ORAL CXCR4 ANTAGONIST MAVORIXAFOR TREATMENT IN WHIM SYNDROME: RESULTS OF AN OPEN LABEL PHASE 2 STUDY WITH LONG-TERM EXTENSION.

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INTRODUCTION

- **W**arts, **H**ypogammaglobulinemia, **I**nfections, and **M**yelokathexis (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[1-2] 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[3] for the ongoing Phase 3 trial of mavorixafor in patients with WHIM syndrome (4WHIM).

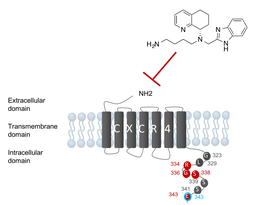

Figure 1. Gain of function mutations in the CXCR4 receptor. *The structure of the human CXCR4 receptor contains extracellular, transmembrane and intracellular domains. Highlighted here are previously published[4] mutated C-terminal (COOH) residues reported to cause WHIM syndrome. Heterozygous Autosomal Dominant Gain-of-Function CXCR4 mutations cause WHIM syndrome and truncate the carboxy-terminus by (1) premature termination, indicated in red, or (2) frameshift, indicated in grey. Both a stop mutation and a single amino acid substitution that cause WHIM syndrome are reported in position 343, indicated in red and blue.*

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.

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 for absolute neutrophil counts (AUC_{ANC}) and absolute lymphocyte counts (AUC_{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** (**TAT_{ANC}**) as the time, in hours, during which ANC remained above 500 cells/µL, and **Time Above Threshold for ALC (**TAT_{ALC}**)** as the time, in hours, during which ALC remained above 1000 cells/µL.
- Annualized infection rate at each dose was compared to the year prior to the study.
- Dermatological response evaluated the number of warts on the hands and feet.
- The data cut-off date for this analysis was June 14th, 2019

Inclusion criteria:
- Adult patients (≥18 years)
- Pathogenic CXCR4 mutation
- ANC ≤400/µL and/or ALC ≤650/µL

Trial registered at:
www.clinicaltrials.gov NCT03005327

Exclusion criteria:
- Treatment with plerixafor in prior 2 months
- and/or G-CSF in prior 2 weeks
- and/or any prohibited medication based on Cytochrome P450
- and/or P-glycoprotein interaction within the prior 2 weeks

RESULTS

- We enrolled 8 patients with genetically confirmed WHIM syndrome.
- All patients presented pathogenic gain-of-function mutations in the CXCR4 gene: 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).

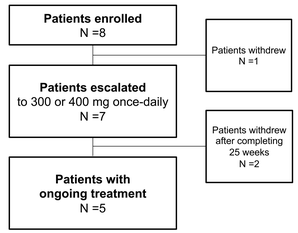

Figure 2: Study flowchart

- 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 TAT_{ANC} 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 TAT_{ALC} was 16.9 (±5.8) hours.

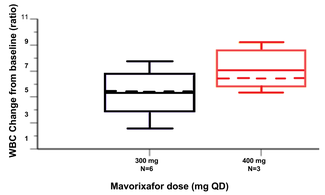

Figure 3: Box plots of WBC change from baseline ratio at 300 mg and 400 mg

- 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 400 mg was also observed.
- We found an average 75% reduction in the number of cutaneous warts.

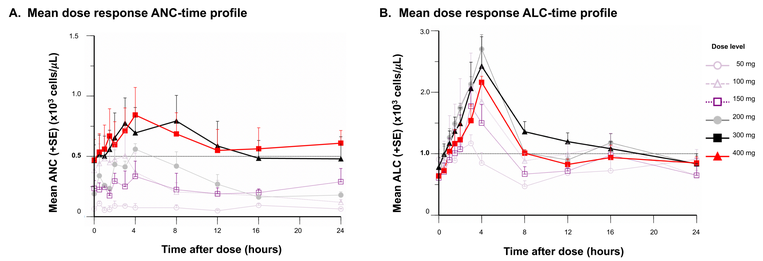

Figure 4: Mean dose response ANC-time (panel A) and ALC-time profiles (panel B) over 24 hours. Dashed lines indicate the ANC target threshold of 500 neutrophils/µL and the ALC target threshold of 1000 cells/µL.

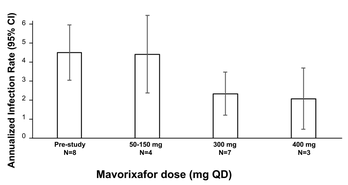

Figure 5: Reduction in the annualized infection rate upon treatment with mavorixafor 300 mg and 400 mg QD compared to the 12 months prior and to lower doses of mavorixafor (50 to 150 mg QD).

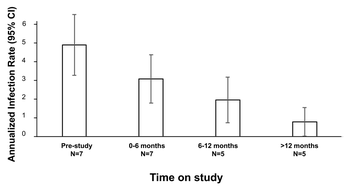

Figure 6: Reduction in the annualized infection rate over time upon treatment with mavorixafor in patients treated at 300 mg and/or 400 mg QD.

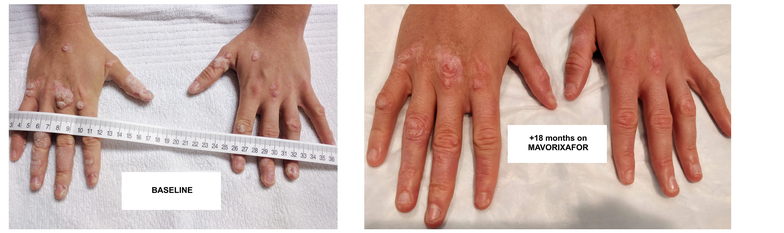

Figure 7: Reduction in the number of cutaneous warts during long-term, once-daily mavorixafor treatment. Patient was treated with increasing doses of mavorixafor for a total of 18 months. The patient was not given imiquimod or other dermatological treatments for warts. Left panel shows warts on hands at baseline. Right panel shows hands 18 months later, after 14 months at 400 mg mavorixafor. A significant decrease in wart burden could be seen after 6 months on treatment.

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 TAT_{ANC} 4.5-fold or more versus the TAT_{ANC} at lower doses. We suggest that TAT_{ANC}, 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
  - TAT_{ANC} 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

1. **Dale D-C *et al.*** X4P-001: A Novel Molecularly-Targeted Oral Therapy for WHIM Syndrome *59th Annual Meeting of the American Society for Hematology (ASH)* 2017.

2. **Dale D-C *et al.*** Phase 2 Study of X4P-001: A Targeted Oral Therapy for Patients with WHIM Syndrome. Poster PS1056. *23rd Congress of the European Hematology Association (EHA) 2018.*

3. **Dale D-C *et al.*** Determination of Phase 3 Dose for X4P-001 in Patients with WHIM Syndrome *60th Annual Meeting of the American Society of Hematology, (ASH) 2018.*

4. **Heusinkveld L-E *et al.*** WHIM Syndrome: from Pathogenesis Towards Personalized Medicine and Cure. *J Clin Immunol.* 2019;39(6):532–556.

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