(median change -780, -610 and -214 [5.25 mg/kg] and -534, -404 and -122 [3.5 mg/kg], respectively). Levels subsequently recovered slightly until redosing at Week 48, followed by a second (comparable) nadir. Lower CD4/CD8 ratios were due to preferential reductions in CD4 versus CD8 cells. Reductions were also observed in CD4 naïve and memory (CD45RA and CD45RO) T-helper cells, and to a lesser extent in CD8 naïve and memory cytotoxic T cells. B-cell (CD19) marker also revealed rapid reductions to nadir values at Weeks 9 and 16, followed by more marked recovery than observed with T-cells.
Conclusions: Treatment with cladribine tablets differentially affected CD4, CD8 and CD19 subpopulations. These findings may suggest a direct effect on T-cell function, humoral B cell activity and antigen-presenting cell activity, which may be involved in immune-mediated disease pathogenesis.

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P817

Early onset of effect of treatment with cladribine tablets for relapsing-remitting multiple sclerosis in the 96-week, phase III, double-blind, placebo-controlled CLARITY study

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Background: Cladribine is activated specifically in lymphocyte subtypes resulting in targeted and sustained immunomodulation, which provides the rationale for use of cladribine tablets as a short-course annual treatment in multiple sclerosis (MS). We investigated the time of onset of treatment effect with cladribine tablets relative to placebo, in the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study in patients with relapsing-remitting MS (RRMS).
Methods: Patients with RRMS (McDonald criteria; Expanded Disability Status Scale [EDSS] score 0-5.5) were randomised 1:1:1 to cladribine tablets (cumulative dose of 5.25 or 3.5 mg/kg), or matching placebo. Cladribine tablets were given in short courses (once daily for 4-5 days) in 4 or 2 consecutive months (28-day periods) in the first 48 weeks, then 2 short courses at Weeks 48 and 52 (for both groups). Qualifying relapses were evaluated serially throughout the study, and MRI parameters (T1-Gd+, active T2, and combined unique [CU] lesions per patient per scan) were evaluated at 24, 48 and 96 weeks post-randomisation.
Results: The ITT population comprised 456, 433 and 437 patients randomised to 5.25 mg/kg, 3.5 mg/kg or placebo groups, respectively. Differences in qualifying relapse rate between active treatment groups vs. placebo were apparent as early as 4 weeks post first treatment course (5.25 and 3.5 mg/kg vs. placebo: 0.27 and 0.23 vs. 0.42, respectively). Statistically significant differences for all three MRI parameters were also evident at the first assessment (mean number of lesions per patient per scan in the 5.25 and 3.5 mg/kg vs. placebo groups at Week 24: 0.07 and 0.07 vs. 0.97 for T1 Gd+ lesions, 0.33 and 0.45 vs. 1.59 for active T2 lesions, and 0.38 and 0.49 vs. 1.91 for CU lesions, respectively).
Conclusions: Treatment with cladribine tablets resulted in early onset of effect in clinical and MRI outcomes. Taken together with the favourable tolerability and safety results observed in this study (reported elsewhere), these findings provide strong support for annual short-course treatment with cladribine tablets in patients with MS.

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P818

Cladribine tablets produce sustained improvements in relapsing-remitting multiple sclerosis in the 96-week, phase III, double-blind, placebo-controlled CLARITY study

