LEADER 3D: Use of the Win Ratio Method to Demonstrate Clinical Benefit from a Composite Endpoint for a Rare Disease

Mavorixafor (Xolremdi)

Before reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. The small population affected by a rare disease presents additional considerations that must be addressed and also calls for appropriate flexibility. **Please note this case study is not intended or designed to provide specific strategies for obtaining product approval.** Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Learning Objectives

After reading this case study you will:

- Have a greater understanding of the win ratio statistical method.
- Be aware of how a win ratio method can be leveraged to demonstrate clinical benefit from a composite endpoint, resulting in a traditional approval.
- Be familiar with the relevant FDA guidance documents that discuss concepts covered within this case study (e.g., use of multiple endpoints).

To access FDA guidance documents for rare disease drug development organized by topic, please scan this QR code.

Case Study Summary

This case study highlights the use of the win ratio method in the U.S. Food and Drug Administration (FDA) approval of mavorixafor (Xolremdi), a selective CXC chemokine receptor type 4 (CXCR4) antagonist developed, in this case, for the treatment of WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome to increase the number of circulating mature neutrophils and lymphocytes. The win ratio method provided the Applicant a way to prioritize the components of a composite clinical endpoint based on their relative clinical importance, demonstrating statistically significant treatment benefit where traditional analyses had not.

Mavorixafor is the first FDA-approved therapy for WHIM syndrome. The Applicant engaged with FDA throughout development, beginning with early discussions of trial design, endpoint selection, and statistical approaches. The Applicant submitted results from their single, randomized, double-blind, placebo-controlled trial (Study X4P-001-103), with prespecified analyses submitted as part of the new drug application. For more information on the regulatory history of this application, please refer to page 95 of the Integrated Review for mavorixafor (Xolremdi). During review, FDA evaluated both the Applicant's statistical method and the primary win ratio method recommended by FDA during the study design phase, ultimately resulting in use of the win ratio method to more appropriately capture treatment benefit in the composite clinical endpoint given the limitations of the small trial.

Key Concept: The Win Ratio Method

The win ratio method is a statistical approach developed to improve the analysis of composite endpoints in clinical investigations. Traditional analyses often treat all components of a composite endpoint equally or rely on "time-to-first event", which can obscure clinically meaningful differences when endpoint components vary in importance or frequency.

The win ratio method addresses this limitation by ranking components hierarchically, giving priority to outcomes of greater clinical importance.

The method works by comparing participants in the treatment and control arms in a pairwise fashion. Each pair is evaluated first for the most important outcome: the participant with the more favorable result on that outcome is declared the "winner". If the pair is tied, the comparison proceeds to the next outcome in the hierarchy. The win ratio is then calculated as the total number of wins divided by the total number of losses across all pairs, with confidence intervals and p-values derived using established statistical methods.[1] (Both matched and unmatched comparisons can be used, depending on study design.)

The win ratio method is appropriate when:

- A trial uses a composite endpoint that combines outcomes of varying clinical importance and there is clear consensus regarding the hierarchy of those outcomes.
- A hierarchical evaluation of outcomes provides a more clinically relevant interpretation than treating all events equally.

Key benefits of the win ratio method include:

- Emphasizing outcomes that matter most to patients and clinicians.
- Avoiding dilution of treatment effects by less important or more variable components.
- Providing an intuitive interpretation of treatment effect, expressed as the ratio of "wins" to "losses".

As a result, the win ratio method may be useful in clinical development, especially in settings where traditional methods may not adequately reflect the true clinical impact of an intervention.

Introduction to the Rare Disease: WHIM Syndrome

WHIM syndrome is rare and estimated to occur in approximately 1 in 5 million live births. It is a serious and life-threatening immunodeficiency caused by gain-of-function mutations in the *CXCR4* gene which encodes the CXCR4 receptor. These mutations prolong CXCR4 receptor signaling with its ligand C-X-C motif chemokine 12 (CXCL12), resulting in the abnormal retention of maturing myeloid and lymphoid cells in the bone marrow, a process known as myelokathexis. This leads to chronic neutropenia, lymphopenia, and hypogammaglobulinemia, which compromise immune function and predispose patients to recurrent bacterial and viral infections.

