

Modeling Longitudinal Count Data Disease Dynamics: A Bayesian Continuous-Time Markov Analysis of Povorcitinib in Hidradenitis Suppurativa

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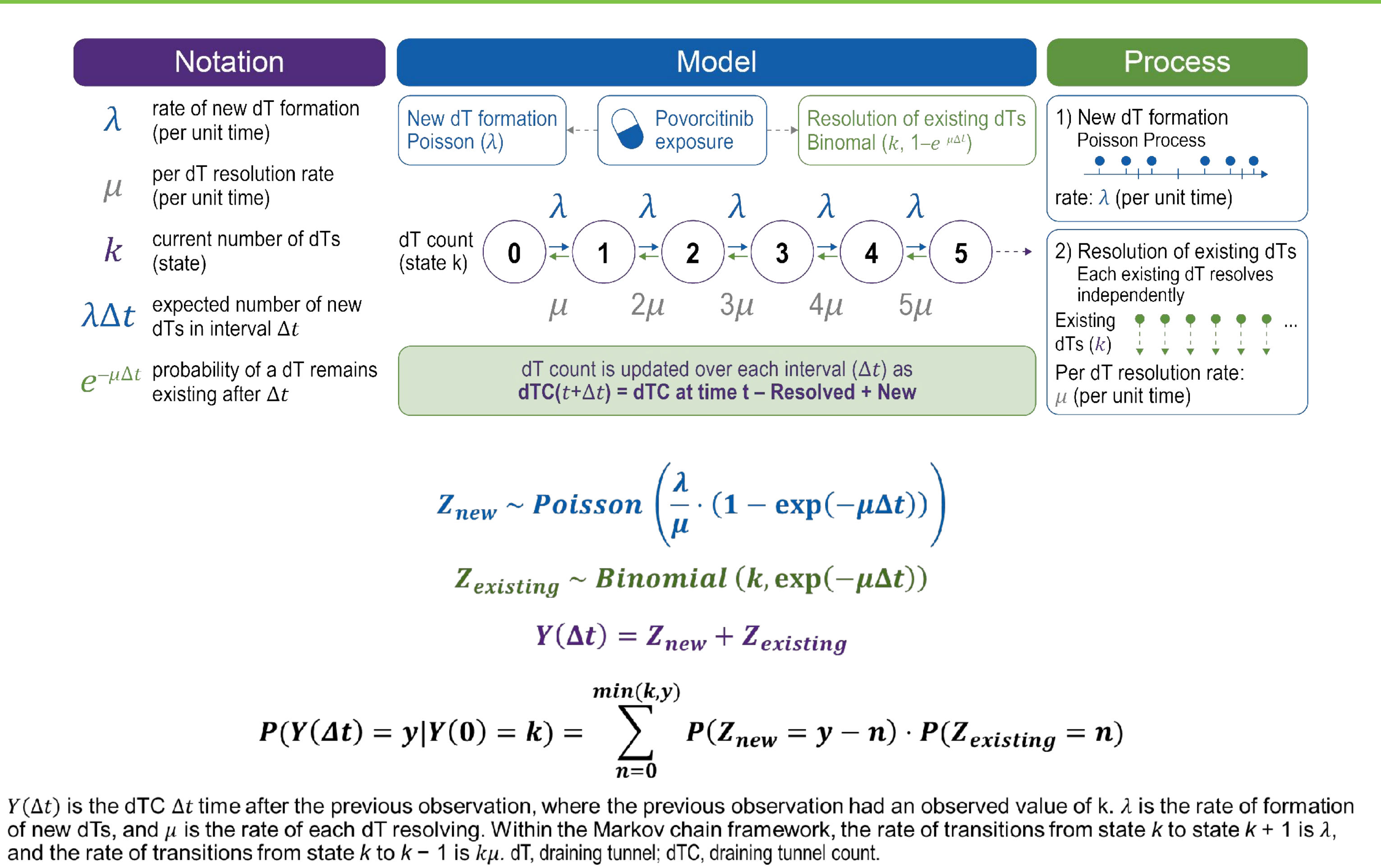
Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent nodules, abscesses, and draining tunnels (dT) that contribute substantially to disease burden.¹ The presence of dTs is indicative of irreversible tissue damage, and a surrogate marker of a more challenging to treat HS, making dT count (dTC) a clinically meaningful endpoint. Povorcitinib is an oral, highly selective Janus kinase 1 inhibitor with demonstrated efficacy in reducing dTC in the phase 3 STOP-HS1 and –HS2 studies.² Because dTC changes dynamically over time, a continuous-time Markov model (birth-death process) was developed to characterize the longitudinal relationship between povorcitinib exposure and dTC in patients with moderate to severe HS

