Genetics in Medicine Open (2026) ■, 104398

ELSEVIER

Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

ACMG THERAPEUTICS BULLETIN

Mavorixafor (Xolremdi) for individuals with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

Mark Dulchavsky[1], Xiao Peng[2], Mark Hannibal[1], Harry Lesmana[3,4]; on behalf of the ACMG Therapeutics Committee[5,*]

Disclaimer: This therapeutics bulletin is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. It is reflective of information available at the time of acceptance to publication and may not include newer updates that have since become available. Adherence to this therapeutics bulletin is completely voluntary and does not necessarily assure a successful medical outcome. This therapeutics bulletin should not be considered inclusive of all proper procedures, treatments, and tests or exclusive of other procedures, treatments, and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure, treatment or test, clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen.

Clinicians are encouraged to document the reasons for the use of a particular procedure, treatment, or test, whether or not it is in conformance with this therapeutics bulletin. Clinicians also are advised to take notice of the date this therapeutics bulletin was accepted to publication, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures. Where individual authors are listed, the views expressed may not reflect those of authors' employers or affiliated institutions.

The mention of any therapeutic approach, product, or sponsor in this therapeutics bulletin does not constitute endorsement or sponsorship by the American College of Medical Genetics and Genomics (ACMG). The ACMG does not endorse or recommend any specific therapeutic approach or product mentioned in this therapeutics bulletin.

ARTICLE INFO

Article history:
Received 2 April 2026
Accepted 2 April 2026
Available online xxxx

Keywords:
CXCR4
Immunodeficiency
Mavorixafor
Neutropenia
WHIM syndrome

Background

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an autosomal dominant inborn error of immunity caused by pathogenic gain-of-function variants in CXC chemokine receptor 4 (*CXCR4*) (HGNC:2561) with an estimated incidence of 0.2 per million births.[1–3] *CXCR4* variants that result in hyperactive signaling from this receptor cause retention of immune cells in the bone marrow with peripheral neutropenia and lymphopenia, termed myelokathexis.[2] Despite peripheral cytopenias, individuals with WHIM

This article was a work product of the Therapeutics Committee of the ACMG, and the Article Publishing Charge (APC) was waived. No industry sponsorship was received for this work.

The Board of Directors of the American College of Medical Genetics and Genomics approved this bulletin on 13 March 2026.

*Correspondence: ACMG. *Email address:* documents@acmg.net

Affiliations are at the end of the document.

doi: https://doi.org/10.1016/j.gimo.2026.104398

syndrome do not commonly suffer from invasive infections characteristic of other chronic neutropenic disorders.[4,5] However, they do develop hypogammaglobulinemia and thus show increased susceptibility to recurrent respiratory infections, especially from encapsulated bacteria (such as *Streptococcus pneumoniae* or *Haemophilus influenzae*).[3,4,6] There is also susceptibility to skin infections with molluscum contagiosum and, more concerningly, risk for virally induced malignancy from human papilloma virus and Epstein-Barr virus infections.[6–8] A significant subset of patients develops broken immune tolerance, leading to systemic and organ-specific complications from adaptive immune dysregulation and autoinflammation.[6] Some patients may also present with congenital anomalies at birth.[4,6]

Management and Treatment

There are no consensus guidelines for management of WHIM syndrome. Antimicrobial prophylaxis and immunoglobulin replacement therapy can be considered in persons with recurrent infections.[4,5] The use of granulocyte colony-stimulating factor (G-CSF) is controversial because many WHIM affected individuals are able to mount a granulocytic response to infections, but it can be used for patients that are unable to normalize neutrophil counts.[5] Hematopoietic stem cell transplantation can be curative but is rarely pursued because of the disease's chronicity, variable phenotypic severity, and transplant-related risks; most notably infectious complications.[9]

Newly Approved Therapy

Indication and approved treatment population

Mavorixafor (Xolremdi) is an orally bioavailable small-molecule CXCR4 antagonist administered once daily. On April 29, 2024, it received FDA approval for treatment of individuals aged 12 years and older with WHIM syndrome. Approval was granted under priority review, fast track, rare pediatric disease, and orphan drug designations.[10]

Mechanism of action

Pathogenic *CXCR4* variants disrupt normal receptor autoregulation by impairing endocytosis and intracellular recycling, resulting in persistent surface expression and constitutive signaling of the receptor. This leads to abnormal retention of hematopoietic cells within the bone marrow microenvironment. Mavorixafor is a selective CXCR4 antagonist that inhibits this excessive CXCR4 signaling, thus promoting mobilization and egress of neutrophils and lymphocytes into peripheral circulation.[11]

Outcomes and efficacy

Across phase 1-3 clinical trials, mavorixafor has consistently shown the ability to induce leukocytosis among healthy volunteers and individuals with WHIM syndrome.[11–13] The pivotal randomized, placebo-controlled phase 3 trial (NCT03995108) includes 14 participants with WHIM syndrome treated with mavorixafor.[12] Participants in the mavorixafor treatment group spent less time severely neutropenic by an average of 12.3 hours (95% CI = 7.2-17.4) and lymphopenic by an average of 11.3 hours (95% CI = 7.5-15.0) than those in the placebo arm when measured over 24 hours over the 52-week study period. The treatment group experienced a 40% reduction (95% CI = 20%-40%) in the annualized rate of infections (1.7 per year) compared with the placebo group (4.2 per year). Subjective improvement in cutaneous warts was also reported in multiple studies, although standardized clinical scoring tools did not demonstrate statistically significant differences in this trial.[12,13]

Adverse effects and toxicity

Common treatment-related adverse events include thrombocytopenia, pityriasis or other skin rashes, rhinitis, epistaxis, vomiting, and dizziness.[11,12] Three participants in the phase 3 trial treatment group developed thrombocytopenia under various clinical circumstances, although the authors report this as unrelated to treatment because most participants experienced an increase in platelet count upon starting mavorixafor.[12] Mavorixafor may also induce QT-prolongation. Mavorixafor does not carry any boxed warnings for prescribers.

