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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Moderate to Severe Psoriasis Therapy with Etanercept and Ustekinumab in the United States

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Abstract

Background Limited information is available on the cost effectiveness of ustekinumab and alternative biologic treatments in a United States (US) setting. Given the recent head-to-head clinical trial study of ustekinumab and etanercept, an economic model comparing the two treatments can be constructed. Etanercept and ustekinumab are indicated for the treatment of chronic moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy.

Objective Clinical trials have evaluated the efficacy of ustekinumab, an anti-cytokine biologic, for the treatment of moderate to severe psoriasis. This study evaluated the cost effectiveness of ustekinumab compared with etanercept from a US societal perspective.

Methods A Markov model was constructed to simulate the incremental cost per quality-adjusted life-year (QALY) gained every 12 weeks over a base-case 3-year time horizon. A hypothetical patient cohort was based on the characteristics of the phase III Active Comparator Psoriasis Trial (ACCEPT). The main outcome measures were costs and QALYs, which were estimated from the US societal perspective. Costs, utilities, treatment strategy, and resource use estimates were obtained from relevant literature. All costs were adjusted to 2011 US dollars. A 3 % annual discount rate was applied to costs and QALYs. Incremental cost-effectiveness ratios were in US dollars per QALY gained.

Results For the base-case 3-year time horizon, the incremental cost-effectiveness ratio comparing ustekinumab 90 mg with etanercept 50 mg was US$384,401 per QALY gained. Ustekinumab 45 mg dominates etanercept 50 mg for the same time horizon. These results were robust to sensitivity analyses involving treatment strategy, transition probabilities, valuing outcomes, and resource use and costs. The probabilistic sensitivity analysis suggests ustekinumab 90 mg has a minimal (4 %) chance of being cost effective compared with etanercept 50 mg at a willingness-to-pay threshold of US$150,000 per QALY improvement. For the same threshold, ustekinumab 45 mg has a high (88 %) chance of being cost effective compared with etanercept 50 mg.

Conclusion Under typical US willingness-to-pay cutoffs, ustekinumab 90 mg is not cost effective compared with etanercept 50 mg therapy in moderate to severe psoriasis patients for the base-case 3-year time horizon. Ustekinumab 45 mg dominates etanercept 50 mg therapy for an equivalent patient psoriasis severity and time horizon.

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Key Points for Decision Makers

- Ustekinumab 45 mg dominates (i.e., is less costly and more effective than) etanercept 50 mg for the base-case 3-year time horizon in US psoriasis patients with no previous treatment with either therapy.
- Ustekinumab 90 mg is not cost effective compared with etanercept 50 mg for the base-case 3-year time horizon when applying a US willingness-to-pay threshold of US$120,000–US$150,000 per quality-adjusted life-year (QALY).
- The uncertainty surrounding the cost-effectiveness estimates, for a range of cost-effectiveness thresholds, is represented in this study's cost-effectiveness acceptability curve. Ustekinumab 90 mg has a low likelihood of being cost effective compared with etanercept 50 mg at a threshold of US$150,000 per QALY. At the same threshold, ustekinumab 45 mg has a high likelihood of being cost effective compared with etanercept 50 mg.

1 Introduction

Psoriasis is a chronic autoimmune-related skin disease characterized by an accelerated rate of turnover of the skin, appearing as red, scaly plaques [1]. Psoriasis affects approximately 2 % of the population [1, 2]. Approximately 20 % of the psoriasis population experiences moderate to severe psoriasis, which affects more than 5 % of the body surface area [2]. General recommendations for the treatment of psoriasis include topical agents (for limited disease involvement), phototherapy (when topical therapies fail to produce an adequate response), and/or traditional systemic immunosuppressive agents (e.g., methotrexate and cyclosporine) [2].

Biologic therapies are routinely used when one or more traditional systemic agents produce inadequate response, are not tolerated due to adverse effects, or are unsuitable because of comorbidity presence [3]. Tumor necrosis factor inhibitors etanercept, adalimumab, and infliximab are efficacious for psoriasis patients, with improved safety profiles relative to traditional systemic agents [4]. More recently, the interleukin-12 and interleukin-23 inhibitor ustekinumab was shown to be effective for the treatment of psoriasis [5–7]. Currently, there are no treatment algorithms to guide providers when switching between and commencing biologic therapies within the United States (US) [2, 4]. Switching between biologic therapies has become common practice when patients experience treatment failure from one biologic therapy [4]. Ustekinumab is a valuable clinical alternative for these cases.

The higher cost of biological therapies compared with traditional treatments have generated interest in the management of moderate to severe psoriasis. The estimated annual costs for phototherapy and traditional systemic agent treatments for moderate to severe psoriasis is US$1,600–US$10,000 (year 2002 values) [8]. The estimated annual cost of biologic treatment is US$16,000– US$37,000 (year 2002 values) [8]. The additional costs for biologic therapies pose a significant challenge to limited health systems resources. Therefore, the choice of biologic treatments that offer value for money can potentially generate healthcare expenditure savings and consequently increase available funds for more pressing healthcare needs [9–11]. To aid in this choice, cost-effectiveness analyses can assist healthcare decision makers (i.e., payers) in applying cost-effective strategies to uncover overused services that offer little value for money [10, 11].

Given the latest US Food and Drug Administration (FDA) approval of ustekinumab for the treatment of psoriasis, a cost-effectiveness analysis comparing ustekinumab with previously approved biologics can be useful to US healthcare decision makers. The head-to-head phase III Active Comparator Psoriasis Trial (ACCEPT) comparison of ustekinumab and etanercept has found a significant clinical superiority of ustekinumab for the treatment of patients with moderate to severe psoriasis [7]. This randomized clinical trial forms the basis for conducting a cost-effectiveness analysis between these two drugs. Previous studies examined ACCEPT in terms of cost per responder and cost per QALY from a Canadian perspective [12, 13]. This study analyzes the cost per QALY of ustekinumab and etanercept from a US perspective.

2 Study Objective

Psoriasis patients experiencing inadequate response or contraindication to conventional (i.e., methotrexate, cyclosporine, or psoralen plus ultraviolet A) systemic therapy are typically treated with costly biologic therapies such as etanercept or ustekinumab. In this study, we evaluate the cost effectiveness of ustekinumab compared with etanercept from the US societal perspective. The objective of our cost-effectiveness analysis was to estimate the incremental cost (in 2011 US dollars) per quality-adjusted life-year (QALY) gained between (i) etanercept 50 mg, (ii) ustekinumab 45 mg, and (iii) ustekinumab 90 mg therapies for adult patients with moderate to severe psoriasis.

3 Methods

3.1 Base-Case Model Description

This study employs the cost per QALY in the incremental cost-effectiveness ratio (ICER) similar to the Gold et al. [9] reference case analysis approach [14]. This analysis compares ustekinumab 45 and 90 mg with etanercept 50 mg (i.e., the reference case). Etanercept 50 mg was chosen as the reference case because the Medical Board of the National Psoriasis Foundation (NPF) does not specify a standard of care for patients commencing biologic treatment for moderate to severe psoriasis [2]. Therefore, our model compares ustekinumab 45 and 90 mg to the existing therapeutic alternative, etanercept 50 mg. A Markov model was constructed in Microsoft Excel. The main outcome measures modeled were costs and QALYs from a US societal perspective. The model classifies a cost-effective treatment as an intervention with a cost-effectiveness ratio of less than three times gross domestic product per capita. This US threshold was approximately US$120,000–US$150,000 in 2011 [15, 16].

The model characteristics were based on ACCEPT, comparing ustekinumab and etanercept safety and efficacy [7]. For example, patients with moderate to severe refractory psoriasis with no previous treatment with ustekinumab or etanercept were included in the trial. In ACCEPT, patients were randomly assigned to one of three treatment groups (45 or 90 mg of ustekinumab or 50 mg of etanercept). The Psoriasis Area and Severity Index (PASI) evaluated efficacy, which is accepted as a US FDA primary endpoint in assessing therapies for psoriasis [17]. The PASI is a score based on the extent of psoriatic involvement of body surface area, as well as the severity of scale formation, erythema, and plaque induration of the body [7]. At week 12, the ACCEPT study demonstrates ustekinumab 45 and 90 mg provides superior efficacy, as measured by the proportion of patients with a reduction in baseline PASI score of at least 75 % (PASI75), and similar safety relative to etanercept 50 mg. *P* values for the comparison of PASI75 improvement rates between ustekinumab 45 mg versus etanercept 50 mg and ustekinumab 90 mg versus etanercept 50 mg were 0.01 and <0.001, respectively.