Methods

Data from a phase 2 study (NCT04476043) and two phase 3 studies (STOP-HS1/-HS2 [NCT05620823, NCT05620836]) of povorcitinib in HS were analyzed. A continuous-time Markov model, equivalent to a M/M/∞ queueing process, was developed in which each state represented a dTC value. The model structure and underlying transition process are summarized in Figure 1

Figure 1. Schematic Overview of the Continuous-Time Markov Birth-Death Model



The model was parameterized using the stationary mean of dTC ($\tau = \lambda/\mu$) and a turnover parameter $\rho = \lambda \cdot \mu$, with povorcitinib exposure incorporated as a piecewise-constant time-varying predictor of mean dTC

$$\log(\tau_i(t)) = \tau_0 + X_i^T \beta_\tau + f_\tau(Cavg_{ss,i}, X_i, \theta) + \zeta_\tau I_\zeta + \eta_i^T$$

Note: $\tau_i(t)$ is the expected stationary mean dTC, τ_0 is the population typical value, X_i is the covariate vector, β_τ is the vector of covariate coefficients, $Cavg_{ss,i}$ is the steady-state average concentration, θ denotes the exposure-response parameters, ζ_τ is the baseline period effect, I_ζ is the baseline indicator, and η_i is the individual random effect. The model equation is the same for ρ , except that the baseline offset and random effect terms were not used. dTC, draining tunnel count.

Covariates were evaluated on structural parameters based on clinical relevance, including:

- Age
- Body mass index
- Pan-immune-inflammation value (PIV; surrogate parameter to more broadly quantify systemic inflammation)
- Prior treatment with an anti-tumor necrosis factor alpha (anti-TNF-α) for HS; subpopulation of patients with potentially more recalcitrant disease

Model development used a Bayesian framework with weakly informative priors and was implemented in Stan through the brms interface.^{3,4} Predictive performance guided model selection, and simulations quantified dose-dependent differences in dTC response and onset

Results

Figure 2. Model-Predicted Mean Percentage of Achieving Zero dTC (Baseline dTC ≥1 Population)

