4WHIM: Evaluating the Oral CXCR4 Antagonist Mavorixafor in Patients With WHIM Syndrome via a Global, Phase 3, Randomized, Placebo-Controlled Trial With Open-Label Extension

David C. Dale,[1] Laia Alsina,[2] Antoine Azar,[3] Raffaele Badolato,[4] Yves Bertrand,[5] Navid Ezra,[6] Henrik Hasle,[7] Hyoung Jin Kang,[8] Sorena Kiani-Alikhan,[9] Taco Kuijpers,[10] Alexander Kulagin,[11] Daman Langguth,[12] Carina Levin,[13] Olaf Neth,[14] Jane Peake,[15] Anna Shcherbina,[16] Teresa K. Tarrant,[17] Matthias G. Vossen,[18] Christian A. Wysocki,[19] Andrea Belschner,[20] Diego Cadavid,[20] Yanping Hu,[20] Honghua Jiang,[20] Richard MacLeod,[20] Weihua Tang,[20] Michael Tillinger, [20] Jean Donadieu[21]

[1]Department of Medicine, University of Washington, Seattle, WA, USA; [2]Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu Barcelona, Institut de Recerca Sant Joan de Déu, Barcelona, Spain; [3]Division of Allergy and Clinical Immunology, Johns Hopkins University, Baltimore, MD, USA; [4]Department of Pediatrics, Angelo Nocivelli Institute of Molecular Medicine, University of Brescia, Brescia, Italy; [5]Institute of Pediatric Hematology and Oncology (IHOPe), Civil Hospital of Lyon, Lyon, France; [6]California Dermatology Institute, Thousand Oaks, CA, USA; [7]Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark; [8]Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Cancer Research Institute, Wide River Institute of Immunology, Seoul National University Children's Hospital, Seoul, Korea; [9]Department of Immunology, Barts Health NHS Trust, London, United Kingdom; [10]Department of Paediatric Immunology, Rheumatology and Infectious Diseases, Amsterdam University Medical Center, Amsterdam, The Netherlands; [11]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russia; [12]Immunology Department, Sullivan Nicolaides Pathology Auchenflower, Queensland, Australia; [13]Pediatric Hematology Unit, Emek Medical Center, Afula and the Ruth and Bruce Rappaport Faculty of Medicine Technion, Haifa, Israel; [14]Pediatric, Infectious Diseases, Rheumatology and Immunology Department, Hospital Virgen del Rocío, Institute of Biomedicine of Sevilla (IBiS), Seville, Spain; [15]Department of Allergy and Immunology, Queensland Children's Hospital, University of Queensland, South Brisbane, Queensland, Australia; [16]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia; [17]Division of Rheumatology and Immunology, Department of Medicine, Duke University, Durham, NC, USA; [18]Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Medical University of Vienna, Vienna, Austria; [19]Division of Allergy and Immunology, Departments of Pediatrics and Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA; [20]X4 Pharmaceuticals, Boston, MA, USA; [21]Service d'Hémato-Oncologie Pédiatrique, Hopital Trousseau, Paris, France

Background

- Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome is a primary immunodeficiency classically caused by gain-of-function mutations in *CXCR4*, leading to dysregulated immune cell maturation and trafficking. This causes retention of leukocytes in the bone marrow (myelokathexis), resulting in neutropenia, leukopenia, and sometimes, hypogammaglobulinemia.[1-3]
- Patients with WHIM syndrome experience recurrent sinopulmonary infections and unusual susceptibility to human papillomavirus (HPV), causing predisposition to warts and malignancy.[1-3]
- Currently, there are no approved treatments for WHIM syndrome. All management strategies are symptomatic only, do not address the underlying mechanism of WHIM syndrome, and are not effective for HPV infections.[4]
- Mavorixafor is an investigational, oral CXCR4 antagonist that directly inhibits CXCR4-enhanced signaling in WHIM syndrome pathogenesis. It has been shown to increase white blood cell counts, decrease annualized infection rate, and reduce cutaneous warts in patients with WHIM syndrome in an open-label phase 2 clinical trial (NCT03005327).[4]
- Here, we describe the design, key baseline characteristics, and status of 4WHIM, a global, phase 3, randomized, double-blind, placebo-controlled, trial (NCT03995108) with open-label extension evaluating the safety and efficacy of mavorixafor in patients with WHIM syndrome.[5]

