### Efficacy and Safety of Eculizumab in Aquaporin-4 Antibody Positive (AQP4-IgG+) Neuromyelitis Optica Spectrum Disorder (NMOSD): A Phase 3, Randomized, Double Blind, Placebo-Controlled, Multicenter Trial (PREVENT) (Emerging Science 009)

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**Studies**

Complement activation is a major component of CNS inflammation and astrocyte injury in NMOSD. Eculizumab is a humanized monoclonal antibody against C5. This therapy was tested in a global phase 3 trial, PREVENT.

**Methods**

PREVENT was a randomized, double blind, time to event trial, designed to end when there were 24 on-trial relapses as adjudicated by a blinded independent expert panel. This panel was established midway through the study. AQP4-IgG+ NMOSD adult patients were randomized 2:1 to eculizumab 1200 mg IV every 2 weeks (after a loading dose protocol of 900 mg IV weekly x4) or placebo. The continued use of stable-dose immunosuppressive therapy was permitted (glucocorticoids, azathioprine, mycophenolate, cyclophosphamide, methotrexate, mizoribine, tacrolimus).

**Results**

N=143 patients were randomized (91% females, median age 45 years), and N=124 completed the study; N=80/96 (83.3%) in the eculizumab arm, and N=44/47 (93.6%) in the placebo arm. Baseline annualized relapse rate (ARR) was 1.94 and 2.07 in the eculizumab and placebo group; immunosuppression was being used in 78.1% and 72.3% respectively. The study was stopped after 23 adjudicated on-trial relapses (N=3 with eculizumab, N=20 with placebo). Primary endpoint (time to first relapse) was reduced by 94.2% with eculizumab (P<0.0001). At 48 weeks 97.9% of the eculizumab group were relapse free vs. 63.2% of the placebo group. Adjudicated on-trial ARR was significantly lower with eculizumab 0.02 vs. 0.35 (P<0.0001). Mean change in the EDSS score was -0.18 vs. +0.12 (NS). Upper respiratory tract infections and headaches were more common with eculizumab. Most treatment emergent adverse events were mild to moderate. There were no meningococcal infections. There was one death in the eculizumab arm due to pulmonary empyema, but it did not involve microorganisms associated with complement deficiency.

**Conclusions**

Eculizumab significantly reduced relapse risk in patients with AQP4-IgG+ NMOSD. The safety profile was similar to that in other indications. (Note: There is a novel anti-C5 ravulizumab with a longer half-life, that is given Q8 weeks. This will be studied in the future).
Double-masked, placebo-controlled study with open-label period to evaluate the efficacy and safety of inebilizumab in adult subjects with neuromyelitis optica spectrum disorders – top line efficacy and safety results (Plenary Session 02.001)

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There are no approved therapies for NMOSD, but empiric data suggests depleting B cells may be useful. Inebilizumab is a humanized anti-CD19 monoclonal antibody that depletes pro-B cells, B cells, and plasmablasts, as well as some plasma cells.

N-MOmentum is a phase 3, double-masked, randomized, placebo controlled trial of inebilizumab (MEDI-555) in NMOSD. A three-member eligibility committee confirmed entry criteria for AQP4-IgG negative subjects. Participants were randomized 3 to 1 to treatment with inebilizumab or placebo. No concurrent immune suppressants were permitted. The placebo-controlled period was limited to 6.5 months. Primary outcome was time to first adjudicated attack. Open label extension study inebilizumab was offered to those with an adjudicated attack, or who completed the controlled phase of the study.

N-MOmentum enrolled 231 NMOSD patients; 91% were AQP4-IgG+. Patients received two 300 mg IV doses of inebilizumab on days 1 and 15 (N=174), or placebo (N=56), and were then followed for 28 weeks. Inebilizumab reduced the attack risk by 77.3% (89% attack free vs. 58%) in AQP4-IgG+ patients (P<0.0001), and by 72.8% (P<0.0001) in the entire treated population (87% attack free vs. 60%). Inebilizumab reduced worsening from baseline EDSS (15.5% vs. 33.9%, P=0.005); reduced hospitalizations (10/174 vs. 8/56, P=0.01), reduced cumulative total active MRI lesions (79/174 vs. 32/56, P=0.0034). These two arms showed similar rates of adverse events. There were 2 deaths in the open label period (due to a severe attack, and a brain event of unclear etiology).

