# Pharmacometric-Pharmacoeconomic Modeling and Simulation in Atopic Dermatitis: Informing Early Drug Development Decisions for a Hypothetical New Therapeutic

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## Introduction

Early drug development decision making, such as the definition and assessment of target product profile (TPP) characteristics, rarely includes pharmacoeconomic (PE) considerations. The disciplines of phamacometrics (PM) and 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 complete and accurate understanding of the probability of success for new therapeutics.

This study explores the potential value of combining PM and PE modeling and simulation in early drug development decision making. The work replicates an actual health economics assessment of dupilumab (DU) with the addition of a PM model and compares outcomes between DU and a hypothetical new therapeutic, Drug X. The analyses exemplify assessments payors use to drive discussions about cost effectiveness (CE) of new therapeutics, but with a change in context to early development decision making.

## Objectives

The objective was to assess the expected impact of selected target product profile (TPP) characteristics on the cost effectiveness (CE) of a hypothetical novel therapeutic, Drug X, in atopic dermatitis (AD) relative to a reference therapeutic, dupilumab (DU).

Specific characteristics of interest included: Emax (maximum drug effect), ET50 (time to reach half-maximal drug effect), and persistence of therapy (POT).

Target Criterion: A two-fold increase in the probability of CE at a willingness to pay (WTP) threshold of $100,000, relative to DU.

## Methods

A pharmacometric (PM) - pharmacoeconomic (PE) model was developed to describe the PM-PE relationship for DU. The PM-PE model for hypothetical Drug X was based on the same structure, with select modifications of PM model parameters, relative to the DU reference. PM model data sources included digitized longitudinal meta-data from published studies.

The PM model described longitudinal eczema area and severity index (EASI) score as a fractional decrease from baseline EASI (E0) score, including effects for placebo response (Pbo), topical corticosteroids (TCS), and drug effects (Drug) over time ($t$) for study $i$ and timepoint $j$. The offset of TCS response is characterized by rate constant koff and offset lag time $\mu$ (Equation 1).

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

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

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

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

**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, responder (EASI 50, EASI 75, EASI 99), and death, with each state associated with quality adjusted life years (QALYs). Efficacy is the proportion of the population that responds to drug at week 16; responders transition back to non-response or death from their responder state over time.

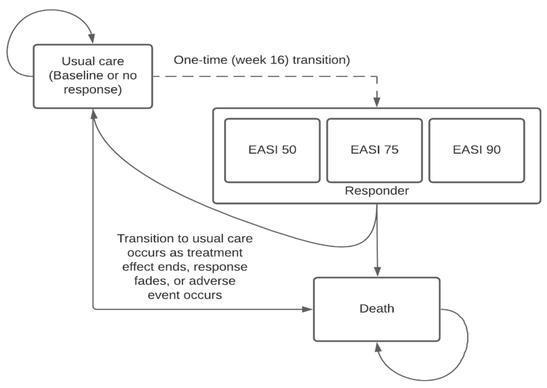


**Figure 1.** Pharmacoeconomic model structure for atopic dermatitis (Zimmerman *et al.*)

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 are relative to the DU reference. 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 vs. 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