Clinical manifestations of WHIM syndrome are wide-ranging. Patients often experience recurrent respiratory tract and skin infections, bacterial meningitis, and sepsis, as well as persistent Human Papillomavirus (HPV)-associated warts that can be extensive and difficult to manage. Infections have a direct impact on morbidity and mortality and are present in almost all patients with WHIM syndrome. Over time, repeated infections can cause irreversible complications such as bronchiectasis, hearing loss, and organ damage,

FDA Guidance Corner

In this case study, the approval of mavorixafor illustrates the use of a fit-for-purpose statistical analysis in one adequate and well-controlled investigation with confirmatory evidence to fulfill the statutory standard for substantial evidence of effectiveness (SEE). This guidance represents the Agency's current thinking on drug development for rare diseases and provides important considerations for sponsors working in these areas.

Guidance for Industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023)

Approval of any drug — for either a rare or a common disease or condition — must be based on substantial evidence of the drug's effectiveness for its intended use and sufficient information to conclude that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. Sponsors should demonstrate evidence of effectiveness in an identified population from adequate and well-controlled clinical investigations. FDA regulations provide flexibility in how the regulatory standard may be met. FDA exercise[s] its scientific judgment in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs. This flexibility extends from the early stages of development to the design of adequate and

[1] Pocock, SJ, CA Ariti, TJ Collier, & D Wang, (2012). The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European heart journal, 33(2), 176-182.

necessitating lifelong surveillance and medical management. Although warts may confer an increased risk of HPV-driven malignancies, they are not experienced by all patients with WHIM syndrome.[2]

Current Treatment Options

Before the approval of mavorixafor, there were no FDA-approved treatments for WHIM syndrome, and management relied on supportive approaches intended to reduce complications. The most common available strategies for management of WHIM syndrome included:

- Antibiotic prophylaxis or treatment to address recurrent bacterial infections.
- Immunoglobulin replacement therapy (IgG) to compensate for hypogammaglobulinemia and reduce the frequency of infections.
- Granulocyte-colony stimulating factor (G-CSF) used off-label to increase circulating neutrophils.

In rare cases, hematopoietic stem cell transplantation (HSCT) has been attempted with the goal of curing WHIM syndrome. However, HSCT is associated with high rates of morbidity and mortality and is further limited by donor availability. Despite supportive strategies, these options only provided a partial benefit to patients and were insufficient to fully address the underlying immune dysfunction, leaving a significant unmet medical need for more effective therapies.

well-controlled clinical investigations required to demonstrate effectiveness to support marketing approval and to establish safety data needed for the intended use.

Sponsors should select endpoints considering the objectives of each clinical investigation in the context of the overall clinical development program. Endpoint selection, especially considerations related to novel endpoints (that could be clinical outcomes or biomarkers as surrogate endpoints), is an important aspect of rare disease drug development. Sponsors are encouraged to engage early with the Agency to discuss endpoint development. Clinical investigations within a drug development program generally build upon the knowledge gained in early studies to guide the design and endpoint selection for later stages of development.

For many rare diseases, well-characterized efficacy endpoints appropriate for the disease are not available. The frequency of assessments and patients' (and caregivers') involvement in the selection, development, or modification of existing clinical outcome assessment measures and available instruments can improve the chances of success for the development program.

Sponsors should explore and address concerns about clinical investigation design (such as control arms and randomization) with patients, caregivers, and clinical investigators early in planning stages to avoid undermining clinical investigation recruitment and retention. Sponsors can sometimes address patient and family concerns by using modified clinical investigation designs, when appropriate, to demonstrate effectiveness and identify important safety signals. It is important that plans to use innovative clinical investigation designs be discussed in advance with the review division, ideally at the pre-investigational new drug application (pre-IND) meeting.

[2] Geier, CB, M Ellison, R Cruz, et al, 2022, Disease Progression of WHIM Syndrome in an International Cohort of 66 Pediatric and Adult Patients, J Clin Immunol, 42(8):1748-1765.

Mavorixafor Mechanism of Action

WHIM syndrome is driven by gain-of-function mutations in the *CXCR4* gene, which encodes a G protein-coupled receptor. Under normal physiology, the CXCR4 receptor binds to its ligand, CXCL12, to regulate the trafficking and homing of hematopoietic and immune cells.[3] Ligand binding activates intracellular signaling pathways that help retain developing neutrophils and lymphocytes in the bone marrow until they mature. In WHIM syndrome, CXCR4 mutations result in hyperactive receptor signaling. Instead of undergoing normal desensitization and internalization after ligand binding, mutant CXCR4 remains abnormally responsive to CXCL12 and produces prolonged intracellular signaling responses.[4] This sustained signaling results in myelokathexis, the retention of neutrophils and lymphocytes in the bone marrow and leads to chronic neutropenia and lymphopenia. Mavorixafor is a selective oral CXCR4 antagonist that blocks CXCL12 binding and signaling. By inhibiting this pathway, mavorixafor promotes the mobilization of mature neutrophils and lymphocytes into the bloodstream, improving immune cell availability. **Figure 1** illustrates the mechanism of action of mavorixafor, illustrating how inhibition of CXCR4 signaling restores normal trafficking of immune cells from the bone marrow into circulation.

