

mavorixafor

Category:

Best Product for Orphan/Rare Diseases

Company Name:

X4 Pharmaceuticals, Inc.

Product/Solution Name:

mavorixafor

Compound/Tech Name:

mavorixafor

Trade Name:

XOLREMDI® (U.S.)

Corporate Name:

X4P-001

Date of Approval:

2024-04-26

Indications:

WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) (approved in U.S., pending in EU), Primary Chronic Neutropenia (Phase 3 ongoing)

Therapeutic Areas:

Primary Chronic Neutropenic conditions

General Information File Document upload:

**X4 Pharma Mavorixafor Prix Galien Submission FINAL
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Background information and need for drug / device:

Until recently, there had been no innovation for patients with chronic neutropenia in more than 30 years.

X4 Pharmaceuticals was founded in 2014 with a vision to create a company focused on rare diseases with few/no treatment options, turning our scientific insights into clinical benefit. Ten years later, we have done just that.

At founding, we licensed a development candidate from Genzyme/Sanofi and set about studying the drug across rare disease indications where we thought it could make the greatest impact for patients. The candidate was mavorixafor, the first orally bioavailable CXCR4 inhibitor, a mechanism that enables the mobilization of white blood cells (including neutrophils and lymphocytes) from the bone marrow into blood. (1,2,3)

We first pursued the indication of WHIM syndrome, an ultra-rare combined primary immunodeficiency and chronic neutropenic disorder caused by variants in the CXCR4 gene. (4) At the time, there were no approved treatments for the estimated 1,000 U.S. population - patients were treated symptomatically and/or with chronic, prophylactic antibiotics. "WHIM" stands for: Warts, due to HPV, variable Hypogammaglobulinemia, Infections, and Myelokathexis, the retention of mature neutrophils in the bone marrow, (5) and is characterized by severe chronic neutropenia, lymphopenia, and an increased risk of malignancy.

We successfully obtained Orphan Drug, Rare Pediatric Disease, Breakthrough Therapy, and Fast Track Designations in the U.S. for mavorixafor in WHIM, helping us accelerate development and, ultimately, approval.

Following successful clinical development, we received U.S. FDA approval for mavorixafor in April 2024 as a once-daily oral treatment for patients ≥ 12 years with WHIM syndrome. (6,7) We launched mavorixafor in May 2024 as XOLREMDI® - the first drug approved for WHIM anywhere in the world. Approval is pending in the EU, where mavorixafor has also been awarded Orphan Designation for WHIM.

During early development of mavorixafor, we observed that the drug was able to raise neutrophil counts, in addition to counts of other white blood cells, in healthy individuals. This led us to hypothesize that mavorixafor could also benefit people with neutropenia not caused by CXCR4 dysfunction, and we set about tackling chronic neutropenia, a larger, but still rare disease market, affecting ~50,000 in the U.S.

Chronic neutropenia (CN) is defined as having <1500 cells/ μL in the peripheral blood for 3 months or longer. (8,9) In the absence of efficacious treatment, CN can be fatal, as it increases the risk of severe, life-threatening infections that require frequent hospitalization, significantly impacting patients' quality of life. (10,11,12)

The only FDA-approved treatment for CN is injectable human recombinant granulocyte-colony stimulating factor (G-CSF), approved in the early 1990s for severe CN. (13) G-CSF is far from an ideal treatment, with reported side effects that include bone pain, splenomegaly, thrombocytopenia, glomerulonephritis, vasculitis, and osteoporosis, (14,15,16) and long-term treatment, especially at high doses, is correlated with an increased risk of leukemia in some. (16,17)

Following our successful Phase 2 clinical study of mavorixafor in certain CN disorders, we are now conducting a global, pivotal Phase 3 trial targeting the estimated 15,000 in the U.S. with significant unmet needs.

Background File Document upload:

N/A

History of the development of the solution/product:

Mavorixafor in WHIM

Following a successful Phase 2 study, we investigated oral, once-daily mavorixafor in people with WHIM syndrome in a global, pivotal, randomized, double-blind, placebo-controlled, 52-week Phase 3 trial (4WHIM). The trial enrolled participants aged ≥ 12 years with WHIM syndrome and absolute neutrophil count (ANC) $\leq 400/\mu\text{L}$. The primary endpoint was a measurement of the time above threshold of ANC $\geq 500/\mu\text{L}$ (or TAT-ANC) versus placebo as assessed every 3-months over the 52-week study. Secondary endpoints included TAT for absolute lymphocyte count $\geq 1000/\mu\text{L}$ (TAT-ALC) and changes in other white blood cell counts; and annualized infection rate; infection duration and total infection score (combined infection number/severity) among others.