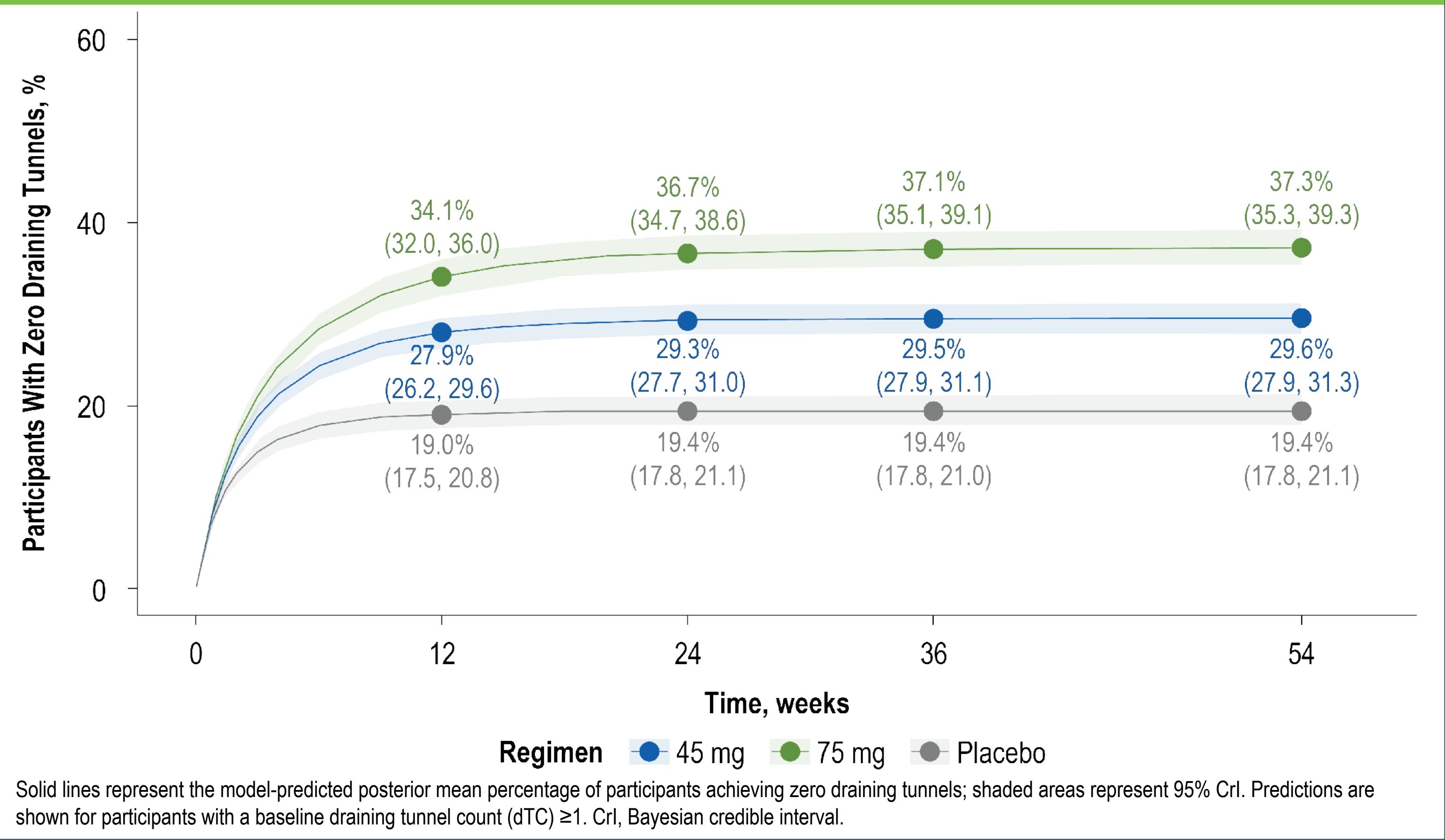


Table 1. Model-Predicted Duration of Zero dTC

Metric	Placebo	45 mg QD	75 mg QD
Achieved dTC=0 within 54 weeks, proportion	0.638 (0.569, 0.709)	0.755 (0.696, 0.813)	0.814 (0.763, 0.861)
Duration of dTC=0, weeks (54 max)	9.88 (7.45, 12.5)	14.6 (11.8, 17.8)	18.0 (14.9, 21.5)
Achieved dTC=0 within 24 weeks, proportion	0.527 (0.456, 0.597)	0.633 (0.569, 0.697)	0.692 (0.629, 0.750)
Proportion of time with dTC=0 after achieving first zero dT* (Restricted to those who achieved dTC=0 by Week 24)	0.365 (0.312, 0.417)	0.454 (0.408, 0.500)	0.516 (0.475, 0.559)