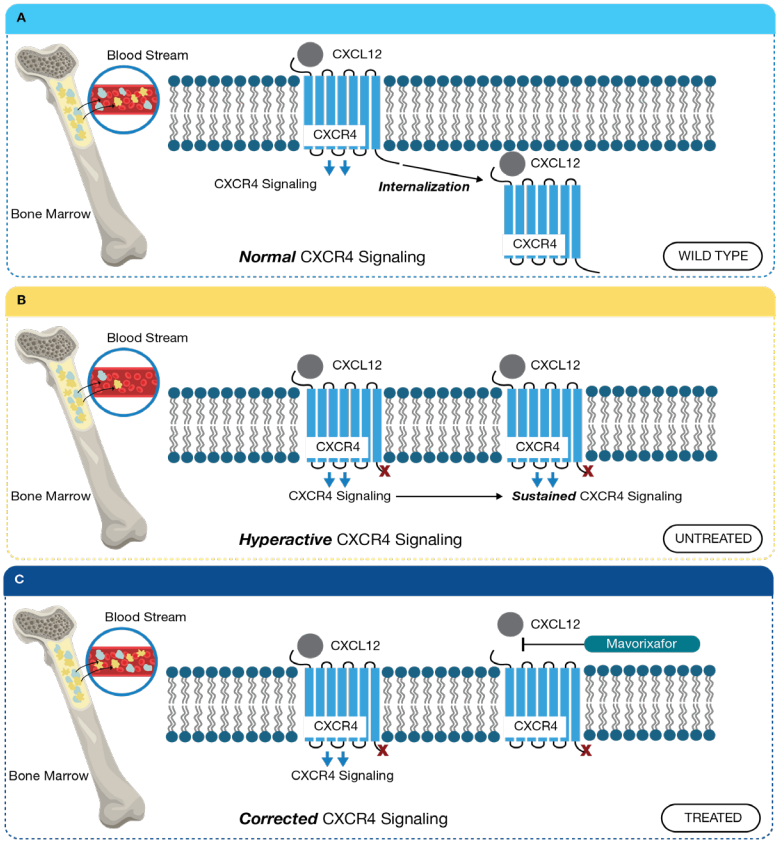


Figure 1: *CXCR4/CXCL12 Signaling in Normal Physiology, WHIM Syndrome, and Treatment with Mavorixafor. Panel A: Under normal conditions, CXCR4/CXCL12 signaling regulates immune cell trafficking, allowing mature neutrophils and lymphocytes to exit the bone marrow and enter circulation. Panel B: In WHIM syndrome, gain-of-function in CXCR4 causes prolonged receptor signaling, leading to abnormal retention of mature immune cells in the bone marrow (myelokathexis) and reduced numbers of circulating neutrophils and lymphocytes. Panel C: Treatment with mavorixafor, a selective CXCR4 antagonist, blocks excessive CXCR4/CXCL12 signaling, restores normal immune cell exit from the bone marrow, and increases the availability of functional neutrophils and lymphocytes in peripheral blood to improve immune defense.*[5]