Patients enter our model when either etanercept or ustekinumab therapy was initiated. The structure of the model is based on a three-state Markov approach using PASI measures of health state. Each cycle of the model is 12 weeks, which represents the duration for response assessment defined in ACCEPT [7]. After each cycle, patients move to the full response state (a baseline PASI score reduction of at least 75 %; PASI75), the partial response state (a baseline PASI score reduction of 50–74 %; PASI50-74), or the nonresponse state (a baseline PASI score reduction of less than 50 %; PASI<50) (Fig. 1).

The US FDA considers the PASI75 health state as the benchmark of primary endpoints for psoriasis therapies [17]. The PASI50-74 health state is relevant to our model's US societal perspective because the NPF considers a PASI50-74 as a clinically meaningful degree of improvement for patients [17]. Mortality was omitted in the base-case model because there was not enough evidence from the ACCEPT study to conclude significantly different mortality rates between treatment groups. However, severe psoriasis is associated with an increased risk of death [18]. While the base-case model omitted mortality, we conducted sensitivity analyses on the effect of mortality on main outcomes.

3.2 Time Horizon

Our base-case model draws conclusions from 12-week clinical trial data. As a chronic disease, modeling psoriasis with a meaningful time horizon is based on whether efficacy from 12-week data continues. This lack of information beyond 12 weeks reflects the evidence base for all psoriasis treatments, not just the new biological therapies [19]. However, biologic treatments for psoriasis have been modeled with a maximum time horizon of 10 years, which was based on international consensus guidelines of long-term psoriasis therapy [19–21]. While this time horizon was

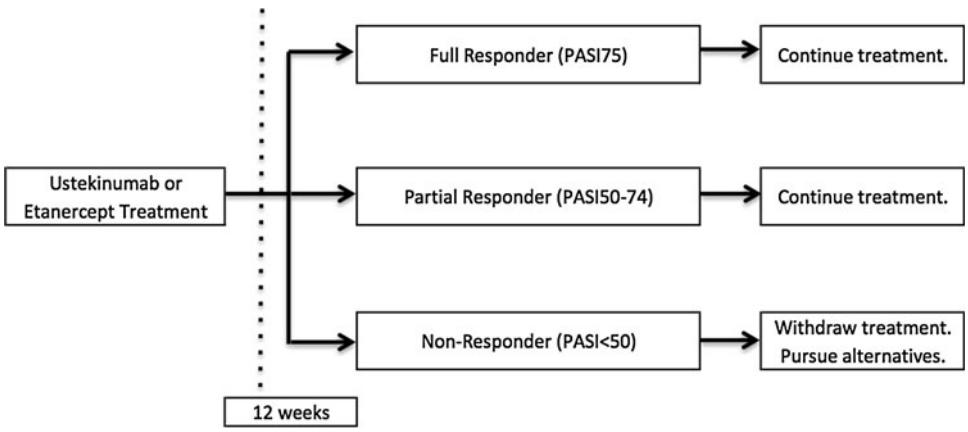

Fig. 1 Conceptual base-case model structure. *PASI* Psoriasis Area Severity Index, *PASI75* decrease in PASI of 75 % or better, *PASI50-74* decrease in PASI of 50–74 %, *PASI<50* decrease in PASI of less than 50 %. The model structure is continued for 12-week cycles

shown as an appropriate ceiling for long-term analysis, we strengthen previous approaches by incorporating safety monitoring results for both drugs to our model time horizon.

Long-term safety profiles defined the base-case time horizon. The comparable safety profiles between the two drugs provide the rationale for extrapolating the ACCEPT 12-week control period to long-term analyses [22, 23]. The etanercept 50 mg safety profile was assessed up to 144 weeks (2.8 years) while ustekinumab 45 and 90 mg safety profiles were assessed up to 208 weeks (4 years) [22, 23]. Thus, the base-case time horizon is 3 years. The time horizon was varied from 12 weeks to 5 years in sensitivity analyses.

3.3 Patient Cohort

Hypothetical patients entered the model as adults experiencing moderate to severe psoriasis with the same baseline characteristics and inclusion criteria as the ACCEPT study [7]. Across treatment groups, the male percentage range was 63.6–70.9 % while the mean age range was 44.8–45.7 years. Patient eligibility criteria include inadequate response, intolerance, or contraindication to at least one conventional systemic agent for psoriasis treatment. The model simulated a 1,000 patient cohort.

3.4 Treatment Strategy

The treatment strategy of etanercept and ustekinumab for our model is based on the treatment design of ACCEPT [7]. From a US context, this treatment strategy is consistent with the recommendations by the American Academy of Dermatology (AAD) and NPF, and FDA-licensed doses [2, 3, 24, 25]. The etanercept dosing schedule comprises subcutaneous injection of 50 mg twice per week for 3 months (12 weeks) followed by 50 mg once per week. The ustekinumab dosing schedule comprises subcutaneous injection of 45 or 90 mg at baseline, 4 weeks, and every 12 weeks. Patients in the base-case model receive each subcutaneous injection under clinician supervision regardless of therapy. Clinician-supervised injections are consistent with the US prescribing indications of ustekinumab and etanercept [24, 25]. Table 1 describes the annual number of doses per patient for both drugs.

US prescribing indications for etanercept that suggest starting doses of 25 or 50 mg once weekly, in addition to the recommended 50 mg twice-weekly dose, are efficacious [24]. Therefore, the etanercept starting dose therapies of 25 or 50 mg once weekly for etanercept were assessed in sensitivity analyses. In addition, etanercept 50 mg can be self-administered by patients within the US [24]. The effect of etanercept patient self-administration on main outcomes was also assessed in a sensitivity analysis.

Table 1 Annual base-case costs per patient (2011 US$)

Treatment year	Therapy type	Number of doses	Direct costs							Indirect costs	
			Drug cost [38][b]	Office visits [40][c]	PPD [30, 37]	LFT [37]	CBC [37]	Physical [37]	Retail OTC [39]	Compensation [41][d]	Total cost per patient
1	Etanercept 50 mg	64	26,643	4,414	13	80	76	136	29	6,034	37,425
	Ustekinumab 45 mg	5	26,372	345	13	80	76	136	23	471	27,516
	Ustekinumab 90 mg	5	52,744	345	13	80	76	136	19	471	53,884
2, 3, 4, 5	Etanercept 50 mg	52	21,648	3,586	13	80	76	136	29	4,903	30,471
	Ustekinumab 45 mg	5 (4)[a]	26,372 (21,098)	345 (276)	13	80	76	136	23	471 (377)	27,516 (22,079)
	Ustekinumab 90 mg	5 (4)[a]	52,744 (42,195)	345 (276)	13	80	76	136	19	471 (377)	53,884 (43,172)

[a] Patients receive four ustekinumab doses during years 3 and 4

[b] Etanercept 50 mg dose cost US$416.30, ustekinumab 45 mg dose cost US$5,274.41, ustekinumab 90 mg dose US$10,548.81

[c] US$68.97 per office visit per dose, Current Procedural Terminology (*CPT*) code 99213; purified protein derivation (*PPD*): US$10 (2004 values) per tuberculin test per year; liver function test (*LFT*): US$15.43 (2004 values) per four LFTs per year; complete blood cell count (*CBC*): US$14.68 (2004 values) per four CBCs per year; physical: US$105.66 (2004 values) per physical examination per year; over the counter (*OTC*): annual per patient OTC drugs were estimated from common adverse event rates within ACCEPT [7]

[d] Indirect costs assume 4 hours of lost time per physician-supervised dose with US$23.57 hourly compensation

Patients achieving a reduction from baseline PASI score of ≥50 % (PASI50) at the end of each cycle are considered treatment responders. This assumption is based on the position by the NPF that a PASI50 is a clinically meaningful improvement for patients [17]. Patients responding to treatment continue with maintenance therapy (i.e., treatment beyond the initial 12 weeks) of etanercept or ustekinumab. Responding patients discontinue treatment for various reasons such as adverse events and treatment failure [19]. Similar to Woolacott et al. [19], this study applied a fixed annual 20 % discontinuation rate for patients responding to treatment (i.e., those with a PASI50-74 or PASI75 health state). Discontinuing patients experience a PASI<50 health state and are affected by this health state's costs and outcomes. We conducted a sensitivity analysis around this rate because there is limited evidence to suggest this discontinuation rate is appropriate in a US setting.

