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ORIGINAL RESEARCH

Cost-Effectiveness of Acthar Gel Versus Standard of Care for the Treatment of Exacerbations in Moderate-to-Severe Systemic Lupus Erythematosus

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ABSTRACT

Introduction: Despite current standard of care (SoC), there is an unmet need for the treatment of active systemic lupus erythematosus (SLE). The study assessed the cost-effectiveness of Acthar® Gel (repository corticotropin injection) versus SoC treatment in patients with active, moderate-to-severe SLE from the US payer and societal perspectives over 2 and 3 years.

Methods: Cost-effectiveness model was developed using a probabilistic cohort-level state-transition approach. Patients received Acthar Gel in an exacerbation state, and the outcomes were assessed at the end of a 3-month cycle for response achievement based on the probability of treatment success with Acthar Gel. Patients may sustain the response or experience an exacerbation. For the base case scenario, moderate-to-severe SLE was defined as British Isles Lupus Assessment Group (BILAG)-2004 $\geq$ 20 or SLE Disease Activity Index 2000 (SLEDAI-2K) $\geq$ 10 and clinical response was based on SLE responder index (SRI)-4. Clinical response, productivity loss, and utility were derived from a phase 4 SLE trial; cost and disutility estimates were sourced from the literature.

Results: From a payer perspective, Acthar Gel versus SoC resulted in an incremental cost-effectiveness ratio (ICER) of $133,110 per quality-adjusted life-year (QALY) and $94,818 per QALY over 2 and 3 years, respectively. From a societal perspective, Acthar Gel versus SoC results in an ICER of $70,827 per QALY and $32,525 per QALY over 2 and 3 years, respectively. Results from the sensitivity and scenario analyses are consistent with those of the base case model.

Conclusions: Acthar Gel is a cost-effective, value-based treatment option for appropriate patients with moderate-to-severe SLE at a willingness-to-pay threshold of $150,000 over 2–3 years from the US payer and societal perspectives. Acthar Gel results in the reduction of direct medical and indirect costs.

Keywords: Acthar® Gel; Cost-effectiveness analysis; Repository corticotropin injection; Systemic lupus erythematosus

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Key Summary Points

Why carry out this study?

Acthar® Gel (repository corticotropin injection) is approved by the US Food and Drug Administration for use during an exacerbation or as maintenance therapy in systemic lupus erythematosus (SLE).

Acthar Gel has been shown to be safe and provides durable benefits among patients with moderate-to-severe SLE who have persistently active SLE despite aggressive treatment. However, data on the economic benefit of Acthar Gel in moderate-to-severe SLE are limited.

Assessment of the economic benefit of Acthar Gel for treatment-experienced patients with moderate-to-severe SLE by integrating the information on efficacy, effectiveness, cost, and patient outcomes is important to support decision-making.

What was learned from the study?

Treatment with Acthar Gel is a cost-effective, value-based strategy for active, moderate-to-severe SLE versus standard of care at a willingness-to-pay threshold of $150,000 over 2 and 3 years from the US payer and societal perspectives. These findings suggest that the use of Acthar Gel may considerably improve clinical and health outcomes among patients with moderate-to-severe SLE with a reduction in direct medical and indirect costs.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic non-organ specific autoimmune inflammatory disease and is characterized by a dysregulation of the immune system [1]. SLE involves many vital organs and systems such as the kidneys, brain, heart, dermatologic manifestations, and blood [1, 2]. SLE is characterized by heterogeneity of clinical manifestations and periods of remission and relapse and may present with various constitutional and organ-specific symptoms. Approximately 204,295 people in the US have definite or suspected SLE based on the American College of Rheumatology 1997 revised classification criteria for SLE [3]. Reported incidence rates for SLE in North America range from 1.2 to 8.7 per 100,000 person-years [4], and prevalence rates in studies of US populations range from 5 to 241 per 100,000 people [5]. About 90% of people living with SLE are women [6]. Approximately three-fourths of patients experience moderate-to-severe SLE [7]. SLE results in functional impairment, reduced productivity, poor quality of life (QoL), unemployment, increased mortality, and increased healthcare utilization [8–10]. Furthermore, an increase in SLE disease severity results in greater flare frequency and severity, thereby adding to the existing economic burden on patients and the healthcare system [7]. Increase in flare frequency is related to impaired functional and psychologic well-being, family functioning, and the number of monthly healthy days [11] as well as increased productivity loss and healthcare utilization [12].

