LB1.1 Late Breaking News

LB1.1 Phase 2 results of the RADIANCE trial: a randomized, double-blind, placebo-controlled trial of oral RPC1063 in relapsing multiple sclerosis

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Background: RPC1063 is an oral, selective sphingosine 1-phosphate 1 receptor modulator in clinical development for the treatment of relapsing multiple sclerosis (RMS).

Objectives: Demonstrate the superior efficacy of low (LD, 0.5 mg) and high (HD, 1.0 mg) dose RPC1063 vs. placebo (PBO), and characterize the safety of RPC1063 in patients with RMS.

Methods: RADIANCE is an international, combined Phase 2/3 trial. In the 24-week, Phase 2 portion, 258 patients were randomized (1:1:1) to PBO (n=88), LD (n=87) or HD (n=83). The primary endpoint was the cumulative number of total gadolinium-enhancing (GdE) lesions on MRI at Wks 12-24, and annualized relapse rate (ARR). Safety was assessed using vital signs, labs, ECG, Holter monitoring, PFT, OCT and adverse events (AEs). Patients were titrated to their assigned dose over one week to mitigate first dose heart rate effects.

Results: 98% of patients completed the trial. Cumulative total Wk 12-24 GdE lesions was reduced 86% in both RPC1063 arms vs. PBO (mean ± SD: PBO 11.1 ± 29.9, LD 1.5 ± 3.7, HD 1.5 ± 3.4, both p< 0.0001). Numbers of GdE lesions at Wk 24 were significantly reduced 91% and 94% (PBO 3.2 ± 9.8, LD 0.3 ± 0.9, HD 0.2 ± 0.6, both p<0.0001) and cumulative Wks 12-24 new/enlarging T2 lesions from Wks 12-24, and annualized relapse rate (ARR). Safety was assessed using vital signs, labs, ECG, Holter monitoring, PFT, OCT and adverse events (AEs). Patients were titrated to their assigned dose over one week to mitigate first dose heart rate effects.

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LB1.2 The long-term effectiveness and cost-effectiveness of interferon-beta and glatiramer acetate: 6-year analysis of the UK MS risk-sharing scheme

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Background: In 2002, the UK’s National Institute of Clinical Excellence concluded that the multiple sclerosis disease modifying therapies (DMTs) would only be cost-effective if the relative short term benefits on disability persisted over an extended period. Given their price, the Risk-sharing Scheme was established to ensure cost-effective provision of interferon-beta (IFb) and glatiramer acetate (GA) in the UK.

Objectives: We aimed to measure long-term effectiveness of these treatments in order to permit price adjustment should prospectively collected disability data deviate from the predicted course of treated patients modelled from natural history data. We report here findings after 6 years of active follow-up.

Methods: Over 5,000 patients treated with either IFb or GA, from 72 UK sites, were enrolled into a 10 year cohort between 2002-2005, with annual EDSS scores recorded. An independent Scientific Advisory Group pre-specified the analysis plan. After experience with the 2 year interim analysis (Boggild et al), the British Columbia MS database was selected as the best natural history comparator and two parallel analyses were undertaken using a continuous Markov and a multi-level model (MLM) with age of onset as a covariate. The hazard ratio for all the DMTs in aggregate was taken to be 0.62 (a 38% relative reduction in the rate of disease progression) if the drugs were to remain on target for cost-effectiveness.
Results: After 6 years of follow-up, the observed increase in EDSS for patients with active relapsing remitting (RR) MS was less than the modelled natural history cohort. The observed progression for EDSS (the primary outcome) was consistent with a relative rate of progression of 0.58 (Markov model) or 0.56 (MLM) which was better than predicted. For EDSS, the relative rates were 0.76 (Markov model) and 0.61 (MLM) respectively. A range of sensitivity analyses examining the potential for various biases such as loss to follow-up continue to show a better outcome than in the untreated cohort.

Conclusions: This is the largest observational study measuring the effect and cost-effectiveness of the IFb preparations and GA, and provides evidence that as a therapeutic group they alter the natural history of RR MS in the real life setting. If sustained over 20 years, the magnitude of the treatment effect observed would be consistent with the pre-defined cost-effectiveness target of £36,000 ($61,000, €45,000) /QALY.

LB1.3
Effect of THC-CBD oromucosal spray (Sativex) on measures of spasticity in multiple sclerosis: a double-blind, placebo-controlled, crossover study
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Background: THC-CBD oromucosal spray (Sativex) has proven effective in reducing symptoms associated with spasticity in multiple sclerosis-MS. Little is known on the correlates of such effects on objective measures of spasticity (e.g. spinal H reflex) or corticospinal excitability.

Objectives: to assess clinical-neurophysiological correlates of Sativex on spasticity in MS.