Inebilizumab appears to be an effective treatment for NMOSD. (Note: In the open label extension people are receiving 300 mg IV inebilizumab Q6 months).

### Efficacy of satralizumab (SA237) in subgroups of patients in SAkuraSKY: a phase III double-blind, placebo-controlled, add-on study in patients with neuromyelitis optica spectrum disorder (NMOSD) (Scientific Session 43.008)

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Satralizumab is a humanized recycling anti-interleukin-6 receptor (IL6-R) IgG2 monoclonal antibody. In SAkuraSKY, a phase III trial, it significantly reduced the risk of a protocol defined relapse in NMOSD patients by 62% (P=0.0184) compared to placebo. This analysis evaluated the efficacy of satralizumab in subgroups of patients from this study.

SAkuraSKY is a randomized, double-blind, phase III study of satralizumab (120 mg SC at weeks 0, 2, 4 and then Q4W) compared to placebo, as add-on to NMOSD patients on baseline stable immunosuppressants (azathioprine, mycophenolate) and/or corticosteroid therapy.

Primary endpoint was time to first protocol defined relapse. Pre-specified subgroup analyses included assessing response by AQP4-Ab status, baseline treatment, and region. Between-group hazard ratios were based on Cox proportional hazards model.

N=83 patients (aged 13-73 years) were randomized in a 1:1 ratio. Satralizumab showed a 79% risk reduction in protocol defined relapse compared to placebo in the AQP4-IgG+ subgroup. Proportion relapse free at 48 weeks was 91.5% vs. 59.9%, and at 96 weeks were 91.5% vs. 53.3%.

For the AQP4-IgG negative subgroup protocol-defined relapse risk reduction was 34% vs. placebo. Proportion relapse free at week 48 was 84.4% vs. 75.5%, and at week 96 was 56.3% vs. 67.1%

Subgroup data indicates satralizumab is effective in reducing protocol defined relapse in NMOSD, but especially in AQP4-IgG+ patients.
### Spontaneous Intracerebral Hemorrhage During Administration of Alemtuzumab for Multiple Sclerosis: A Case Series (Scientific Session 26.005)

**Christina Azevedo**  
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| Alemtuzumab is known to carry risk of immune thrombotic thrombocytopenia, which can lead to intracerebral hemorrhage. However spontaneous intracerebral hemorrhage has been reported during the initial week of drug administration. The etiology is unknown. | This is a retrospective analysis of five cases that occurred at four MS centers. | The five MS patients were females aged 38 to 49 years, with relapsing MS for 8 to 21 years. All had tried ≥2 prior DMTs. None had a history of bleeding, stroke, hypertension or aneurysm. Spontaneous intracerebral hemorrhage occurred on days 3, 4 or 5 of their initial alemtuzumab treatment cycle. Four bleeds affected the basal ganglia, and one was lobar. In 4 patients, blood pressure trended up during the infusion week. Platelet counts decreased by ≥30% (mean 40.1%) on the day of the bleed. Three patients were mildly thrombocytopenic (100,000 to 150,000 x10^9/L). | Rising systolic blood pressure throughout the infusion week was the only indicator of the impending intracerebral hemorrhage. Mild thrombocytopenia may have contributed. An increase in mean systolic blood pressure of ≥20 mmHg, or ≥20% above baseline during the infusion week, should prompt concern for increased risk of intracerebral hemorrhage. (Note: This complication seems confined to the US. In a comment it was noted that the US tends to hydrate patients more vs. Europe, and that this might be a factor). |

### Reduced risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab extended interval dosing (EID): updated analysis of the TOUCH Prescribing Program database (Scientific Session 26.006)