The goal of available SLE treatments is the management of symptoms and disease flares [8]. Effective management of chronically active disease and disease flare is crucial to reduce the risk of accumulated organ and tissue damage over time, thereby reducing end-organ damage related to morbidity and mortality and the economic burden of SLE on patients [2, 13–16]. In addition, SLE treatments should also improve patient QoL [2]. A change of treatment should be considered based on the disease activity (flares) and severity [15, 16]. Treatments include the use of steroidal and nonsteroidal anti-inflammatory drugs, glucocorticoids, immunosuppressives, antimalarials, and biologic agents. Despite treatment with these agents, there is an unmet need for value-based treatments in managing persistently active SLE [16].

Acthar® Gel (repository corticotropin injection) is approved by the US Food and Drug Administration for treatment during an exacerbation or as maintenance therapy in selected

cases of systemic lupus erythematosus. The therapy is also indicated for inducing a diuresis or remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or due to lupus erythematosus [17]. It is unclear or there are limited data available examining gender or racial differences in the effectiveness of this treatment for this indication. Acthar Gel is a naturally sourced complex mixture of adrenocorticotropic hormone analogues and other pituitary peptides that interacts with all five melanocortin receptors. Its therapeutic effects in SLE may be attributed to the activation of several potential anti-inflammatory pathways through both glucocorticoid-dependent and -independent mechanisms [17]. Acthar Gel has been shown to be safe and provide durable and beneficial effects among patients with moderate-to-severe SLE who have persistently active SLE despite aggressive treatment with conventional medications [2, 18, 19]. Furthermore, in an efficacy trial of Acthar Gel in patients with moderate-to-severe SLE, the findings supported the utility of Acthar Gel for treating persistently active SLE [20]. Acthar Gel treatment resulted in a reduction in 28-point swollen joint count and/or tender joint count and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)-Activity score in a proliferation-inducing ligand cytokine. Post hoc analyses demonstrated a greater proportion of British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) responders for Acthar Gel compared to placebo as early as Week 4 and sustained response through Week 24 [20]. Furthermore, patients in the Acthar Gel group had greater SLE Responder Index (SRI)-4 response compared to the placebo group with better SLE Disease Activity Index-2000 (SLEDAI 2K) and CLASI-Activity [20]. Improvement in the Lupus QoL, specifically pain, planning, and fatigue domains, as well as the Work Productivity and Activity Impairment (WPAI)-Lupus percent impairment while the Working domain was observed among patients with high baseline disease activity on Acthar Gel versus placebo [21]. Acthar Gel therapy also led to reductions in B cell activating factor and IL-6 cytokines, total B-cells, and atypical activated memory B cells, particularly in patients with high baseline disease activity [22].

There is substantial evidence suggesting a favorable clinical profile of Acthar Gel; however, data on the economic benefit of Acthar Gel in moderate-to-severe SLE are limited. Only one study utilizing administrative claims data reported that patients receiving Acthar Gel had lower utilization and costs for medical services [8]. It is important to evaluate the economic benefit of Acthar Gel for treatment-experienced patients with moderate-to-severe SLE integrating the information on efficacy, effectiveness, cost, and patient outcomes to support decision-making. To address this knowledge gap, the objective of the current analysis was to estimate the cost-effectiveness of Acthar Gel versus standard of care (SoC) in patients with active, moderate-to-severe SLE despite aggressive treatment from the US payer and societal perspectives over 3 years.

METHODS

Model Structure

A probabilistic cohort-level state-transition approach was used to develop the cost-effectiveness model in Microsoft® Excel 2019. This is a novel method to evaluate the short-term cost-effectiveness of Acthar Gel in persistently active, moderate-to-severe SLE. The incremental cost-effectiveness ratio (ICER) of Acthar Gel versus SoC was assessed using the direct medical costs, indirect costs, and quality-adjusted life-years (QALYs) over 3 years from the US payer and societal perspectives.