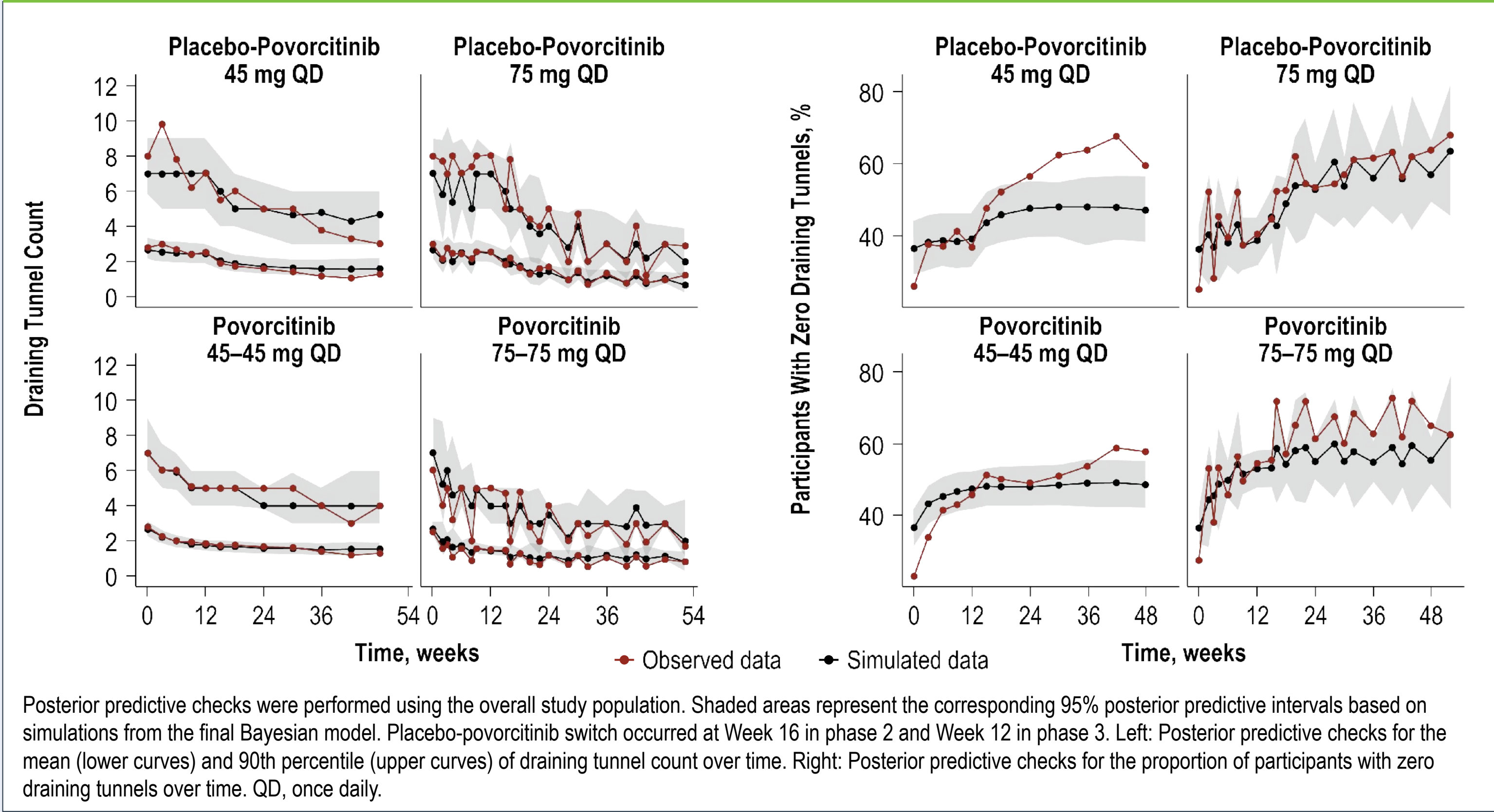
Analysis was restricted to simulated participants with baseline dTC ≥1. Results are based on model simulations and are presented as posterior mean (95% CrI). CrI, Bayesian credible interval; dT, draining tunnel; dTC, draining tunnel count; QD, once daily.

Table 2. Model-Predicted Percentage of Achieving Zero dTC

Group	Dose	Week 12*	Week 24	Week 36	Week 54
Naive + baseline PIV ≥349†	45 mg QD	24.7 (22.5, 26.9)	26.2 (24.0, 28.5)	26.5 (24.5, 28.7)	26.6 (24.5, 28.9)
	75 mg QD	30.7 (28.2, 33.3)	33.8 (31.2, 36.4)	34.4 (31.9, 37.0)	34.6 (32.1, 37.2)
Naive + baseline PIV <349†	45 mg QD	36.5 (33.8, 39.2)	38.8 (36.1, 41.5)	39.1 (36.3, 41.9)	39.2 (36.5, 42.1)
	75 mg QD	44.9 (41.7, 48.0)	49.1 (45.9, 52.2)	49.7 (46.7, 52.7)	49.9 (46.8, 52.9)
Experienced + baseline PIV ≥349†	45 mg QD	17.8 (15.5, 20.3)	17.9 (15.6, 20.5)	17.9 (15.6, 20.4)	17.9 (15.4, 20.4)
	75 mg QD	20.5 (17.9, 23.1)	20.6 (17.9, 23.3)	20.6 (17.8, 23.4)	20.6 (17.8, 23.4)
Experienced + baseline PIV <349†	45 mg QD	28.4 (24.9, 32.1)	28.6 (24.9, 32.3)	28.5 (24.9, 32.3)	28.5 (25.0, 32.2)
	75 mg QD	33.2 (29.1, 37.5)	33.5 (29.0, 38.1)	33.4 (29.4, 37.6)	33.4 (29.2, 37.5)

Analysis was restricted to simulated participants with baseline dTC ≥1. Results are based on model simulations and are presented as posterior mean (95% CrI). * End of placebo-controlled period. † Naive: no prior anti-TNF-α treatment for HS; Experienced: prior anti-TNF-α treatment for HS; PIV cutoff was based on the observed median baseline value of 349. CrI, Bayesian credible interval; dTC, draining tunnel count; PIV, pan-immune-inflammation value; QD, once daily; TNF, tumor necrosis factor.

