NVS	Trial Data - Top-Line Results	Phase III - STR1VE	302149
AVXS-101	Spinal Muscular Atrophy	Novartis AG	NVS	Trial Data - Updated Results	Phase I/II - IRB13-00627 (SMA Type 1)	302158

Biomedtracker 2018 AAN Events

Drug	Indication	Lead Company	Ticker	Event Type	Trial Name	Link
Olesoxime	Spinal Muscular Atrophy	Roche Holding AG	RHHBY	Trial Data - Top-Line Results	Phase II - OLEOS (Long-Term Safety)	302462
RG7916	Spinal Muscular Atrophy	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase II - FIREFISH	302138
RG7916	Spinal Muscular Atrophy	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase II - SUNFISH	302320
RG7916	Spinal Muscular Atrophy	Roche Holding AG	RHHBY	Trial Data - Updated Results	Phase II - JEWELFISH	302485
Spinraza	Spinal Muscular Atrophy	Biogen, Inc.	BIIB	Trial Data - Updated Results	Phase II - EMBRACE	302041
Dalazatide	Sporadic Inclusion Body Myositis (sIBM)	Kineta, Inc.		Trial Data - Preclinical Results	Preclinical Studies	302409
Ingrezza	Tardive Dyskinesia	Neurocrine Biosciences, Inc.	NBIX	Trial Data - Updated Results	Phase III - Kinect 3	302383
Ingrezza	Tardive Dyskinesia	Neurocrine Biosciences, Inc.	NBIX	Trial Data - Updated Results	Phase III - Kinect 4	302321
ABX-1431	Tourette's Syndrome	Abide Therapeutics Inc.		Trial Data - Updated Results	Phase Ib - PN015	305116
Inotersen	Transthyretin (TTR)-related Hereditary Amyloidosis (Familial Amyloid Polyneuropathy)	Ionis Pharmaceuticals, Inc.	IONS	Trial Data - Updated Results	Phase II/III - NEURO-TTR	302046
Inotersen	Transthyretin (TTR)-related Hereditary Amyloidosis (Familial Amyloid Polyneuropathy)	Ionis Pharmaceuticals, Inc.	IONS	Trial Data - Updated Results	Phase II/III - NEURO-TTR (Ext.)	302024
Patisiran	Transthyretin (TTR)-related Hereditary Amyloidosis (Familial Amyloid Polyneuropathy)	Alnylam Pharmaceuticals, Inc.	ALNY	Trial Data - Retrospective Analysis	Phase III - APOLLO	302122