All patients entered the model cycle 0 in the exacerbation state and initiated treatment with Acthar Gel or SoC. The model used a natural history matrix and applied the probability of treatment success with Acthar Gel during each treatment cycle based on the clinical trial. Treatments were administered consistent with the current recommendations and clinical practices; Acthar Gel is administered to patients in an exacerbation state. Patients were monitored at the end of a 3-month cycle for the achievement of response. Following the

achievement of response, patients could have had a durable response or experienced an exacerbation. Patients who did not achieve a response were assumed to discontinue Acthar Gel. Patients who experienced exacerbation received Acthar Gel and moved into a response or non-response state, based on the probability of treatment success with Acthar Gel. Patients in the response or non-response state were allowed to experience an exacerbation in subsequent cycles. Costs and utilities are calculated for each state every 3 months over a 3-year time horizon. The model assumed that patients in the non-response and exacerbation states experience an additional decrement in utilities for the duration of one cycle due to the ongoing disease burden (Fig. 1).

This study does not involve any human participants, human data, and/or human material. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Key Inputs

Clinical Inputs

The principal evidence source used to derive clinical parameter values was a phase 4 multicenter, randomized, double-blind, placebo-controlled study. This trial was conducted across 54 study sites in Argentina, Chile, Mexico, Peru, and the US. Adults aged ≥ 18 years with active SLE (≥ 4 of 11 American College of Rheumatology criteria; SLEDAI-2K score ≥ 6 at screening; and clinical SLEDAI-2K [excluding laboratory results] score ≥ 4 at both screening and randomization) and with moderate-to-severe rash and/or arthritis by BILAG-2004 scores A or B in the mucocutaneous or musculoskeletal domains at both screening and randomization were enrolled in the study. Patients were administered 80 U of Acthar Gel or matching placebo subcutaneously every other day for 4 weeks and then twice per week for an additional 20 weeks. The modified intent-to-treat population, defined as patients who received at least one dose of the study drug and contributed any post-baseline efficacy data, comprised 169 patients; 84 patients received Acthar Gel and 85 received placebo. Details of this clinical trial have been described elsewhere [20].

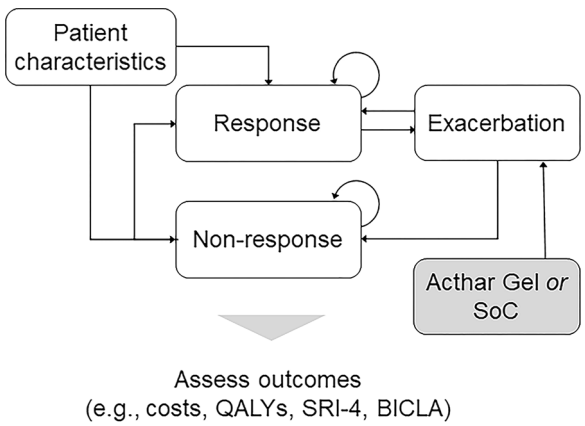

Fig. 1 Schematic of the probabilistic cohort-level state-transition model. *BICLA* British Isles Lupus Assessment Group-based Composite Lupus Assessment, *QALY* quality-adjusted life-year, *SLE* systemic lupus erythematosus, *SoC* standard of care, *SRI-4* SLE Responder Index

Moderate-to-severe SLE was defined as patients with BILAG-2004 ≥ 20 or SLEDAI-2K ≥ 10. These benchmarks were considered to align with the moderate-to-severe SLE defined in the Phase 4 SLE trial [20]. There are no established benchmarks for defining moderate-to-severe SLE based on BILAG-2004 and SLEDAI-2K. Both SLEDAI ≥ 6 [23, 24] and SLEDAI ≥ 10 [25] have been used; however, SLEDAI-2K ≥ 10 provides a more conservative definition for this population. No specific benchmark has been defined for BILAG-2004. Furthermore, the relationship between these clinical measures is not known; thus, each of these measures was considered to define moderate-to-severe SLE.