4WHIM Eligibility and Baseline Characteristics

4WHIM Is a Global, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Trial

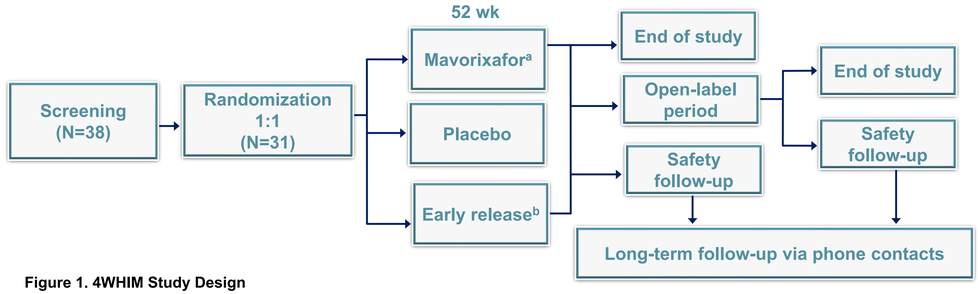

Figure 1. 4WHIM Study Design
[a]Adult patients will receive 400 mg orally daily; adolescent patients aged 12-17 years weighing >50 kg will receive 400 mg orally daily, while those weighing ≤50 kg will receive 200 mg orally daily. [b]Participants suffering from severe infections may be early released and join the open-label extension if they meet prespecified conditions as determined by an independent adjudication committee.
WHIM, Warts, Hypogammaglobulinemia, Infections, Myelokathexis.

Key Eligibility Criteria for Enrollment in the WHIM Phase 3 Clinical Trial

- Patients aged ≥12 years with a clinical diagnosis of WHIM syndrome
- Genotype-confirmed *CXCR4* mutation consistent with WHIM syndrome phenotype
- Absolute neutrophil count (ANC) ≤400 cells/μL during screening without clinical evidence of infection

Primary and Secondary End Points for WHIM Phase 3 Clinical Trial

Primary End Point

- Number of hours above ANC threshold (500 cells/μL) over a 24-hour period, assessed every 3 months for 52 weeks

Key Secondary End Points

- Time above threshold for absolute lymphocyte count (TAT_{ALC}) ≥1000 cells/μL over a 24-hour period assessed every 3 months for 12 months
- Composite clinical efficacy end point for mavorixafor based on total infection score and total wart change score
- Total wart change score for mavorixafor based on central, blinded, independent review of 3 target skin regions
- Total infection score for mavorixafor based on number and severity of infections adjudicated by blinded, independent review

4WHIM Is Fully Enrolled With 31 Patients

Geographic Distribution of Patients Enrolled in WHIM Phase 3 Clinical Trial

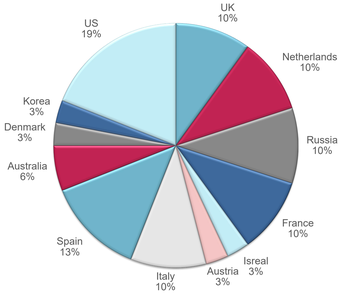

Figure 2. 31 patients enrolled from 12 countries worldwide.

Clinical and Mutational Status of Patients Enrolled in WHIM Phase 3 Clinical Trial

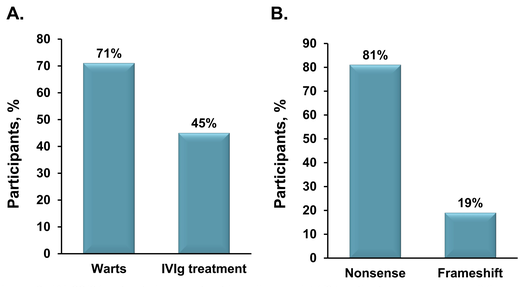

Figure 3. (A) 22/31 patients had warts at baseline, and 14/31 patients were receiving IVIg treatment. **(B)** 25/31 had nonsense mutations of *CXCR4*. IVIg, intravenous immunoglobulin G.

Sex and Age Distribution of Patients Enrolled in WHIM Phase 3 Clinical Trial

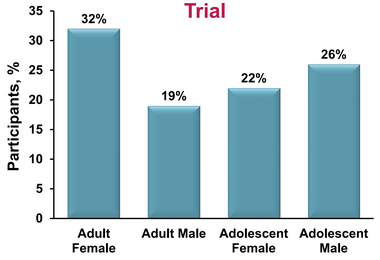

Figure 4. 18 females and 13 males enrolled in the study. 10/31 were adult females, 6/31 were adult males, 8/31 were adolescent females, and 7/31 were adolescent males.

Dose Allocation for Patients Enrolled in WHIM Phase 3 Clinical Trial

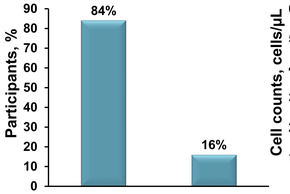

Figure 5. 26/31 enrolled patients will receive 400 mg of mavorixafor.

ANC and ALC at Screening

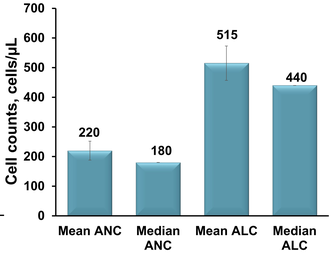

Figure 6. Mean and median ANC and ALC counts at screening. ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

Conclusions

- **1st** — This is the first double-blind, placebo-controlled, randomized trial in patients with WHIM syndrome
- 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 mavorixafor, an orally bioavailable targeted therapy for WHIM syndrome
- Top-line clinical results are expected in Q4 2022

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