W-032

Joint Exposure-Response Longitudinal Modeling of Modified Mayo Score and Dropout in Patients with Moderate to Severely Active Ulcerative Colitis.

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INTRODUCTION

Etrasimod is an oral sphingosine 1-phosphate (S1P) receptor modulator that is approved for the treatment of moderate to severely active ulcerative colitis with a dose of 2 mg once daily. Efficacy was evaluated using the Mayo score which is composed of three components: rectal bleeding (RB), stool frequency (SF), and endoscopy findings (endoscopic score [ES], Geboes Index, Physicians Global Assessment). Each component is scored on a scale from 0 to 3 with the combined score being the sum of each of the component scores (0 is best, 3 is worst). A longitudinal joint model with dropout was developed to characterize the five Mayo score measures over time together with the dropout [1]. The average concentration of etrasimod at steady state was the exposure metric that best correlates with the efficacy.

DATA

The model was built using the Phase 2 studies APD344-003/005 and the Phase 3 studies APD334-301, APD334-302/308 [2]. There was a total of 943 subjects and 20,783 efficacy observations (**see Table 1**). The dropout spikes at Week 12 (**Figure 1**) which is the transition time from the end of the induction period (Week 12) to the maintenance period in a treat-through design.

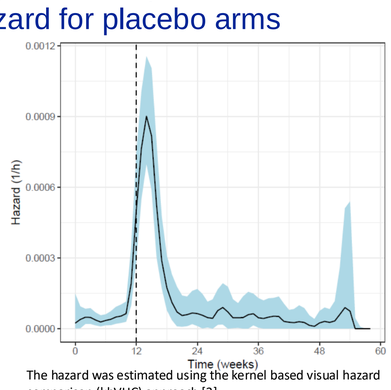
Table 1. Summary of Demographics and Efficacy Score Counts

	Continuous		Categorical			Efficacy Scores (N)	
	Age (yrs)	Bodyweight (kg)	Sex N (%)	Race N (%)	Study N (%)		
Median	39	72	Male: 536 (56.8)	White: 794 (84.2)	Study 003: 156 (16.5)	Rectal bleeding	7334
Mean (Std. Dev.)	40.8 (13.7)	73.4 (16.8)	Female: 404 (42.8)	Black: 14 (1.5)	Study 301: 433 (45.9)	Stool frequency	7334
Range (Min; Max)	(16; 78)	(35; 140)	Missing: 3 (0.3)	Asian: 107 (11.3)	Study 302: 354 (37.5)	Endoscopic score	2159
N (%)	943 (100.0)	943 (100.0)		Multiple/Other: 25 (1.3)		Physician's Global Assessment	2223
Missing (%)	3 (0.3)	3 (0.3)		Missing: 3 (0.3)		Geboes Index	1733

RESULTS

The joint longitudinal-dropout model was able to better capture the relationship between efficacy and exposure by incorporating the dropout, which was more likely in patients with little to no response to treatment. The model was able to characterize the dropout over time (**Figure 2**). The VPCs show that the model also does a much better job characterizing the longitudinal relationship with the efficacy scores (**Figure 3)** including for outcomes calculated from the 5 efficacy subscores (eg Clinical Remission).

Figure 1. Nonparametric estimate of hazard for placebo arms



The hazard was estimated using the kernel based visual hazard comparison (kbVHC) approach [3].

Figure 2. Visual Predictive Check of Dropout

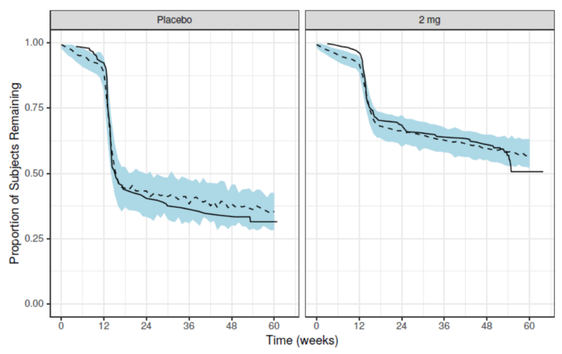
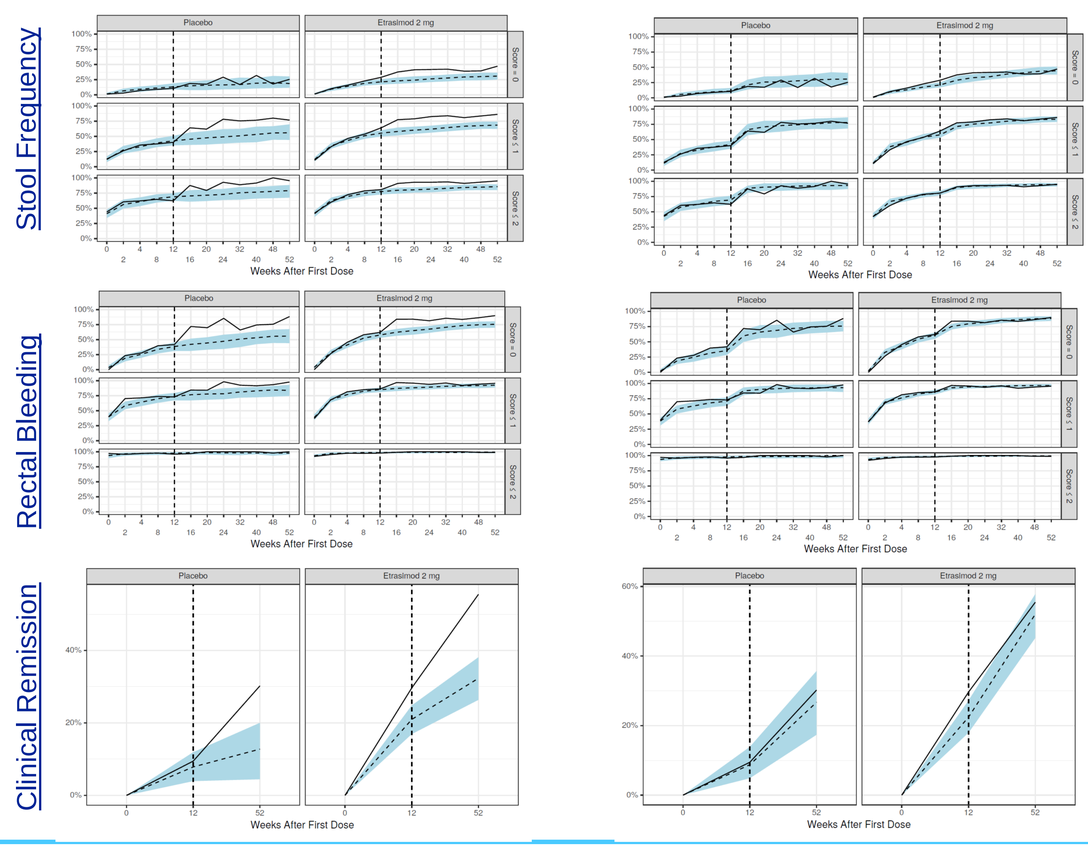