The clinical response was based on the proportion of SRI-4 or BICLA responders sourced from the Phase 4 SLE trial [20]. The probability of exacerbation was based on the rate of flares among adults with SLE sourced from the literature; the overall rate was 3.5 flares per year [7]. A 3-month probability of an exacerbation in SLE was 0.58 [7]. The relative risk reduction in exacerbation was calculated based on the type of clinical measure to define moderate-to-severe SLE and the type of clinical response evaluated. The relative risk reduction was applied to SRI-4 or BICLA responders on Acthar Gel and SoC.

Table 1 Clinical parameters among patients with moderate-to-severe SLE

Parameter	SRI-4 responders	BICLA responders
Proportion of responders[a]		
Acthar Gel		
BILAG-2004		
3 months	40.0%	60.0%
6 months	52.5%	65.0%
SLEDAI-2K		
3 months	48.9%	58.7%
6 months	61.7%	58.7%
Placebo		
BILAG-2004		
3 months	27.8%	27.8%
6 months	38.9%	58.3%
SLEDAI-2K		
3 months	38.6%	23.3%
6 months	40.9%	34.9%
Exacerbation risk reduction with Acthar Gel[b]		
BILAG-2004	0.200	0.148
SLEDAI-2K	0.297	0.306

BILAG British Isles Lupus Assessment Group, *BICLA* BILAG-based Composite Lupus Assessment, *SLE* systemic lupus erythematosus, *SLEDAI-2K* SLE Disease Activity Index 2000, *SRI-4* SLE Responder Index

[a]Derived from data on file (Phase 4 SLE trial) [20]

[b]Calculation based on annual flare rate (Hammond 2021) [7] and response rate on the type of clinical measure to define moderate-to-severe SLE and the type of clinical response evaluated (Phase 4 SLE trial) [20]

The annual rates were converted to the monthly probability of exacerbation (Table 1). The transition probabilities from exacerbation to response were based on the probability of treatment success at the end of the 3-month cycle to align with the clinical trial assessment. Transition probabilities varied by type of clinical measure to define moderate-to-severe SLE and the type of clinical response evaluated.

Healthcare Resource Utilization and Costs

Costs considered in the present model included treatment costs, direct medical costs, and indirect costs (Table 2). Treatment costs included the cost of Acthar Gel as well as concomitant medications (corticosteroids, disease-modifying anti-rheumatic drug [DMARDs], and biologics) for patients on Acthar Gel. Wholesale acquisition costs for Acthar Gel were obtained from the IBM Micromedex® Red Book [26]. The dose strength and dosing of Acthar Gel were based on dispensing data from specialty pharmacies, from the last 12 months as of March 29, 2019. The proportion of patients using corticosteroids, DMARDs, and biologics was sourced from the literature [27]. Wholesale acquisition costs were used for the cost of biologics (specifically, belimumab) [26], and the costs of corticosteroids and DMARDs were sourced from the literature [28].

Direct medical costs comprised inpatient, outpatient, emergency department, and physician office visit-related costs [9]. SLE affects multiple organs and may result in organ damage that may require surgery and/or transplant. The risk of organ damage is higher for patients who have persistently active SLE. The model also considered both organ damage and surgical costs for patients who did not respond to Acthar Gel and those who experienced a new exacerbation. Organ damage and surgery rates as well as related costs were sourced from the literature [29–34]. Costs related to the use of opioids for pain and opioid abuse were also applied to the model. Estimates from the literature suggest that up to 23% of patients with SLE are regular users of opioids and the effects of DMARDs are minimal in reducing opioid use [35]. Although the literature supports the efficacy of short-term opioids for the improvement of pain, long-term use is associated with reduced efficacy and increased safety concerns. Opioid use for pain management and opioid abuse costs were sourced from the literature [36] and applied to patients in the non-response and exacerbation state.

