Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults

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ABSTRACT

Introduction: Dupilumab significantly improves signs and symptoms of atopic dermatitis (AD), including pruritus, symptoms of anxiety and depression, and health-related quality of life versus placebo in adults with moderate-to-severe AD. Since the cost-effectiveness of dupilumab has not been evaluated, the objective of this analysis was to estimate a value-based price range in which dupilumab would be considered cost-effective compared with supportive care (SC) for treatment of moderate-to-severe AD in an adult population.

Methods: A health economic model was developed to evaluate from the US payer perspective the long-term costs and benefits of dupilumab treatment administered every other week (q2w). Dupilumab q2w was compared with SC; robustness of assumptions and results were tested using sensitivity and scenario analyses. Clinical data were derived from the dupilumab LIBERTY AD SOLO trials; healthcare use and cost data were from health insurance claims histories of adult patients with AD. The annual price of maintenance therapy with dupilumab to be considered cost-effective was estimated for decision thresholds of US$100,000 and $150,000 per quality-adjusted life-year (QALY) gained.

Results: In the base case, the annual maintenance price for dupilumab therapy to be considered cost-effective would be $28,770 at a $100,000 per QALY gained threshold, and $39,940 at a $150,000 threshold. Results were generally robust to parameter variations in one-way and probabilistic sensitivity analyses.

Conclusion: Dupilumab q2w compared with SC is cost-effective for the treatment of moderate-to-severe AD in US adults at an annual price of maintenance therapy in the range of $29,000–$40,000 at the $100,000–$150,000 per QALY thresholds.

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INTRODUCTION

Patients with moderate-to-severe atopic dermatitis (AD) report a multidimensional burden that encompasses intense pruritus, sleep disturbances, the presence of anxiety and depression, reductions in function and productivity, and lower health-related quality of life (HRQoL) [1–9]. Despite the development of treatment guidelines [10–13], currently available pharmacologic options for the management of moderate-to-severe AD are less than optimal with regard to both long-term efficacy and safety [10–14].

Dupilumab is a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor-α. This binding to IL-4α inhibits signaling of the Th2 cytokines IL-4 and IL-13 that contribute to the pathogenesis of AD [15]. Results from two phase 3, double-blind, placebo-controlled studies (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2) showed that, after 16 weeks of monotherapy, subcutaneous dupilumab 300 mg administered every other week (q2w) resulted in significantly greater improvements compared with placebo for signs and symptoms of AD, including pruritus, symptoms of anxiety and depression, and HRQoL [16, 17].

Value-based frameworks requiring estimation of overall cost-effectiveness (CE) have been recommended to help clinicians and payers compare the value of medications and other health technologies across multiple therapeutic areas on a common scale [18]. CE analyses lend themselves to such a comparison by utilizing a measure of quality-adjusted life expectancy defined as a quality-adjusted life-year (QALY). The objective of this analysis was to estimate a price range in which dupilumab would be considered cost-effective compared with supportive care (SC) for the treatment of moderate-to-severe AD in US adults based on generally accepted CE decision thresholds.

METHODS

While this article does not contain any new studies with human subjects, the described analyses used assumptions and inputs from two clinical trials that were performed with the oversight of the local institutional review board or ethics committee at each participating study center [16].

Model Structure

The analytical structure took the form of a decision tree linked to a Markov model, programmed in Excel (Microsoft, Redmond, WA, USA), to evaluate the annual value-based price of dupilumab maintenance therapy from the US payer perspective [19]. The lifetime model estimated the value-based price, with costs and QALYs discounted at 3% per year [20]. The model structure was similar to previous analyses undertaken for biologics in chronic immunologic skin conditions such as psoriasis [21–27] and psoriatic arthritis [28–32].

Patients with moderate-to-severe AD were first assigned in the short-term (16-week) decision tree (Fig. 1a) to treatment with either dupilumab (administered as a 300-mg subcutaneous injection q2w) plus emollients, or SC, considered to be emollients as required since there are currently no recommendations for targeted management of this AD population. The 16-week decision point corresponded to the time point for assessment of the primary outcomes in the SOLO trials [16]. At 16 weeks, patients entered the Markov model for long-term maintenance treatment, with dupilumab treatment responders (i.e., those that achieved ≥75% improvement in EASI score) continuing on dupilumab, and dupilumab non-responders switching to SC. The patients on SC treatment remained in the Markov model. At the end of each 4-month Markov cycle, dupilumab patients in the maintenance treatment health state could continue to respond, transition to SC treatment for any reason, or die (Fig. 1b). The presence of AD does not increase the likelihood of death in the model. Those on SC treatment remained in the...
same health state until death. A half-cycle correction was applied to the Markov calculations so that benefits and costs were accrued in the middle of each cycle.