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Background: Cladribine is activated specifically in lymphocyte subtypes resulting in targeted and sustained immunomodulation, which provides the rationale for use of cladribine tablets as a short-course annual treatment in multiple sclerosis. Here we investigated multiple clinical and MRI efficacy parameters over time to assess the persistence of treatment effect with cladribine tablets relative to placebo, from the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study in patients with RRMS.
Methods: Patients with RRMS (McDonald criteria; Expanded Disability Status Scale [EDSS] score 0-5.5) were randomised 1:1:1 to cladribine tablets (cumulative dose of 5.25 or 3.5 mg/kg), or matching placebo. Cladribine tablets were given in short courses (once daily for 4-5 days) in 4 or 2 consecutive months (28-day periods) in the first 48 weeks, then 2 short courses at Weeks 48 and 52 (both groups). Efficacy endpoints included the annualised qualifying relapse rate (primary), the proportion of relapse-free patients, and MRI activity measures vs. placebo (T1-Gd+, active T2, and combined unique [CU] lesions/patient/scan).
Results: The ITT population comprised 456, 433 and 437 patients randomised to 5.25 mg/kg, 3.5 mg/kg or placebo groups, respectively. In the cladribine 5.25 mg/kg, 3.5 mg/kg and placebo groups 95.6%, 93.8% and 66.6% patients, respectively, were T1-Gd+ lesion-free at Week 24; 94.1%, 94.2% and 77.1% patients were T1-Gd+ lesion-free at Week 96; 78.1%, 76.2% and 49.7% patients were T2 lesion-free at Week 24; and 82.2%, 82.2% and 61.6% patients were T2 lesion-free at Week 96. The proportions of patients that were relapse-free in the cladribine 5.25 mg/kg, 3.5 mg/kg and placebo groups were, 91.2%, 92.1% and 82.8%, respectively, at Week 24; 86.0%, 85.9% and 74.1% at Week 48; and 78.9%, 79.7% and 60.9% at Week 96. Reductions in relapse rate and MRI lesion count were also observed at these time points.
Conclusions: Treatment with cladribine tablets resulted in sustained, consistent benefits on clinical and MRI outcomes. The early beneficial effects across several MRI parameters of disease activity were sustained at Week 96, 44 weeks after the last treatment dose. Taken together with the rapid improvement and favourable tolerability and safety results observed in this study (reported elsewhere), these findings provide strong support for annual short-course treatment with cladribine tablets in patients with MS.

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P819

Glatiramer acetate 20mg subcutaneous twice-weekly versus daily injections: results of a pilot, prospective, randomised, and rater-blinded clinical and MRI 2-year study in relapsing-remitting multiple sclerosis

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Objective: The optimal dose of glatiramer acetate (GA) in RRMS remains unknown. We have previously shown that GA administered on alternate days appears to be as effective as daily GA. There is considerable interest in studying a more patient friendly dosing regimen of GA that may be as efficacious and better tolerated than daily GA.
Methods: We conducted a prospective, randomized, rater-blinded study to compare the clinical and MRI outcomes of GA 20 mg SC administered twice a week to GA administered daily. RRMS patients

receiving GA 20 mg SC daily for at least one year were randomized to either continue in the same fashion or switch to GA 20 mg SC twice weekly. Clinical assessments including EDSS were performed every 6 months and brain MRI scans were obtained at baseline and month 24.
Results: 48 RRMS were randomized into two equal groups of either GA 20 mg SC daily or GA 20 mg SC bi-weekly. Both groups were well-matched for clinical demographics and MRI features at baseline. All patients remained in the study for the entire duration. After two years, the annualized relapse rate, mean EDSS, proportion of relapse-free patients, and the proportion of patients without disease progression were similar in the two groups. Brain MRI also did not demonstrate any significant differences in T2W or T1W lesion, or in the percentage brain volume change between the two groups. However, the incidence of lipoatrophy, local injection site reactions, and immediate-post injection systemic reactions were significantly lower in the GA twice-weekly group. Detailed analysis of the results will be presented.
Conclusion: This study provides further evidence that GA administered less frequently than daily may be as efficacious and better tolerated than GA administered daily. This may have a significant impact on improving compliance and tolerability while maintaining the desired immunomodulating effect of GA. Furthermore, this may also have a favorable economic impact. Larger, multi-center studies are warranted to confirm our findings and address a critical need of the MS patient community.

P820

Conversion of new inflammatory lesions to persistent black holes in patients with relapsing multiple sclerosis participating in a phase 2 trial of DNA vaccine encoding myelin basic protein (BHT-3009)