Methods: Subjects with progressive MS (43, 20 females, EDSS 3.5-6) and clinical evidence of spasticity (modified Ashworth scale -MAS >1) were randomized to a 2-week titration plus 2-week stable dose of either active THC-CBD (Sativex) or placebo formulation, followed by a second cross-over cycle after 2-week washout, in a double-blind fashion. Clinical-neurophysiological measures were obtained before and at the end of each phase: MAS, spasticity and pain numeric rating scales-NRS, 10-mt walk, fatigue severity scale, bilateral soleus H/M ratio; Motor Evoked Potential amplitude at 120% threshold and 100% stimulator output, and intracortical inhibition/facilitation. Five subjects dropped 2 (during real treatment: 1 for dizziness, 1 subjective weakness; 3 on post-real washout: 1 acute pancreatitis, 1 to enter a rehabilitation program, 1 for family reasons), 4 were not analyzed due to positive THC urine testing on washout. The effect of treatment on changes from baseline was tested using paired Student’s t; treatment sequence effect was tested using repeated measures ANOVA, after verifying homogeneity of baselines between subgroups and over time.

Results: A significant treatment effect was found on MAS with higher improvement after real vs placebo (-1.51 ± 2.20 vs 0.16±2.55; p = 0.009); improvement in MAS and in NRS spasticity were significantly correlated (r 0.38, p 0.025). MAS responders (at least 20% improvement) were significantly more frequent during real treatment (41.2%) vs placebo (11.8%; χ²=5.56, p 0.018). Neurophysiological measures did not significantly differ according to treatment and were not significantly correlated cross-sectionally/longitudinally with clinical parameters, except for a trend between percent changes in MAS and in H/M (r 0.34, p 0.051).

Conclusions: Our findings confirm clinical beneficial effect of THC-CBD on MS spasticity. The lack of corresponding changes on corticospinal excitability and on the monosynaptic component of the stretch reflex point to the relevance of other spinal and supraspinal mechanisms involved in spasticity physiopathology.

LB1.4
The Genomic map of multiple sclerosis: over 45 novel susceptibility variants and translation of genetics to biology
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Background: Prior MS susceptibility maps are incomplete and have limited annotation.

Objectives: To identify MS susceptibility associations outside of the validated MS susceptibility loci and uncover new biological processes that drive the onset of MS.

Methods: A genome-wide discovery study of ~8 million SNPs in each of 14,802 multiple sclerosis (MS) cases and 26,703 controls was followed by a deep replication study of >80,000 SNPs in over 19,217 MS cases and 17,842 controls. The 4,716 SNPs with p< 0.05 in the discovery study are included. Functional evaluations of the results are conducted using DEPICT for pathway analysis, as well as analyses of immune cell RNA expression data from ImmVar and reference epigenomic maps from the Epigenome Roadmap and ENCODE projects.

Results: At the end of the replication study, over 45 new susceptibility variants are identified with 10 MHC and >150 non-MHC SNPs meet a threshold of genome-wide significance (p-value < 5 x 10^-8). Importantly, the depth of the replication effort identifies multiple, independent effects in many regions that were previously unresolvable: for example, the EVI5 region has up to four independent susceptibility variants. Uncovering this multiplicity of associations in certain regions is critical to our efforts to model the biological consequences of MS susceptibility variants and to develop predictive algorithms. With >150 independent susceptibility effects and a high resolution analysis of each locus in hand, we have created a reference map of MS susceptibility and now turn to the task of understanding the biology of MS susceptibility.

With the new MS map and multiple approaches to epigenomic annotation and functional evaluations, it is clear that non-TH1/Th17/Treg processes are important in the onset of MS. Myeloid, NK and CD8 cells are now implicated, and B and dendritic cell functions are suggested to be altered by MS variants. Leveraging RNA data from 405 subjects with purified CD4 T and monocytes, 29% of MS variants with RNA effects are unique to monocytes, which is now the same as for T cells (29%). Pathway analyses highlight enrichment of NK and B cell activation molecular networks in addition to T cell effects.
Conclusions: With over 45 additional susceptibility variants, we now present a comprehensive view of MS genetic susceptibility and provide a detailed map of proximal biological effects that identify new molecular pathways involved in the transition from health to MS.

L.B1.5
Co-associations of multiple sclerosis with schizophrenia and bipolar disorder: record linkage studies
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Background: Recent studies have highlighted similar risk factors for patients with schizophrenia, bipolar disorder and multiple sclerosis (MS), including immunogenetic associations, vitamin D deficiency and infections.

Objectives: We sought to test whether MS patients are at an increased risk of schizophrenia and bipolar disorder using a large database of hospital admissions in England (Hospital Episode Statistics).

Methods: We analysed a database of linked statistical records of hospital admissions and death certificates for the whole of England (1999-2011, population 52 million). Rate ratios for psychiatric disease were determined, comparing schizophrenia and bipolar disorder rates in a cohort of all people in England admitted with MS (N=82,176) and rates in a comparison cohort of patients admitted for various other mainly minor medical and surgical conditions (N=9,818,240). Rates were based on person-days, and were standardised by age (in five-year age groups), sex, calendar year of first recorded admission, region of residence, and quintile of patients’ Index of Multiple Deprivation score (as a measure of socioeconomic status) using the indirect method of standardisation.