Nonresponders to treatment experience a <50 % PASI reduction from baseline (PASI < 50). The model assumes nonresponders discontinue therapy of etanercept or ustekinumab for the remainder of the study and pursue alternative biologic treatments (e.g., alafacept, efalizumab, infliximab). This characteristic provides a realistic treatment scenario of patients experiencing moderate to severe psoriasis [4]. Switching from one biological therapy to another, either for primary or secondary lack of efficacy or for adverse events, has become common practice [4].

3.5 Valuing Outcomes

Utilities estimated from the general population were identified because this study incorporates the societal perspective. The relevant study by Schmitt et al. [26] measures how society values a psoriatic patient's sense of well-being. This study was conducted in Germany and included a random sample of 139 adults aged 18 years or older from the general population to assess health utilities using the time trade-off method. The sample was reported to be 59.7 % female with an average age of 39.6 years old. For the time trade-off procedure, participants were asked to choose between living for their remaining life expectancy in the health state of interest (i.e., psoriasis) or a shorter duration in perfect health. Schmitt et al. [26] provides the basis for the base-case model's PASI75, PASI50-74, and PASI<50 health state utilities, which are 0.93, 0.75, and 0.56, respectively.

Utilities can also be estimated from the Dermatologic Life Quality Index (DLQI) [13, 19, 27]. The DLQI is used in clinical trials as the dermatology-specific health-related quality-of-life outcome measure for psoriasis patients [5, 6]. Using a linear regression, Currie and Conway [27] mapped DLQI scores to psoriasis patient EuroQol-5D (EQ-5D) utilities. This study consisted of a sample of 94 psoriasis patients from the United Kingdom (UK). Despite this available method for estimating utilities, the Schmitt et al. [26] study is more applicable to a US societal perspective for the following reasons. First, Currie and Conway [27] estimated utilities from psoriasis patients whereas Schmitt et al. [26] estimated utilities from the general population. Therefore, the Schmitt et al. [26] utilities are relevant to the societal perspective. Second, while international differences may limit its application to a US setting, the Schmitt et al. [26] study is relevant to the US because their health state descriptions for controlled and uncontrolled psoriasis is consistent with the definitions of the NPF [28]. Thus, the base-case analysis considers the Schmitt et al. [26] utilities and we conduct sensitivity analyses using the Currie and Conway [27] measure.

The treatment strategy for patients in the PASI<50 health state is to pursue alternative biologics. Consequently, they experience an improvement in utility from these treatments. Katugampola et al. [29] reviewed all biologic clinical trials that have used the DLQI as an outcome measure. More recently, the DLQI has also been used for ustekinumab [5, 6]. From these studies, we estimated the average utility gain associated with alternative biologic treatments from the procedure by Currie and Conway [27]. The limitations of this procedure to our model were discussed. However, it is the only current method available that maps DLQI to utilities, therefore we conducted sensitivity analyses around this parameter.

Not all patients in the PASI<50 health state experienced an improvement in utility. The proportion of PASI<50 patients experiencing a utility improvement was based on 12-week efficacies for alternative biologic treatments [30]. The remaining proportion experienced the PASI<50 utility estimated from Schmitt et al. [26]. This parameter entered the model as a fixed 12-week 50 % rate and a sensitivity analysis was conducted to address the limited evidence to inform this parameter.

3.6 Transition Probabilities

Etanercept and ustekinumab transition probabilities were derived from the ACCEPT study and were transformed to 12-week probabilities using a constant hazard rate transition model [7, 13, 31, 32]. The ACCEPT study clinical response during the 12-week control period was extrapolated beyond 12 weeks for several reasons. First, comparable safety profiles for the two drugs provide evidence that discontinuation rates remain relatively constant for approximately 3–4 years. Second, our model's health states measure clinical response as PASI improvement compared with baseline. We assume the proportions of patients experiencing PASI improvements at the end of ACCEPT's

control period are maintained. This rationale is supported by long-term efficacy data beyond 12 weeks for each drug [5, 6, 20, 33–36]. Third, extrapolating psoriasis studies with short control periods, such as ACCEPT, to 10 years was accepted by health technology appraisers for the UK National Institute of Health and Clinical Excellence and Canadian dermatologists [13].

Probability of response beyond the initial 12 weeks in ACCEPT assumes constant rates of clinical response (i.e., PASI improvement compared with baseline). The proportions of patients achieving PASI improvements associated with our model's health states are constant over time. Patients achieving a PASI75 improvement for ustekinumab (45 and 90 mg) and etanercept were reported in ACCEPT [7]. A limitation of the ACCEPT study is the absence of 12-week PASI50 responders, which are used to estimate PASI50-74 improvements. The Pan et al. [13] study makes up for part of this limitation by reporting 12-week ACCEPT PASI50 responders for ustekinumab 45 mg and etanercept 50 mg patients. To estimate equivalent ustekinumab 90 mg responders, we applied the average of PASI50 responders from previous ustekinumab clinical trials [5, 6]. This estimate was varied in sensitivity analyses to describe its effect on main outcomes.

Discontinuation rates have been used to measure patients that stop treatment for various reasons such as adverse events or treatment failure [13, 19]. Our model assumes a fixed annual 20 % discontinuation rate for responding patients (i.e., patients with a PASI50) regardless of therapy, which is consistent with similar studies [13, 19]. There is limited evidence to inform this discontinuation rate for the US, therefore we conducted sensitivity analyses around this rate, similar to Pan et al. [13].

3.7 Resource Use and Costs

Resource use for responding patients was determined and estimated from ongoing monitoring and dosing recommendations by the AAD [2, 3]. Direct costs and rates of use for ongoing monitoring procedures were obtained from previous cost-effectiveness analyses employing costs relevant to the US and recommendations by the AAD [2, 3, 24, 25, 37]. Ustekinumab and etanercept drug prices were based on Medicare Part B average sales prices (ASP) [38]. Costs and rates of use of over-the-counter medications to treat common adverse events was based on retail prices and ACCEPT [7, 39]. The cost of physician office visits and clinical procedures were obtained from the Medicare and Medicaid Services Physician Fee Schedule [40].

Indirect costs for receiving subcutaneous injections at the physician's office are included from a societal perspective. Relevant time costs consider traveling, waiting, and actually receiving treatment at the physician's office [9]. Patients were assumed to experience a 4-hour loss of time per injection for ustekinumab and etanercept treatments. We conducted sensitivity analyses around this 4-hour lost time for both treatments. The indirect costs of time lost by these patients were estimated from the average hourly compensation rate from the US Bureau of Labor Statistics [41]. The consumer price index reported by the US Bureau of Labor Statistics was used to adjust the annual base-case direct and indirect costs to 2011 US dollars (Table 1) [42].

Patients self-administering etanercept also experience loss of time from traveling, waiting, and actually receiving treatment at convenient locations other than the physician's office. Patients receiving treatments at a convenient location consume less time than at the physician's office. However, there remains uncertainty in the magnitude of this reduced time. Actual self-injection times are minimal and can be approximated from self-administered adalimumab [43]. However, patients experience additional time costs related to drug procurement and treatment preparation and disposal at a convenient location. There is limited evidence to inform these time costs. Therefore, we conservatively assume patients experience one hour of lost time per dose when self-administering etanercept.

Self-administering patients are expected to see their physician to monitor adverse effects. Self-administering patients travel to the physician four times per year for a physical and lab tests. Therefore, these patients experience costs for four office visits per year. We use previously published cost estimates for physician services when self-administering etanercept [37].