Model inputs are shown in Table 1 and are detailed below.

**Patients**

The model considered patients with characteristics similar to those in the SOLO trials [16], which were performed with the oversight of the local institutional review board or ethics committee at each participating trial center; adults with moderate-to-severe AD, 58% male, mean age of 38 years, median disease duration of 26 years, and a median EASI score of 29.9. The mean baseline utility value was 0.61 [17] and was calculated from patient responses on the EQ-5D [33]. Age and gender mix were used to model patient survival via general US population life tables [34], and patients receiving dupilumab were assumed to have the same baseline mortality as the SC group.

**Clinical**

In the base case analysis, therapeutic response was defined as ≥75% improvement in EASI score (EASI 75). The model inputs of 48% and 13% of dupilumab q2w and SC patients, respectively, reflect data pooled from the SOLO trials for the proportions of patients who achieved the EASI 75 response (P < 0.0001). Dupilumab discontinuation was modeled using data from the open label extension from the SOLO 1 and SOLO 2 studies, where 6.3% (Regeneron Pharmaceuticals, Inc., data on file, 2017) of previously responding patients discontinued by 52 weeks. This annual value was converted to a 4-month probability for use in
Table 1  Model inputs

| Parameter                                      | Mean  | Sampling distribution | Uncertainty               | References                  |
|------------------------------------------------|-------|-----------------------|---------------------------|-----------------------------|
| EASI 75 response                               |       |                       |                           |                             |
| Dupilumab                                      | 48%   | Beta                  | Alpha = 218, beta = 239   | Simpson et al. [16]         |
| SC                                             | 13%   | Beta                  | Alpha = 61, beta = 399    | Simpson et al. [16]         |
| Annual discontinuation probability             | 6.3%  | Beta                  | Alpha = 24, beta = 357    | Regeneron data on file (2017)|
| Dupilumab compliance weeks 0–16                | 95.2% | Beta                  | Alpha = 7081, beta = 359  | Regeneron data on file (2017)|
| Dupilumab compliance maintenance phase         | 98.6% | Beta                  | Alpha = 3692, beta = 52   | Regeneron data on file (2017)|
| Adverse event incidence                        |       |                       |                           |                             |
| Injection site reaction                        | 11.0% | Beta                  | Alpha = 51, beta = 414    | Simpson et al. [16]         |
| Allergic conjunctivitis                        | 3.0%  | Beta                  | Alpha = 14, beta = 451    | Simpson et al. [16]         |
| Infectious conjunctivitis                      | 4.3%  | Beta                  | Alpha = 20, beta = 445    | Simpson et al. [16]         |
| SC                                             |       |                       |                           |                             |
| Injection site reaction                        | 0.0%  | Not varied            | –                         | Assumption                  |
| Allergic conjunctivitis                        | 0.9%  | Beta                  | Alpha = 4, beta = 452     | Simpson et al. [16]         |
| Infectious conjunctivitis                      | 0.7%  | Beta                  | Alpha = 3, beta = 452     | Simpson et al. [16]         |
| Cost of subcutaneous training                  | $73   | Gamma                 | SE assumed to be 10% of mean | Optum 360 [46]             |
| Responder annual cost                          | $7557 | Gamma                 | SE = $125.33              | Shrestha et al. [47]        |
| Non-responder annual cost                      | $15,320 | Gamma              | SE = $274.31              | Shrestha et al. [47]        |
| Adverse event management                       |       |                       |                           |                             |
| Injection site reaction                        | $108  | Gamma                 | SE assumed to be 10% of mean | Optum 360 [46]             |
| Allergic conjunctivitis                        | $73   | Gamma                 | SE assumed to be 10% of mean | Optum 360 [46]             |
| Infectious conjunctivitis                      | $139  | Gamma                 | SE assumed to be 10% of mean | Optum 360 [46]; Smith and Waycaster [48] |
the model and assumed constant over the modeled time horizon.