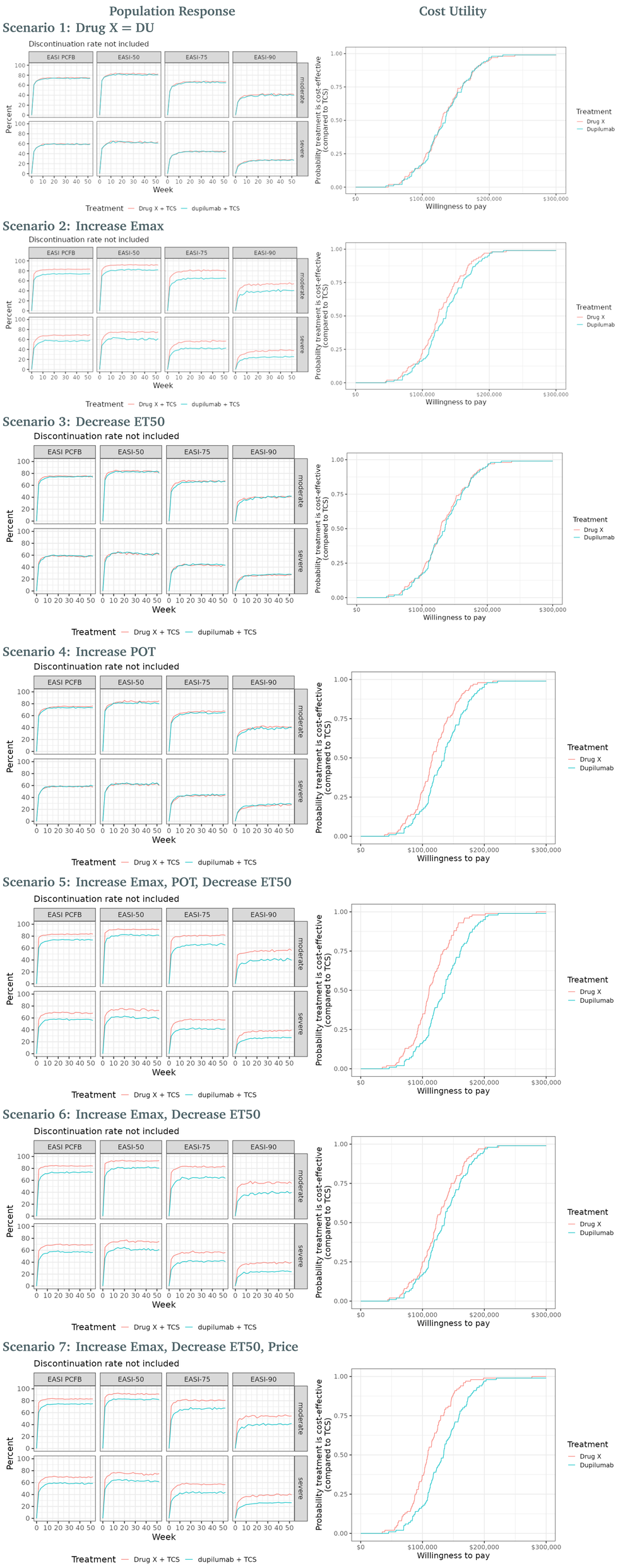


**Figure 2.** Expected population EASI responses over time (left column) and probability of cost-effectiveness vs. willingness to pay (right column) are presented for both Drug X and dupilumab across simulation scenarios.

The population efficacy response projections and a cost utility analysis are presented for each simulation scenario (Figure 2).

### Population Efficacy Response

For each simulation scenario, four population efficacy response endpoints are displayed over time: (left to right) the typical EASI percent change from baseline (PCFB), and the percent of individuals achieving EASI 50, EASI 75, and EASI 90 responses, respectively. Efficacy endpoints are plotted for Drug X (red) and DU (blue) for both moderate (top row) and severe (bottom row) disease phenotypes.

### Cost Utility Analyses

The cost utility analysis examines the price per QALY over time for Drug X and DU relative to TCS. For two drugs, the difference in cumulative QALYs divided by the difference in cumulative costs of treatment form the incremental cost effectiveness ratio (ICER), the primary estimand of interest. In this example, we compare the ICERs of Drug X and DU to TCS. Payors determine an acceptable ICER that they are willing to reimburse at; this is their WTP threshold. For each simulation scenario, the cost-utility analysis displays the probability of cost effectiveness for Drug X (red) and DU (blue) relative to TCS across a range of WTP thresholds.

### Impact of TPP Characteristics

Simulations with the combined PM-PE model allowed for the exploration of the impact of potential TPP characteristics on the cost effectiveness of each drug relative to TCS. Results are presented graphically (Figure 2.) and with key performance metrics summarized for each scenario (Table 2.) Results are presented as probability of cost effectiveness at a WTP threshold of $100,000 for Drug X and for DU, followed by the ratio of these probabilities (CU Ratio) for Drug X to DU, and the difference in QALYs between Drug X and DU (90% prediction interval).

| 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) |

**Table 2.** Results of PM-PE Model Simulation Scenarios.

The increase in Emax for Drug X relative to DU did improve the population mean response profile, but did not impact QALYs or probability of CE at any WTP level (Scenarios 2 and 6). Improvement in onset (ET50) had no impact. The Drug X to DU CU ratio for these scenarios was near 1.

Improvements in POT did result in an increase of approximately 1 QALY and improved probability of CE for DX relative to DU (30% vs 15%, respectively, at a WTP of $100,000). In both Scenarios 4 and 5 the Drug X to DU CU ratio was at least 2, achieving the Target Criterion for CE. In order to achieve a similar probability of cost effectiveness without the improved POT, a decrease in Drug X pricing of approximately 10% relative to DU would be necessary (Scenario 7).

### Limitations and Assumptions

In these simulations, the discontinuation rate for DU therapy was informed by real world data, which suggested a discontinuation rate of 17% ( 83% persistence of therapy) at 1 year (Silverberg *et al.*).

In the published PE analysis, value was driven by a general "Responder" health state. Differentiation of the economic value between improved efficacy response categories (e.g. EASI 90 vs EASI 70) may lead to improved cost effectiveness with improvements in efficacy related TPP characteristics.

The PE model utilized in this study assumes a traditional definition of cost-effectiveness. Inclusion of additional value dimensions, such as those represented in the health economic Value Flower may lead to different conclusions about the impact of TPP characteristics.

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## Conclusion

TPP characteristics that differentiate Drug X from DU on efficacy do not necessarily translate to increased QALYs or probability of CE. It may be important to consider the impact of new drug characteristics on CE when setting the TPP and in early development decision making.

## References

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