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<p>| Natalizumab therapy is associated with an increased risk of PML. This is an update on EID in the TOUCH data as of June 2018, and the impact on risk of PML compared to standard interval dosing (SID). | The TOUCH database up to June 1, 2018 was examined using three previously specified pre-planned analyses: primary analysis over the last 18 months; secondary analysis of prolonged period of EID/SID occurring at any time; and tertiary analysis of dosing history consisting primarily of EID/SID. Most EID patients in the primary and secondary analyses had prior SID therapy. Anti-JC virus positive individuals with dosing intervals of ≥3 to ≤12 weeks were included. PML hazard ratios for EID and SID were compared using Cox regression models and Kaplan-Meier estimates. | This 2018 update, of data originally presented as of 2017, increased the number of analyses in all three analyses: primary 14,305 SID vs. 2,226 EID; secondary 16,648 SID vs. 3,726 EID; and tertiary 24,870 SID vs. 931 EID. For all analyses EID patients had longer median natalizumab exposure. PML hazard ratio was 0.10 (P&lt;0.001) for the primary analysis, and 0.20 (P&lt;0.001) for the secondary analysis in favor of EID. No EID PML cases were noted in the tertiary analysis. This translates to 90% PML reduction in the primary, 80% in the secondary, and no PML in the tertiary group. | This updated analysis of TOUCH demonstrates that natalizumab EID is associated with significantly lower PML risk compared to standard Q4 week dosing. Most often extended dosing involves every 6 to 8 weeks, often initiated after year 1 of natalizumab therapy. (Note: There is an ongoing phase 3B NOVA trial, testing 6 week EID vs. SID therapy). |
| A Novel Functional Composite Endpoint to Characterize Disease Progression in Patients with Secondary Progressive Multiple Sclerosis (Scientific Session 12.006) | Physical disability is measured by the Expanded Disability Status Scale (EDSS). Cognitive processing speed is measured by the Symbol Digit Modality Test (SDMT). Both are highly relevant to evaluate MS patients with the secondary progressive (SP) MS phenotype. They are proposed as a novel functional composite endpoint in SPMS. | The placebo controlled phase III EXPAND trial, testing siponimod 2 mg PO daily, was examined. Time to 6 months confirmed disability progression on EDSS and SDMT (4 point confirmed worsening from baseline) were used. | Of N=1,645 SPMS patients, N=358 had EDSS progression; N=279 (78%) of them had no progression on SDMT. N=287 had SDMT progression; N=208 (72%) of them did not progress on EDSS. Compared to placebo, siponimod reduced risk of progression on EDSS (P=0.0058), on SDMT (P=0.0163), and on the composite endpoint (P=0.0008). At the end of the study, 62% of the siponimod arm vs. 52% of the placebo arm remained free of the composite endpoint disability measure. | Combining EDSS and SDMT resulted in higher sensitivity for change and therapeutic effect in this large SPMS trial. If this is confirmed in other patient samples, introduction of this composite measure might allow for lower sample sizes in future clinical trials. | Ludwig Kappos Basel, Switzerland |
| Pregnancy-related relapses in a large, contemporary multiple sclerosis cohort: no increased risk in the postpartum period (Scientific Session 6.007) | Prior studies indicate decreased risk of relapse during pregnancy for relapsing multiple sclerosis (MS), particularly the first trimester, but significant rebound risk in the early postpartum (especially first 3 months) period. This data comes principally from the pre-DMT era, and when MRIs were not in widespread use. | 466 pregnancies were identified among N=375 women with MS in the Kaiser Permanente Southern and Northern California electronic health record (EHR) between 2008-2016. Prospectively collected complete EHR data on mother and child, and interview-administered surveys, were used. | 14.6% of the MS cohort had a clinically isolated syndrome. 38% were not on any DMT in the year prior to conception. 8.4% had a relapse during pregnancy. In the postpartum year 26.4% relapsed, 87% breastfed, 35% breastfed exclusively, and 41.2% resumed a DMT. Annualized relapse rate (ARR) declined from 0.39 pre-pregnancy to 0.14-0.07 (P&lt;0.0001) during pregnancy. In the first 3 months postpartum ARR was 0.27 (P=0.03) and returned to pre-pregnancy rates at 4-6 months (0.37). Exclusive breastfeeding for at least 2 months reduced postpartum relapse risk by 40% (P=0.0093), while resuming a DMT (largely an injectable) had no statistically significant effect (P=0.62). | This study reports a novel finding: no rebound increase in ARR above pre-pregnancy baseline in the 3 months postpartum. Pregnancy relapse rate was low (8.4%). The authors speculated this likely reflected a combination of (exclusive) breastfeeding, early CIS inclusion, and use of a population based setting. (Note: This finding of no postpartum rebound is in contrast to several other studies, and will have to be confirmed). | Annette Langer-Gould Palo Alto, California |</p>
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<th><strong>Response to Treatment According to Progressive Disease Type: Analysis from a Phase II Progressive MS Trial of Ibudilast (Scientific Session 12.007)</strong></th>
<th>Primary progressive MS (PPMS) and secondary progressive MS (SPMS) are increasingly viewed as being more similar (a shared neurodegenerative disease phase) than different. The goal of this study was to determine the impact of oral ibudilast on disease course in PPMS vs. SPMS.</th>
<th>SPRINT-MS was a randomized placebo-controlled 96 week phase II trial that found a positive effect of ibudilast vs. placebo on brain measures of integrity in a combined progressive MS cohort of PPMS (N=134) and SPMS (N=121). Separate linear mixed models were used in PPMS and SPMS to evaluate rate of change in the primary outcome (progression of brain atrophy) measured by brain parenchymal fraction. Baseline demographics and disease measures were included where appropriate.</th>
<th>Post hoc analysis showed a marginally significant 3 way interaction between treatment effect and disease course (P=0.0576). The overall treatment effect was primarily driven by PPMS patients (P=0.005), not by SPMS patients (P=0.97). This difference may have been driven (at least in part) by faster atrophy progression in the PPMS placebo group compared to SPMS placebo (P=0.016). Although backwards selection retained age, T2 lesion volume, RNFL and longitudinal diffusivity as significant baseline covariates (P&lt;0.05), the adjusted difference in treatment effect was still marginally significant (P=0.0715) and driven by PPMS (P=0.007).</th>
