Objective: Efficacy and safety of erenumab, a human anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, were evaluated in patients with episodic migraine (EM) in a phase 3 trial (NCT02483585). Background: CGRP plays an important role in migraine pathophysiology. Erenumab is a fully human monoclonal antibody that inhibits the CGRP receptor and is being evaluated as a prophylactic treatment for migraine. Design/Methods: 577 adults with EM were randomized 1:1 to subcutaneous, monthly placebo or erenumab (70mg). Primary endpoint was change in monthly migraine days (MMDs) from baseline to weeks 9-12 of a 12-week double-blind phase. Secondary endpoints were achievement of ≥50% reduction in MMDs, change in acute migraine-specific medication use, and ≥5-point reduction in Physical Impairment (PI) and Impact on Everyday Activities (EA) measured by the Migraine Physical Function Impact Diary. Statistical significance was determined after adjustment for multiple comparisons. Results: Patients reported a mean 8.3 MMDs at baseline. Those receiving erenumab experienced a mean -2.9-day change (reduction) from baseline in MMDs, compared to a -1.8-day reduction for placebo (p<0.001). A ≥50% reduction in MMDs was achieved by 40% and 30% in erenumab and placebo groups (odds ratio: 1.6; p=0.010). Monthly acute migraine-specific medication use was reduced by mean -1.2 and -0.6 days (p=0.002). Respective ≥5-point reductions (improvement) in PI were achieved by 33% and 27% of patients (p=0.13) and in EA by 40% and 36% (p=0.26). The safety profile of erenumab was similar to placebo. Most frequently reported AEs across both groups were upper respiratory tract infection, injection site pain, and nasopharyngitis. Conclusions: Erenumab statistically significantly reduced migraine frequency, acute migraine-specific medication use, and a greater proportion of patients achieved ≥50% reduction in MMDs compared to placebo in this phase 3 trial in EM.

Study Supported By:
Study funded by Amgen Inc.
Non-invasive Vagus Nerve Stimulation for the Acute Treatment of Episodic and Chronic Cluster Headache: Findings From the Randomized, Double-blind, Sham-Controlled ACT2 Study

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Objective: Evaluate non-invasive vagus nerve stimulation (nVNS; gammaCore®) as acute treatment in episodic or chronic cluster headache (eCH, cCH). Background: Clinical observations and recent studies support nVNS use in CH. Design/Methods: Adults with CH received nVNS or sham therapy during a 2-week double-blind period. At attack onset, subjects self-administered three consecutive 120-second stimulations to the vagus nerve (cervical branch). If the attack was not aborted within 9 minutes, three additional stimulations were permitted. Subjects were to refrain from using rescue treatments for 15 minutes after treatment initiation; efficacy end points were assessed at this time. The primary end point was the proportion of attacks that achieved pain-free status (pain score=0). Additional end points included change in pain intensity (0-4 point scale) and proportions of subjects with responder status (pain score=0-1) for ≥50% of attacks. Results: Efficacy evaluations included 48 nVNS-treated (14 eCH, 34 cCH) and 44 sham-treated (13 eCH, 31 cCH) subjects. In the total cohort, proportions of attacks with pain-free status did not differ significantly between treatments (nVNS, 14%; sham, 12%); in the eCH subgroup, nVNS (48%) was superior to sham (6%; PP=0.01); the cCH subgroup showed no significant treatment difference (nVNS, ?1.2; sham, ?1.0). Proportions of subjects with responder status for ≥50% of attacks were significantly higher with nVNS in the total cohort (nVNS, 40%; sham, 14%; PPConclusions: This study supports the acute use of nVNS in patients with eCH but not cCH.

Study Supported By:
This study was sponsored by electroCore, LLC.
Objective: TOLEDO (NCT02006121) is the first prospective, randomized, multicenter, double-blind study to investigate the efficacy of apomorphine subcutaneous infusion (APO) versus placebo in Parkinson’s disease (PD) patients with motor fluctuations not well controlled on optimized medical treatment. Background: Although extensive data from open-label studies with APO demonstrate its efficacy in reducing OFF time, dyskinesias and oral levodopa dose in patients with severe motor fluctuations that are poorly controlled by conventional therapy, evidence from randomized, blinded studies has been lacking. Design/Methods: Patients from 23 centers in 7 countries were randomized to receive APO during their waking time (16±2 hours; ≤8 mg/hour), or placebo saline infusion using the same pump system. Based on efficacy and tolerability, the hourly flow rate of the infusion and dose of concomitant antiparkinsonian medication were adjusted during the first 4 weeks. The primary endpoint was the absolute change in OFF time from baseline to Week 12 based on patient diaries. Results: Compared with placebo (n=53), APO (n=53) provided significantly greater reduction (improvement) in OFF time between baseline and Week 12 (-0.58 hours versus -2.47 hours, respectively), a difference between treatment groups of -1.89 hours (95% CI: -3.16, -0.62; p=0.0025). The reduction in OFF time with APO was observed within the first week of treatment and sustained over 12 weeks, and was associated with a significantly greater increase in ON time without troublesome dyskinesia. The beneficial effects of APO were reflected in higher scores for Patient Global Impression of Change versus placebo at Week 12 (p<0.001). APO was generally well tolerated and no unexpected adverse events were observed. Conclusions: These results show Level 1 evidence that APO provides a significant and clinically meaningful reduction in OFF time without increasing dyskinesias in patients whose motor fluctuations cannot be controlled with current standard of care, filling an important knowledge gap.

Study Supported By:
Britannia Pharmaceuticals Ltd.
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Intraputaminal AADC gene therapy for advanced Parkinson’s disease: Interim Results of a Phase 1b Trial

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Objective: This trial was designed to evaluate the safety of gene therapy with human aromatic L-amino acid decarboxylase (AADC) AAV-hAADC using large infusion volumes and intraoperative MRI to improve delivery.

Background: Levodopa therapy for Parkinson’s disease (PD) becomes less effective over time, possibly due to progressive loss of aromatic L-amino acid decarboxylase (AADC) which converts levodopa into dopamine. In a prior study of AAV-hAADC using low volume (100µl) infusions into bilateral putamen, we obtained limited anatomical coverage.

