INTRODUCTION

• Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome is a rare primary immunodeficiency caused by C-terminal autosomal dominant gain-of-function mutations in the gene encoding the CXCR4 receptor.

• Existing treatments do not address the pathophysiology of the disease and have limited efficacy on the clinical manifestations of the disease, and, in particular, on bacterial infections and HPV-induced warts.

• Mavorixafor, a selective allosteric antagonist of the CXCR4 receptor that targets the mechanism of disease of WHIM syndrome, is the first oral, once-daily treatment in development for this disease.

• Previous reports of this Phase 2 study demonstrated mavorixafor to be well tolerated, with the ability to sustainably increase neutrophil and lymphocyte counts in the blood. Data from this Phase 2 study informed the design of and 400 mg dose selection for the ongoing Phase 3 trial of mavorixafor in patients with WHIM syndrome (4WHIM).

METHODS

- Open-label, prospective, international, dose-escalation Phase 2 study.
- Study conducted at two clinical trial sites located in Australia and the United States.
- Dose-escalation occurred over 25 to 52 weeks up to 400 mg once daily, based on the threshold-adjusted area under the curve (AUC) for absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC) with thresholds of 600 cells/μL for ANC and 1000 cells/μL for ALC over 24-hours.
- We defined Time Above Threshold for ANC (TATANC) as the time, in hours, during which ANC remained above 600 cells/μL, and Time Above Threshold for ALC (TATAUC) as the time, in hours, during which ALC remained above 1000 cells/μL.
- Annualized infection rate at each dose was compared to the prior year to study the Dermatological response evaluated the number of warts on the hands and feet.
- The data cut-off date for this analysis was June 14th, 2019.

OBJECTIVES

This dose-finding Phase 2 clinical trial assessed the safety and long-term efficacy of mavorixafor in patients with WHIM syndrome. We report here the effects of long-term treatment on hematologic and clinical outcomes.

RESULTS

- We enrolled 8 patients with genetically confirmed WHIM syndrome.
- All patients presented pathogenic gain-of-function mutations in the CXCR4 factor: R334X (6/8), E343X (1/8) and S324Pfs365X (1/8).
- Median follow-up was 16.5 months (mean 15.4 months, range 6 days to 28.6 months).
- Patients received escalated doses of mavorixafor 50 mg (N=2), 100 mg (N=4), 150 mg (N=2), 200 mg (N=3), 300 mg (N=7) and 400 mg (N=3). Not all patients received all doses.
- Mavorixafor was well tolerated with no treatment-related serious adverse events.
- At a median follow-up of 16.5 months, we observed durable, dose-dependent increases of white blood cell (WBC), ANC and ALC counts.
- At doses of 300 or 400 mg/day, the mean TATANC was 12.6 ± 9.8 hours (N=7) compared to 2.8 ± 3.5 hours or less for patients (N=4) treated at doses of 150 mg or lower. The mean TATAUC was 16.9 ± 5.8 hours.
- We report a decreased yearly infection rate from 4.63 [95% CI 3.3, 6.3] events in the 12 months prior to the trial to 2.27 [95% CI 1.4, 3.5] events on mavorixafor 300 mg and 400 mg once daily. Continuous reduction in the yearly infection rate over time during treatment with 300mg and/or 400mg was also observed.
- We found an average 75% reduction in the number of cutaneous warts.

CONCLUSIONS

• Mavorixafor was well tolerated in WHIM patients for up to 28.6 months (June 2019);
• 5 patients remain on the extension study as of May 2020.
• Mavorixafor 400 mg orally once daily increased total white blood cell, neutrophil and lymphocyte counts in WHIM patients.
• Mavorixafor at doses of 300 and 400 mg was shown to increase the TATANC 4.5-fold or more versus the TATANC at lower doses. We suggest that TATANC, the number of hours during which the absolute neutrophil count is raised above the 500 cells/μL threshold, is an objective and consistent biomarker of the response to CXCR4 antagonist therapy in WHIM patients that correlates with clinical endpoints (Figures 4-7), reflecting global immunological improvement and leukocyte mobilization.
• Long-term follow-up revealed significant reductions in both infection rates and wart numbers in WHIM patients treated with mavorixafor for at least 6 months.
• The Phase 2 study data informed the ongoing "4WHIM" Phase 3 clinical study design:
  • Mavorixafor 400 mg dosed orally once daily is the selected dose
  • TATANC is the primary endpoint
  • Infection rate and wart burden are clinical endpoints.
• Together, these results suggest that mavorixafor is a promising targeted therapy that, by down-regulating CXCR4/CXCL12 signalling, could lead to improved and durable clinical efficacy in patients with WHIM syndrome.

ACKNOWLEDGEMENTS

We thank all the patients who participated in this study.

REFERENCES


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