Patients in the PASI<50 health state incur direct costs for treatments and medical services. The base-case annual average healthcare costs of US$10,593 (year 2007 values) for these patients were obtained from Yu et al. [44]. This cost was fixed per cycle for the model duration and varied in a sensitivity analysis. The Yu et al. [44] study was applicable to our model because it grouped costs for patients with moderate to severe psoriasis, which is relevant to patients experiencing a PASI<50 improvement. Similar healthcare costs have been reported [45–47]. A 3 % annual discount rate was applied to all costs and QALYs [9]. A sensitivity analysis estimated the effect of variations in annual discount rates on outcomes.

3.8 Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) of 5,000 repetitions explored the base-case model uncertainty and was executed using distributions shown in Table 2. A series of sensitivity analyses were conducted to compare with the base-case results and assess the base-case assumptions (Table 3). From Table 3, we explain the set of sensitivity analysis cases that test specific assumptions in our model.

Table 2 Base-case probabilistic sensitivity analysis input parameter distributions (adjusted to 2011 US$)

Input parameter	Base-case input	Distribution	Distribution parameters		Reference
Annual healthcare utilization (2007)[a,b]	$10,593	Lognormal	Mean: $10,593	Standard deviation: 19,194	44
Utility: PASI75 health state[c]	0.93	Beta	Alpha: 3.49	Beta: 0.55	26
Utility: PASI50-74 health state[c]	0.75	Beta	Alpha: 50.98	Beta: 15.78	26
Utility: PASI<50 health state[c]	0.56	Beta	Alpha: 2.76	Beta: 2.08	26
Utility: PASI<50 responders to alternative treatments[d]	0.84	Beta	Alpha: 47.13	Beta: 9.30	27, 29
Treatment: Etanercept 50 mg[e]					
Proportion of PASI75 responders per 12 weeks	0.57	Beta	Alpha: 51.19	Beta: 48.84	5–7, 33, 34
Proportion of PASI50-74 responders per 12 weeks	0.26	Beta	Alpha: 3.14	Beta: 1.49	5–7, 33, 34
Proportion of PASI<50 responders per 12 weeks	0.18	Beta	Alpha: 19.48	Beta: 68.25	5–7, 33, 34
Treatment: Ustekinumab 45 mg[e]					
Proportion of PASI75 responders per 12 weeks	0.68	Beta	Alpha: 168.27	Beta: 187.19	5–7, 33, 34
Proportion of PASI50-74 responders per 12 weeks	0.19	Beta	Alpha: 121.75	Beta: 574.25	5–7, 33, 34
Proportion of PASI<50 responders per 12 weeks	0.13	Beta	Alpha: 65.54	Beta: 359.59	5–7, 33, 34
Treatment: Ustekinumab 90 mg[e]					
Proportion of PASI75 responders per 12 weeks	0.74	Beta	Alpha: 59.92	Beta: 23.36	5–7, 33, 34
Proportion of PASI50-74 responders per 12 weeks	0.14	Beta	Alpha: 18.29	Beta: 98.48	5–7, 33, 34
Proportion of PASI<50 responders per 12 weeks	0.12	Beta	Alpha: 47.57	Beta: 336.58	5–7, 33, 34
Etanercept 50 mg dose	$416	Triangular[f]	Min: $375	Max: $458	38
Ustekinumab 45 mg dose	$5,274	Triangular	Min: $4,747	Max: $5,802	38
Ustekinumab 90 mg dose	$10,549	Triangular	Min: $9,494	Max: $11,604	38
Common adverse event treatment for etanercept 50 mg[g]	$6.66	Triangular	Min: $6.00	Max: $7.33	7, 39
Common adverse event treatment for ustekinumab 45 mg[g]	$5.20	Triangular	Min: $4.68	Max: $5.72	7, 39
Common adverse event treatment for ustekinumab 90 mg[g]	$4.40	Triangular	Min: $3.96	Max: $4.84	7, 39
Office visit	$69	Triangular	Min: $62	Max: $76	40
Hourly compensation (2010)[b]	$23	Triangular	Min: $20	Max: $25	41
Tuberculin test (2004)[b]	$10	Triangular	Min: $9	Max: $11	30, 37
Liver function test (2004)[b]	$15	Triangular	Min: $14	Max: $17	37
Complete blood cell count test (2004)[b]	$15	Triangular	Min: $13	Max: $16	37
Physical examination (2004)[b]	$106	Triangular	Min: $95	Max: $116	37
Proportion PASI<50 responders to alternative treatments per 12 weeks	0.50	Triangular	Min: 0.45	Max: 0.55	30
Annual discount rate	0.030	Triangular	Min: 0.027	Max: 0.033	9
Patient hours spent for subcutaneous injection at physician's office	4.0	Triangular	Min: 3.6	Max: 4.4	NA

Min minimum, *Max* maximum, *NA* not applicable, *PASI* Psoriasis Area and Severity Index

[a] The model converted arithmetic means and standard deviations from the literature to geometric mean and geometric standard deviations

[b] Costs were converted to 2011 U.S. dollars

[c] Beta distribution parameters were defined from the estimated interquartile range in Schmitt et al. [26]

[d] Beta distribution parameters were defined from the estimated mean and variance of utility scores across all relevant therapies

[e] Beta distribution parameters were defined for the proportion of PASI responders per 12 weeks from the referenced clinical trials

[f] Triangular distributions were applied to parameters with limited information to inform variance

[g] Per patient per 12 weeks independent of health states

Table 3 Base-case model assumptions

Method section	Assumptions	Sensitivity analysis	References
Model description	1. Mortality is omitted from the base case because there is not enough evidence from the ACCEPT study to conclude the presence of significantly different mortality rates between treatment groups	See Table 6, Case VI	[7, 22, 23]
Time horizon	2. Extrapolating beyond the 12-week control period from ACCEPT to a 3-year time horizon is based on long-term safety data	See Table 4, Case V	[5, 6, 19–23]
Hypothetical patient cohort	3. Patients entered the model as adult patients with moderate to severe psoriasis characterized as the baseline characteristics and inclusion criteria in the ACCEPT study	NA	[7]
	4. Patients had no previous treatment with ustekinumab or etanercept	NA	[7]
Treatment strategy	5. From a US context, the model's treatment strategy is consistent with the recommendations by the AAD, the US FDA-licensed doses, and the treatment design of ACCEPT	See Table 7, Test 8 and 9	[2, 3, 7, 24, 25]
	6. Patients discontinue treatment at an annual fixed 20 % rate	See Table 5, Case III	[13, 19]
	7. All patients received subcutaneous injections for each drug under clinician supervision, which is consistent with US prescribing indications for either etanercept or ustekinumab	See Table 5, Case II	[24, 25]
	8. Patients respond to ustekinumab or etanercept treatment while in PASI50-74 and PASI75 health states	NA	[17]
	9. Patients discontinue treatment and pursue alternative biologic treatments while in the PASI<50 health state	NA	[4, 17]
Valuing outcomes	10. Utility values for PASI75, PASI50-74, and PASI<50 health states were based on scenarios for controlled and uncontrolled psoriasis from the general population	See Table 5, Case I	[26]
	11. Patients experience an average improvement in utility, estimated from mapped DLQI scores to EQ-5D utilities, while pursuing alternative biologic treatments	See Table 7, Test 2	[27, 29]
	12. A fixed proportion of PASI<50 respond to alternative biologic treatments per cycle	See Table 7, Test 3	[27, 29, 30]
Transition probabilities	13. 12-week probabilities were estimated using a constant hazard rate transition model	See Table 2	[5–7, 13, 31, 32]
	14. Probability of response beyond the initial 12 weeks in ACCEPT assumes constant rates of clinical response (i.e., PASI improvement compared with baseline)	See Table 4, Case V and Table 7, Test 7	[5–7, 13, 19, 20, 22, 23]
Resource use and costs	15. Direct costs and rates of use for ongoing monitoring procedures were obtained from previous studies employing costs relevant to the US and recommendations by the AAD	See Table 2	[2, 3, 24, 25, 33–36]
	16. Ustekinumab and etanercept unit drug prices were based on Medicare ASP	See Table 5, Case IV	[38]
	17. Costs and rates of use of OTC medication to treat common adverse events were based on retail prices and ACCEPT	See Table 2	[7, 39]
	18. The cost of physician office visits and clinical procedures were based on the Physician Fee Schedule	See Table 2	[40]
	19. Psoriasis patients experience a 4-hour loss of time per injection per year for ustekinumab and etanercept treatments	See Table 7, Test 6	NA
	20. Patients achieving a PASI<50 incur annual average healthcare costs for treatments and medical services	See Table 7, Test 1	[44]

