Ocrelizumab Treatment Effect on Upper Limb Function in PPMS Patients with Disability: Subgroup Results of the ORATORIO Study to Inform the ORATORIO-HAND Study

Gavin Giovannoni\textsuperscript{1}, Laura Airas\textsuperscript{2}, Riley Bove\textsuperscript{3}, Alexey Boyko\textsuperscript{4}, Gary Cutter\textsuperscript{5}, Jeremy Hobart\textsuperscript{6}, Jens Kuhle\textsuperscript{7}, Jiwon Oh\textsuperscript{9}, Carmen Tur\textsuperscript{9}, Monika Garas\textsuperscript{10}, Fabian Model\textsuperscript{10}, Marianna Manfrini\textsuperscript{9}, Jerry S Wolinsky\textsuperscript{11}

\textsuperscript{1}Queen Mary University of London, \textsuperscript{2}University of Turku, \textsuperscript{3}Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, \textsuperscript{4}Department of Neurosurgery and Medical Genetics, Pirogov Russian National Research Medical University, Yusupov Hospital, \textsuperscript{5}University of Alabama At Birmingham, \textsuperscript{6}University of Plymouth, \textsuperscript{7}Neurologic Clinic and Policlinic, Departments of Medicine, Biomedicine and Clinical Research, University Hospital Basel, \textsuperscript{8}St. Michael’s Hospital, University of Toronto, \textsuperscript{9}University College London, \textsuperscript{10}F. Hoffmann-La Roche Ltd, \textsuperscript{11}McGovern Medical School, UTHealth

Objective:
To assess ocrelizumab efficacy on upper limb function in more disabled/older patients with primary progressive multiple sclerosis (PPMS) from the Phase III ORATORIO study (NCT01194570) to inform the design of the Phase IIIb ORATORIO-HAND study.

Background:
Ocrelizumab demonstrated efficacy versus placebo in reducing upper limb dysfunction (9-Hole Peg Test [9HPT]) in ORATORIO (Expanded Disability Status Scale [EDSS] \(\leq 6.5\)). Ocrelizumab benefit in more disabled PPMS patients ineligible for inclusion in ORATORIO would fulfill an unmet need.

Design/Methods:
ORATORIO PPMS patients (N=732; EDSS 3.0–6.5; age 18–55 years) were randomized (2:1) to ocrelizumab or placebo for \(\geq 120\) weeks and until a pre-specified number of EDSS progression events occurred. Efficacy of ocrelizumab in preventing progression of upper limb function as measured by 12-week confirmed 20% worsening in 9HPT (average of both hands) was investigated in baseline subgroups: EDSS \(\geq 6.0\) (N=220), age >45 years (N=384), and 9HPT time \(\leq 25\) seconds (N=434).

Results:
Ocrelizumab reduced upper limb disability progression in more disabled/older PPMS patients. Risk reductions versus placebo in 9HPT progression were similar in patients with baseline EDSS score <6.0 and \(\geq 6.0\) (40% versus 38%, \(p=0.92\)), and baseline 9HPT time \(\leq 25\)s and >25s (49% versus 44%, \(p=0.82\)). Progression events mainly occurred in patients with 9HPT >25s versus \(\leq 25\)s (placebo: 34.3% vs 17.8%; ocrelizumab: 21.5% vs 9.9%); a weak trend for greater efficacy in patients \(\leq 45\) years versus >45 years was observed (\(p=0.29\)).

Conclusions:
ORATORIO-HAND is designed to further investigate the efficacy of ocrelizumab on upper limb function. Based on the 9HPT progression rates observed in ORATORIO, 1000 eligible patients (EDSS 3.0–8.0, age 18–65 years, 9HPT >25s), randomized (1:1) to ocrelizumab or placebo for \(\geq 120\) weeks (until a pre-specified number of progression events occur) will enable the assessment of ocrelizumab efficacy on confirmed 9HPT progression (primary endpoint). Screening will begin Q1 2019.