<th>The overall treatment effect of ibudilast on brain atrophy progression appears to be driven by patients with PPMS and not SPMS. In part this may be because of faster atrophy progression rates in untreated PPMS. (Note: This is a caution to include an evaluation of treatment impacts not just on progressive MS, but on PP vs. SPMS when dealing with combined populations).</th>
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<td><strong>Efficacy and Safety of Fingolimod 0.5 mg and 0.25 mg Versus Glatiramer Acetate 20 mg in Patients with Relapsing-Remitting Multiple Sclerosis – ASSESS Study Group (Scientific Session 56.009)</strong></td>
<td>Fingolimod 0.5 mg has demonstrated superior efficacy over placebo and IM interferon beta-1a in phase III trials. The FDA mandated that a post marketing lower dose of fingolimod be examined. The ASSESS study evaluated fingolimod (0.5 mg and 0.25 mg) vs. glatiramer acetate (GA) 20 mg SC daily in a 12 month relapsing trial.</td>
<td>ASSESS is a phase 3B randomized, multicenter rater and dose blinded study. Patients were randomized to fingolimod 0.5 mg (N=352), 0.25 mg (N=370) or SC GA 20 mg daily (N=342). Superiority of fingolimod was tested hierarchically: 0.5 mg vs. GA, followed by 0.25 mg vs. GA, Primary endpoint was reduced annualized relapse rate (ARR). Secondary endpoints were MRI measures of disease activity at 12 months. Safety and tolerability were also assessed.</td>
<td>N=859 (80.7%) patients completed the study. Over 12 months ARR with fingolimod 0.5 mg and GA were 0.153 vs. 0.258 (relative reduction 40.7%, P=0.0138). Fingolimod 0.25 mg achieved a risk reduction of 14.6%, but was not statistically significant. Fingolimod 0.5 mg and 0.25 mg significantly reduced the mean number of new/enlarging T2 lesions (relative reduction 54.4% and 42.1%, P&lt;0.0001), and contrast lesions (relative risk 55.6% for both doses, P=0.0167 and P=0.0011). Adverse events for fingolimod were within the known safety profile. More discontinuations were reported with GA (due to injection related events, consent withdrawal, and unsatisfactory therapeutic effects).</td>
<td>Fingolimod 0.5 mg is the optimal efficacy dose, and is the first DMT to show superior efficacy vs. GA in a controlled head to head study. Safety findings were compatible with the established profile. (Note: This study indicates 0.25 mg fingolimod has less efficacy than 0.5 mg fingolimod).</td>
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| Pharmacokinetics, Pharmacodynamics and Exposure-Response Analyses of Ocrelizumab in Patients with Multiple Sclerosis (Neuroscience in the Clinic Session 4.001) | Ocrelizumab is a CD20+ B cell selective monoclonal antibody approved to treat relapsing forms of MS and primary progressive (PP) MS. The goal was to describe population pharmacokinetics, pharmacodynamics, and exposure-efficacy/safety relationships of ocrelizumab in MS. | Ocrelizumab phase II/III trial data were analyzed using a non-linear mixed-effects model to describe ocrelizumab population and pharmacokinetic modeling, and assess covariate results. Relationships to phase III study endpoints (annualized relapse rate [ARR], 12/24 week confirmed disability progression) and safety parameters (serious adverse events, serious infections, and infusion related reactions) were assessed. | A two compartment model with time-dependent clearance and body weight as main covariates described accurately ocrelizumab pharmacokinetics in patients with relapsing MS (N=941) and PPMS (N=482). Exposure (area under serum concentration-time curve) was 26% higher in patients with relapsing MS <60 kg, and 21% lower in those >90 kg vs. a 75 kg reference patient. Blood B cell depletion correlated with ocrelizumab exposure. Patients with relapsing MS obtained similar benefits with regard to ARR independent of exposure. However risk reductions in 12/24 week CDP was exposure dependent in relapsing MS (12-week CDP hazard ratios by exposure quartiles 1-4: 0.77, 0.80, 0.45, 0.33 vs. IFNβ-1a) and PPMS (12-week CDP hazard ratios by exposure quartiles 1-4: 0.87, 0.83, 0.78, 0.59 vs. placebo). Safety parameters were similar across exposure quartiles. | There is greater B cell depletion with higher ocrelizumab exposure. ARR and MRI outcomes were not exposure dependent. However ratios of disability progression were associated with higher ocrelizumab exposure and lower median B cell levels prior to the next infusions. Higher ocrelizumab exposure and greater B cell depletion may be important for control of disability progression. (Note: Are more obese patients underdosed? Are we underdosin most patients with regard to impacting progression? This needs to be addressed). |
| Monitoring of Subclinical Disease Activity by Serum Neurofilament Light Chain Levels (Scientific Session 37.005) | Neurofilament light protein (NfL) serum level is associated with disease activity in MS. Its practical value to detect subclinical MRI activity is not established. The goal of the study was to investigate the ability of serum NfL to identify brain MRI activity. | This longitudinal study included N=163 relapsing patients (405 samples) from the SET cohort, and N=179 relapsing patients (664 samples) from the GeneMSA cohort. Serum Nfl levels were evaluated annually using Simoa. Age adjusted NfL percentiles were based on normative data from healthy controls. In each cohort MRI scans were performed annually using 1.5T scanner and a uniform protocol. The accuracy of different NfL cut-offs for the detection of active lesions (new/enlarging lesions, contrast lesions) compared with the preceding year’s MRI was assessed on annual scans. | Nfl levels exceeded the 90th percentile in 25.4% of the SET and 26.5% of the GeneMSA samples. 81.6% of the SET and 48.9% of the GeneMSA cohort with Nfl ≥90th percentile showed MRI activity. Nfl levels <30th percentile was observed in 32.8% of the SET and 19.4% of the GeneMSA samples, and reflected negligible MRI activity. Only 0.8% (SET) and 5.4% (GeneMSA) of patients developed ≥3 active lesions; 6.0% (SET) and 5.4% (GeneMSA) developed ≥2 active lesions; and 29.3% (SET) and 10.9% (GeneMSA) showed any MRI activity (≥1 active lesion). All results were confirmed in sub-analyses of clinically stable patients. | Low serum Nfl levels help identify MS patients with very low recent MRI disease activity. This result suggests that Nfl assessment may help to spare the need for annual brain MRI monitoring in clinically stable patient with very low Nfl levels. |
### BASIC SCIENCE