Figure 3. VPCs With and Without Accounting for Dropout



CONCLUSIONS

The longitudinal joint model was able to characterize the exposure-response relationship with modified mayo score components and dropout. By jointly modeling the efficacy and the dropout rate, the model helped to understand the effect that the enriched population – resulting from increased dropouts driven by poor response to treatment – had on the efficacy predictions.

METHODS

Longitudinal Efficacy Model

Differential odds model for each score in which the probability of achieving a certain score at time t is described

$$g\{Pr[S_m(t) \le k]\} = \alpha_{km} + \left[f_{pm}(t) + f_{dm}(t)\right] \cdot \delta_k + \eta_{bm}$$

Where:

- g() is the logit link function
- S_m is the score for one of SF, RB, ES, or Geboes Index
- k is one of the potential value for the score
- α_{km} is the intercept
- f_{pm} is a function describing the placebo effect
- f_{dm} is a function describing the drug effect
- δ_k is the different effect for a score of k (with $\delta_0 = 1$)
- η_{bm} is the random effect for baseline IIV ($\eta_{bm} \sim N(0, \omega_{bm}^2)$)

The intercept, α_{km}, was parameterized as $(\alpha_{1m}, d_{1m}, d_{2m}, d_{3m})$ with $d_{im} > 0$ such that $\alpha_{im} = \alpha_{(i+1)m} - d_{im}$ for $i < 1$, and $\alpha_{im} = \alpha_{(i-1)m} - d_{im}$ for $i > 1$.

Inter-individual random effects and structural model parameters were shared between scores to allow the more frequently collected scores to inform the sparsely collected scores related to endoscopy readings (ES, PGA, and Geboes Index). This was accomplished via a shared latent variable.

$$\frac{dR(t)}{dt} = k_{in} \cdot \left(1 - \text{Slope} \cdot C_{avg,ss}\right) - k_{out} \cdot R(t)$$

Where:

- R(t) is a latent variable
- $C_{avg,ss}$ is the average etrasimod concentration at steady state.
- k_{in}, k_{out}, and Slope are parameters in an inhibition on k_{in} indirect response model.

The reduction in R(t) was then used to drive drug effect for each subscore:

$$f_{dm}(t) = DE_m \cdot \left(1 - R(t)\right)$$

$$f_{pm}(t) = P_{max,m} \cdot \left(1 - \exp\left(-k_p t\right)\right)$$

Where:

- $P_{max,m}$ is the maximum (asymptotic) placebo effect for subscore m; and
- k_p is the rate constant for the placebo effect timecourse (shared between scores).

Joint Longitudinal-Dropout Model

A model involving the joint likelihood of longitudinal response and dropout was developed, using a link function involving the baseline, placebo effect, and drug effect (via the latent variable R(t).

$$h(t;\theta_i) = h_0(t) \cdot \exp\left(-\beta \cdot f(t;\theta_i)\right)$$

Where:

- h() is the hazard function (h_0 is the baseline hazard)
- θ_i is the vector of longitudinal model parameters for subject i
- f is a link function
- β is the link parameter, capturing the strength of the association between the efficacy response and dropout.

Dropout was well described by the baseline hazard function as follows:

$$h_0(t) = \begin{cases} \lambda & t_{start} > t \text{ or } t > t_{start} + t_{dur} \\ \lambda \cdot \left(1 + \text{AMP} \cdot \sin\left(\dfrac{2\pi}{2t_{dur}} \cdot (t - t_{start})\right)\right) & t_{start} \le t \le t_{start} + t_{dur} \end{cases}$$

Where:

- λ is the baseline dropout rate
- t_{start} is the starting time of the spike and
- t_{dur} is the duration of the hazard spike
- Amp is the amplitude of the hazard spike

The link function involved baseline, placebo, and drug effects, taking the average of each across the 5 subscores:

$$f(t;\theta_i) = \frac{1}{5}\sum_{m=1}^{5}\eta_{bm,i} + \frac{1}{5}\left(\sum_{m=1}^{5}P_{max,m}\right)\left(1 - \exp\left(-k_{p,i}t\right)\right) + \frac{1}{5}\left(\sum_{m=1}^{5}DE_m\right)\left(1 - R(t)\right)$$

REFERENCES

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3. Goulooze et al. "Kernel-based visual hazard comparison (kbVHC): a simulation-free diagnostic for parametric repeated time-to-event models." The AAPS journal 20 (2018): 1-11.