Effect of Etrasimod On Circulating Lymphocyte Subsets: Data From a Randomized Phase 1 Study in Healthy Japanese and Caucasian Men

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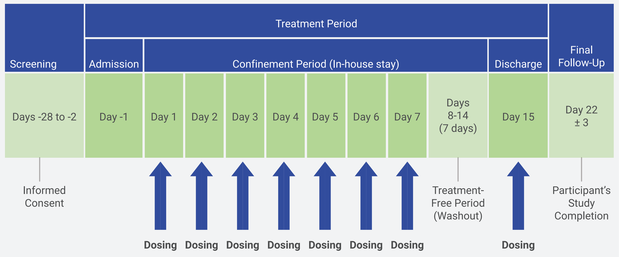
BACKGROUND

- Etrasimod is an orally administered selective sphingosine 1-phosphate (S1P) receptor 1,4,5 modulator that reduces peripheral lymphocytes and subsequently impedes their recruitment to sites of inflammation[1,2]
- Etrasimod is currently in development for chronic immune-mediated inflammatory diseases of ulcerative colitis, Crohn's disease, eosinophilic esophagitis, atopic dermatitis, and alopecia areata
- Reducing pro-inflammatory immune cells without causing broad immunosuppression is an important treatment goal in patients with these diseases
- This study evaluated the effect of etrasimod on circulating lymphocyte subsets in healthy volunteers to improve understanding of its proposed mechanism of action

METHODS

- In this phase 1, single-blind (participant only) pharmacokinetic (PK) and pharmacodynamic study, 49 healthy Japanese and Caucasian men were randomized to receive oral etrasimod 1 mg (n=20; 10 Japanese and 10 Caucasian), etrasimod 2 mg (n=20; 10 Japanese and 10 Caucasian), or matching placebo (n=9; 4 Japanese and 5 Caucasian)
- Participants received etrasimod or matching placebo once daily on Days 1-7, followed by a 7-day washout and a single dose on Day 15 (**Figure 1**)
- Absolute lymphocyte counts (ALC) were determined by complete blood count with differential. Samples were collected pre-dose on Days 1-7 and 15. On Days 8-14, the CBC blood samples were collected at approximately the same collection time as Days 1-7.
- Immune cell subsets were evaluated by flow cytometry from isolated peripheral blood mononuclear cells (PBMCs) collected pre-dose on Days 1, 3, 5, 7, and 15
  - Data for changes in immune cell subsets are presented as pooled for Japanese and Caucasian groups
  - Change from baseline on immune cell subtypes was evaluated using a mixed-effects model
  - Paired t-tests were computed to evaluate significant subtype modulations in etrasimod-treated groups versus placebo at Day 7

Figure 1. Study Design



RESULTS

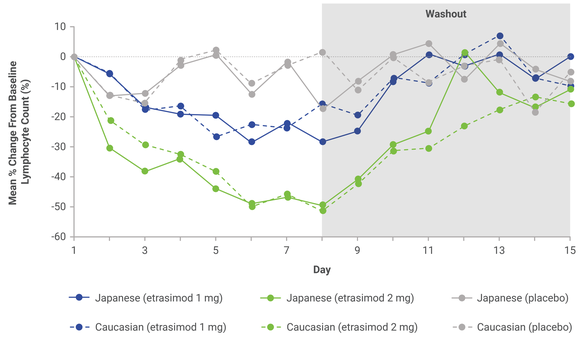
PARTICIPANTS

- 49 participants were included in the study and received ≥1 dose of study treatment

ABSOLUTE LYMPHOCYTE COUNT OVER TIME

- Compared with placebo, etrasimod 1 and 2 mg dosed daily for 7 days resulted in a dose-dependent reduction in ALC. The greatest mean percent change from baseline was -53.6% (8.7 SD) in the Japanese (etrasimod 2 mg) group and -54.1 (7.5) in the Caucasian (etrasimod 2 mg) group (**Figure 2**).
- By Day 15 pre-dose (7 days post-dose), total lymphocyte counts had returned to near baseline (mean percent of baseline ≥ 84%) and individual counts were within the normal range in 100% of participants.
- Changes in ALC were similar between Japanese and Caucasian groups

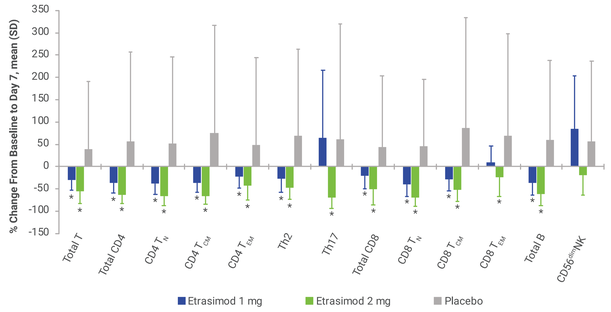
Figure 2. Mean Percent Change From Baseline in Lymphocyte Count Over Time