AAD American Academy of Dermatology, *ACCEPT* phase III Active Comparator Psoriasis Trial, *ASP* average sales price, *DLQI* Dermatologic Life Quality Index, *FDA* Food and Drug Administration, *NA* not applicable, *OTC* over the counter, *PASI* Psoriasis Area Severity Index, *US* United States

3.8.1 *Case I: Utility Gains from Dermatologic Life Quality Index (DLQI)*

The ACCEPT study does not include DLQI measures, therefore EQ-5D utility gains from DLQI changes were obtained from ustekinumab and etanercept clinical trials [5–7, 36, 48]. From these trials, average baseline DLQI, and subsequently average baseline EQ-5D utility, can be estimated for 45 and 90 mg ustekinumab and 50 mg etanercept treatments [5, 6, 36, 48]. However, the absence of 12-week DLQI change by PASI response category limits the estimation of the respective EQ-5D utility gains. The

Pan et al. [13] study overcomes this limitation by reporting EQ-5D utility gains by PASI response category from ustekinumab clinical trials [5, 6]. Case I applies these utility gains to estimated average baseline EQ-5D utilities [5, 6, 13, 36, 48].

3.8.2 Case II: Self-Administration of Etanercept 50 mg

The US prescribing indications for etanercept allow patients to self-administer while ustekinumab patients cannot [24, 25]. There is limited experimental and observational evidence to inform rates of psoriasis patient use of self-administered versus clinician supervised etanercept injections. Relevant information for etanercept self-administration choice is from rheumatoid arthritis patients, where 48 % of respondents prefer to administer their own treatment [49]. Therefore, Case II approximates 50 % of etanercept patients self-administer at treatment initiation for the duration that they respond to treatment. This proportion is a fixed value per 12-week cycle because we are not aware of evidence to advise whether this parameter changes over time. Case II also measures the effect of all patients (100 %) choosing to self-administer etanercept for the duration of the model.

3.8.3 Case III: Discontinuation

The base case 20 % fixed annual discontinuation rate was incorporated into our model similar to previous studies [13, 19]. Case III varies this rate at ranges previously tested (i.e., 0 and 90 %) [13].

3.8.4 Case IV: Drug Costs

The base-case model incorporates Medicare ASP for ustekinumab and etanercept. Wholesale acquisition costs (WAC) have been reported for ustekinumab and etanercept under the premise that these prices exclude discounts or mark-ups by wholesalers or distributors [12]. This case applies WAC prices for both drugs to the model. Moreover, the contractual price between the drug manufacturer and the insurer (other than Medicare ASP) are highly confidential in the US. Threshold sensitivity analyses around the base-case drug prices were conducted to estimate the effect of variations in these prices on incremental costs.

3.8.5 Case V: Time Horizon

The base-case results extrapolate effectiveness and safety beyond the 12-week ACCEPT trial's controlled period. We provide 12-week results to consider this short duration. We are not aware of US guidance for acceptable psoriasis model time horizons. Therefore, we report 1- and 5-year results to accommodate the long-term disease characteristics of psoriasis.

3.8.6 Case VI: Mortality

The base-case model assumes no difference in mortality rates between the ustekinumab and etanercept treatments. While long-term safety studies for both drugs show comparable mortality rates to each other and to US populations, patients with severe psoriasis experience excess risk of death [18, 22, 23]. This case includes mortality as an additional health state for all time horizons reported for Case V. Rates of mortality incorporated all-cause and disease-specific mortality risk [18, 50].

4 Results

4.1 Base-Case Model

The base-case incremental cost per QALY gained (ICER) for the three arms are reported in Table 4. The ICER comparing ustekinumab 45 mg with 90 mg is not relevant to our study because randomization was stratified by baseline weight in ACCEPT. From Table 4, ustekinumab 45 mg dominated etanercept 50 mg because it is less costly and more effective. The ICER comparing ustekinumab 90 mg versus etanercept 50 mg was US$384,401. As a result, ustekinumab 90 mg was not cost effective when compared with our model's US$120,000–US$150,000 willingness-to-pay threshold.

4.2 Sensitivity Analysis

The results from Cases I, II, III, and IV are shown in Table 5. Case I indicates EQ-5D utility gains mapped from DLQI decreased incremental QALYs compared with the base case. Despite this reduction, ustekinumab 45 and 90 mg remained dominant and not cost effective compared with etanercept 50 mg, respectively.

Case II varied the proportion of patients self-administering etanercept 50 mg at treatment initiation to 50 and 100 %. The 50 % proportion of self-administering patients did not affect the outcomes when compared with the base case. However, when 100 % of patients self-administer etanercept 50 mg at treatment initiation, ustekinumab 45 mg did not dominate etanercept 50 mg. When compared with our model's threshold, ustekinumab 45 mg was cost effective while ustekinumab 90 mg remained not cost effective. The results from Case II suggest as the proportion of people choosing to self-administer etanercept 50 mg at treatment initiation increase, etanercept 50 mg becomes less costly. This trend can be attributed to the

Table 4 Cost-effectiveness results for the base case and Case V sensitivity analysis

Time horizon	Intervention	Incremental cost (US$)	Incremental effectiveness (QALYs)	Incremental cost per Incremental QALY (US$)
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
12 weeks	Ustekinumab 45 mg	(2,044)	0.006	Dominant
	Ustekinumab 90 mg	7,649	0.011	687,034
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
1 year	Ustekinumab 45 mg	(3,858)	0.024	Dominant
	Ustekinumab 90 mg	18,303	0.042	434,043
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
3 years	Ustekinumab 45 mg	(3,919)	0.040	Dominant
(Base case)[a]	Ustekinumab 90 mg	27,257	0.071	384,401
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
5 years	Ustekinumab 45 mg	(3,664)	0.046	Dominant
	Ustekinumab 90 mg	29,735	0.080	370,646

Parentheses indicate negative costs; all costs and QALYs discounted at 3 %

QALY quality-adjusted life-year

[a] Overall costs for etanercept 50 mg, ustekinumab 45 mg, and ustekinumab 90 mg are US$54,845, US$50,926, and US$82,103, respectively. Overall QALYs for etanercept 50 mg, ustekinumab 45 mg, and ustekinumab 90 mg are 2.109, 2.149, and 2.180, respectively

reduced indirect costs experienced by patients self-administering.

The cost-effectiveness outcomes from Case III suggest varying discontinuation rates at 0 and 90 % do not substantively differ from the base case. Ustekinumab 45 mg dominated etanercept 50 mg at these two rates while ustekinumab 90 mg remained not cost effective.

Case IV demonstrates ICERs estimated from WAC do not meaningfully differ from the base case. The related threshold sensitivity analysis (Fig. 2) shows changes in drug costs on incremental costs. Ustekinumab 45 mg becomes more costly than etanercept 50 mg when all drug costs increase by 80 %, ustekinumab 45 mg drug costs increase by 20 %, and etanercept 50 mg drug costs decrease by 20 %. Ustekinumab 90 mg becomes less costly than etanercept 50 mg when all drug costs decrease by 80 % and ustekinumab 90 mg drug costs decrease by 50 %. Ustekinumab 90 mg remained more costly than etanercept 50 mg when etanercept 50 mg drug costs increase by 100 %.

Case V explored the effect of varying time horizons on the base-case ICERs (Table 4). At 12 weeks, ustekinumab 45 mg dominates etanercept 50 mg while ustekinumab 90 mg was not cost effective. These 12-week outcomes persisted up to 5 years. Case VI (Table 6) extends the results of Case V by testing whether mortality affects this extrapolation. Case VI shows that including mortality does not noticeably affect the model outcomes when compared with Case V.

