Pharmacometric-Pharmacoeconomic Modeling and Simulation to Assess Target Product Profile Characteristics in Early Drug Development: Application to Atopic Dermatitis

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Introduction

Early drug development decisions rarely include formal assessment of the relationships between potential target product profile (TPP) characteristics and cost effectiveness (CE). The disciplines of pharmacometrics (PM) and pharmacoeconomics (PE) are closely aligned and intersect at the goal of a quantitative understanding of the system. Connection of these two disciplines is a logical extension of typical PM objectives and should lead to a more comprehensive understanding of the probability of success for new therapeutics. This study investigated those relationships for a hypothetical new drug DrugX (DX) in atopic dermatitis (AD) relative to a reference treatment, dupilumab (DU). The analyses exemplify assessments payors use to drive discussions about CE of new therapeutics in context of early development decision making. The specific target criterion was a two-fold increase in the probability of CE at a willingness to pay (WTP) threshold of $100,000, relative to DU.

Methods

A PM-PE model was developed to describe the PM-PE relationship for DU. The PM-PE model for DX was based on the same structure, with modifications of PM model parameters, relative to DU. Literature meta-data were digitized from published studies, and the PM model described longitudinal eczema area and severity index (EASI) score as a fractional decrease from baseline EASI score, including effects for placebo response, topical corticosteroids (TCS), and drug effects (Equation 1).

$$\mathrm{EASI}(t_{ij}|\mathrm{drug}_i) = \frac{\mathrm{E0}_i}{1 + g_{\mathrm{Pbo}}(t_{ij}) + g_{\mathrm{TCS}}(t_{ij}) + g_{\mathrm{Drug}}(t_{ij})}$$

$$g_{\mathrm{Pbo}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{Pbo}} \times t_i}{\mathrm{ET50}_{\mathrm{Pbo}} + t_i}$$

$$g_{\mathrm{TCS}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{TCS}i,i} \times t_i}{\mathrm{ET50}_{\mathrm{TCS}} + t_i} \times e^{-k_{\mathrm{off,TCS}}\ (t_i - \mu_{\mathrm{TCS}})}$$

$$g_{\mathrm{Drug}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{Drug},i} \times t_i}{\mathrm{ET50}_{\mathrm{Drug}} + t_i}$$

Equation 1. Longitudinal pharmacometric model for drug effects on the EASI endpoint in atopic dermatitis

The PE model was derived from a published PE analysis of dupilumab in AD and was characterized as a Markov model with transition probabilities between health states: non-responder, EASI response, and death, linked to state-specific quality-adjusted life years (QALYs). Monte Carlo simulations varied DX properties relative to DU parameters: maximum fractional efficacy (Emax), inter-individual variability, onset time (T50), and persistence of therapy (POT) (Figure 1).

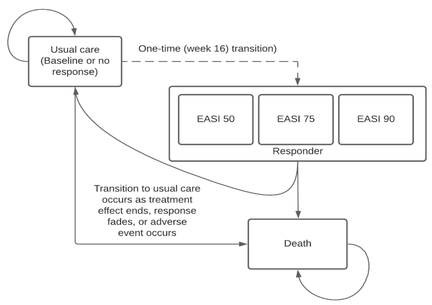

Figure 1. Pharmacoeconomic model structure for atopic dermatitis (Zimmerman *et al.*)

Simulation scenarios included variations of Drug X properties relative to DU: increased Emax, shorter onset time (ET50), and improved persistence of therapy (POT) (also noted as a decreased discontinuation rate) for a population of mixed moderate/severe disease phenotypes (Table 1). All parameter modifications were relative to the DU reference. The real-world discontinuation rate for DU (which informed simulations) was 17% (~83% POT) at 1 year (Silverberg *et al.*). Replicate simulations were implemented in an interactive tool developed in R and Shiny, running on the Metworx platform. Results were summarized for each scenario as the difference in (Drug X - DU) QALYs and probability of CE versus WTP.

	Drug X Model Parameters Relative to Dupilumab			
Scenario	Emax	ET50	Discontinuation Rate	Price
1	1	1	1	1
2	5	1	1	1
3	1	0.5	1	1
4	1	1	0.5	1
5	5	0.5	0.5	1
6	5	0.5	1	1
7	5	0.5	1	0.9

Table 1. PM-PE model simulation scenarios

Results

Population efficacy (typical EASI percent change and EASI 50/75/90 over time) and cost-utility (price-per-QALY relative to TCS) were projected (Figure 2). Incremental CE ratios (ICER = Δcost/ΔQALY) were compared for DX and DU to TCS. PM-PE model simulations assessed the impact of TPP characteristics on CE probability across a range of WTP thresholds. At a $100,000 WTP threshold for DX and DU, the CU Ratio for DX to DU, and the ΔQALY (90% prediction interval) were summarized (Table 2). Relative to DU, improvements in DX Emax and ET50 improved mean efficacy but did not affect QALYs or CE probability (at any WTP level). Reduced IIV had no impact on CE. Improved POT added ~1 QALY and raised CE probability for DX relative to DU (30% versus 15%, respectively); without the POT improvement, a cost effective DX would require a ~10% price reduction relative to DU.

