Model-Predicted Lymphocyte Response and Recovery Profiles for the Sphingosine 1-Phosphate Receptor Modulators Ozanimod and Etrasimod

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BACKGROUND

- Sphingosine 1-phosphate receptor (S1PR) modulators inhibit lymphocyte egress from lymph nodes, thereby reducing the number of peripheral lymphocytes available to be recruited to sites of inflammation[1,2]
- Ozanimod is an S1PR modulator approved for the treatment of multiple sclerosis and ulcerative colitis (UC)[3,4]
  - The lymphocyte-lowering response to ozanimod treatment and recovery following drug discontinuation is mainly driven by pharmacokinetic (PK) exposure and half-life (≈11 days) of its active metabolite (CC112273)[5]
- Etrasimod is an S1PR modulator in clinical development for the treatment of immune-mediated inflammatory disorders, including inflammatory bowel disease
  - The lymphocyte-lowering response to etrasimod treatment and recovery following drug discontinuation is mainly driven by PK exposure and half-life of the parent drug (≈30 hours), as it has no major active (or inactive) circulating metabolites[6]
- Exposure-response models describing observed/published PK and pharmacodynamic (PD) data can facilitate comparisons between compounds
- Here, we present a model-predicted, head-to-head comparison of lymphocyte response profiles for once-daily dosing of ozanimod and etrasimod, including lymphocyte recovery following discontinuation of either drug

CONCLUSIONS

- Model predictions of lymphocyte response and recovery profiles indicate that etrasimod is expected to achieve lymphocyte nadir more quickly and require less time to recover to the normal range after drug discontinuation compared with ozanimod
- Rapid drug washout and reconstitution of the immune system may be desirable when considering resolution of infection, switching therapies, and family planning

Disclosures

C. A. Lee, D. A. Oh, H. K. Komori, and J. S. Grundy are employees of Arena Pharmaceuticals, a wholly-owned subsidiary of Pfizer Inc, New York, NY, USA. **T. Waterhouse** and **M. Heathman** are employees of Metrum Research Group, which received funding from Arena Pharmaceuticals for conduct of the reported analyses.

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METHODS

Observed PK and PD Data

Ozanimod

- The following were used for PK and PK/PD model development:
  - Published "summary-level" observed PK and PD data of ozanimod's active metabolite (CC112273) and lymphocyte response, respectively
  - Mean and standard deviation (SD) PK profiles (following single doses of 0.5 and 1 mg ozanimod)[5]
  - Mean and standard error of the mean (SEM) percent change from baseline lymphocyte count profiles (placebo and various ozanimod fixed and dose-escalation dosing regimens ranging from 0.3 to 2 mg/day)[7]

Etrasimod

- Etrasimod population PK/PD model development used observed, individual subject PD lymphocyte data consisting of 6400 observations from 548 subjects, obtained from 7 phase 1 studies in healthy volunteers and 3 phase 2 studies in subjects with either UC or atopic dermatitis
  - Evaluated etrasimod single and multiple dose levels ranged from 0.1-5 mg and 0.35-4 mg once daily, respectively
  - Post hoc PK parameter estimates for each of the individual 548 evaluated subjects were obtained from a previously developed population PK model (not shown)

Model Development and Validation

- Data manipulation, visualization, and simulations were conducted using version 3.6.2 of R (http://www.rproject.org)
- All population PK and PK/PD analyses were conducted via nonlinear mixed-effects modeling with a qualified installation of the nonlinear mixed-effects modeling (NONMEM) software, version 7.4 (ICON Development Solutions)

Etrasimod

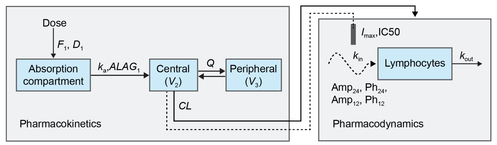
- A previously developed and validated population PK model for etrasimod (not shown) was used to generate individual subject post hoc PK parameter estimates for use in a sequential modeling approach for etrasimod population PK/PD model development
- The etrasimod population PK/PD model (**Figure 1**) was an indirect response model in which etrasimod concentrations inhibit egress of lymphocytes from lymph nodes to the systemic circulation (lymphocyte trafficking), with a circadian rhythm model component also included to account for diurnal changes in lymphocyte counts throughout the day
  - The IIV of the model parameters was described by an additive model in the log domain; the residual error model included both proportional and additive error terms
  - A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented
    - The final PK/PD model included covariate effects for age, body weight, sex, race, subject status, and ethnicity