Additional sensitivity analyses are reported in Table 7. The majority of these analyses test our model assumptions in Table 3. Test 1 shows ±30 % variations in healthcare costs for PASI<50 do not differ from the base-case model. Tests 2 and 3 provide sensitivity analyses for model assumptions 11 and 12, respectively. There were minimal differences in outcomes when compared with the base case. Tests 4 and 5 demonstrate variations in patient hourly compensation and annual discount rates do not considerably alter the outcomes relative to the base case. Test 6 addresses model assumption 19. This sensitivity analysis indicates increasing patient time lost per treatment dose decreases incremental costs for ustekinumab 45 and 90 mg.

Relevant studies on ACCEPT do not report ustekinumab 90 mg PASI50 responders [7, 13]. The base-case model takes the average PASI50 responders from previous ustekinumab 90 mg studies [5, 6]. Test 7 demonstrates minimal differences in outcomes, relative to the base case, when Phoenix I and Phoenix II ustekinumab 90 mg PASI50 responders are applied to the model, respectively.

The etanercept US prescribing indications suggest once weekly 25 or 50 mg starting doses, in addition to the recommended 50 mg twice-weekly dose, were shown to be efficacious [24]. Tests 8 and 9 consider these starting doses as possible treatment scenarios using clinical trial data comparing these two regimens [36]. The 50 mg once-weekly maintenance dose is the expected dosing schedule after the 25 mg once-weekly starting dose [24]. There is limited evidence to inform PASI response rates for this dosing schedule, therefore we limit the 25 mg once-weekly starting dose time horizon to 12 weeks. From Test 8, a starting dose of once weekly 25 mg etanercept is less costly with similar effectiveness when compared with the twice-weekly starting dose regimen. However, ustekinumab 45 and 90 mg were not cost effective for up to a 12-week time horizon.

Table 5 Sensitivity analysis cases

Case	Sensitivity analysis	Intervention	Incremental cost (2011 US$)	Incremental effectiveness (QALYs)	Incremental cost per incremental QALY (2011 US$)[d]
		Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
Base case	None	Ustekinumab 45 mg	(3,919)	0.040	Dominant
		Ustekinumab 90 mg	27,257	0.071	384,401
	PASI<50 utility gain: 0.040	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
I	PASI50-74 utility gain: 0.170	Ustekinumab 45 mg	(3,919)	0.011	Dominant
	PASI75 utility gain[e]: 0.235	Ustekinumab 90 mg	27,257	0.004	6,348,360
		Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
	50 %	Ustekinumab 45 mg	(627)	0.040	Dominant
II[a]		Ustekinumab 90 mg	30,550	0.071	430,828
		Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
	100 %	Ustekinumab 45 mg	3,864	0.040	96,310
		Ustekinumab 90 mg	35,040	0.071	494,161
		Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
	0 %	Ustekinumab 45 mg	(4,153)	0.046	Dominant
III[b]		Ustekinumab 90 mg	32,210	0.083	388,086
		Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
	90 %	Ustekinumab 45 mg	(3,424)	0.027	Dominant
		Ustekinumab 90 mg	18,959	0.046	408,600
	Etanercept 50 mg cost: US$407.28	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
IV[c]	Ustekinumab 45 mg cost: US$4,891.49	Ustekinumab 45 mg	(5,270)	0.040	Dominant
	Ustekinumab 90 mg cost: US$9,782.97	Ustekinumab 90 mg	24,613	0.071	347,106

Parentheses indicate negative costs

PASI Psoriasis Area Severity Index

[a] The proportion of patients self-administering at treatment initiation for etanercept 50 mg

[b] Annual fixed discontinuation rate

[c] Wholesale acquisition cost prices (2010 US$) [12]

[d] 3-year time horizon with 3 % discount rate

[e] Average utility gain between PASI75 to <90 and PASI90

The 50 mg once-weekly starting dose was extended beyond 12 weeks because clinical trials measure PASI response rates into 50 mg once-weekly maintenance [33, 35]. The relatively stable PASI75 response rates provide the rationale to extend the 12-week clinical trial data to the base-case 3-year time horizon [33, 35, 36]. Test 9 indicates ustekinumab 45 mg is not cost effective at 12 weeks and is cost effective at a 3-year time horizon. Ustekinumab 90 mg is not cost effective for up to a 3-year time horizon.

Patients may continue on etanercept 50 mg twice weekly beyond the initial 12 weeks due to inadequate response. Test 10 considers this scenario by extending the twice-weekly etanercept 50 mg dose to 24 weeks and then once weekly for 3 years. For this test, extended exposure of etanercept 50 mg twice weekly had a similar safety profile to etanercept 50 mg once weekly [51]. Therefore, only the base case of 12 doses was increased to 24, for an additional 12 weeks, because PASI response was assumed to be constant. Incremental effectiveness for extending twice-weekly etanercept 50 mg did not differ from the base case. The incremental costs decreased for ustekinumab 45 and 90 mg. However, ustekinumab 45 and 90 mg remained dominant and not cost effective, respectively. We are not aware of studies that inform us whether an additional 12-week extension of twice-weekly etanercept 50 mg is relevant to the US setting. Additional work can examine feasible scenarios where clinicians experience a loss of patient efficacy when moving beyond the 12-week starting dose period.

Fig. 3 shows the acceptability curve for the base-case comparison of ustekinumab 90 mg and ustekinumab 45 mg compared with etanercept 50 mg, respectively. The probability that ustekinumab 90 mg is cost effective compared with etanercept 50 mg is 4 % for a willingness-to-pay threshold of US$150,000 per QALY. For the same threshold, ustekinumab 45 mg has an 88 % probability of being cost effective compared with etanercept 50 mg.

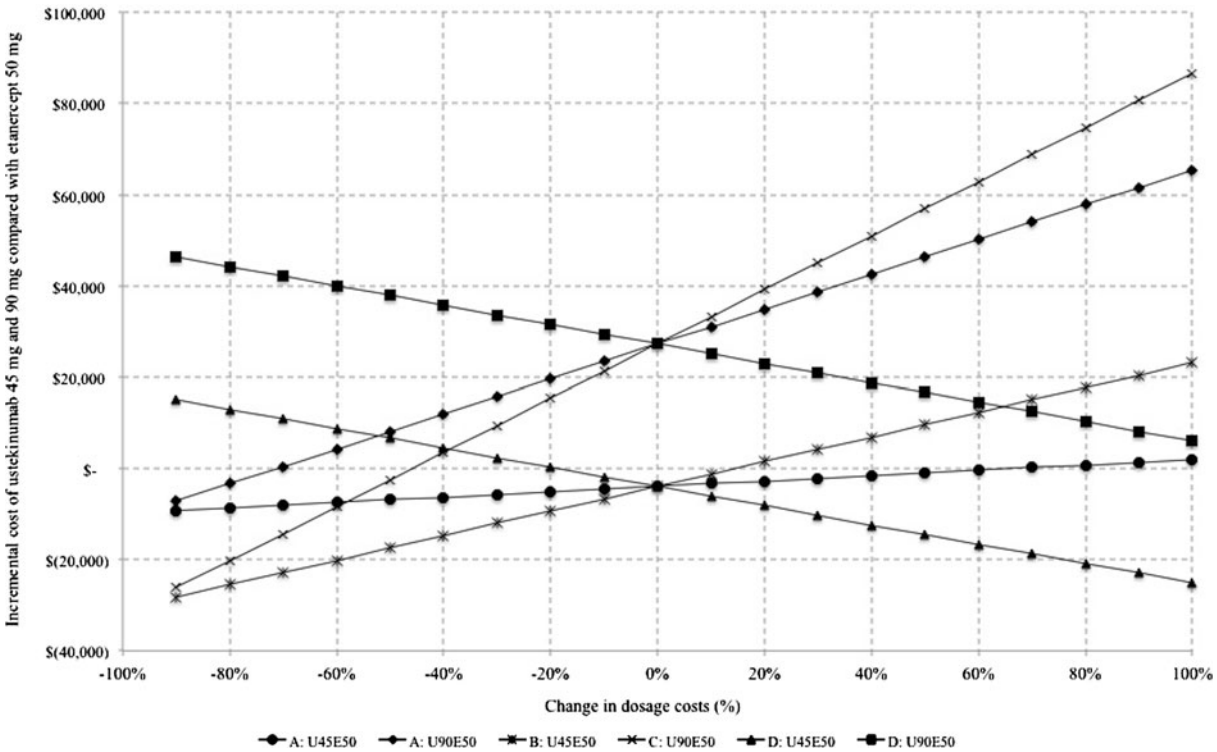

Fig. 2 U45E50 (ustekinumab 45 mg compared with etanercept 50 mg) and U90E50 (ustekinumab 90 mg compared with etanercept 50 mg) threshold sensitivity analyses on incremental costs as a function of percent change in dosage costs. All costs are in US$. *A* change in all dose costs, *B* change in U45 dose costs only, *C* change in U90 dose costs only, *D* change in E50 dose costs only