The Single Adequate and Well-Controlled Investigation

Trial Design

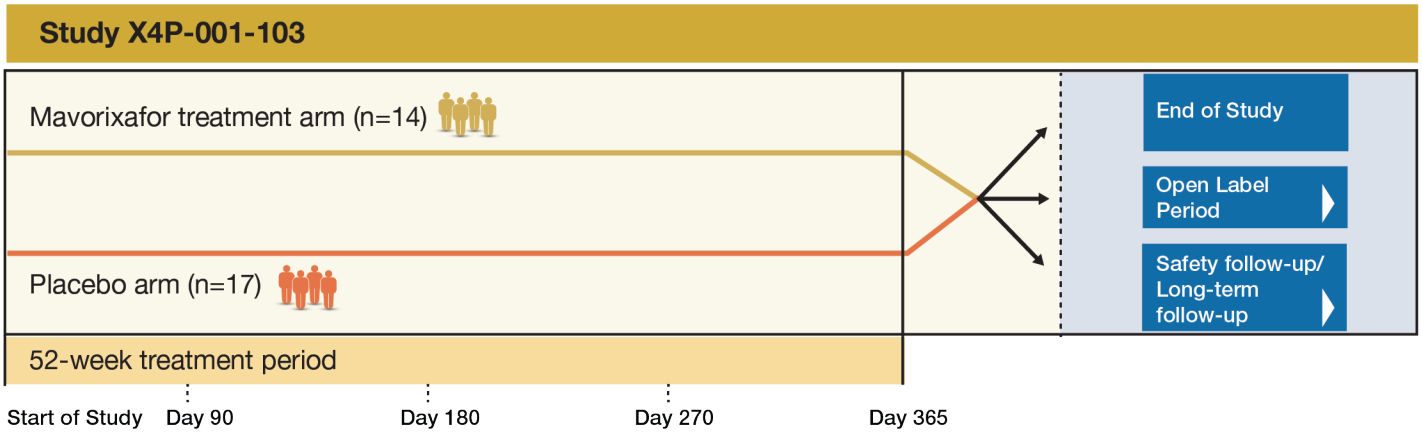
The pivotal trial for mavorixafor (Study X4P-001-103) was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (**Figure 2**). A total of 31 participants aged 12 years and older with WHIM syndrome and baseline absolute neutrophil counts (ANC) of 400 cells/μL or less were enrolled and randomized 1:1 to receive either once-daily oral mavorixafor or placebo for 52 weeks, with assessments conducted at baseline and at three-month intervals throughout the study.

[3] Bianchi, ME and R Mezzapelle, 2020, The Chemokine Receptor CXCR4 in Cell Proliferation and Tissue Regeneration, Front Immunol, 11:2109.

[4] Kawai, T, & HL Malech, (2009). WHIM syndrome: congenital immune deficiency disease. Current opinion in hematology, 16(1), 20-26.

[5] Figure 1 was generated using information provided on page 19 of the Integrated Review for mavorixafor (Xolremdi), NDA 218709

Figure 2: *Randomized, double-blind, placebo-controlled design of Study X4P-001-103*[6]



Study Results

The primary endpoint of the trial was the time above threshold-ANC (TAT_{ANC}), defined as the number of hours in a 24-hour period that ANC remained at or above 500 cells/μL, assessed at four timepoints during the 52-week study. Treatment with mavorixafor demonstrated a statistically significant improvement compared with placebo, with participants in the active arm averaging 15.0 hours above the threshold versus 2.8 hours in the placebo arm. This corresponded to a least-squares mean difference of 12.3 hours and was highly significant ($p<0.00001$).

The first key secondary endpoint was time above threshold-absolute lymphocyte count (TAT_{ALC}), defined as the number of hours per day that ALC remained at or above 1000 cells/μL. Mavorixafor again demonstrated a significant improvement, with participants in the treatment group averaging 15.8 hours compared with 4.6 hours for placebo, a difference of 11.3 hours ($p<0.0001$). The other key secondary endpoint, the composite clinical efficacy endpoint (total infection score and total wart change score) did not achieve a statistically significant result with the prespecified analysis of covariance (ANCOVA). Specifically, when evaluated individually, no treatment effect was observed for the wart change score; and while infection scores were lower in the treatment arm, this difference did not achieve statistical significance under the Applicant's analysis plan.

The results of the primary and select secondary endpoints established the pharmacodynamic (PD) effects of mavorixafor on mobilization of neutrophils and lymphocytes. However, the composite endpoint was reflective of clinical benefit unlike either of

FDA Guidance Corner

In this case study, the Applicant's prespecified ANCOVA analysis based on the sum of ranks of the two individual components of the composite clinical efficacy endpoint, infections and warts, appeared to underestimate the treatment benefit of reducing infections.

This guidance, which represents the Agency's current thinking on the use and analysis of multiple endpoints in clinical trials, outlines strategies for addressing endpoint selection, analysis, and interpretation.

Guidance for Industry *Multiple Endpoints for Clinical Trials* (October 2022)

Most clinical trials performed in drug development contain multiple endpoints to assess the effects of the drug and to document the ability of the drug to favorably affect one or more disease characteristics. Endpoints in adequate and well-controlled drug trials are usually grouped hierarchically, often according to their clinical importance, but also taking into consideration the expected frequency of the endpoint events and anticipated drug effects. The critical determination for grouping endpoints is whether they are intended to establish effectiveness to support approval or intended to demonstrate additional meaningful effects. Endpoints critical to establish effectiveness for approval are often designated as primary

[6] Figure 2 was generated using information provided on page 31 of the Integrated Review for mavorixafor (Xolremdi), NDA 218709

the PD endpoints, which were not considered validated surrogate measures of clinical benefit in WHIM syndrome. The Applicant's prespecified analysis of the composite clinical endpoint failed to achieve statistical significance, and therefore, did not establish clinical benefit, which highlights the challenges of demonstrating efficacy in a small, rare disease patient population with heterogeneous clinical manifestations. Although the Applicant's prespecified analysis did not show significance, the Agency conducted analyses using the win ratio method – a recommendation made by FDA earlier in the development program – as an alternative statistical approach to more appropriately evaluate the composite endpoint and clinical benefit (i.e., how a patient feels, functions, or survives).