Results: Out of 96 European non-MHC MSSNPs available in the study dataset, 69 (71.9%) associated in the same direction in African Americans as in Europeans, demonstrating an excess of concordance (binomial test p=1.1x10^{-5}). However, only 21 MSSNPs (21.9%) were formally replicated in African Americans (one-tailed test p<0.05), which was within the range of expectation considering the average statistical power of this dataset (binomial test p=0.8941). Among the 86 MS loci where European MSSNPs were not replicated or not available, eight regions included significant risk-tagging SNPs within the LD blocks of the European MSSNPs, suggesting occasional success in narrowing MS-associated loci. In addition seven novel candidate MS loci were identified, one of which (top SNP: rs2702177) on chromosome 1 was replicated in the independent sample set (replication one-tailed p=0.034, joint p=6.3x10^{-5}).

Conclusions: These results show a partial replication of European MS variants in African Americans, suggesting shared genetic contributions to MS risk. At the same time, in some MS-associated loci, different SNPs may more appropriately tag risk in non-European populations.

L.B1.6
Genetic determinants of multiple sclerosis in African Americans
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Background: While substantial progress has been made in the past decade to identify genetic variants associated with multiple sclerosis (MS) risk in populations of European descent, it remains unclear whether these variants also influence disease susceptibility in non-European populations with lower rates of prevalence.

Objectives: We assess whether the most updated non-MHC MS-associated single nucleotide polymorphisms (MSSNPs) discovered in individuals with European ancestry (Nature Genet, 2013; 45:1353-60) also influence susceptibility in African Americans. We also search for novel African American MS-associated loci.

Methods: With the ImmunoChip custom genotyping array, we analyzed 803 African American MS cases and 1,516 controls across a total of 130,15 SNPs that passed quality controls. An association analysis was conducted with rigorous adjustments for admixture and stratification, and the replication status for the European MSSNPs was evaluated. Significantly associated SNPs (p<10^{-5}) outside the established risk loci (1Mb centromeric and 1Mb telomeric from the designated MSSNPs) were defined as candidates tagging potential novel MS loci in African Americans and were further tested in an independent cohort consisting of 620 African American cases and 1,565 controls.

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L.B1.7
The life extension protein Klotho enhances remyelination following cuprizone-induced demyelination
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Background: While substantial progress has been made in the past decade to identify genetic variants associated with multiple sclerosis (MS) risk in populations of European descent, it remains unclear whether these variants also influence disease susceptibility in non-European populations with lower rates of prevalence.

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Conclusions: These results show a partial replication of European MS variants in African Americans, suggesting shared genetic contributions to MS risk. At the same time, in some MS-associated loci, different SNPs may more appropriately tag risk in non-European populations.
Background: The generation of new oligodendrocytes (OLs) and myelin are prominent features of white-matter lesions during early stages of MS. However, the majority of chronically demyelinated white matter lesions in MS brains show limited remyelination due to reduced recruitment of oligodendrocyte precursor cells (OPCs), failure of OPCs to generate OLs, and failure of OL maturation into myelin forming cells. Klotho was identified in 1997 as a gene mutated in the klotho mouse, which has an extremely shortened life span and displays multiple phenotypes resembling human premature-aging, while Klotho overexpressing mice live 30% longer than wild type (WT) mice. The decrease in Klotho in the aging brain white matter, at the same time when myelin deficits are also observed, implies a connection between Klotho expression and myelin integrity. Klotho knockout mice suffer from severe CNS hypomyelination. Furthermore, the exogenous addition of Klotho enhances OL maturation with increased expression of major myelin proteins, suggesting that Klotho plays an important role in OL maturation and myelination in the CNS.

Objectives: We aimed to assess whether overexpression of Klotho in mice enhances remyelination in the cuprizone model. A positive outcome would indicate that increasing Klotho expression could improve remyelination in demyelinating CNS diseases.

Methods: Ten weeks old Klotho overexpressing (KL-OE) mice and WT littermates were fed cuprizone (0.3% (w/w), which was mixed into chow pellets and was available ad libitum for 6 weeks. During these 6 weeks, the mice received daily injections of rapamycin to inhibit OPC proliferation. From week 7, cuprizone-containing chow was replaced with normal diet, rapamycin injections were discontinued and mice were allowed to remyelinate for 3 weeks. For histological analysis a specific region of corpus callosum (CC) was dissected and embedded in Epon. Two slides were stained with para-phenylenediamine (PPD). The average number of PPD stained myelinated axons per unit area was used for statistical analysis.

Results: The number of myelinated axons in KL-OE mice per unit length of the CC was 1.88 times higher (p = 0.019) than in WT animals. In addition, the density of myelinated axons per unit area increased by 1.76 fold (p = 0.026) in the KL-OE animals.

Conclusions: This is the first in vivo description for the role of Klotho as a regulator of remyelination in the white matter. Thus, small molecule Klotho-enhancing compounds could become novel therapeutics for myelin repair in MS.