Table 6 Cost-effectiveness results for the Case VI sensitivity analysis

Time horizon	Intervention	Incremental cost (US$)	Incremental effectiveness (QALYs)	Incremental cost per incremental QALY (US$)
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
12 weeks	Ustekinumab 45 mg	(2,044)	0.006	Dominant
	Ustekinumab 90 mg	7,649	0.011	687,034
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
1 year	Ustekinumab 45 mg	(3,859)	0.023	Dominant
	Ustekinumab 90 mg	18,271	0.042	434,813
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
3 years	Ustekinumab 45 mg	(3,971)	0.040	Dominant
	Ustekinumab 90 mg	27,232	0.071	385,923
	Etanercept 50 mg	REFERENCE	REFERENCE	REFERENCE
5 years	Ustekinumab 45 mg	(3,785)	0.046	Dominant
	Ustekinumab 90 mg	29,909	0.080	372,895

Parentheses indicate negative costs; all costs and QALYs discounted at 3 %

QALY quality-adjusted life-year

5 Discussion

In this Markov model, we examined the comparative cost effectiveness of etanercept 50 mg, ustekinumab 45 and 90 mg for moderate to severe psoriasis patients. The model comprised outcomes, resource use and costs, and treatment strategies relevant to the US societal perspective. For the base-case 3-year period, ustekinumab 45 mg dominates etanercept 50 mg (i.e., more effective and less costly). For the same time period, ustekinumab 90 mg was not cost

Table 7 Sensitivity analysis tests

Test	Analysis performed	U45–E50			U90–E50		
		Incremental cost (2011 US$)	Incremental effectiveness (QALYs)	ICER (US$)	Incremental cost (2011 US$)	Incremental effectiveness (QALYs)	ICER (US$)
	Base case	(3,919)	0.040	Dominant	27,257	0.071	384,401
1	Annual healthcare costs for PASI<50 +30 %[a]	(4,630)	0.040	Dominant	26,166	0.071	369,012
	Annual healthcare costs for PASI<50 −30 %[a]	(3,209)	0.040	Dominant	28,349	0.071	399,790
2	Utility gain for PASI<50 responders to alternative treatments +10 %	(3,919)	0.032	Dominant	27,257	0.059	459,893
	Utility gain for PASI<50 responders to alternative treatments −10 %	(3,919)	0.048	Dominant	27,257	0.083	330,198
3	Proportion of PASI<50 responders to alternative treatments 0 %	(3,919)	0.066	Dominant	27,257	0.109	249,461
	Proportion of PASI<50 responders to alternative treatments 90 %	(3,919)	0.020	Dominant	27,257	0.040	677,642
4	Patient hourly compensation +5 %	(4,135)	0.040	Dominant	27,044	0.071	381,394
	Patient hourly compensation −5 %	(3,704)	0.040	Dominant	27,471	0.071	387,407
5	Annual discount rate: 0 %	(3,968)	0.042	Dominant	28,102	0.073	382,428
	Annual discount rate: 5 %	(3,887)	0.039	Dominant	26,730	0.069	385,687
6	Patient time lost per treatment dose: 2 h	(1,763)	0.040	Dominant	29,390	0.071	414,469
	Patient time lost per treatment dose: 8 h	(8,231)	0.040	Dominant	22,993	0.071	324,265
7	Ustekinumab 90 mg PASI50 responders: Phoenix I[b]	(3,919)	0.040	Dominant	24,745	0.065	379,032
	Ustekinumab 90 mg PASI50 responders: Phoenix II[b]	(3,919)	0.040	Dominant	30,062	0.077	392,576
8	Etanercept 25 mg once weekly: 12-week time horizon	5,419	0.006	848,894	15,111	0.011	1,357,351
9	Etanercept 50 mg once weekly: 12-week time horizon	3,447	0.006	539,970	13,139	0.011	1,180,219
	Etanercept 50 mg once weekly: 3-year time horizon	8,779	0.084	104,829	39,956	0.115	348,842
10	Extending twice weekly etanercept 50 mg to 24 weeks	(8,209)	0.040	Dominant	22,968	0.071	323,905

E50 etanercept 50 mg, *ICER* incremental cost per incremental QALY, *NA* not applicable, *PASI* Psoriasis Area and Severity Index, *PASI<50* less than 50 % improvement in PASI score, *QALY* quality-adjusted life-year, *U45* ustekinumab 45 mg, *U90* ustekinumab 90 mg

[a] ±30 % to describe the sensitivity of reported costs from Yu et al. [44]

[b] PASI50 responders are not reported in ACCEPT and Pan et al. [13]. The base-case model takes the average PASI50 responders from Phoenix I and Phoenix II. This analysis applies PASI50 responders from Phoenix I or Phoenix II, respectively [5–7, 13]

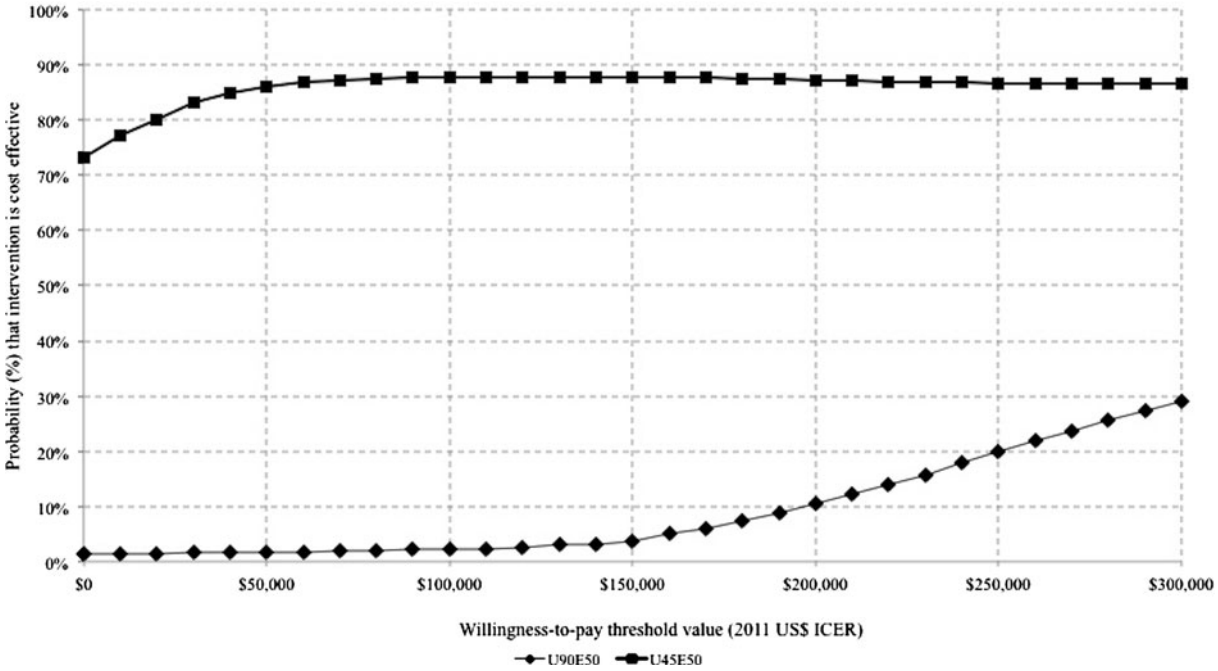

Fig. 3 Cost-effectiveness acceptability curves for the base-case probability that ustekinumab 90 mg and 45 mg is cost effective compared with etanercept 50 mg (U90E50 and U45E50, respectively) as a function of a decision maker's willingness-to-pay threshold. *ICER* incremental cost-effectiveness ratio, expressed as incremental cost per incremental quality-adjusted life-year (QALY)

effective using our model's US willingness-to-pay threshold. The model assumptions were evaluated in multiple sensitivity analyses and the majority of the results do not substantially differ from the base-case outcomes.