Adverse Events

Adverse events associated with injection site reaction and conjunctivitis were included in the model, with the incidence of these events (Table 1) drawn from the SOLO trials [16]. While injection site reactions were assumed to occur once and were included in the first cycle, allergic and infectious conjunctivitis were included in each cycle.

Costs

As indicated in Table 1, dupilumab compliance was taken from all patients in the first 16 weeks of the SOLO trials. Post-16 weeks, compliance was calculated for responders who would maintain a q2w dosing schedule. Given the overall low cost and uncertainty in emollient use (i.e., the difficulty in costing the topicals that are used in varying amounts and frequencies), a simplified assumption was made to exclude the cost of emollients from the model. A one-time cost of patient training for dupilumab subcutaneous injection was assumed to occur at the start of the decision tree. Other medical costs (i.e., physician visits, emergency room use, hospitalizations) as shown in Table 1 were derived from a separate study that assessed costs of AD by severity using a commercial claims database; a commercial claims database was deemed to be most representative of patients with AD. Responders were assumed to have similar costs and healthcare resource utilization as patients with lower AD severity; there was no assumption for costs for regular follow-up visits or laboratory testing specifically related to dupilumab treatment, since no such follow-up is mandated [35]. Non-responders were assumed to incur the costs and health care resource utilization of AD patients with higher AD severity.

Costs associated with commonly observed adverse events included in the model (Table 1) were estimated based on the need for at least one physician visit. While injection site reactions might also require over-the-counter (OTC) emollients and allergic conjunctivitis might also require OTC eye drops, OTC costs were not included. However, conjunctivitis may require prescription antibiotics, and an average cost was included.

Costs are reported in December 2016 US dollars with unit costs from previous years inflated using the medical component of the Consumer Price Index [36].

Utility Values

The SOLO trials included the widely used, generic, 5-dimension, 3-level EuroQol (EQ-5D) as a

| Parameter                      | Mean | Sampling distribution | Uncertainty               | References          |
|-------------------------------|------|-----------------------|---------------------------|---------------------|
| Other infections              | $139 | Gamma                 | SE assumed to be 10% of mean | Optum 360 [46]; Smith and Waycaster [48] |

Utility value change from baseline

All patients

| Parameter | Mean | Sampling distribution | Uncertainty | References |
|-----------|------|-----------------------|-------------|------------|
| Dupilumab | 0.21 | Beta                  | SE = 0.01   | Simpson et al. [17] |
| SC        | 0.03 | Beta                  | SE = 0.01   | Simpson et al. [17] |
| Dupilumab responders | 0.25 | Beta                  | SE = 0.01   | Simpson et al. [17] |

EASI Eczema Area and Severity Index, SE standard error, SC supportive care
measure of HRQoL [33]. Utility values derived from the EQ-5D represent the patient’s preference for being in or avoiding certain states of health, and generally range from 0 (death) to 1 (perfect health). Utility values are combined with the time spent in a health state to estimate QALYs [37]. A QALY can be described as 1 year of life in perfect health, with fractions of QALYs interpreted as either the proportion of the year spent in perfect health or the percent reduction in HRQoL over a full year, i.e., 0.5 QALYs can represent 6 months of life in perfect health or 12 months of life with HRQoL reduced by 50%.

Least squares mean change from baseline for the utility values were calculated from EQ-5D responses from the SOLO trials and were combined with baseline utility values to estimate health-state-specific values [17]. The treatment-specific utility values (Table 1) for all patients were applied to the 16-week decision tree. Dupilumab responders carried forward treatment- and response-specific utility values into the Markov model. SC patients retained the 16-week observed utility values in the SC treatment health state. The model did not include the disutility (e.g., negative quality of life) associated with adverse events, a conservative assumption as serious adverse events occurred more frequently in the SC arm than the dupilumab arm (5% vs. 2%) of the SOLO trials [16].