The Win Ratio Method for the Analysis of the Composite Clinical Endpoint

Although the prespecified primary endpoint demonstrated superiority of mavorixafor over placebo, FDA placed particular focus on the composite endpoint. The primary endpoint, TAT_{ANC}, was a PD measure of neutrophil mobilization. While statistically significant, this endpoint did not directly measure clinical benefit and was not a validated surrogate endpoint in WHIM syndrome. Because of this limitation, FDA emphasized the importance of the key secondary composite endpoint, which was considered the most clinically meaningful measure of benefit, as it directly reflected disease manifestations experienced by patients (i.e., infections and warts). The pivotal trial for mavorixafor only enrolled 31 participants worldwide and included a composite clinical efficacy endpoint that combined infection scores and wart burden. The Applicant's proposed primary analysis with ANCOVA was based on the sum of ranks of the two individual components, which weighted infections and warts equally. Using this approach, the study did not demonstrate superiority of mavorixafor over placebo for the composite endpoint, despite trends favoring mavorixafor in infection outcomes. The lack of significance was driven in part by the wart-related outcomes, which showed no improvement with treatment and contributed to variability across participants.

During discussions with the Applicant that occurred early in the course of their development program, the Agency recommended use of the win ratio method to analyze the composite clinical endpoint.[7,8] This statistical approach may be used to evaluate

endpoints. Secondary endpoints can provide useful description to support the primary endpoint(s) and/or demonstrate additional clinically important effects. Exploratory endpoints can include endpoints for research purposes or for new hypotheses generation.

There are some disorders for which more than one clinical outcome in a clinical trial is important, and all outcomes are expected to be affected by the treatment. Rather than using each as a separate primary endpoint (creating multiplicity) or selecting just one to be the primary endpoint and designating the others as secondary endpoints, it could be appropriate to combine those clinical outcomes into a single variable. This is often called a composite endpoint, where an endpoint is defined as the occurrence or realization in a subject of any one of the specified components.

The choice of the components of a composite endpoint should be made carefully. The treatment effect on the composite event rate can be interpreted as characterizing the overall clinical effect when the individual events all have reasonably similar clinical importance. The effect on the composite endpoint, however, will not be a reasonable indicator of the effect on all of the components or an accurate description of the drug's benefit if the clinical importance of different components is substantially different and the treatment effect is chiefly on the least important event. Furthermore, it is possible that a component with greater importance would be adversely affected by the treatment, even if one or more event types of lesser importance are favorably affected, so that although the overall outcome still has a favorable statistical result, doubt may arise about the treatment's clinical value. In this case, although the overall statistical analysis indicates the treatment is beneficial, careful examination of the data could call this conclusion into question. For this reason, as well as for a greater depth of understanding of the treatment's effects, analyses of the components of the composite endpoint are important and can influence interpretation of the overall study results.

[7] For more information on the regulatory history of this application, please refer to page 95 of the Integrated Review for mavorixafor (Xolremdi), NDA 218709

[8] For more information on specific types of meetings and engagement mechanisms available to applicants and related timing, please refer to Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.

composite endpoints in settings where individual components differ in clinical importance. In contrast to ANCOVA and other methods that give equal weight to all components, the win ratio method applies a hierarchical framework, ranking outcomes by clinical priority (which was done in consultation with FDA during the study design phase). In this case, infections were designated as the highest-priority outcome due to their direct impact on morbidity and mortality, as well as their presence in almost all patients with WHIM syndrome, compared to warts which were given a lower priority as not all patients experience warts.

In this trial, the composite endpoint was based on the infection scores (calculated as the sum of documented infections, weighted by severity) and the wart score (based on the number and extent of cutaneous warts, as assessed clinically). For the win ratio analysis, each participant on mavorixafor was paired with each participant on placebo. A "win" was assigned if the treated participant had a lower infection score than the placebo participant. If infection outcomes were identical, the comparison proceeded to the wart outcomes, with a win assigned to the participant with fewer or reduced warts. Ties were recorded when both infection and wart outcomes were the same. The overall win ratio was then derived from the number of wins divided by the number of losses across all pairs.