Design/Methods: Ten subjects with advanced PD received bilateral infusion of AAV-hAADC vector (0.83 x 10^{12} vg/ml) co-infused with gadoteridol. Five subjects in cohort 1 received up to 450 µl/putamen and 5 subjects in cohort 2 received up to 900 µl/putamen. 18F-dopa PET was obtained at baseline and 6 months post-procedure to assess gene expression.

Results: Twenty one percent of the putamen was covered by vector in cohort 1 and 34% in cohort 2. Treatment was well tolerated with no vector related SAEs. There was one post-procedure pulmonary embolus which resolved. Enzyme activity increased on 18F-dopa PET by 13% in cohort 1 and 56% in cohort 2. Five subjects in cohort 1 and 3 in cohort 2 have completed the 12-month evaluation. At 12 months, mean off-medication UPDRS motor scores fell by 16.4 points in cohort 1 and 14.3 in cohort 2. On-medication scores increased 1.8 points in cohort 1, but fell 9.3 in cohort 2. Due to improved motor function, daily levodopa equivalents were reduced an average of 10% for cohort 1 and 35% for cohort 2. On-time without troublesome dyskinesias, measured by motor diaries, increased by 1.6 hours in cohort 1 and 4.1 hrs in cohort 2 at 12 months.

Conclusions: These interim results show that AAV-hAADC gene therapy using intraoperative MRI is well-tolerated, provides dose-dependent gene expression and potential clinical efficacy.

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Motor effects and safety of IPX203, an investigational extended-release formulation of carbidopa-levodopa, in advanced Parkinson’s disease: A single-dose Phase 2 study

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Objective: Evaluate the efficacy and safety of IPX203 vs. immediate-release (IR) carbidopa-levodopa (CD-LD) and vs. extended-release (ER) CD-LD (IPX066, RYTARY®) in patients with advanced Parkinson’s disease (PD). Background: Motor fluctuations and dyskinesias often accompany treatment with IR CD-LD in advanced PD. ER reduces “off” time and improves “on” time without troublesome dyskinesia vs. IR. IPX203 is an investigational extended-release capsule formulation of CD-LD aimed at further improving the clinical response over that from ER. Design/Methods: An open-label, rater-blinded, randomized, crossover study compared the response of advanced PD patients to single doses of IR, ER, and IPX203. Patients on a stable IR regimen (≥400 mg LD/day, given ≥4x/day) were rated by trained personnel as “off” or as “on” with or without troublesome dyskinesia every 30 min after dosing. The Unified PD Rating Scale (MDS-UPDRS) Part III was completed hourly for 10 hours after dosing. Adverse events (AEs) were also recorded. Results: Twenty-five of 26 patients completed all 3 periods. The proportion of patients turning “on” by hour 1 was similar between IR, ER, and IPX203. IPX203 decreased mean (±SD) “off” time (4.5±2.0 hr) vs. IR (7.2±1.3 hr, p<.0001) and vs. ER (5.4±1.9 hr, p<.05). IPX203 correspondingly increased “on” time vs. both comparators without significantly increasing troublesome dyskinesia. IPX203 increased the duration of both a 4-point improvement [IPX203: 6.1 hr; IR: 3.7 hr (p<.0001); ER: 5.2 hr (p<.05)] and a 13-point improvement [IPX203: 4.8 hr; IR: 2.2 hr (p<.0001); ER: 3.6 hr (p<.05)] in the MDS-UPDRS Part III. AEs were reported by 28.0% (IR), 8.0% (ER), and 19.2% (IPX203) of patients. AEs reported by ≥2 patients in any treatment were nausea, dizziness, and hypertension; no serious AEs were reported. Conclusions: IPX203 significantly increased the duration of motor symptom improvement compared to both IR and ER CD-LD, without increasing troublesome dyskinesia.

Study Supported By: Impax Laboratories, Inc.
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Results of a Phase 1 Study of ABBV-8E12 in Patients with Progressive Supranuclear Palsy and Phase 2 Study Design in Alzheimer’s Disease and PSP

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Objective: To present the results of a phase 1 study of ABBV-8E12 in patients with Progressive Supranuclear Palsy (PSP) and phase 2 study designs. Background: ABBV-8E12 is a humanized anti-tau monoclonal antibody being developed for the treatment of PSP and Alzheimer’s disease (AD). Design/Methods: The phase 1 study was a double-blind, placebo-controlled, single dose study assessing the safety, tolerability, and pharmacokinetics of ABBV-8E12 in PSP patients (NCT02494024). Patients were randomized 3:1 to drug or placebo and received an intravenous dose of ABBV-8E12 (2.5, 7.5, 15, 25, 50 mg/kg) or placebo. Safety was monitored for 84 days post-dosing. Results: Thirty patients were enrolled/randomized. At screening, the mean (SD) patient age was 69.4 (7.4) years and the mean PSP Rating Scale score was 35.6 (7.6). Twenty-seven patients completed the 84-day follow-up and 1 (3.3%) patient withdrew from the study due to AE. AEs occurred in 21 of the 30 (70%) participants. AEs with the highest incidence were dermatitis (n=5) and fall (n=5). Noncompartmental analysis based on the complete pharmacokinetic dataset indicates dose-proportional increases in AUC and Cmax. A phase 2 study evaluating the 52-week efficacy and safety of ABBV-8E12 in PSP patients is currently recruiting (NCT02985879). Eligible patients (n=180) will meet criteria for possible/probable PSP and have symptoms for <5 years. A separate phase 2 study is designed to evaluate the safety and efficacy of ABBV-8E12 in patients (n=400) with early Alzheimer’s disease (AD) for up to 96 weeks (NCT02880956). Conclusions: When administered as a single dose up to 50 mg/kg in PSP patients, ABBV-8E12 exhibited an acceptable safety and tolerability profile to support repeat-dose testing in patients with tauopathies.