### Sensitivity Analyses

One-way sensitivity and scenario analyses explored the impact of plausible variations of single input parameters on the model results. One scenario analysis used the EASI 50 threshold (i.e., percent of patients with ≥50% improvement in EASI score), which was achieved by 67% and 23% of dupilumab q2w and placebo patients, respectively [16]. Other scenario analyses were performed for time horizons (1 year, 5 years, and 10 years) and discontinuation rates (0, 3, 6, and 12%). Probabilistic sensitivity analysis using Monte Carlo simulation with 10,000 iterations explored the effects of joint uncertainty (i.e., varying all parameters simultaneously using the pre-specified distributions shown in Table 1) on model results. A scatter plot was used to graphically display the variation in incremental price and QALYs for dupilumab compared with SC, while a CE acceptability curve was developed to show the probability that dupilumab is cost-effective at various cost per QALY decision thresholds. For simplicity, the probabilistic sensitivity analysis was implemented at a value-based price calculated using a $125,000 per QALY gained threshold, which is midway between the $100,000 and $150,000 thresholds.

### RESULTS

#### Base Case

As shown in Table 2 for the base case, dupilumab is estimated to produce 1.12 more QALYs

| Outcome                      | Dupilumab | SC    | Difference |
|------------------------------|-----------|-------|------------|
| Other medical costs          | $299,155  | $331,430 | −$32,275  |
| Administration costs         | $73       | $0    | $73        |
| Adverse events costs         | $221      | $108  | $112       |
| Total non-dupilumab drug costs | $299,449 | $331,538 | $32,089   |
| Total QALYs                  | 15.95     | 14.83 | 1.12       |
| Years with response          | 7.21      | 3.05  | 4.16       |

### Table 2 Base case results

$QALY$ quality-adjusted life-year, $SC$ supportive care

△ Adis
over the lifetime horizon compared with SC (15.95 vs. 14.83), with the difference attributed to greater time spent in the response state (over 7 years for dupilumab compared with 3 for SC). Cost offsets of approximately $32,000 were obtained for other medical costs. Adverse event costs were similar between treatments.

Under a $100,000 per QALY gained decision threshold, the annual maintenance price for dupilumab therapy to be considered cost-effective would be $28,769. With a $150,000 per QALY gained threshold, the annual maintenance price for dupilumab therapy to be cost-effective would increase to $39,941 (Table 2).

One-Way Sensitivity Analysis

The one-way sensitivity analysis showed that the model was robust to the changes in input parameters across their ranges (Fig. 2a, b). The

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Fig. 2 Tornado diagrams of one-way sensitivity analysis. a Value-based pricing based on $100,000 per QALY gained threshold. b Value-based pricing based on $150,000 per QALY gained threshold. Vertical lines separating low and high bounds indicate the base case annual maintenance prices at which dupilumab therapy would be considered cost-effective at the given threshold. AD atopic dermatitis, SC supportive care.
ranges of the annual value-based price of dupilumab were $26,468–$34,928 for the $100,000 per QALY gained decision threshold and $36,490–$48,492 for the $150,000 per QALY gained decision threshold.

### Scenario Analyses

In the scenario analyses (Table 3), there was an overall decrease in the annual value-based price of dupilumab maintenance therapy when the dupilumab discontinuation rate was greater than baseline and when the time horizon was less than lifetime. This decrease, resulting from a shorter time horizon, was due in part to the dupilumab loading dose being accounted for over a shorter time period. In contrast, the annual value-based price of dupilumab maintenance therapy increased slightly when patients remained on therapy longer than the base case (i.e., a lower discontinuation rate). When the response criterion for continuation was lowered to EASI 50, the value-based price decreased as more patients are continuing treatment and incurring drug costs.

### Probabilistic Sensitivity Analysis

Results of 10,000 iterations of the probabilistic sensitivity analysis are summarized in the form of a CE scatter plot (Fig. 3a) and an acceptability curve (Fig. 3b). The dupilumab price corresponding to an incremental CE ratio of $125,000 per QALY gained was $34,355 per year. The CE acceptability curve shows that simultaneous variation of model parameters has limited impact on the results, with 100% of the iterations falling below the $150,000 threshold.

### DISCUSSION

The economic model and analyses described were designed to evaluate the long-term treatment costs and benefits of dupilumab for the treatment of moderate-to-severe adult AD patients over the course of their lifetime. The results suggest that, based on the increase in QALYs achieved with dupilumab relative to SC, dupilumab is cost-effective compared with SC across a range of annual maintenance prices in this patient population.