When applied to the pivotal trial, the win ratio method revealed a statistically significant treatment benefit. In the unstratified analysis (Table 1), the win ratio was 2.76 (p=0.00025), showing that participants on mavorixafor were nearly three times more likely to achieve better outcomes than those on placebo.

Highlights

Prioritization of Composite Endpoint Components in the Win Ratio Method

When composite endpoints include outcomes that differ in clinical importance, statistical analyses may prioritize components based on higher importance. For mavorixafor, the total infection score was prioritized over the total wart change score based on the following clinical considerations:

- Infections represent the most significant clinical manifestation of WHIM syndrome, and recurrent infections are the primary disease burden experienced by patients.
- Nearly all individuals with WHIM syndrome experience infections during their lifetime, with varying severity and frequency.
- Not all patients develop warts, and some individuals with WHIM syndrome never experience them.
- Infections may lead to urgent or potentially-life threatening complications, as well as long term medical consequences, whereas warts generally represent a less severe manifestation of the disease.

Table 1: *Win Ratio Analysis* for the Composite Clinical Efficacy Endpoint (Infection Score First, Then Wart Score) – Unstratified Analysis – Randomized Placebo-Controlled Period (ITT Population), Study X4P-001-103* [9]

Category	n**	Win Ratio	95% CI for Win Ratio	Normal P-Value
Mavorixafor wins on total infection score	174	174/63=2.76	(1.60,4.76)	0.00025
Placebo wins on total infection score	63			
Mavorixafor wins on total wart change score	0			
Placebo wins on total wart change score	0			
None of the above (tie)	1			

**The method compared each mavorixafor-treated patient to each placebo-treated patient in a pair-wise manner that proceeded in a hierarchical fashion using total infection score, followed by total wart change score if patients could not be differentiated based on total infection score. The total infection score was calculated by summing up the number of infection events weighted by severity and divided by the total exposure time (in years). Total wart change score was calculated by summing up the regional wart change scores from three target regions (lesions).*
***n is number of wins*

[9] Table 1 was generated using information provided on page 54 of the Integrated Review for mavorixafor (Xolremdi), NDA 218709

A stratified analysis, which adjusted for baseline use of immunoglobulin replacement therapy, produced a similar result, with a win ratio of 2.31 (p=0.003). Both analyses demonstrated clear superiority of mavorixafor, in contrast with the null result obtained using ANCOVA, which diluted the signal of benefit and contributed to a nonsignificant result for the composite endpoint.

The use of the win ratio method was important because it ensured that the component of the composite endpoint most clinically meaningful to patients and regulators (i.e., reduced severity/frequency of infections) was given greater weight than the wart score, which was variable across the study population and did not consistently respond to treatment. Furthermore, the method demonstrated that mavorixafor provided measurable clinical benefit, strengthening the overall evidence for approval. For more information on the clinical benefit to patients, please refer to pages 52-57 of the Integrated Review for mavorixafor (Xolremdi). This case illustrates the potential role of the win ratio method as a fit-for-purpose statistical tool in rare disease investigations where small populations, heterogeneity of clinical manifestations, and the use of composite endpoints can complicate interpretation of treatment effect. By prioritizing outcomes according to clinical importance when appropriate, the win ratio method may provide a clearer assessment of benefit than traditional analyses. Thus, this case example highlights the importance of selecting the optimal statistical analysis method for a specific application.

FDA Guidance Corner

In this case study, the win ratio proved more appropriate than ANCOVA in demonstrating statistical significance in a small trial population with heterogeneous disease presentation. Sponsors should work with the relevant review division regarding questions relating to the most appropriate statistical approaches for their development programs. This guidance represents the Agency's current thinking on best practices for communication during drug development.

Guidance for Industry *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017)

The purpose of this guidance is to describe best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors and FDA at critical junctures in drug development, which may facilitate earlier availability of safe and effective drugs to the American public. Meetings between FDA and a sponsor at critical junctures in drug development can be especially helpful in minimizing wasteful expenditures of time and resources and thus in speeding the drug development and evaluation process. These milestone meetings under PDUFA include pre-IND, end-of-phase 1 (EOP1), end-of-phase 2 (EOP2), and pre-NDA/BLA meetings.

