Reduced Rate of Brain Atrophy in Patients With PPMS Receiving Ocrelizumab Earlier and Continuously Versus Those Initiating Ocrelizumab Later: Results of ORATORIO 5-Year Follow-Up

Douglas L. Arnold1,2, Gavin Giovannoni3, Hans-Peter Hartung4, Stephen L. Hauser5, Ludwig Kappos6, Xavier Montalban7,8, Jerry S. Wolinsky9, Karine Coutant19, Kalpesh Prajapati10, Fabian Model10, Lahar Mehta11, Anthony Traboulsee12

1McGill University, 2NeuroRx Research, 3Queen Mary University of London, 4Department of Neurology, UKD, Center of Neurology and Neuropsychiatry and LVR-Klinikum, Heinrich Heine University Duesseldorf, 5University of California San Francisco, 6University Hospital Basel, University of Basel, 7Division of Neurology, University of Toronto, 8Vall d’Hebron University Hospital, 9McGovern Medical School, UTHealth, 10F. Hoffmann-La Roche Ltd, 11Genentech, Inc., 12University of British Columbia

Objective:
To assess the efficacy of switching to or maintaining ocrelizumab therapy on brain atrophy in the open-label extension (OLE) of the ORATORIO Phase III trial (NCT01194570) in primary progressive multiple sclerosis (PPMS) through 5 years of follow-up.

Background:
Prior analyses of ORATORIO and ORATORIO OLE demonstrated not only that ocrelizumab reduced the risk of 24-week confirmed disability progression versus placebo in the double-blind period (DBP) by 25% (p=0.037), but also had a consistent and sustained treatment benefit over 5 years of DBP/OLE favoring earlier and continuous treatment with ocrelizumab. For whole brain volume (WBV), a 17.5% (p=0.02) relative reduction of brain volume loss from Week 24 to Week 120 was demonstrated in the DBP (secondary endpoint).

Design/Methods:
At the end of the ORATORIO DBP (after 132–216 weeks on-treatment), patients remained on randomized treatment until the trial outcome was ascertained. Patients entered the OLE ~3–9 months after DBP cut-off and either continued ocrelizumab or switched from placebo to ocrelizumab. Changes in WBV are reported for Week 120 (last MRI assessment during DBP) and for Week 96 of the OLE (~240–336 weeks after randomization).

Results:
At Week 120, the percentage change from baseline in WBV was –1.472%/–1.304% for placebo/ocrelizumab (Δ=0.168%; p=0.085). For Week 96 of the OLE, the corresponding percentage change from original study baseline was –2.960%/–2.595% (Δ=0.366%; p=0.043). Consistent trends were observed for cortical gray and white matter volumes.

Conclusions:
ORATORIO uniquely demonstrates a long-term reduction in brain atrophy with continuous ocrelizumab versus placebo-ocrelizumab switch in patients with PPMS, as measured over 5 years of DBP/OLE follow-up. Reduced rates of brain atrophy were consistently observed for whole brain, cortical gray and white matter volume in patients with PPMS receiving ocrelizumab earlier and continuously than when initiation of ocrelizumab was delayed.