Figure 3. Posterior Predictive Check by Treatment Arm



Overall Treatment Response

A clear exposure-response relationship was identified, with dose-dependent reductions in dTC. The predicted proportion of participants achieving zero dTs increased rapidly during the first 12 weeks and reached near steady state after approximately 24 weeks (Figure 2). By Week 54, 37.3% of participants receiving 75 mg QD were predicted to achieve zero dTs compared with 29.6% for 45 mg QD. The 75 mg QD regimen also resulted in lower mean dTC and a longer cumulative duration of zero dTs over 54 weeks (18.0 vs 14.6 weeks; Table 1). The final model provided an adequate description of the observed data and reproduced the observed exposure-response relationship well (Figure 3)

Effects of Baseline Inflammation and Prior Anti-TNF-α-Naïve Therapy

Baseline PIV (a surrogate for systemic inflammation) and prior anti-TNF-α therapy (a surrogate for recalcitrant disease) were important predictors of treatment response. Anti-TNF-α-naïve participants with lower baseline PIV had the highest predicted proportion of participants achieving zero dTs, whereas anti-TNF-α-experienced participants with higher baseline PIV had the lowest (Table 2). Despite differences in absolute response across subgroups, the 75 mg QD regimen consistently outperformed the 45 mg QD regimen throughout the study

Effect of Baseline Disease Severity

Baseline dTC was an important determinant of response trajectories. Although participants with higher baseline dTC maintained higher absolute dTC throughout treatment, they achieved larger absolute reductions and greater percentage improvements from baseline (Table 3). The simulated dTC trajectories showed earlier and greater reductions with the 75 mg QD regimen than with the 45 mg QD regimen across all baseline severity groups, with the treatment benefit maintained through Week 54

Table 3. Model-Predicted Population Mean Draining Tunnel Count

Baseline	Dose	Week 0	Week 12	Week 24	Week 36	Week 54
dTC=1, 2	45 mg QD	1.39 (1.38, 1.41)	0.916 (0.864, 0.971)	0.912 (0.859, 0.968)	0.911 (0.859, 0.966)	0.911 (0.860, 0.966)
	75 mg QD	1.39 (1.38, 1.41)	0.706 (0.660, 0.754)	0.690 (0.642, 0.740)	0.689 (0.642, 0.740)	0.689 (0.643, 0.737)
dTC=3, 4	45 mg QD	3.42 (3.40, 3.45)	1.98 (1.87, 2.09)	1.88 (1.77, 1.99)	1.87 (1.76, 1.98)	1.87 (1.76, 1.98)
	75 mg QD	3.42 (3.40, 3.45)	1.58 (1.48, 1.68)	1.44 (1.35, 1.55)	1.43 (1.33, 1.53)	1.42 (1.33, 1.52)
dTC ≥5	45 mg QD	9.09 (8.62, 9.63)	5.67 (5.20, 6.19)	5.07 (4.63, 5.54)	4.91 (4.48, 5.37)	4.86 (4.44, 5.31)
	75 mg QD	9.09 (8.62, 9.63)	4.80 (4.38, 5.26)	4.09 (3.70, 4.52)	3.92 (3.55, 4.35)	3.85 (3.50, 4.26)

Analysis was restricted to simulated participants with baseline dTC ≥1. Results are based on model simulations and are presented as posterior mean (95% CrI). CrI, Bayesian credible interval; dTC, draining tunnel count; QD, once daily.

Conclusions

- A continuous-time Markov framework was developed to characterize longitudinal dT dynamics in HS, support povorcitinib dose differentiation, and enable simulation of dosing regimens not evaluated in clinical trials. Unlike discrete-time Markov or indirect response models, the framework naturally accommodates irregular visit schedules and correlations between repeated observations while retaining a closed-form likelihood without numerical ordinary differential equation solutions
- Both the 45 mg and 75 mg QD doses demonstrated continued improvement beyond Week 12, suggesting accrual of treatment benefit beyond the placebo-controlled period. The 75 mg QD dose produced greater reductions in dTCs than the 45 mg QD dose, particularly in patients with baseline dTC ≥5, suggesting a deeper treatment effect at the higher dose
- These findings, together with the simulation-ready framework linking exposure to discrete disease-state transitions, support model-informed dose optimization in drug development

Disclosures

MW and TW are employees of Metrum Research Group and were paid consultants of Incyte Corporation at the time this research was conducted. YW, KS, VP, LS, and JW are employees of Incyte Corporation. The work was funded by Incyte Corporation.

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