Pre-IND meetings are valuable for understanding the mechanism of actions of the drug and possible study designs and initiating dialogue regarding drug development in its early stages. They can prevent clinical hold issues from arising and aid sponsors in developing a complete IND. EOP2 meetings are of considerable importance in determining the safety of, and sufficiency of data (e.g., on dose selection) for, proceeding to phase 3, and for planning a complete and well-designed phase 3 development program. Pre-NDA/BLA meetings are helpful in acquainting FDA reviewers with the format and content of the planned marketing application, including labeling and risk management activities (if applicable), presentation and organization of data, dataset structure, acceptability of data for submission, as well as the projected submission date of the marketing application. They are also intended to uncover major issues, identify studies intended to establish the drug's safety and effectiveness, discuss the status of pediatric studies, and discuss statistical analysis methods, or the results of analyses. Premeeting preparation is critical for achieving a successful meeting with productive discussion and exchange of information. Sponsors should submit a limited number of clearly worded and targeted questions that directly address concerns about the drug development programs, and sponsors' meeting packages should be well organized and tabbed or bookmarked to enhance the reviewers' navigation within the packages both in preparation for and during the meetings. The FDA regulatory project manager (RPM) should send preliminary responses to sponsor questions before the meeting so that the meeting time can be dedicated to unresolved issues for which more discussion is needed. In the preliminary responses, FDA should provide high-level recommendations for important issues identified during the review of the meeting package, even if questions concerning those issues were not explicitly posed by the sponsor.

Conclusion

The approval of mavorixafor for the treatment of WHIM syndrome represents an important milestone in addressing a long-standing unmet medical need in a rare immunodeficiency. The pivotal trial demonstrated significant effects on infection by applying the win ratio method to prioritize infections over wart outcomes in the composite clinical efficacy endpoint. This approach revealed a clear and statistically significant reduction in infections, supporting the conclusion that mavorixafor provides clinically meaningful benefit for patients with WHIM syndrome. This case underscores the importance of fit-for-purpose statistical methodologies in rare disease drug development, particularly when trials rely upon composite endpoints that vary in clinical relevance. It also highlights the value of early and ongoing engagement with the Agency to refine statistical analysis plans. Lessons from this case may inform future programs where endpoint prioritization is essential to demonstrating SEE in trials with small, heterogeneous patient populations.

Key Concept: Substantial Evidence of Effectiveness

In most rare disease drug development programs, data from one adequate and well-controlled clinical investigation plus confirmatory evidence are leveraged to demonstrate substantial evidence of effectiveness.

Case Study Relevance to Key Concept: For mavorixafor, SEE was established through one adequate and well-controlled investigation plus confirmatory evidence. The pivotal Phase 3 trial, Study X4P-001-103, served as the single adequate and well-controlled investigation. It was a randomized, double-blind, placebo-controlled trial that demonstrated statistical significance after reanalysis using the win ratio method demonstrating superiority of the efficacy endpoint of infections, which was considered the most clinically meaningful.

The confirmatory evidence came from Study X4P-001-MKKA, which provided mechanistic PD data demonstrating that mavorixafor antagonism of CXCR4 corrected the underlying defect in immune cell trafficking. Together, the results of Study X4P-001-103 and the PD data from Study X4P-001-MKKA established an evidence package that met the statutory requirements for SEE. For additional information on establishing substantial evidence of effectiveness with one adequate and well-controlled investigation, please see draft guidance for industry: *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* draft FDA guidance document which, when final, will represent the Agency's current thinking on topics in the case study.

Key Takeaways

- For many rare diseases, clinically meaningful assessment may require composite endpoints and hierarchical analysis. When disease manifestations are heterogeneous and some components are variable, methods that prioritize the most important clinical outcomes may better capture benefit within a feasible study duration. For mavorixafor, infections were prioritized over wart outcomes, and a hierarchical comparison (win ratio) provided a clearer picture of clinical benefit compared to equal-weight approaches.
- The acceptability of composite endpoints and the analytical method used to evaluate them are context dependent. FDA evaluates the choice of components, their hierarchy/ordering, and the statistical analysis plan on a case-by-case basis, considering the disease, patient population, and mechanism of action.
- Careful statistical analysis planning (e.g., strategies for addressing analyses of composite or multiple endpoints) and pre-specification along with early and ongoing FDA-sponsor communication helps resolve analytical challenges. In this case, dialogue with the Agency helped address limitations of the prespecified ANCOVA approach, leading to use of the win ratio method, which aligned the analysis with outcomes important to patients with WHIM syndrome and yielded interpretable evidence to support marketing approval.
- Sponsors should work with the appropriate review division to obtain alignment on the most appropriate fit-for-purpose statistical methods for a development program (e.g., prior to initiating the pivotal trial).
- The win ratio method is appropriate when the components can be ranked by clinical priority.
- Statistical analysis plans should be discussed with FDA at the study design phase.