Mavorixafor achieved statistically significantly greater TAT-ANC than placebo (15.0 hours versus 2.8 hours, $P < 0.001$) and greater TAT-ALC (15.8 hours versus 4.6 hours, $P < 0.001$) in the 31-participant study. In addition, higher absolute WBC, ANC, and ALC levels were seen with mavorixafor than placebo at each timepoint assessed. Most importantly, the changes observed in blood counts resulted in a statistically significant 60% lower rate of annualized infection versus placebo ($P = 0.007$) and total infection scores were 40% lower (7.4 versus 12.3). Treatment with mavorixafor reduced infection frequency, severity, duration, and also the use of antibiotics. In addition, the open label extension (2-year study) showed benefit in wart burden (18), a challenging hallmark of the disease. Mavorixafor was well tolerated in participants. (19)

Mavorixafor in Chronic Neutropenia

We conducted an open-label, multicenter Phase 1b/Phase 2 clinical trial to assess oral mavorixafor, with or without injectable G-CSF, in participants with CN disorders, including idiopathic, cyclic, and congenital neutropenia.

In the Phase 1b portion of the study, participants received one dose of oral mavorixafor and were assessed for magnitude of ANC response and tolerability. 100% of participants (n=25) responded to treatment, demonstrating a meaningful increase in ANC over the 24-hour period, and mavorixafor was generally well tolerated alone or dosed concurrently with G-CSF. (20)

The Phase 2 portion of the trial (n=23) assessed the safety, tolerability, and the impact on participants' neutropenia of oral, once-daily mavorixafor +/- injectable G-CSF over a 6-month period. During the study, physicians had the option to reduce G-CSF dosing in participants on combination therapy following the 8-week visit.

Results from the two treatment groups (21,22): mavorixafor monotherapy (n = 10 at baseline) and mavorixafor + G-CSF (n=13 at baseline) showed:

- Mavorixafor monotherapy durably and meaningfully increased mean ANC beginning at Month 1, continuing through Months 3 and 6.
- Mavorixafor + G-CSF also durably and meaningfully maintained mean ANC above the lower limit of normal from baseline through Month 6.
- Investigators and participants chose to substantially reduce injectable G-CSF therapy in 9 of 12 eligible participants, with 89% having G-CSF adjusted at the earliest timepoint possible. Three participants had G-CSF treatment discontinued before Month 6. All 9 participants maintained normal ANC throughout the study.
- The overall safety profile was consistent with prior studies.

A neutrophil function sub-study also showed that mavorixafor-treated participants' neutrophils were as functional as healthy donor samples. (20)

Development File Document upload:

N/A

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

Mavorixafor: Unlocking Potential Immune System Restoration for Rare Diseases

Mavorixafor represents a groundbreaking innovation as the first and only FDA-approved treatment for individuals with WHIM syndrome, a rare/serious primary immunodeficiency. Yet, its potential impact extends far beyond a single disease. By uniquely enhancing both innate (neutrophil-mediated) and adaptive (lymphocyte-mediated) immune responses, mavorixafor holds promise for transforming the treatment landscape across a broad spectrum of immunodeficiencies and immune-related conditions.

Transformative Mechanism of Action with Broad Relevance

Mavorixafor's novel mechanism - selective CXCR4 antagonism - modulates immune cell trafficking, enabling the immune system to respond more effectively to pathogens. In the pivotal Phase 3 trial in WHIM syndrome, treatment with mavorixafor not only reduced the frequency of bacterial and viral infections but also led to a significant reduction in the use of antibiotics and antivirals. This dual benefit not only improved patient outcomes but also offers a path toward reducing antimicrobial misuse and resistance - an escalating global public health crisis.

Impact Beyond Infection: Implications for Cancer and Chronic Immune Disorders

In WHIM syndrome, where HPV-driven wart burden is common and associated with early-onset cancers, mavorixafor has been shown to significantly reduce wart severity, suggesting an ability to disrupt HPV persistence and potentially lower cancer risk in this population. Furthermore, early clinical and translational research demonstrates that mavorixafor increases immune cell infiltration and activation within the tumor microenvironment. This includes a favorable shift in immune gene signatures that supports its potential as an adjunct or foundational therapy in immuno-oncology.

Personalized Benefits and Population Health Impact

Beyond clinical endpoints, mavorixafor has changed lives. Testimonials from individuals with WHIM currently receiving XOLREMDI (mavorixafor) provide powerful human evidence of its impact:

- "I now know what it's like to have a normal immune system - it has had a profound impact on my enjoyment of life."
- "My immune system works so much better now - I don't have warts all over my body, I don't get skin infections anymore, and I'm generally a healthy person."
- "I didn't know how sick I was until I felt better!"
- "My white blood cell count is now very close to normal limits. I feel more energetic than I have in years, haven't missed any work due to illness, and have become more engaged professionally and socially."

These individual experiences underscore the broader health, social, and economic value of restoring immune function.

A Platform for Global Innovation

We believe mavorixafor's chronic, oral, and well-tolerated profile opens the door for long-term use across numerous immune-mediated diseases. Its CXCR4 antagonism mechanism is supported by a growing body of evidence suggesting therapeutic potential in:

- HIV/AIDS prevention (23)
- Oncology: enhancing checkpoint inhibitor response (24)
- Broad immunodeficiencies, both rare and acquired

We are humbled to witness the early impact of mavorixafor on the lives of individuals with WHIM syndrome and are inspired by the emerging science that suggests even greater potential. Mavorixafor exemplifies how deep mechanistic understanding can lead to transformative therapies with far-reaching implications for global human health.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

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