The population PK/PD model validation for etrasimod lymphocyte response involved a longitudinal visual predictive check, Bayesian model fits, and goodness-of-fit plots

Ozanimod

- The population PK model for metabolite CC112273 summary-level PK data used a 2-compartment model with zero-order absorption
  - Structural model parameters were estimated using a least-squares fit to the published observed mean (SD) concentration-time data
  - Interindividual variability (IIV) and residual unexplained variability (RUV) were determined by trial and error using comparison of confidence intervals (CIs) to the published observed mean (SD) values
    - The IIV was described by log-normal distributions, and RUV was described by a combined additive and proportional error model
- The population PK/PD model for summary-level ozanimod lymphocyte response over time was based on a published direct maximum effect (E_{max}) model[8]
  - A nominal baseline lymphocyte count of 2×10^9/L was used in model calibration
  - Structural model parameters were as published[8]
  - The IIV of the model parameters was described by log-normal distributions; RUV was described by a combined additive and proportional error model
    - Variability terms were determined by trial and error, with systematic comparison of CIs (assessed by simulation of 10,000 replicates) of the mean (SEM) with the published observed mean (SEM) lymphocyte-time data
- The population PK and PK/PD models for ozanimod were validated by performing simulations with multiple doses and comparing with the relevant published observed summary-level data
  - The initial population PK/PD model simulation predicted a mean baseline lymphocyte count of 1.97×10^9/L (slightly higher than the published observed results from the ozanimod RADIANCE study [1.83×10^9/L]); thus, a correction factor of 0.93 was applied to the ozanimod simulations

Figure 1. Diagram of Etrasimod Population PK/PD Base Model



ALAG$_1$, oral absorption lag time; Amp_{12}, amplitude for 12-hour period; Amp_{24}, amplitude for 24-hour period; CL, systemic clearance; D_1, duration of zero-order absorption; F_1, relative bioavailability; IC50, concentration required to achieve half the maximum inhibition; I_{max}, maximum inhibition; k_a, absorption rate constant; K_{in}, egress rate constant, k_{out}, removal rate constant, Ph_{12}, phase for 12-hour period; Ph_{24}, phase for 24-hour period; Q, intercompartmental clearance; V_2, central volume of distribution; V_3, peripheral volume of distribution.

Population PK/PD Model Primary Endpoints and Simulations

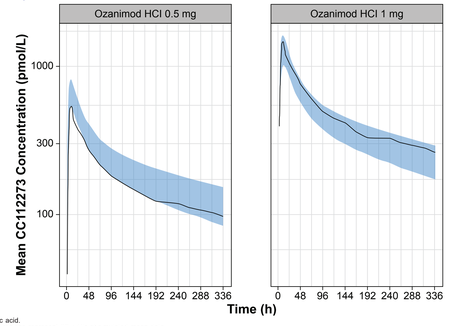
- The primary modeling endpoints for both ozanimod and etrasimod included the following:
  - Predicted time to reach median steady-state lymphocyte nadir following once-daily dosing
  - Predicted time for lymphocytes to return to above the lower limit of normal in 90% of subjects after dosing discontinuation
- Simulations from both models of 10,000 virtual participants given ozanimod (initial 7-day titration: 0.23 mg on days 1-4, 0.46 mg on days 5-7, and 0.92 mg on day 8 and thereafter for 11 weeks) or etrasimod (2 mg for 12 weeks) were produced and compared
  - In addition, primary modeling endpoints were determined and compared between these dosing regimens

