Pharmacokinetics and Circulating Total Lymphocyte Count
Pharmacodynamic Response From Single and Multiple Oral Doses of Etrasimod in Japanese and Caucasian Healthy Male Subjects

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Introduction
• Etrasimod (APD334) is an oral, synthetic, selective sphingosine 1-phosphate (S1P) receptor modulator in development for chronic immune-mediated inflammatory disorders
  - Etrasimod selectively targets S1P receptors 1, 4, and 5 (S1P1, S1P4, and S1P5). S1P regulates lymphocyte egress from lymphoid organs and
  - Etrasimod demonstrated efficacy in patients with moderately to severely active ulcerative colitis
• In the present phase 1 study, we evaluated etrasimod PK and pharmacodynamics (PD) in healthy male subjects of Japanese or Caucasian descent

Methods
• This single-blinded (subject only), placebo-controlled, phase 1 study included 49 healthy male subjects in 4 treatment groups randomized to receive etrasimod or placebo (10 etrasimod and 2 placebo per group)
• Treatment groups were: Japanese, etrasimod 1 mg; Japanese, etrasimod 2 mg; Caucasian, etrasimod 1 mg; and Caucasian, etrasimod 2 mg
• Subjects met one of the following ethnicity criteria:
  - Japanese: both of the subject’s biological parents and all four grandparents had to be Japanese
  - Caucasian: had to be of Northern, South American, South American, or Middle Eastern descent
• Subjects received etrasimod at matching placebo once daily (QD) from Days 1 to 7, followed by a 7-day washout and a single dose on Day 15 (Figure 1)
  - Blood was sampled multiple times on Days 1 and 7 for plasma single- and multiple-dose PK assessment and each morning from Day 1 through Day 15 to assess lymphocyte counts and calculate lymphocyte PD parameters, including the minimum and maximum response values after dosing (Cmin, Cmax, respectively) and net area under the effect curve (AUC). Cmin is the area to the bottom baseline and below the curve minus the area that is both below baseline and above the curve

Results
Subjects
• Total body weight (TBW) of subjects receiving etrasimod was lower in subjects of Japanese descent compared with subjects of Caucasian descent

Pharmacokinetics
• Etrasimod peak concentration (Cmax) and total plasma exposure (AUC) values in both ethnic groups were dose-proportional following either a single dose or multiple doses (Table 2)
• Etrasimod mean Cmax and AUC were slightly higher in Japanese subjects compared with Caucasian subjects following either a single dose or multiple doses

Lymphocyte Pharmacodynamics
• Dose-dependent, progressive decreases in mean absolute and percent change from baseline lymphocyte counts were observed across all four treatment groups from Day 2 to Day 8, followed by a subsequent increase to near baseline levels during the 7-day washout period (Figure 2)
  - No statistically significant differences were observed between Japanese and Caucasian subjects for lymphocyte Cmax, or AUC, based on least square (LS) mean values

Conclusions
• Single and multiple dose etrasimod mean peak (Cmax) and total plasma exposure (AUC) measures were slightly to moderately higher in Japanese subjects compared with Caucasian desent, but were similar after dose-body weight normalisation
• No statistically significant differences were observed between subjects of Japanese and Caucasian descent for lymphocyte PD parameters of Rh, Rho, or AUC upon administration of multiple doses of etrasimod
• These results demonstrate a lack of clinically meaningful PK or PD (lymphocyte response) ethnic differences between healthy male subjects of Japanese and Caucasian descent

References

Figure 1. Study Design

Figure 2. Mean (A) Lymphocyte Count and (B) Change from Baseline Lymphocyte Count (%) Over Time

Table 1. Subject Demographic and Baseline Characteristics

Table 2. Summary of Etrasimod Single Dose and Multiple Dose Plasma PK Parameters in Japanese and Caucasian Male Subjects

Table 3. Summary of Japanese/Caucasian GMR of Cmax and AUC after Single and Multiple Doses

Table 4. Summary of Baseline and Nadir Lymphocyte Counts and Time to Nadir

Table 5. Summary of Lymphocyte PD Parameters in Subjects Treated With Etrasimod (Day 1 to Day 15)

Table 4

Table 5

**Summary of Japanese/Caucasian GMR of Cmax and AUC after Single and Multiple Doses**

**Summary of Baseline and Nadir Lymphocyte Counts and Time to Nadir**

**Summary of Lymphocyte PD Parameters in Subjects Treated With Etrasimod (Day 1 to Day 15)**