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Background: There is evidence that persistent T1-hypointense lesions, (persistent black holes, PBH) correlate better than T2 lesions with irreversible tissue damage, axonal loss and disability progression, In a Phase 2 Trial of a DNA Vaccine encoding Myelin Basic Protein (BHT-3009) in relapsing remitting multiple sclerosis (RRMS) the median percentage change in T1-hypointense lesion volume was -3.76% in the low dose treatment group compared with 0% for placebo (p=0.08) (Garren et al, Ann. Neurol. 2008).
Objective: To determine the evolution of new inflammatory lesions to PBH and examine changes in lesion characteristics, such as size and degree of hypointensity, in BHT-3009 treated patients compared with placebo.
Methods: A post-hoc, rater-blinded evaluation of MRI scans collected during year 1 of the phase 2 trial was performed in RRMS patients, randomly assigned to receive placebo 0.5mg BHT-3009 or 1.5mg BHT-3009. New and enlarging lesions (candidate lesions: CL) were selected at the first and second on-study MRI (month 2 and 4) and were tracked on month 12 for T1-signal evolution. Lesions hypointense on T1-weighted pre contrast images of months 2 and 4 were considered acute black holes (ABH) and lesions not enhancing and hypointense on month 12 were considered PBH. Size and degree of hypointensity of ABH and PBH were also determined.
Results: 650 CL were found in 155 of 267 patients in the per protocol population, 180 CL in 50/87 patients on placebo, 239 CL in 57/96 patients on 0.5 mg BHT-3009 and 231 CL in 48/84 patients on 1.5 mg. 462/650 CL were Gd enhancing. Average proportions of CL evolving into PBH were 50/180 (0.28) for placebo, 55/239 (0.23) for low dose and 49/231 (0.21) for high dose treated patients. The mean proportion of CL per patient developing into PBH was 0.25 in the two treatment groups (0.28 in the low dose and 0.21 in the high dose treatment group) and 0.29 in the placebo arm.
Conclusions: In this exploratory analysis a trend to lower proportions of CL and CL per patient evolving into PBH in treated patients compared with placebo was detected.

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Immunosuppression

P821

Cancer risk in a MS population treated with immunosuppressants

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Background: Use of the immunosuppressant drugs (mitoxantrone, methotrexate, azatioprine, etc..) are linked to cancer risk.
Objective: we evaluated the presence of cancer in our multiple sclerosis (MS) cohort.
Methods: In a population of 616 MS patients, we followed up 73 patients, previously treated (43) or actually in treatment (30) with immunosuppressants: 10 with mitoxantrone (MTX) until the maximum cumulative dose, 49 with azatioprine (AZA), 2 with methotrexate (MTH), 2 with ciclofosfamide (CTX). 10 patients received more than 1 immunosupressant. The mean follow up period since first drug administration was 104.9±62 months (min: 32 months, max: 348 months). Mean treatment period was 65±51 months (min: 12 months, max: 312 months).
Results: One patient treated with CTX developed an uterine cancer two years after CTX withdrawal. The age at cancer diagnosis was 26 years. No cancer was developed in patients treated with MTX, AZA and MTH.
Conclusion: The prevalence rate of uterine cancer in our MS cohort (1.3%) was higher than in the general population (0.01%).

P822

ASPIRE (Azathioprine Secondary Progressive Interferon treated patients Randomised Evaluation) study: 2-year double-blind and 1-year open, randomised, multicentre, pilot study. Multiple Sclerosis Functional Composite (MSFC) and magnetic resonance data

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Combination therapy has been routinely used in autoimmune disease and, in the last years, even for multiple sclerosis (MS). The aim of the study was to assess the efficacy, safety and tolerability of azathioprine (AZA) when added to IFN β-1b in patients with secondary progressive MS who had an incomplete response to IFN β-1b. The study provides an overall evaluation of illness stabilization, with the primary endpoint being the variation in MS functional composite (MSFC) over the 2-year double-blind and 1-year open treatment period. Secondary endpoints were Expanded Disability Status Scale (EDSS) variability, quality of life (QOL) effects according to the MSQOL-54 Instrument, magnetic resonance (MRI) data, neutralizing antibodies and cytochine evaluations.
85 patients completed randomization, 42 with azathioprine and IFN β-1b and 43 with placebo and IFN β-1b treatment. At the end of 36 months 45 patients completed the study (23 and 21 respectively), resulting in an high number of drop-outs. MSQOL-54 and safety data analyzed showed a slight worsening in AZA group.
MSFC data were compared to basal data and showed a slight worsening at 36 months in azathioprine group in comparison to placebo.
MRI data showed a reduction in enhancing lesions only at 12 months of treatment in AZA group, while there was not consistent variation in the two groups at 24 and 36 months.