Table 2 Healthcare resource use and costs

Parameter	Value			References
Healthcare resource use and costs (2022 USD)				
Treatment costs				
Cost of Acthar Gel	$41,459			Red Book 2022 [26]
Acthar Gel use (12 months)	8.57 packs			Data on File[a]
Medication utilization				
Proportion of patients	**Acthar Gel**	**SoC**		
Corticosteroids	58.0%	100.0%		Myung 2017 [27]
DMARDs	37.0%	50.0%		Myung 2017 [27]
Biologics	9.0%	14.0%		Myung 2017 [27]
Cost of medications				
Corticosteroids	$410			AHRQ 2007 [28]
DMARDs	$2909			AHRQ 2007 [28]
Biologics	$55,312			Red Book 2022 [26]
Healthcare costs	**Mild**	**Moderate**	**Severe**	
Inpatient	$3444	$5325	$16,609	Murimi-Worstell 2021 [9]
Outpatient	$11,589	$13,669	$27,208	Murimi-Worstell 2021 [9]
ER	$399	$825	$1046	Murimi-Worstell 2021 [9]
Physician office	$2314	$3446	$4346	Murimi-Worstell 2021 [9]
Surgery				
Surgery rate				
Kidney Transplant	2.4%			Lionaki 2014 [29]
Splenectomy	3.1%			You 2004 [30]
Total hip or knee replacement	33.2%			Mukherjee 2015 [58]
Surgery-related costs				
Kidney Transplant	$127,337			Axelrod 2016 [31]
Splenectomy	$21,923			Hamlat 2012 [32]
Total hip or knee replacement	$47,412			Clair 2016 [33]
Organ damage				
Organ damage rate				
Cardiovascular	30.1%			Pierotti 2015 [34]
Diabetes	19.0%			Pierotti 2015 [34]
Gastrointestinal	22.2%			Pierotti 2015 [34]
Malignancy	36.3%			Pierotti 2015 [34]

Table 2 continued

Parameter	Value		References
Musculoskeletal	64.5%		Pierotti 2015 [34]
Neuropsychiatric	46.9%		Pierotti 2015 [34]
Ocular	60.5%		Pierotti 2015 [34]
Peripheral vascular	20.9%		Pierotti 2015 [34]
Pulmonary	34.3%		Pierotti 2015 [34]
Renal	26.0%		Pierotti 2015 [34]
Organ damage-related costs			
Cardiovascular	$2729		Pierotti 2015 [34]
Diabetes	$5726		Pierotti 2015 [34]
Gastrointestinal	$505		Pierotti 2015 [34]
Malignancy	$1601		Pierotti 2015 [34]
Musculoskeletal	$23,310		Pierotti 2015 [34]
Neuropsychiatric	$8998		Pierotti 2015 [34]
Ocular	$556		Pierotti 2015 [34]
Peripheral vascular	$1860		Pierotti 2015 [34]
Pulmonary	$51,775		Pierotti 2015 [34]
Renal	$15,842		Pierotti 2015 [34]
Pain-related costs			
Opioid use for pain			
Opioid use	23.0%		Somers 2019 [35]
Cost of opioid use	$24,722		Luo 2021 [36]
Substance use disorder			
SLE-related opioid abuse (> 1 year of opioid use)	68.0%		Somers 2019 [35]
SLE patients on ≥ 2 opioids	22.0%		Somers 2019 [35]
Opioid abuse and overdose	$24,503		Luo 2021 [36]
Work Productivity Loss[b]	**Acthar Gel**	**SoC**	
Absenteeism	7.8%	17.6%	Phase 4 SLE trial [21]
Presenteeism	27.3%	51.8%	Phase 4 SLE trial [21]
Activity impairment	34.3%	58.1%	Phase 4 SLE trial [21]
SF-6D utility			
Response	0.654		Phase 4 SLE trial [21]

Table 2 continued

Parameter	Value	References
Non-response	0.595	Phase 4 SLE trial [21]
Disutilities		
Disutilities: patient outcomes		
Chronic OCS use	− 0.023	ICER 2018 [40]
Exacerbation (new flare)	− 0.360	Pollard 2015 [41]
Exacerbation Requiring Steroid Burst	− 0.100	ICER 2018 [40]
Planning	− 0.106	Pollard 2015 [41]
Body image	− 0.102	Pollard 2015 [41]
Intimate relationships	− 0.020	Pollard 2015 [41]
Burden to others	− 0.059	Pollard 2015 [41]
Disutilities: surgery		
Kidney transplant	− 0.170	Li 2017 [42]
Splenectomy	− 0.168	Synder 2008 [43]
Total hip or knee replacement	− 0.261	Benson 2016 [44]
Disutilities: organ damage		
Cardiovascular	− 0.076	Di Tanna 2021 [45]
Diabetes (type 2)	− 0.110	Matza 2007 [46]
Gastrointestinal	− 0.240	Worbes-Cerezo 2019 [47]
Malignancy	− 0.110	Choi 2015 [48]
Musculoskeletal	− 0.030	Törmälehto 2018 [49]
Neuropsychiatric	− 0.640	Pollard 2015 [41]
Ocular	− 0.029	Brown 2009 [50]
Peripheral vascular	− 0.076	Assumption [same as cardiovascular]
Pulmonary	− 0.327	Moayeri 2016 [51]
Renal	− 0.260	Cooper 2020 [52]

