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PB1938 4WHIM: EVALUATING MAVORIXAFOR, AN ORAL CXCR4 ANTAGONIST, IN PATIENTS WITH WHIM SYNDROME VIA A GLOBAL PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED TRIAL WITH OPEN-LABEL EXTENSION

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background: Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome is a primary immunodeficiency characterized by retention of leukocytes in the bone marrow (myelokathexis), resulting in neutropenia, leukopenia, and in some cases hypogammaglobulinemia. WHIM syndrome is classically caused by gain-of-function mutations in *CXCR4,* with the resulting hyperactivation of the CXCR4-CXCL12 pathway. Patients diagnosed with WHIM syndrome have a heterogeneous phenotype yet typically experience recurrent sinopulmonary infections and unusual susceptibility to human papillomavirus (HPV), resulting in predisposition to warts and malignancy. There are no approved medications for WHIM syndrome. To date, all management strategies are symptomatic only, failing to address the underlying mechanism of WHIM syndrome, and are mostly ineffective for HPV infections. Mavorixafor is an investigational, oral CXCR4 antagonist that directly inhibits CXCR4-enhanced signaling in WHIM syndrome pathogenesis, and has been shown to increase white blood cell counts, decrease annualized infection rate, and reduce cutaneous warts in an open-label phase 2 clinical trial (NCT03005327) for patients with WHIM syndrome.

Aims: Here, we describe the design, baseline characteristics, and status of a global phase 3, double-blind, placebo-controlled, randomized trial (4WHIM, NCT03995108) with open-label extension evaluating the safety and efficacy

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of mavorixafor in patients with WHIM syndrome.

Methods: Eligibility for enrollment included age ≥12 years, diagnosis of WHIM syndrome, confirmed *CXCR4* mutation, and absolute neutrophil count (ANC) ≤400 cells/μL without clinical evidence of active systemic infection. Patients were randomized in a 1:1 ratio to receive mavorixafor (adults, 400 mg; adolescents weighing ≤50 kg, 200mg; adolescents weighing >50 kg, 400mg) or placebo orally once daily. The primary endpoint is defined as number of hours above ANC threshold (500 cells/μL) over a 24-hour period, assessed every 3 months for 52 weeks. Secondary endpoints include the composite end point of infection and warts, infection rates and severity, change from baseline in cutaneous warts, and number of hours above absolute lymphocyte count (ALC) of ≥1000 cells/μL over a 24-hour period, and patient-reported quality-of-life assessment using age-appropriate questionnaires.

Results: Enrollment for the trial has been completed, with a total of 31 patients enrolled globally. Demographics of the enrolled population include: 48% adolescents (age 12-18 years), 42% male, 71% with warts, 81% with nonsense *CXCR4* mutations, and 19% with frameshift *CXCR4* mutations. Mean and median ANC and ALC at screening visit were 220 cells/μL and 180 cells/μL, and 515 cells/μL and 440 cells/μL respectively.

Summary/Conclusion: 4WHIM is the first double-blind, placebo-controlled, randomized trial in patients with WHIM syndrome; top-line clinical results are expected in Q4 2022. The study enrolled children (aged ≥ 12 years) and adults, all with genetically confirmed *CXCR4* variants consisting of both nonsense and frameshift mutations. The patients all presented with severe neutropenia and lymphopenia and a high percentage of the patients had warts. This study represents an important next step in the development of the novel, orally bioavailable, targeted therapy mavorixafor for the treatment of patients with WHIM syndrome.

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