Study Supported By:
This work was funded by C2N Diagnostics and AbbVie Inc. C2N and AbbVie participated in the study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving the publication. Amy M. Spiegel, PhD, of AbbVie Inc., provided medical writing assistance.
Sustained seizure reduction with adjunctive everolimus for treatment-refractory seizures associated with tuberous sclerosis complex (TSC): Long-term results from the phase 3 EXIST-3 study

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Objective: Assess long-term efficacy and safety of everolimus as adjunctive therapy for TSC-associated treatment-refractory seizures. Background: Epilepsy occurs in 85% of patients with TSC; ~60% become refractory to antiepileptic drugs (AEDs). EXIST-3 (NCT01713946) demonstrated significantly reduced seizure frequency with everolimus versus placebo. Design/Methods: Patients (2-65 years) with TSC-associated refractory seizures receiving 1-3 AEDs were included. Following the 18-week core phase, patients could enter the extension phase and receive everolimus (target exposure=3-15 ng/mL) until ≥48 weeks. Efficacy endpoints included change from baseline in average weekly seizure frequency (response rate [RR], ≥50% reduction), and median percentage reduction (PR) in seizure frequency. Results: 361/366 patients received everolimus in core or extension phases. RR at week 18 was 31% (95%CI:26.2-36.1; N=352) versus 46.6% (95%CI:40.9-52.5; N=298) at 1 year and 57.7% (95%CI:49.7-65.4; N=163) at 2 years. Greater benefit was observed in younger patients at 1 year of follow-up. Median PR in seizure frequency was 31.7% (95%CI:28.5-36.1) at week 18 versus 46.7% (95%CI:40.2-54) at 1 year and 56.9% (95%CI:50-68.4) at 2 years. Ninety-five patients discontinued everolimus before 2 years; 103 patients had <2 years of follow up at study cut-off. Sensitivity analysis (early discontinued patients considered non-responders) showed RR of 30.2% (95%CI:25.5-35.2; N=361) at week 18 versus 38.8% (95%CI:33.7-44.1; N=358) at 1 year and 41% (95%CI:34.6-47.7; N=229) at 2 years, confirming sustained benefit over time. No increase in emergence of treatment-related adverse events (AEs) over time was observed (<6 months, 77.8%; 6-12 months, 46.2%; 2nd year, 45.5%). Grade 3/4 AEs (any cause) occurred in 40.2% of patients. Forty-seven patients (13%) discontinued due to AEs, primarily pneumonia (1.7%) and stomatitis (1.4%). Two deaths (pneumonia, SUDEP) were reported. Conclusions: Sustained reductions in TSC-associated treatment-refractory seizures over time were achieved with adjunctive everolimus. Safety profile was consistent with the core phase; AE emergence frequency did not increase over time.

Study Supported By: Novartis Pharmaceutical Corporation
Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE3)

Anup Patel, MD; Orrin Devinsky, MD, FAAN; J. Helen Cross; Vicente Villanueva; Elaine Wirrell, MD; Kevan VanLandingham, MD, PhD; Claire Roberts; Daniel Checketts; Sameer Zuberi

Objective: Evaluate efficacy of add-on CBD for the treatment of drop seizures associated with LGS. Background: Class 1 evidence of efficacy with CBD in epilepsy is needed. This is the second controlled trial of CBD oral solution in LGS. Design/Methods: Eligible patients were 2–55 years old with a clinical diagnosis of LGS, ≥8 drop seizures during 4-week baseline, and documented failures on ≥1 antiepileptic drug (AED). Patients were randomized (1:1:1) to receive CBD 20mg/kg/day, CBD 10mg/kg/day, or placebo for 14 weeks (2-week titration; 12-week dose maintenance). The primary efficacy endpoint was percentage change from baseline in drop seizures/month over the 14-week treatment period for CBD vs placebo. Results: 225 patients were randomized (76 CBD 20mg/kg, 73 CBD 10mg/kg, 76 placebo); 9 CBD 20mg/kg, 2 CBD 10mg/kg, and 2 placebo patients withdrew early. Groups were similar at baseline; mean age was 16 years (30% of patients ≥18 years) and median monthly drop seizure frequency was 85 (IQR: 44, 168). Patients had previously failed a median of 6 and were taking a median of 3 AEDs. Reduction in drop seizure frequency was significantly greater for CBD 20mg/kg (42%) and CBD 10mg/kg (37%) than placebo (17%; p=0.0047 and p=0.0016). Adverse events (AEs) occurred in 94% of CBD 20mg/kg, 84% of CBD 10mg/kg, and 72% of placebo patients, and most were mild or moderate; the two most common were somnolence and decreased appetite. Treatment-related serious AEs were reported in 5 CBD 20mg/kg, 2 CBD 10mg/kg, and 0 placebo patients. Some elevations in transaminases were seen. There were no deaths. Of the 212 completers, 99% entered the open-label extension study. Conclusions: Results suggest that CBD add-on therapy for the treatment of drop seizures associated with LGS may be efficacious, with more adverse events than placebo but generally well-tolerated. (NCT02224560)

Study Supported By:
GW Research, Ltd
Objective: The phase 3, multicenter, randomized, double-blind, sham-procedure controlled CHERISH study (NCT02292537) assessed the efficacy and safety of nusinersen in children with later-onset SMA. Background: Nusinersen is an antisense oligonucleotide for the treatment of SMA that alters SMN2 gene splicing to promote the production of full-length SMN protein. Design/Methods: Children with symptomatic SMA aged 2-12 years were randomized 2:1 (stratified based on screening age <6 versus ≥6 years) to receive 4 doses of intrathecal nusinersen (12mg non-scaled) or sham procedure over 15 months. Key inclusion criteria include confirmed 5q SMA and onset of SMA clinical symptoms at age >6 months. The primary endpoint was change in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at month 15. Secondary endpoints included proportion of children with ≥3-point increase in HFMSE score, proportion with achievement of new WHO motor milestones, and change in revised Upper Limb Module (RULM) test at month 15. Safety/tolerability were also assessed. Results: At the time of this pre-specified interim analysis (August 31, 2016), CHERISH enrolled 126 children. A highly clinically and statistically significant difference in motor function as assessed by mean HFMSE score at 15 months was observed between the nusinersen and sham-control group (least square mean treatment difference [95% CI]=5.9 [3.7,8.1] points; \( P=0.0000002 \)). HFMSE scores increased ≥3 points in 57.3% of nusinersen-treated versus 20.5% of sham-treated children; 17.1% versus 10.5% achieved new WHO motor milestones, respectively. Greater improvement in RULM score was observed in the nusinersen versus sham-control group (least square mean treatment difference=3.4 points). Nusinersen demonstrated a favorable safety profile consistent with other published results, and no children discontinued the study or treatment. Additional secondary endpoints will be reported. Conclusions: Significant improvements in motor function were observed in nusinersen-versus sham-treated children. Nusinersen demonstrated a favorable safety profile. Children from CHERISH will be transitioned into the SHINE (NCT02594124) open-label extension study.