| Metabolic interference protects against a mouse model of multiple sclerosis (Scientific Session 55.003) | Activated leukocytes show marked metabolic changes with preferential use of glycolysis for cellular energy generation. Blocking glycolysis inhibits effector T cell differentiation, and promotes regulatory T cell formation. This study evaluated whether a combination of three drugs inhibiting glycolysis and glutamine metabolism, which were shown to prevent allograft rejection in mice, could treat a mouse model of multiple sclerosis (MS). | Experimental allergic/autoimmune encephalitis (EAE) was induced in wild type female C57BL/6 mice at 11 weeks of age. Starting on the day of induction and continuing through the course of 40 days, mice received via oral gavage a combination therapy of metformin at 150 mg/kg/day (an AMPK activator), 2-deoxyglucose (2-DG, a hexokinase inhibitor and ATP depleting agent) at 500 mg/kg/day, and 6-diazo-5-oxo-L-norleucine (DON, a glutamine metabolism inhibitor) at 0.8 mg/kg/day every other day. This was compared to mice receiving a control solution, with N=10 in each group. Spinal cord tissue was harvested for immunohistochemistry and flow cytometry. | Mice who received the combination therapy showed marked protection against EAE as compared to controls, with significant differences in mean scores from days 15-40 (P<0.0001), total mean score (2.4 vs. 0.48, P<0.00001), disability onset (day 13.6 vs. 22.85, P<0.0005), and peak score of disease (3.65 vs. 1.35, P<0.005). 40% of the treated group showed no clinical symptoms. | A pharmacologic regimen blocking glycolysis and glutamine metabolism demonstrates strong protective effects in a mouse EAE model, supporting a value for metabolic interference in MS and other CNS immune-mediated diseases. |
| Stefan Jordan New York, New York | | | | |