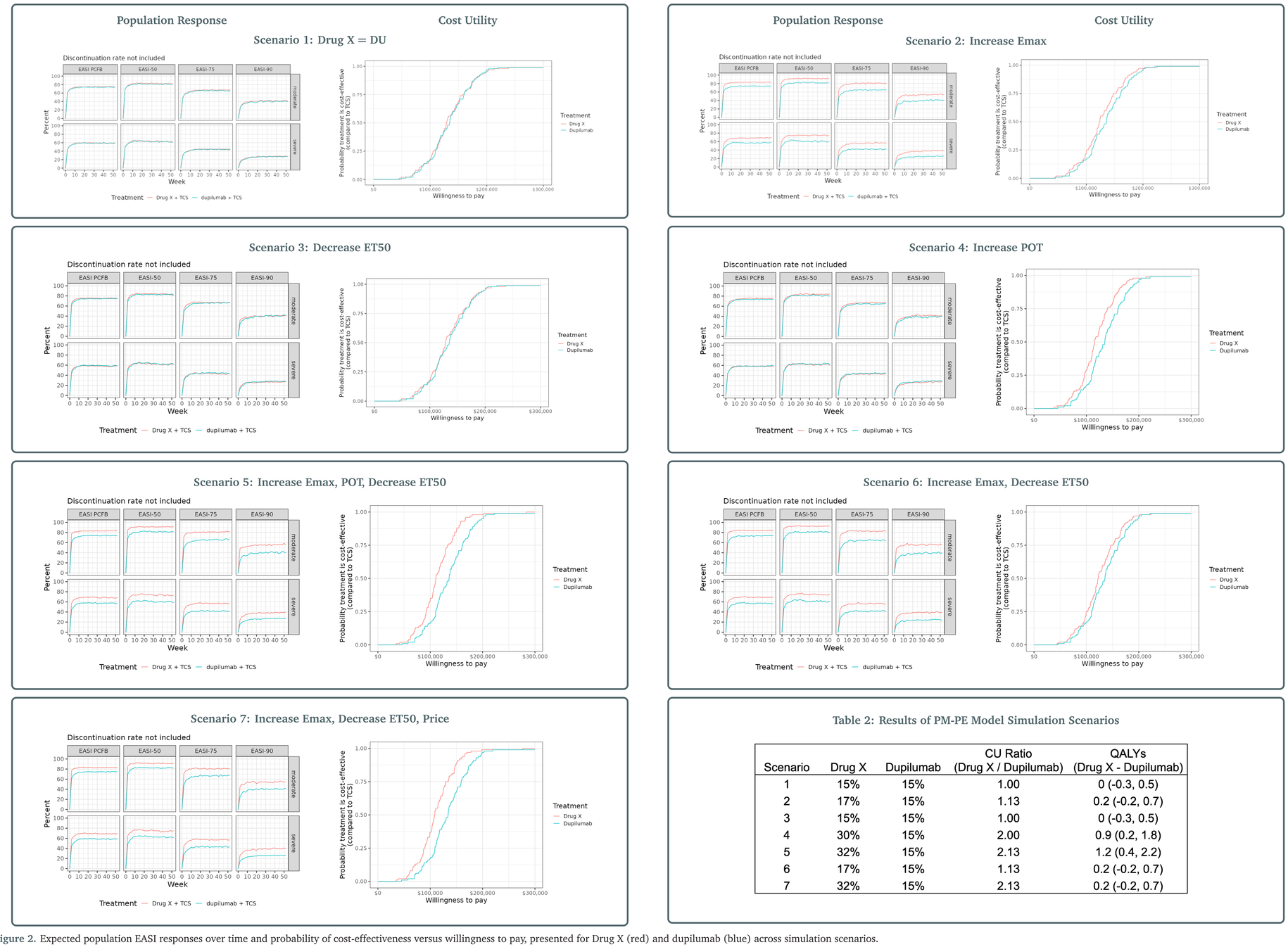

Figure 2. Expected population EASI responses over time and probability of cost-effectiveness versus willingness to pay, presented for Drug X (red) and dupilumab (blue) across simulation scenarios.

Table 2: Results of PM-PE Model Simulation Scenarios

Scenario	Drug X	Dupilumab	CU Ratio (Drug X / Dupilumab)	QALYs (Drug X - Dupilumab)
1	15%	15%	1.00	0 (-0.3, 0.5)
2	17%	15%	1.13	0.2 (-0.2, 0.7)
3	15%	15%	1.00	0 (-0.3, 0.5)
4	30%	15%	2.00	0.9 (0.2, 1.8)
5	32%	15%	2.13	1.2 (0.4, 2.2)
6	17%	15%	1.13	0.2 (-0.2, 0.7)
7	32%	15%	2.13	0.2 (-0.2, 0.7)

Conclusion

TPP characteristics improving efficacy do not necessarily translate to increased QALYs or probability of CE for DX relative to DU. Results may differ under different PE model assumptions (e.g., distinct value of EASI response levels) or with the addition of other Value Flower elements.

References

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