Study Supported By:
Ionis Pharmaceuticals, Inc. and Biogen
Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (CIDP), a multicenter randomized double-blind placebo-controlled trial: the PATH Study

Ivo Van Schaik, MD; Vera Bril, MD; Nan van Geloven; Hans-Peter Hartung, MD, FAAN; Richard Lewis, MD, FAAN; Gen Sobue, MD; John-Philip Lawo, PhD; Orell Mielke, MD; Billie L Durn; David R Cornblath; Ingemar Merkies, MD; on behalf of the PATH study group

Objective: To determine efficacy of IgPro20 for CIDP Background: Approximately two-thirds of CIDP subjects need long-term corticosteroids or intravenous immunoglobulins (IVIg), with IVIg being slightly preferred based on safety profiles. Subcutaneous Ig (SCIg) is an alternative option for Ig delivery but has not previously been investigated in a large-scale clinical trial in CIDP. Design/Methods: Randomized, double-blind trial in CIDP investigating 0.2 and 0.4 g/kg weekly doses of SCIg IgPro20 (Hizentra®, CSL Behring) versus placebo in 172 subjects for maintenance treatment. IVIg-dependent adults with definite or probable CIDP according to EFNS/PNS criteria were eligible. The primary outcome was the percentage of subjects with a CIDP relapse (1-point deterioration on adjusted INCAT disability score) or who were withdrawn for any other reason during the 24-week SCIg-treatment period. Multiple secondary endpoints were assessed. Superiority of at least one IgPro20 dose over placebo was tested one-sided using the Cochran-Armitage trend test for the primary outcome and the Jonckheere-Terpstra tests for secondary outcomes. Results: The primary outcome occurred in 33% of high-dose SCIg, 39% of low-dose SCIg, and 63% of placebo subjects (p < 0.001); CIDP relapse occurred in 19% of high-dose SCIg, 33% of low-dose SCIg and 56% of placebo subjects (p < 0.001), respectively. Both SCIg doses were superior to placebo (low-dose vs placebo p = 0.007; high dose vs placebo p < 0.001). Median INCAT score, MRC sum score, and grip strength remained stable in SCIg subjects. High-dose SCIg prevented the R-ODS decline seen with low-dose SCIg and placebo (p < 0.001). All placebo subjects deteriorated on measures of strength and disability. Causally related adverse events occurred in 47 (27%) subjects (18% placebo, 30% low dose, and 35% high dose). Conclusions: SCIg IgPro20 was efficacious and safe as maintenance treatment. High-dose and low-dose SCIg were both superior to placebo, with the high dose potentially showing better efficacy.

Study Supported By:
Funding: CSL Behring sponsored the study Trial Registration: Clinicaltrials.gov, number NCT01545076
Results of a Phase 1b/2 Study of ATYR1940 in Adult Patients with Limb Girdle Muscular Dystrophy Type 2B (LGMD2B) and Facioscapulohumeral Muscular Dystrophy (FSHD) (ATYR1940-C-004)

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Objective: To evaluate the safety, tolerability, and pharmacodynamic activity of ATYR1940 in patients with LGMD2B and FSHD. Background: LGMD2B and FSHD are debilitating genetic myopathies associated with an immune component and dystrophic changes in muscle. ATYR1940 is a Physiocrine-based protein that is substantially identical to human histidyl-tRNA synthetase and has been shown in preclinical studies to modulate immune responses in skeletal muscle. Design/Methods: This multicenter, open-label study evaluated intra-patient dose escalations of intravenous ATYR1940 from weekly to twice weekly (biw) infusions in patients with genetically confirmed disease and STIR-positive muscles on MRI (FSHD/LGMD2B) or elevated creatine kinase (LGMD2B). Eighteen patients were assigned to Group A or B for one week of placebo, then 12 weeks of ATYR1940. In Group A, 4 FSHD patients received ATYR1940 titrated to 1.0 mg/kg biw; in Group B, 10 LGMD2B and 4 FSHD patients received ATYR1940 titrated to 3.0 mg/kg biw. Safety assessments included: incidence of adverse events, laboratory tests, ECGs, and pulmonary function tests. Exploratory assessments included: manual muscle testing (MMT), the Individualized Neuromuscular Quality of Life (INQoL) questionnaire, targeted MRI, and circulating biomarkers. Results: ATYR1940 was well-tolerated at all doses tested. Adverse events were mild or moderate in intensity. There were no clinically significant changes in other safety assessments. One patient had a reversible infusion-related reaction. Mean change from baseline to Week 14 for MMT was -7.1% for FSHD Group A, 0% for FSHD Group B, and +6.2% for LGMD2B Group B. No consistent changes over time were observed for INQoL scores, circulating biomarkers or MRI. Conclusions: In this pilot, open-label study, ATYR1940 administered up to 3 mg/kg biw was safe and well-tolerated in patients with LGMD2B and FSHD. A mean increase in MMT of 6.2% was observed in the LGMD2B group after 12 weeks of treatment. These data support further evaluation of ATYR1940 for LGMD2B and FSHD.