This model has several advantages over previously reported models from a US context [12, 30, 37, 52]. First, this model is based upon the head-to-head comparison from ACCEPT. While a similar US study was based on the ACCEPT trial, we present a cost per QALY analysis versus a cost per responder analysis [12]. Our model's cost per QALY analysis is consistent with the recommendations from the US Panel on Cost Effectiveness in Health and Medicine [9]. Second, previous studies have used indirect comparisons and meta-analysis procedures [30, 37, 52]. Our study improves upon these comparisons because the direct comparisons from ACCEPT provide high internal validity of efficacy.

Third, this study evaluates the predicament with extrapolating 12-week ACCEPT control data to longer time horizons relevant to the chronic disease characteristics of psoriasis. Previous studies based on ACCEPT limit their time horizons to either 12 weeks or omit 12-week outcomes [12, 13]. It is possible that long-term effectiveness differs from the 12-week ACCEPT control period. Our study responds to this concern by reporting 12-week outcomes. However, future adverse effects and treatment response related to treating chronic psoriasis may not be observed in the course of the 12-week control period. We evaluate these future events by assessing cost effectiveness for up to 5 years. Our study's short- and long-term analyses provide a complete evaluation of expected outcomes applicable to treating chronic psoriasis.

Morbidity and mortality indirect costs are two general types of time costs that are also incorporated in our model through the QALY. First, through the health state descriptions in Schmitt et al. [26], morbidity indirect costs (productivity costs associated with lost/impaired ability to work or engage in leisure activities due to psoriasis-related morbidity) are captured in the QALY calculation. Second, mortality indirect costs (loss of economic productivity due to death) are also captured in the QALY calculation because the QALY captures the full value of time lost in death; consequently, it is naturally incorporated in our model's QALY calculation. Therefore, our model's QALY calculation incorporates the relevant indirect costs associated with moderate to severe psoriasis relevant to the US societal perspective.

In comparing the base-case ICERs generated from Schmitt et al. [26] utilities with those from the Currie and Conway [27] method, it is possible to make a comparison between utilities estimated from the general population and a psoriasis population. The utility gains estimated from the Currie and Conway [27] mapping method are less than the utility gains from the Schmitt et al. [26] direct elicitation study. Therefore, the reduction in incremental QALYs experienced by ustekinumab 45 and 90 mg reflect this

difference in utility gains. The Schmitt et al. [26] utility gains have been discussed as more relevant than the Currie and Conway [27] utilities for our model. By using the Schmitt et al. [26] utilities in the base case, there are fewer concerns on the validity of the subsequent results in the context of a US societal perspective.

The option to self-administer etanercept 50 mg presents a likely treatment scenario that was evaluated in this study. Self-administering etanercept 50 mg treatments decrease overall costs. As the fraction of self-administering etanercept patients increases, ustekinumab becomes more costly than etanercept. This result is based on the increased proportion of etanercept patients that self-administer and the related patient time lost per dose. While there is limited evidence to inform these parameters, the effects of self-administering etanercept 50 mg on ICERs are useful. From Table 1, the infrequent treatments at the physician's office of ustekinumab relative to etanercept generate less indirect costs per patient per year. While self-administering etanercept reduces these indirect costs, ustekinumab 45 mg remains cost effective and ustekinumab 90 mg is not cost effective using a US willingness-to-pay threshold of US$150,000 per QALY.

From a US context, there is limited evidence to suggest appropriate discontinuation rates. This model demonstrates that high rates of discontinuation do not affect long-term cost effectiveness. Our treatment of discontinuation rates is consistent with previous long-term psoriasis analyses [13, 19]. However, there is limited information to inform whether these discontinuation rates differ between treatments or occur intermittently over time. Therefore, the results from this study are applicable when discontinuation rates are fixed over time and equally applied to all therapies.

Excess mortality risk is typically not considered in psoriasis CEA models because there is limited evidence to conclude that there are significantly different mortality rates between drug treatments [13, 19, 52]. The base-case model conservatively assumes mortality does not differentially affect outcomes. However, the US Panel on Cost Effectiveness in Health and Medicine recommends outcomes include mortality risks [9]. In addition, patients with severe psoriasis experience excess mortality, which may affect results for time horizons of 3 or 5 years [18]. However, our model shows that including excess mortality from psoriasis does not materially affect cost-effectiveness outcomes within these time horizons.

In the US setting, the application of cost-effectiveness information in decision making is complex [10, 11]. Cost-effectiveness analyses, such as this model, provide decision makers (i.e., physicians, managed care organizations, or state or federal healthcare programs) with a guide to resource allocation in healthcare [10]. For example, given the confidential price contracts between US private insurers and drug manufacturers, our model's threshold sensitivity analysis gives insight into the effects of different drug pricing assumptions on incremental costs. In addition, our model provides decision makers with an assessment of potential cost savings when etanercept patients self-administer or initiate a once-weekly starting dose regimen.

The ACCEPT study focused on uncontrolled moderate to severe psoriasis patients defined by inadequate response to conventional therapy. In particular, ACCEPT patients had no previous treatment with ustekinumab or etanercept. The results from this model can be generalized to patient groups that fit these criteria. Furthermore, the AAD report biologic agents are routinely used when one or more traditional systemic agents fail to produce an adequate response, are intolerable, or are unsuitable due to comorbidity presence [2, 3]. Therefore, the results from this model are relevant to US patients with refractory psoriasis with a choice to initiate treatment with ustekinumab or etanercept.

While our sensitivity analyses indicate robust results, our model has some limitations. First, ustekinumab 90 mg is prescribed for people weighing >100 kg (220 lb) in the US. The average weight for the ustekinumab 90 mg group in ACCEPT was <100 kg, therefore, the clinical response modeled in our base-case results may differ from clinical practice. Second, published ustekinumab 90 mg PASI50 response rates were not available for ACCEPT [7, 13]. Therefore, we applied average PASI50 response rates from the placebo-controlled trials Phoenix I and II [4, 5]. The sensitivity analysis for this limitation did not affect cost-effectiveness outcomes relative to the base case. Third, this study assumed all once-weekly etanercept 50 mg doses are administered without interruption. Intermittent once-weekly etanercept 50 mg is a possible treatment scenario that was evaluated in open-label studies [53, 54]. However, there is limited evidence from these studies and in the US prescribing indications to inform relevant treatment scenarios for analysis. Future studies should consider realistic treatment scenarios, where appropriate, for intermittent once-weekly etanercept 50 mg in a US setting.

6 Conclusions

Under typical US willingness-to-pay thresholds, ustekinumab 90 mg is not cost effective compared with etanercept 50 mg therapy in moderate to severe psoriasis patients for the base-case 3-year time horizon. In contrast, ustekinumab 45 mg dominates etanercept 50 mg therapy for equivalent patient psoriasis severities and wider time horizons.

Author Contributions Mr. Reginald Villacorta, and Drs. Joel Hay and Andrew Messali had full access to all of the data in the study and

take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Villacorta, Hay, Messali. *Acquisition of data:* Villacorta. *Analysis and interpretation of data:* Villacorta, Hay, Messali. *Drafting of the manuscript:* Villacorta, Hay, Messali. *Critical revision of the manuscript for important intellectual content:* Villacorta, Hay, Messali. *Statistical analysis:* Villacorta, Hay, Messali.

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