Additional Considerations

Mavorixafor represents the first FDA-approved therapy for WHIM syndrome and expands the landscape of targeted therapies for genetically driven immune disease. Interpretation of efficacy and safety data is limited by the small sample sizes inherent to rare disease clinical trials. There is currently insufficient evidence to guide the concurrent use of mavorixafor with other commonly used therapies, such as exogenous immunoglobulin or G-CSF. Roughly half of the treatment and placebo group in the phase 3 trial for mavorixafor underwent regular immunoglobulin supplementation throughout the trial period, and several participants received G-CSF for intercurrent illness or prophylaxis.

A rare phenocopy of WHIM syndrome is caused by biallelic loss-of-function in *CXCR2* (HGNC:6027), which encodes a chemokine receptor that promotes cellular egress from the bone marrow upon activation.[3] Although mavorixafor has general approval for WHIM syndrome, limited preclinical evidence suggests that it may be less effective in the setting of *CXCR2*-mediated disease.[14] Caution is

warranted when considering mavorixafor as a therapeutic agent in this subpopulation.

CXCR4 antagonism could have broader application among other immune cell cytopenias, and mavorixafor is currently under investigation as a therapeutic agent for chronic and congenital neutropenic conditions (NCT04154488).

Conflict of Interest

All workgroup members receive salary for providing clinical services that may be relevant to the content of this document in either the laboratory or patient care setting at their listed affiliations.

Affiliations

[1]Division of Genetics, Metabolism and Genomic Medicine, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI; [2]Division of Genetics, Department of Pediatrics, Children's Hospital at Montefiore, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; [3]Department of Medical Genetics and Genomics, Cleveland Clinic Lerner College of Medicine, Cleveland, OH; [4]Case Western Reserve University, Cleveland, OH; [5]American College of Medical Genetics and Genomics, Bethesda, MD

References

1. Beaussant Cohen SB, Fenneteau O, Plouvier E, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. *Orphanet J Rare Dis*. 2012;7(1):71. http://doi.org/10.1186/1750-1172-7-71
2. Zuelzer WW. "Myelokathexis"–a new form of chronic granulocytopenia. Report of a case. *N Engl J Med*. 1964;270(14):699-704. http://doi.org/10.1056/nejm196404022701402
3. Heusinkveld LE, Majumdar S, Gao JL, McDermott DH, Murphy PM. WHIM syndrome: from pathogenesis towards personalized medicine and cure. *J Clin Immunol*. 2019;39(6):532-556. http://doi.org/10.1007/s10875-019-00665-w
4. Heusinkveld LE, Yim E, Yang A, et al. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. *Expert Opin Orphan Drugs*. 2017;5(10):813-825. http://doi.org/10.1080/21678707.2017.1375403
5. Badolato R, Donadieu J, WHIM Research Group. How I treat warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. *Blood*. 2017;130(23):2491-2498. http://doi.org/10.1182/blood-2017-02-708552
6. Geier CB, Ellison M, Cruz R, et al. Disease progression of WHIM syndrome in an international cohort of 66 pediatric and adult patients. *J Clin Immunol*. 2022;42(8):1748-1765. http://doi.org/10.1007/s10875-022-01312-7
7. Dotta L, Notarangelo LD, Moratto D, et al. Long-term outcome of WHIM syndrome in 18 patients: high risk of lung disease and HPV-related malignancies. *J Allergy Clin Immunol Pract*. 2019;7(5):1568-1577. http://doi.org/10.1016/j.jaip.2019.01.045
8. Moulin C, Beaupain B, Suarez F, et al. CXCR4 WHIM syndrome is a cancer predisposition condition for virus-induced malignancies. *Br J Haematol*. 2024;204(4):1383-1392. http://doi.org/10.1111/bjh.19373
9. Laberko A, Deordieva E, Krivan G, et al. Multicenter experience of hematopoietic stem cell transplantation in WHIM syndrome. *J Clin Immunol*. 2022;42(1):171-182. http://doi.org/10.1007/s10875-021-01155-8
10. FDA approves first drug for WHIM syndrome, a rare disorder that can lead to recurrent, life-threatening infections. US Food and Drug Administration. Accessed January 12, 2026. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-drug-whim-syndrome-rare-disorder-can-lead-recurrent-life-threatening-infections
11. Stone ND, Dunaway SB, Flexner C, et al. Multiple-dose escalation study of the safety, pharmacokinetics, and biologic activity of oral AMD070, a selective CXCR4 receptor inhibitor, in human subjects. *Antimicrob Agents Chemother*. 2007;51(7):2351-2358. http://doi.org/10.1128/aac.00013-07
12. Badolato R, Alsina L, Azar A, et al. A phase 3 randomized trial of mavorixafor, a CXCR4 antagonist, for WHIM syndrome. *Blood*. 2024;144(1):35-45. http://doi.org/10.1182/blood.2023022658
13. Dale DC, Firkin F, Bolyard AA, et al. Results of a phase 2 trial of an oral CXCR4 antagonist, mavorixafor, for treatment of WHIM syndrome. *Blood*. 2020;136(26):2994-3003. http://doi.org/10.1182/blood.2020007197
14. Eash KJ, Greenbaum AM, Gopalan PK, Link DC. CXCR2 and CXCR4 antagonistically regulate neutrophil trafficking from murine bone marrow. *J Clin Invest*. 2010;120(7):2423-2431. http://doi.org/10.1172/jci41649