Study Supported By: aTyr Pharma, Inc.
Dual Responder Analyses of Both Muscle Strength and Activities of Daily Living, Eculizumab Versus Placebo, in Refractory Generalized Myasthenia Gravis (gMG) Patients: Results from the REGAIN Study

James Howard, MD, FAAN; Fanny O’Brien; Jing Jing Wang, MD; Renato Mantegazza

Objective: The Myasthenia Gravis Activities of Daily Living (MG-ADL) is a physician-directed, patient-reported measure of symptom severity related to MG-specific ADLs. The Quantitative Myasthenia Gravis (QMG) tool is a clinician-reported measure of muscle strength. The objective of this analysis was to evaluate the proportion of refractory gMG patients from the REGAIN study treated with eculizumab who responded on both the QMG and the MG-ADL, compared with placebo. Background: REGAIN was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of eculizumab in patients with AChR+-refractory gMG over 26 weeks. Design/Methods: Refractory gMG patients continued to receive a stable dose of immunosuppressive therapy (IST) throughout the study and were randomized to receive eculizumab (n=62) or placebo (n=63). In this ad hoc dual responder analysis, a clinically meaningful response was defined as a reduction of ≥3 points from baseline in the MG-ADL total score, and a reduction of ≥5 points from baseline in the QMG total score, both with no rescue therapy. Results: More patients receiving eculizumab versus placebo achieved clinically meaningful responses at week 26 on both the MG-ADL and QMG scales (Week 26: eculizumab 40% vs placebo 13%, nominal P=0.0004). The benefit of eculizumab treatment was apparent within the first 2 weeks (Week 2: eculizumab 19% vs placebo 6% dual responders, nominal P=0.0297). Improvement with eculizumab was generally observed by week 8 (eculizumab 36% vs placebo 14%, nominal P=0.0060). Conclusions: Three times as many of refractory gMG patients treated with eculizumab experienced improvements in muscle strength that benefited patients’ ADLs compared to the placebo group by week 26. Improvement in the eculizumab-treated patient group was observed early compared with placebo and continued to improve over the course of the study.

Study Supported By:
Alexion Pharmaceuticals, Inc.
Comparison of protein-coding and long, non-coding RNA gene expression signatures to classify multiple sclerosis

Charles Spurlock, PhD; John Tossberg; Subramaniam Sriram, MD; Phillip Crooke; Thomas Aune, PhD

Objective: Develop machine learning classifiers using messenger RNA (mRNA) and long, non-coding RNA (lncRNA) expression data obtained from whole blood to accurately classify multiple sclerosis (MS). Background: lncRNAs are a relatively new class of RNA that play pivotal roles in the regulation of a variety of biological processes including innate and adaptive immune responses. Compared to mRNAs, our understanding of the functional role of lncRNAs in human diseases, including MS, is in its infancy. To date, no blood-based biomarkers have been made commercially available to aid in the diagnosis of MS. Design/Methods: Whole blood collected into PAXgene tubes was obtained from healthy subjects (n=346), patients with a clinically isolated syndrome who transitioned to clinically definite MS (n=84), diagnosed MS patients prior to treatment (n=90), established MS patients receiving therapies (n=212), and other inflammatory (n=132) and non-inflammatory (n=115) neurologic diseases. RNA sequencing was performed using a small subset of healthy control and MS patient samples to derive two sets of 48 highly differentially expressed gene candidates using mRNA and lncRNA gene targets. RT-PCR was performed on all patients recruited (n=979) and a portion of the datasets generated were used to train and independently validate multi-category machine learning classifiers capable of distinguishing MS. Results: We found that differences in expression of annotated lncRNAs ranged in magnitude from 4-fold to 32-fold across our study cohorts while differences in expression of mRNAs were typically less than 4-fold. Compared to mRNAs, lncRNAs exhibit greater discriminatory power and confidence of machine learning predictions with sensitivity and specificity exceeding 90% across case/control comparisons. Conclusions: Use of gene expression data obtained from whole blood and analyzed with machine learning methods delivers a highly accurate, actionable tool for providers who suspect MS.

Study Supported By:
NIH R43 AI124766 and IQuity, Inc.
A ‘surface-in’ gradient of thalamic damage is an early and disease-specific process in pediatric-onset multiple sclerosis

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Objective: To examine whether the distribution of thalamic damage in pediatric multiple sclerosis (MS) reflects a disease-specific ‘surface-in’ process of injury, compared to children with non-MS acquired demyelinating syndromes (non-MS ADS). Background: Subpial cortical pathology in MS is now considered an important contributor to progressive disease. This subpial injury reportedly exhibits a ‘surface-in’ gradient of damage, implicating a distinct disease mechanism (potentially involving soluble CSF factors). However, it remains unknown when during disease course such a process may begin. Reduced thalamic volume has been noted in both adult-onset and pediatric-onset MS. Since the thalamus has both CSF and white matter (WM) interfaces, we considered whether examination of thalamic injury in pediatric-onset MS would demonstrate an MS-specific ‘surface in’ pattern of injury. Design/Methods: 100 children (27 MS; 73 non-MS ADS) were prospectively followed from incident attack with yearly brain MRI (mean follow-up 4.6 years). 282 healthy children with serial MRIs were included as controls. Jacobian determinants, calculated in the thalamus from non-linear registration of scans to the baseline, were averaged over each isodistant surface from CSF, then analyzed using non-linear mixed effect modeling. Results: While the thalamus in both MS and non-MS ADS children failed to exhibit normal growth in thalamic regions adjacent to the WM, only children with MS exhibited an additional and striking ventricular ‘surface-in’ gradient of injury. This MS-specific distance-related abnormality of the thalamic CSF interface was already detectable from the first year of disease ($p = 0.0002$) and became more severe with time ($p = 0.0021$). Conclusions: We identified two distinct patterns of thalamic damage in pediatric demyelinating disease: one pattern, occurring distant from the ventricular surface, is shared by both children with MS and non-MS ADS; the second pattern, unique to MS, suggests that a distinct ‘surface-in’ process occurs in the very earliest MS disease stages.
Delayed-release Dimethyl Fumarate Reduces the Formation of T2 Lesions in Pediatric Patients with Relapsing-Remitting MS: Results From FOCUS, the First Clinical Trial to Evaluate the Neuroradiological Efficacy of an MS Disease-Modifying Therapy in Pediatric Patients