EFFECT OF ETRASIMOD ON IMMUNE CELL SUBSETS

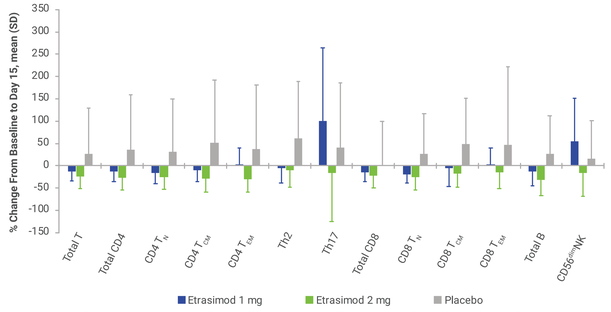
- Compared with placebo, etrasimod induced reductions in mean percent change from baseline to Day 7 in total T cells, total CD4+ and CD8+ T cells, naïve CD4+ and CD8+ T cells, central memory CD4+ and CD8+ T cells, effector memory CD4+ and CD8+ T cells, Th2 and Th17 cells, and total B cells (**Figure 3**)
- Trends in immune cell subsets were similar between Japanese and Caucasian groups
- Etrasimod resulted in greater reductions in naïve and central memory T cells than in effector memory T cells (**Figure 3**)
- No notable treatment effects were seen on innate immune cells such as monocytes, macrophages, or CD56^{dim} NK cells
- Decreased immune cell subsets recovered to ≥ 70% of baseline pre-dose on Day 15, after the 7-day washout period (**Figures 4-7**)

Figure 3. Mean Percent Change From Baseline to Day 7 in Immune Cell Subsets



*P<0.05 compared with placebo.
NK, natural killer cells; T_{CM}, central memory T cells; T_{EM}, effector memory T cells; T_N, naïve T cells; Total B, total B cells (CD20+); Total T, total T cells (CD3+).

Figure 4. Mean Percent Change From Baseline to Day 15 in Immune Cell Subsets



NK, natural killer cells; T_{CM}, central memory T cells; T_{EM}, effector memory T cells; T_N, naïve T cells; Total B, total B cells (CD20+); Total T, total T cells (CD3+).

Figure 5. (A) Total T cells (CD3+) and (B) Total B cells (CD20+) Over Time

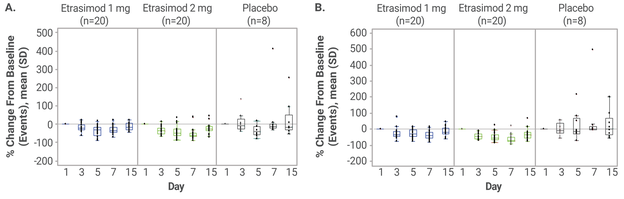


Figure 6. (A) Total CD4+ Naïve T cells and (B) Total CD8+ Naïve T cells Over Time

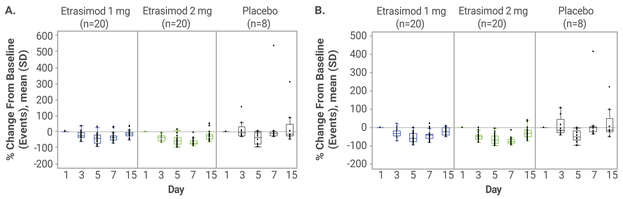
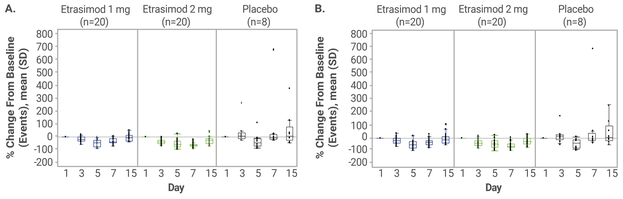


Figure 7. (A) Total CD4+ Central Memory T cells and (B) Total CD8+ Central Memory T cells Over Time



SAFETY

- Etrasimod 1 and 2 mg once-daily dosing regimens were safe and generally well tolerated
- No adverse events related to low lymphocyte values occurred

CONCLUSIONS

- Etrasimod effects on ALC and immune cell subsets were consistent with its known mechanism of action
- Little or no ethnic group differences in effects on ALC and immune cell subsets were observed in this study
- The effect of etrasimod on onset and offset of immune modulation is consistent with etrasimod PK, with a typical half-life of approximately 33 hours
- The differential effects of etrasimod on immune cell subsets may allow for a reduction in inflammation while maintaining immune surveillance
- The lymphocyte subset profile suggests that etrasimod reduces certain immune cells and behaves as a selective immunomodulator rather than as a broad immunosuppressive agent

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REFERENCES:
1. Al-Shamma H et al. *J Pharmacol Exp Ther* 2019;369:311–317.
2. Matloubian M et al. *Nature* 2004;427:355–360.

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DISCLOSURES: HKK, CL, KG, and JG are employees of Arena Pharmaceuticals, Inc. LA was employed at Arena Pharmaceuticals, Inc. at the time of the study.

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