Critical Thinking Questions for a Rare Disease Drug Development Program

Rare disease drug developers should engage FDA early to discuss the selection of endpoints and the statistical methods planned for their analysis. When preparing for and designing a clinical investigation for a rare disease medical product, consider the following questions:

1. **Has FDA engagement addressed the endpoint strategy in sufficient detail?** Were discussions with the Agency used to confirm the appropriateness of endpoint selection?
2. **If a composite endpoint is of interest, has the rationale for its use been clearly justified?** Do the selected components reflect outcomes of clinical importance, and is equal weighting appropriate or is a hierarchical approach more suitable?
3. **Are statistical methods prespecified to address endpoint hierarchy?** Does the statistical analysis plan describe how data from composite or multiple endpoints will be analyzed?
4. **Have alternative statistical methods been appropriately considered?** If traditional analyses may not be sufficient to demonstrate significance, is there a scientifically defensible plan for alternative statistical methods (such as the win ratio method), and has this been discussed with FDA?
5. **Does the choice of endpoints and analysis plan balance statistical rigor with clinical relevance?** Do the proposed endpoints and planned statistical analyses include outcomes of greatest importance to patients and provide confidence that observed effects represent clinical benefit?

We recommend meeting with the Agency early[10] in the drug development program to reach alignment regarding endpoint selection, trial design, and the approach to demonstrate substantial evidence of effectiveness.

Additional Resources

1. Guidance for Industry: Critical Path Innovation Meetings. https://www.fda.gov/media/89497/download
2. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. https://www.fda.gov/media/172311/download
3. Draft Guidance for Industry: Early Drug Development and the Role of Pre-IND Meetings. https://www.fda.gov/media/117322/download

[10] Please refer to the Additional Resources section for guidance on how to engage early with FDA, including information on Critical Path Innovation Meetings, INTERACT Meetings, and Pre-IND Meetings

Case Study References by Order of Appearance

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See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.

See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.

See page 95 of the FDA Integrated Review document for more information on the regulatory history of mavorixafor (Xolremdi), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218709Orig1s000IntegratedR.pdf.

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See Pocock, SJ, CA Ariti, TJ Collier, & D Wang, 2012, The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European heart journal, 33(2), 176-182, available at https://doi.org/10.1093/eurheartj/ehr352.

See guidance for industry Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023) for important considerations in rare disease drug and biologics development, available at https://www.fda.gov/media/119757/download.

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See Geier, CB, M Ellison, R Cruz, et al, 2022, Disease Progression of WHIM Syndrome in an International Cohort of 66 Pediatric and Adult Patients, J Clin Immunol, 42(8):1748-1765, available at https://doi.org/10.1007/s10875-022-01312-7.

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See Bianchi, ME and R Mezzapelle, 2020, The Chemokine Receptor CXCR4 in Cell Proliferation and Tissue Regeneration, Front Immunol, 11:2109, available at https://doi.org/10.3389/fimmu.2020.02109.

See Kawai, T, & HL Malech, (2009). WHIM syndrome: congenital immune deficiency disease. Current opinion in hematology, 16(1), 20-26, available at https://doi.org/10.1097/MOH.0b013e32831ac557.

See page 19 of the FDA Integrated Review document for more information on the mechanism of action for mavorixafor (Xolremdi), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218709Orig1s000IntegratedR.pdf.

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See page 31 of the FDA Integrated Review document for more information on the mavorixafor (Xolremdi) clinical trial design, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218709Orig1s000IntegratedR.pdf.

See guidance for industry Multiple Endpoints in Clinical Trials (October 2022), available at https://www.fda.gov/media/162416/download.

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See page 95 of the FDA Integrated Review document for more information on the regulatory history of mavorixafor (Xolremdi), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218709Orig1s000IntegratedR.pdf.

See draft guidance for industry Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (September 2023), available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic.

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See page 54 of the FDA Integrated Review document for more information on the win ratio analysis used mavorixafor (Xolremdi), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218709Orig1s000IntegratedR.pdf.

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See page 52-57 of the FDA Integrated Review document for mavorixafor (Xolremdi) for more information on the clinical benefit to patients, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218709Orig1s000IntegratedR.pdf.

See guidance for industry Best Practices for Communication Between IND Sponsors and FDA During Drug Development (December 2017), available at https://www.fda.gov/media/94850/download.

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See draft guidance for industry Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (September 2023), available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.