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Objective: To evaluate the effect of delayed-release dimethyl fumarate (DMF) on the formation of T2 lesions, and the safety and pharmacokinetics of DMF, in pediatric relapsing-remitting MS (RRMS) patients. Background: No disease-modifying therapy (DMT) has been demonstrated safe and effective in an interventional trial in pediatric MS patients. Design/Methods: FOCUS (NCT02410200) was a single arm, open-label study in RRMS patients aged 10–17 years. The study comprised an 8-week, off-treatment baseline period, followed by a 24-week treatment period during which patients received oral DMF 240 mg twice daily. Brain MRI scans were obtained at the beginning and at the end of the baseline period, and at weeks 16 and 24 of the treatment period. The primary endpoint was the change in the number of new/newly enlarging T2 hyperintense lesions during the 8-week baseline versus the final 8-week treatment period. Results: Twenty-two patients (14 [64%] female; mean age 15.8 [range: 13–17] years; mean weight 66 kg) were enrolled (12 sites, 10 countries). The mean (SE) change in the number of new/newly enlarging T2 hyperintense lesions was -7.9 (4.2) and the median (90% confidence interval) was -2.0 (-8.0, -1.5, p=0.009). The geometric mean \(C_{\text{max}}\) and AUC\(_{0-12}\) of DMF following the morning dose were 1.6 \(\mu\text{g/mL}\) and 3.4 h*\(\mu\text{g/mL}\), respectively. The most common adverse events were gastrointestinal events, flushing, and MS relapse, occurring in 55%, 45%, and 32% of patients, respectively. Lymphopenia, alanine aminotransferase elevation, and aspartate aminotransferase elevation occurred in 23%, 15%, and 10% of patients, respectively. There were no serious adverse events considered by the investigators to be related to DMF treatment. All 20 patients completing the study enrolled in a 2-year extension study (NCT02555215). Conclusions: In this study, the first clinical trial to examine the neuroradiological efficacy of a DMT in pediatric MS patients, the efficacy, safety, and pharmacokinetics of DMF were consistent with those observed in adult RRMS patients.

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Patients Who Received Alemtuzumab in CARE-MS I or II Show a Low Rate of Conversion From Relapsing-Remitting MS to Secondary Progressive MS Through 6 Years

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**Objective:** To determine the rate of conversion from relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS) through 6 years among CARE-MS I and II alemtuzumab-treated patients. **Background:** Delaying conversion to SPMS is an important treatment goal in MS. In an MSBase patient cohort (17,356 MS patients; median baseline disease duration 3.8 years; median 5.8-year follow-up), 18% of all patients converted to SPMS using a recently developed SPMS definition based on EDSS scores and relapses. In the CARE-MS studies, EDSS scores were stable/improved with alemtuzumab over 6 years in >75% of patients with active RRMS who were treatment-naïve (CARE-MS I; NCT00530348) or had inadequate response (≥1 relapse) to prior therapy (CARE-MS II; NCT00548405), in the absence of continuous treatment (extension study: NCT00930553). **Design/Methods:** Patients with active RRMS received 2 courses of alemtuzumab 12 mg (baseline: 5 consecutive days; 12 months later: 3 consecutive days) in CARE-MS I or II, and in the extension as-needed alemtuzumab for relapse or MRI activity, or another disease-modifying therapy (DMT) per investigator discretion. The definition of SPMS onset was as published by Lorscheider et al. (Brain 2016;139:2395-405). **Results:** Median disease duration at baseline was 1.7 years in CARE-MS I and 3.8 years in CARE-MS II (2.8 pooled). 325/376 (86%) and 344/435 (79%) alemtuzumab-treated patients, respectively, remained on study through Year 6 (669/811 [82%] pooled). Many patients (CARE-MS I: 63%; CARE-MS II: 50%) received no additional treatment in the extension (either alemtuzumab or other DMT). Among alemtuzumab-treated CARE-MS I or II patients, the SPMS definition was met by 4 (1.1%) and 16 (3.7%) patients, respectively, through 6 years (20 [2.5%] pooled). **Conclusions:** Utilizing an objective definition of SPMS based on the EDSS and relapse data, a very low proportion of alemtuzumab-treated patients from the CARE-MS studies progressed to SPMS.

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Symptomatic and objective clinical improvement in progressive multiple sclerosis patients treated with autologous Epstein–Barr virus-specific T cell therapy: Interim results of a phase I trial

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Objective: To determine the safety of treating progressive multiple sclerosis (MS) patients with autologous Epstein–Barr virus (EBV)-specific T cells. Background: Mounting evidence indicates a role for EBV in MS pathogenesis. EBV-infected autoreactive B cells might accumulate in the CNS because of defective cytotoxic CD8⁺ T-cell immunity. Design/Methods: In this trial we administer autologous EBV-specific T cells to patients with progressive MS (EDSS 5.0–8.0). Each patient receives their own T cells stimulated ex vivo to enhance reactivity to EBV nuclear antigen-1, latent membrane protein 1 (LMP1) and LMP2A, and is followed through 26 weeks. Four escalating dose infusions are administered biweekly. Results: To date, four SPMS patients and one PPMS patient have been treated. No significant adverse events have been observed. Three patients experienced symptomatic and objective clinical improvement, which commenced 2–8 weeks after the first infusion and was most marked in the two patients receiving T cells with the highest EBV reactivity. Striking improvement occurred in one SPMS patient, with normalization of lower extremity tone and plantar (Babinski) responses for the first time in 16 years, increased walking distance with walker from 100 meters at baseline and for the previous 5 years to 1200 meters, marked reduction in fatigue, increased manual dexterity, and improvements in lower extremity power, reflexes and sensation. A second SPMS patient had reduced fatigue, increased productivity and improved balance. The third responder (PPMS) had improved color vision, visual acuity and manual dexterity and reduced fatigue, lower extremity spasms and urinary urgency. These data are consistent with prior data from the first patient ever treated (SPMS compassionate use) who experienced reduced fatigue and lower extremity spasms, and improved cognition, hand function and productivity. Conclusions: This is the first report of clinical improvement in a prospective trial of autologous EBV-specific T cells to treat progressive MS patients. Further studies are planned.

