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**Project: Cost Effectiveness of Dupilumab
for Atopic Dermatitis**

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**INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW**

Model Analysis Plan

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APPROACH

The primary aim of this analysis is to estimate the cost-effectiveness of dupilumab for moderate to severe atopic dermatitis compared to the standard of care. The model structure for this assessment is depicted below. The model will be developed in Microsoft Excel.

METHODS

Treatments

The interventions assessed in this model are:

- Dupilumab (Regeneron Pharmaceuticals, Inc., Sanofi)

- Standard of care (SoC)

Standard of care patients will generally be treated with emollients.

Overview and Model Structure

We will develop a Markov model with health states based on treatment response. Treatment response will be measured by the Eczema Area and Severity Index (EASI) score.[1] The EASI evaluates four anatomical regions for extent and severity of disease signs.

Health states will be categorized by the percent decrease in EASI score after a patient begins an intervention: a 50% decrease (EASI 50), a 75% decrease (EASI 75), a 90% decrease (EASI 90), or no response. Patients enter the model in the non-responder state, then can transition to responder states after beginning treatment (Figure 1). Patients can transition from any responder state to non-responder, and from any state to death. Patients cannot transition between responder categories.

Figure 1. Markov model structure
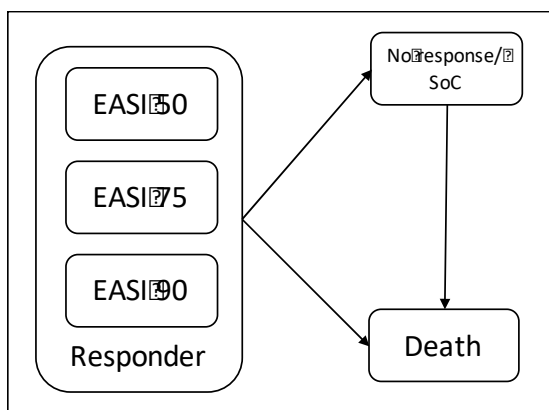
We will use a US health system perspective (i.e., focus on direct medical care costs only) with a 3% discount rate for costs and health outcomes. The model will use 4-month cycles over a lifetime time horizon.

Key Assumptions

We made several assumptions for this model, as follows:

- Patients transition to response states after one cycle.

- Patients do not change response levels after the initial response while on treatment.

- Costs and quality of life for each responder category will represent the average effects for patients with moderate and severe disease at baseline, reflecting an assumption that the proportion of moderate and severe patients within the atopic dermatitis population treated with dupilumab will be similar to that in clinical trials.

- After a patient transitions off treatment, quality of life and costs are equivalent to a patient who was never treated with dupilumab.

- Discontinuation rates for dupilumab are similar to those observed for patients with psoriasis taking biologics, are constant over time, and are equivalent for all the responder categories.

- Patients on standard of care who are responders will transition to non-response at a rate equivalent to recurrence rate for standard of care populations in trials.

- Atopic dermatitis disease and treatments do not affect mortality.

Population

The population for this analysis will be adults ages 18 years and older in the United States with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable.

Input Parameters

Population Demographics

The modeled population will have an assumed mean age of 38 years and be 53% male.[2]

Initial Transition

Patients enter the model in the non-responder/SoC state, then can transition to responder states after an initiation period of 1 cycle. The probabilities for this initial transition are listed in Table 1, as defined based on efficacy from a meta-analysis (Table 1).

Table 1. Distribution of patients after initiation period

	% of patients in each mutually exclusive category		
	EASI 50	EASI 75	EASI 90
SoC	11.77%	8.89%	6.09%
dupilumab	16.50%	18.31%	24.32%

Transition probabilities

Patients on dupilumab will transition from all three responder health states to the no response state as they discontinue dupilumab, rate to be determined.[3] Patients on SoC who are responders will transition to the non-responder state at a recurrence rate of 65.8% every 16 weeks.[4] Patients will transition to death according to U.S. general population mortality rates.[5] Treatment will be assumed to have no effect on mortality.

Costs

An annual cost of care will be applied to all patients. This cost will include all direct costs of care, such as emollients, doctor visits, specialist visits, and hospitalizations. The non-responder/SoC health state will have a baseline cost, and responder categories may have a corresponding lower annual cost. Sources for these costs may include an in-progress evaluation of atopic dermatitis costs from MarketScan data[6], or published literature, such as $349 per year (2005 USD)[7] for standard of care/no treatment, in combination with a possible decrease in costs by responder state. In addition, we will apply an acquisition cost for dupilumab treatment with compliance, as well as a cost for subcutaneous injection training and any relevant monitoring. We will also apply costs for adverse events. All costs will be presented in 2016 dollars.

Utilities

Quality of life utility values will be based on responder states, and will be weighted averages of moderate and severe patients where relevant. The annual utility value for patients in the non-responder/SoC state will be defined by baseline values (potential sources listed in Table 2). If a separate utility value for moderate and severe patients is used, we will take the weighted average of the two values.

Table 2. Potential utility values for non-responder/SoC

Utility Value			Source
Moderate	Severe	Moderate and Severe	
0.770	0.665	--	8
--	0.675	--	9
--	--	To be determined	

Utility values for responder states will be applied per Table 3, to be derived from data on file if available or from other literature sources. We will also apply a disutility for adverse events, subject to data availability.

Table 3. Potential utility values for responder categories

Utility Value			Source
EASI50	EASI75	EASI90	
To be determined			

Adverse Events

Costs and disutilities will be applied on a per event basis for serious adverse events (AEs) at the rates described in Table 4. These rates are based on trial data.

Table 4. Annual rates of serious adverse events (AEs)

	Serious AE rate (annual)
SoC	2.65%
dupilumab	5.70%

Model Outcomes

The model will estimate the amount of time, on average, patients spend in each health state while on dupilumab or SoC treatment. Utility-adjusted time spent in each health state will be summed to provide estimates of quality-adjusted life expectancy for each treatment arm.

Model outcomes of interest will include:

- By intervention:

    o Total costs (discounted)

    o Quality adjusted life expectancy (undiscounted and discounted)

2/16/17

- Pairwise comparisons:

  - Incremental cost-effectiveness ratio versus no treatment/SoC

Sensitivity Analyses

We will run one-way sensitivity analyses to identify the key drivers of model outcomes. Probabilistic sensitivity analysis will be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We may conduct relevant scenario analyses, including differences by severity, inclusion of indirect costs, and time horizons at 1, 5, 10, and 20 years. We will also perform threshold analyses comparing changes in drug price across a range of incremental cost-effectiveness thresholds.

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