Although no formal CE decision thresholds have been established in the US, the base case

| Analysis | Dupilumab value-based annual maintenance price |
|----------|-----------------------------------------------|
|          | $100,000 threshold | Change from base case | $150,000 threshold | Change from base case |
| Response = EASI 50 | $27,752 | −$1017 | $38,698 | −$1243 |
| Time horizon | | | | |
| 1 year | $19,483 | −$9286 | $27,318 | −$12,623 |
| 5 years | $26,859 | −$1910 | $37,345 | −$2596 |
| 10 years | $28,037 | −$732 | $38,946 | −$995 |
| Dupilumab discontinuation probability | | | | |
| 0.0% | $29,518 | $749 | $40,960 | $1019 |
| 3.0% | $29,182 | $413 | $40,502 | $561 |
| 9.0% | $28,417 | −$352 | $39,463 | −$478 |
| 12.0% | $28,023 | −$746 | $38,927 | −$1014 |
used two values, $100,000 and $150,000, that are generally considered acceptable benchmarks of CE [19] and that have also been adopted by the Institute for Clinical and Economic Review (ICER) [38]. The findings indicate that the annual drug price at which dupilumab would be cost-effective ranges from $29,000 to $40,000, for the two thresholds, respectively. The current wholesale acquisition cost (WAC) of a 300-mg injection of dupilumab is $1423.08 [39], translating into an annual WAC of $37,000, which falls within the cost-effective range. In addition, payer discounts and rebates, and patient co-pay or co-insurance offset through co-pay assistance programs, often reduce the actual product price to the payer even further. Accounting for these additional discounts is expected to yield an average annual net price in the low $30,000 range. The results of this analysis are supported by the evidence report for AD recently published by the (ICER) [40]. This report concluded that dupilumab is cost-effective at an annual price range of $30,516–$43,726 at the $100,000–$150,000 per QALY decision threshold range.

Moderate-to-severe AD is associated with a substantial disease burden with respect to clinical signs/symptoms, sleep disturbances, patient function and quality of life, mental health issues (anxiety/depression), and productivity [1, 7–9, 41, 42]. Many adults have been living with AD for nearly their entire lives [9, 16], and AD has been suggested to have a broader impact over the lifetime of the patient by affecting

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Fig. 3 Probabilistic sensitivity analysis. **a** Dupilumab cost-effectiveness scatter plot. **b** Dupilumab cost-effectiveness acceptability curve. SC supportive care
education and career decisions [43, 44]. Recent studies have shown that patients with AD and psoriasis report a similar impairment in HRQoL [45]. Further, in a recent review of biologic drugs for psoriasis by ICER [27], the HRQoL improvement associated with biologic drugs for psoriasis was generally comparable to the mean improvement observed with dupilumab (0.23/0.26 for PASI-75/PASI-90 responders in psoriasis relative to 0.25 for EASI-75 responders in AD). Finally, our model structure was similar to previous economic analyses in psoriasis [21–25, 27] that served as the basis for reimbursement of biologic drugs by health technology assessment bodies in countries that require a formal assessment of a new medicine's CE [e.g., National Institute for Health and Care Excellence (NICE)]. At assumed price levels net of discounts and payer rebates ranging from $35,000 to $55,000 per year, all psoriasis biologic drugs were found to be cost-effective and to provide “reasonably good value for money” in the ICER review of biologic drugs for psoriasis [27].

Study Limitations

Lack of data on long-term effectiveness and discontinuation rates should be noted as a limitation; however, varying the discontinuation rates generally provided robust results with respect to the base case. Additional limitations are that cost differences were not adjusted for other atopic comorbidities, and that we used an estimated cost surrogate for responders and non-responders. Although these costs were derived from claims data, and thus represent real-world costs among patients with AD, the cost stratification may not necessarily reflect treatment response.

CONCLUSIONS

Dupilumab q2w compared with SC is cost-effective for the treatment of moderate-to-severe AD in US adults at an annual maintenance price in the range of $29,000–$40,000 at the $100,000–$150,000 per QALY decision thresholds. Sensitivity analyses showed the results to be robust and generally insensitive to variability in the key model assumptions and variables.

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Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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