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Objective: To assess disease activity based on radiological evidence in patients with relapsing-remitting multiple sclerosis (RRMS) treated with fingolimod for up to 96 months. Background: Efficacy of fingolimod as assessed by clinical and radiological disease activity measures has been well-established in Phase 2 and 3 trials as well as its generally good tolerability in patients with RRMS. Over 180,000 patients have been treated with Gilenya® (fingolimod), with more than 395,000 patient-years of total exposure in clinical trials and post-marketing setting worldwide. Assessment of the long-term effect of disease modifying therapies is important for managing MS in clinical practice. Design/Methods: LONGTERMS is an open-label, single-arm, extension study evaluating the long-term efficacy, safety, and tolerability of fingolimod in patients who previously participated in phase 2/3/3b fingolimod trials. The fingolimod full analysis set included all patients randomized to the approved dose of fingolimod 0.5 mg. The selected MRI endpoints were annualized rate of new or newly enlarging T2 lesions (ARneT2) and the proportion of patients free from gadolinium-enhancing (Gd+) T1 lesions until the end of the study as evaluated by Kaplan-Meier analysis. ARneT2 was evaluated through Month 96. Results: Overall, 3167 patients were included (women, 71.2%; age [mean±SD], 38.0±9.1 years). Median exposure to fingolimod was 526 days (range, 75-3619). At baseline, mean (±SD) duration of MS since diagnosis was 6.2±5.6 years and mean (±SD) Expanded Disability Status Scale was 2.4±1.5. In the full analysis set (N=3127), ARneT2 gradually decreased from 1.362 at Month 12 to 1.011 at Year 3, 0.915 at Year 5, and 0.801 at Year 8, suggesting continued radiological stability. Of the 924 evaluable patients, 48.3% (SE: 14.2) remained free from Gd+ T1 lesions throughout the study. Conclusions: Radiological evidence suggests a continuous long-term effect of fingolimod on disease activity in patients with RRMS.

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3D Mathematical modeling of glioblastoma suggests that transdifferentiated vascular endothelial cells promote resistance to current standard-of-care therapy

**Daniela Bota, MD; Huaming Yan; Monica Romero-López; Lesly Benitez; Kaijun Di; Hermann Frieboes; Christopher Hughes; John Lowengrub**

**Objective:** Glioblastoma (GBM), the most aggressive brain tumor in human patients, is highly heterogeneous and intensively vascularized. Here, we use 3D mathematical modeling to investigate GBM progression and identify novel treatment strategies.

**Background:** Glioma stem/initiating cells (GSC) are found to play a crucial role by increasing cancer aggressiveness and by promoting resistance to therapy. Recently, crosstalk between GSCs and vascular endothelial cells that line capillaries has been shown to considerably promote GSC self-renewal and tumor progression. GSCs have been shown to also transdifferentiate into bona-fide vascular endothelial cells (GEC). GECs inherit mutations present in GSCs and are resistant to traditional anti-angiogenic therapies.

**Design/Methods:** We develop a multispecies mathematical model to investigate the 3D spatiotemporal dynamics of vascularized GBM progression and response to cancer therapies.

**Results:** The model predicts GSCs drive invasive fingering and that GECs spontaneously form a network within the hypoxic core, consistent with published experimental findings. We demonstrate that standard-of-care treatments using DNA-targeted therapy (radiation/chemo) together with anti-angiogenic therapies reduce GBM tumor sizes but increase invasiveness. Anti-GEC treatments block the GEC support of GSCs and reduce tumor sizes but can lead to increased invasiveness. Anti-GSC therapies that promote differentiation or disturb the stem cell niche effectively reduce tumor invasiveness and sizes, but are ultimately limited in reducing tumor sizes because GECs can maintain GSCs. Anti-GEC therapies are required to remove the tumor completely.

**Conclusions:** Our results suggest that a combinatorial regimen targeting the vasculature, GSCs and GECs, using drugs already approved by the FDA, can reduce both tumor sizes and invasiveness and could lead to tumor eradication without recurrence when the treatment is stopped.

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Cholinesterase Inhibitor Use and Cognitive Decline in Mild Cognitive Impairment and Mild Dementia due to Alzheimer Disease

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Objective: Demonstrate the utility of cholinesterase inhibitor use in mild cognitive impairment. Background: Cholinesterase inhibitors (ChEIs) are approved for the symptomatic treatment of Alzheimer disease (AD) but their efficacy is uncertain in mild cognitive impairment (MCI) despite its frequent use. We investigated whether the use of ChEIs benefits cognitive outcomes in MCI compared with mild AD dementia (ADdem). Design/Methods: Data from 2,264 individuals clinically diagnosed with ADdem (Clinical Dementia Rating [CDR]=0.5 or 1) or MCI due to AD(MCI-AD) at Alzheimer Disease Centers were available from the National Alzheimer's Coordinating Center's Uniform Data Set (UDS). Multivariable linear mixed models were run separately for MCI-AD and ADdem to examine the annual change in the CDR sum of boxes (CDR-SB). We compared slopes before and after ChEI initiation among ChEI users, and then compared change in scores during the entire UDS follow-up in ChEI users versus non-users. Results: 35% of 966 MCI-AD and 72% of 1,298 ADdem participants were ChEI users. In both groups, ChEI users had higher education, were less often African American/other race, and more often had at ≥1 APOE e4 allele (p<0.05). Comparing the slopes before and after ChEI initiation, the decline was significantly steeper at ChEI initiation in both groups (e.g., CDR-SB change in MCI-AD: 0.03 points/year before initiation, 0.85 points/year after initiation). Comparing change in scores over the entire UDS follow-up, ChEI users in both the MCI-AD and ADdem groups had a significantly faster cognitive decline compared to the ChEI non-users (e.g., CDR-SB change in MCI-AD: 0.70 points/year among ChEI users, 0.21 points/year among non-users). Conclusions: Preliminary evidence from this study unexpectedly suggests that ChEI prescription and use in individuals with MCI-AD or ADdem may not improve the overall course. This faster decline seen in ChEI users after ChEI initiation may imply the expected decline that resulted in ChEI use.
Seizures are locked to long time-scale rhythms in epilepsy