RESULTS

Ozanimod

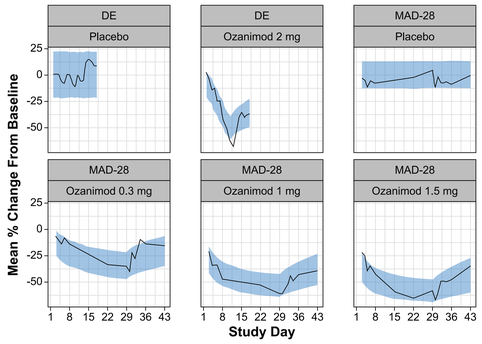
- Population PK model-predicted mean concentration-time profiles of CC112273 (**Figure 2**) and population PK/PD model predicted mean lymphocyte count-time profiles (**Figure 3**) upon dosing of ozanimod appear generally consistent with corresponding published observed mean values[6,7]
- Similarly, respective model predictions of variability in these measures (results not shown) also appear generally consistent with the corresponding published observed variability

Figure 2. Observed (Black Lines) vs Simulated (Blue Shaded Regions[a]) Mean CC112273 Concentrations



HCl, hydrochloric acid.
[a] Blue simulated regions represent 95% CIs of simulated mean data.

Figure 3. Observed (Black Lines) vs Simulated (Blue Shaded Regions[a]) Mean Lymphocyte Percent Changes From Baseline for Placebo and Ozanimod

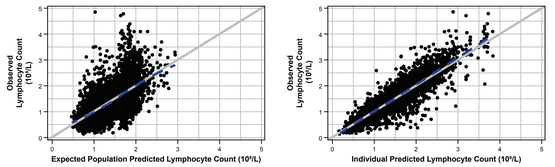


DE, dose escalation cohort; MAD-28, multiple ascending-dose for 28 days cohort.
[a] Blue simulated regions represent 95% CIs of simulated mean data.

Etrasimod

- The population PK/PD final model predicted lymphocyte counts appear generally consistent with corresponding observed values obtained from etrasimod phase 1 and 2 clinical studies (**Figure 4**)

Figure 4. Population Predicted and Individual Predicted vs Observed Lymphocyte Counts From the Final PK/PD Model for Etrasimod[a]

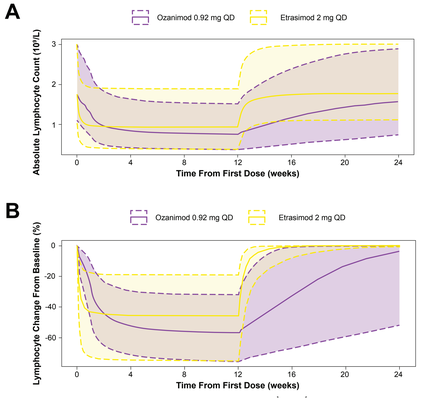


[a] Observed values are indicated by solid black circles. The line of identity (solid gray) is included as a reference (x=y). Dashed blue line represents a LOESS smooth through the data.

Model Simulation and Primary Endpoint Comparisons Between Compounds

- Model-predicted lymphocyte responses over time reached approximately (ie, ≥90%) median steady-state lymphocyte nadir within 24 days for ozanimod and within 5 days for etrasimod (**Figure 5**)
- After drug discontinuation, the model-predicted time for lymphocyte counts (absolute and percent change from baseline) to return to the lower end of normal (0.8×10^9/L or 1.0×10^9/L) for 90% of virtual participants was 48 or 81 days, respectively, for ozanimod and 2 or 4 days, respectively, for etrasimod (**Table 1**)
- Model simulation endpoint results for ozanimod appear generally consistent with corresponding lymphocyte statements from its label[9]

Figure 5. Model-Predicted Simulations of (A) Absolute Lymphocyte Count and (B) Percent Change From Baseline vs Time Profiles for Ozanimod and Etrasimod[a]



QD, once daily.
[a] Solid lines are median; shaded regions are 95% prediction intervals. Ozanimod was given at 0.23 mg QD on days 1-4, 0.46 mg QD on days 5-7, followed by 0.92 mg QD for 11 weeks. Baseline lymphocyte counts in simulations were selected such that the mean matches the mean of baseline for participants in the ozanimod RADIANCE study. Etrasimod was given at 2 mg QD for 12 weeks.

Table 1. Time for Lymphocytes to Return to Normal Range in 90% of Subjects

	Days to Normal Range After Treatment Discontinuation	
Treatment	**LLN: 0.8×10^9/L**	**LLN: 1.0×10^9/L**
Ozanimod 0.92 mg QD	48	82
Etrasimod 2.0 mg QD	2	4

LLN, lower limit of normal; QD, once daily.