| Functional Characterization of Reappearing B cells After Anti-CD20 Mediated B cell Depletion in Two Animal Models of Multiple Sclerosis (Scientific Session 26.004) | Ongoing anti-CD20 monoclonal antibody therapy reduces relapse frequency and CNS lesion development in MS. It is unknown whether B cells must be continuously depleted, or whether alternative anti-CD20 interventions can truly reset the disease-driving B cell function. | C57BL/6 mice received 3 weekly SC injections of 0.2mg murine anti-CD20 or control antibody prior to immunization with a) MOG peptide 35-55, a setting in which B cells remain naïve, or b) MOG protein 1-117, a setting in which B cells get activated. Reappearing B cells were phenotypically analyzed for expression of activation markers, co-stimulatory molecules, B cell receptor diversity and antigen presentation function. | In both models, a fraction of CD20+ antigen-experienced B cells persisted in splenic follicles despite extensive systemic anti-CD20 use. Upon treatment cessation CD20+ B cells simultaneously repopulated in bone marrow and spleen before their reappearance in blood. Returning B cell population showed a shift towards mature differentiated phenotypes containing an increased frequency of myelin-reactive B cells with restricted B cell receptor gene diversity and enhanced capability to activate myelin- | These findings highlight that distinct subpopulations of B cells differ in their sensitivity to anti-CD20 treatment, and suggests that differentiated B cells persisting in secondary lymphoid organs contribute to the recovering B cell pool. |
| Darius Häusler Göttingen, Germany | | | | |
The objective of this study was to characterize reappearing CD20+ B cells in the bone marrow, blood, and secondary lymphoid organs after transient anti-CD20 treatment in murine experimental autoimmune encephalomyelitis (EAE).

Specific T cells, in the model in which B cells are intrinsically activated. By contrast, in the T cell-mediated EAE model, B cells reappeared in a predominantly naïve status with a relative loss of pathogenic APC function.