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Objective: We investigated whether there are rhythms in seizure activity over multiple days, weeks or months (“multidien”) among patients with refractory epilepsy. Background: Epilepsy is defined by the seemingly random occurrence of seizures. However, recent quantitative analyses have described circadian and cluster organization, suggesting that seizures may be temporally regulated over long timescales. An extension of this concept is whether seizure timing is related to fluctuations in Interictal Epileptiform Activity (IEA), a marker of brain irritability. We quantified continuous IEA and seizure detection from 37 patients implanted intracranially for years with the Responsive NeuroStimulation system1 (ambulatory electrocorticography). Design/Methods: We formatted IEA hourly counts into continuous time-series and applied wavelet decomposition to determine any component multidien rhythms. In a subset of 14 patients who had reliable seizure detection, we then estimated the phase timing of seizures in relation to peak periodicities of IEA using circular statistical analyses (mean resultant vector length, Omnibus test). Results: Beyond the expected circadian distribution of IEA (confirmed here), we also found robust superimposed multidien rhythms of IEA. Cycle durations differed between patients, and they were stable over time including some recorded up to 10 years. Both females and males demonstrated these multidien rhythms, and there was no coherence with the lunar cycle. Seizures were phase-locked to the underlying multidien rhythms of IEA, occurring preferentially during the upslope of the period (p<0.05 for 13 out of 14 subjects). Conclusions: Using very long continuous electrocorticography recordings, we found that seizures and IEA are substantially influenced by underlying rhythms in long timescales (several days to weeks or more). These multidien rhythms suggest underlying therapeutic endocrine or metabolic targets that deserve further study. They also highlight opportunities to decrease refractory seizure burden through dynamic predictive therapeutic adjustments.

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The differential effects of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on seizure frequency in patients with drug-resistant epilepsy – A Randomized, double-blind, placebo-controlled trial

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Objective: To investigate the effect of DHA and EPA on seizure rate in patients with DRE. Background: About 30 percent of epileptic patients do not respond to treatment. Cell membrane lipids play a critical role in anti-epileptic drugs’ transport and efficacy. Drug resistant cells have been shown to have altered lipid profiles. In addition, several animal models, as well as some clinical studies, support EPA and DHA as being involved in maintenance and modulation of neuronal functions as well as in the inhibition of neuronal excitability and seizure latency and frequency

Design/Methods: A double-blind, randomized, placebo-controlled clinical trial included ninety nine (n=99) DRE patients, aged 5 -16 (n=85) and 17- 45 (n=14). Patients were recruited from the Neurological Department, Khartoum Hospital, Sudan. After randomization, patients were given 2, 4 or 6 capsules of DHA (417.8 mg DHA and 50.8 mg EPA/capsule, n=33), EPA (385.6 mg EPA and 81.2 mg DHA/capsule, n=33) or placebo (high oleic acid sunflower seed oil, n=33) for one year. The primary outcome measure was the effect of treatment on seizure rate (ITT approach). Results: Fifty-nine patients (n=59) completed the study (59.6%). No treatment-emergent adverse event (TEAE) occurred during the study. The average number of seizures per year were EPA, 113.7±13.1, DHA, 145.5±16.1 and placebo, 182.8±16.1. Age and gender, seizure type adjusted seizure incidence rate ratios (IRRs) of the EPA and DHA groups compared with the placebo were 0.58 (CI= 0.42-0.90, p=0.009, 42% reduction) and 0.61 (CI = 0.39-0.87, p= 0.01, 39% reduction), respectively. There was no difference in IRR between the EPA and DHA groups (p=0.8). Conclusions: This study demonstrates that EPA and DHA are effective in reducing seizure frequency in DRE. Further larger multi-center studies are needed.
**Objective:** To evaluate the efficacy and safety/tolerability of erenumab (AMG 334) in a phase 3 trial of subjects with episodic migraine (EM) (NCT02456740). **Background:** Calcitonin gene-related peptide (CGRP) plays an important role in migraine pathophysiology. Erenumab is a fully human monoclonal antibody that inhibits the CGRP receptor.

**Design/Methods:** In this multinational, double-blind, placebo-controlled trial, adults with EM (n=955) were randomized 1:1:1 to subcutaneous monthly placebo or erenumab 70mg or 140mg for 24 weeks. The primary endpoint was change from baseline in mean monthly migraine days (MMDs) over weeks 13-24. Secondary endpoints were ≥50% reduction in MMDs; change in mean acute migraine-specific medication days; change in mean Physical Impairment (PI) and Impact on Everyday Activities (EA) scores (as measured by the Migraine Physical Function Impact Diary [MPFID]). *p*-values for pairwise comparisons of each erenumab dose with placebo are presented. Statistical significance was determined after adjustment for multiple comparisons.

**Results:** Subjects reported 8.3 MMDs at baseline and experienced -3.2, -3.7, and -1.8-day reductions in the 70mg, 140mg, and placebo groups, respectively (*p*<0.001 for both). A ≥50% reduction in MMDs was achieved by 43%, 50%, and 27% in the 70mg, 140 mg, and placebo groups (*p*<0.001 for both), and monthly acute migraine-specific medication days were reduced by -1.1, -1.6, and -0.2 days (*p*<0.001 for both). Subjects had improved PI scores (-4.2, -4.8, -2.4 points in the 70mg, 140mg, and placebo groups; *p*<0.001) and EA scores (-5.5, -5.9, and -3.3 points; *p*<0.001). The safety/tolerability profile of erenumab was similar to placebo; subjects most frequently reported nasopharyngitis, upper respiratory tract infection, and sinusitis. **Conclusions:** Erenumab 70mg and 140mg significantly reduced migraine frequency and use of migraine-specific medications, reducing migraine’s impact on physical impairment and everyday activities compared with placebo in this EM trial. Numerically greater efficacy was observed for the 140mg dose consistently across all endpoints.

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