DMARD disease-modifying anti-rheumatic drug, *ER* emergency department, *OCS* oral corticosteroid, *SF-6D* Short form-six dimension, *SLE* systemic lupus erythematosus, *USD* United States dollar

[a]Using dispensing data from specialty pharmacies, from the last 12 months as of March 29, 2019

[b]Based on the Work Productivity and Activity Impairment Questionnaire

Furthermore, indirect costs due to the productivity loss for the patients and the additional cost of caregiving were applied in the model from the societal perspective. The proportion of work loss was derived from WPAI scores from the Phase 4 SLE trial [21]. For estimating the indirect costs in the US, the model used $50,910 as the per capita income in the US [37], $4514 for the annual cost of caregiving for SLE [38], and $22,883 for the cost of work-related training [38].

Health Utilities

Both health utilities and disutilities were considered given the multi-organ involvement in SLE (Table 2). Lupus QoL scores were derived from the Phase 4 SLE clinical trial [21]; four domains (emotional health, fatigue, pain, and physical health) from the Lupus QoL measure were mapped to Short form-Six dimension utilities based on the method used in the literature [39]. In addition, disutility for chronic oral corticosteroid use [40], exacerbation (new flare) [41], exacerbation requiring steroid burst [40], surgery [42–44], organ damage [41, 45–52], and health outcomes based on Lupus QoL domains (body image, burden to others, intimate relationships, and planning) [41] were also considered. Disutilities were sourced from the literature. The disutilities were applied based on the scores for each patient in the cycle and were additive.

Analyses

Base Case Analysis

For the base case scenario, moderate-to-severe SLE was defined as BILAG-2004 $\geq$ 20 or SLEDAI-2K $\geq$ 10. BILAG-2004 and SLEDAI-2K were selected to define moderate-to-severe SLE as these measures are primarily used in clinical trials for the selection and classification of patients with SLE [53, 54]. Furthermore, BILAG-2004 assesses different organs/systems, and SLEDAI-2K is a global assessment measure, and thus they complement each other well, thereby providing a comprehensive assessment [54]. Clinical response was based on the SRI-4 as it is a recommended measure in clinical trials [53] and was also the primary endpoint of the Phase 4 SLE trial [20].

The primary outcome in the present model was the discounted incremental ICER defined as the difference in costs divided by the difference in QALYs of Acthar Gel and SoC at 2 and 3 years from both US payer and societal perspectives. From a payer perspective, total costs comprised direct medical costs (costs paid by third party-payers), and from a societal perspective, total costs comprised both direct and indirect costs (productivity loss, work-related training, and caregiving). The secondary outcome included the cost per SRI-4 response. Unless otherwise specified, the costs and QALYs were discounted at 3.0% annually and all costs were adjusted to 2022 US dollars (USD). For the costs obtained from ex-US studies, purchasing power parity exchange rates were used, which adjust for the different costs of buying a similar basket of goods and services in each country, a most commonly used method in economics.

Table 3 Base case results for incremental cost-effectiveness among patients with moderate-to-severe SLE (2022 USD)

Acthar Gel versus SoC[a]	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Payer			
2 years	$117,270	0.881	$133,110
3 years	$129,047	1.361	$94,818
Societal			
2 years	$62,399	0.881	$70,827
3 years	$44,266	1.361	$32,525

BILAG British Isles Lupus Assessment Group, *BICLA* BILAG-based Composite Lupus Assessment, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years, *SLE* systemic lupus erythematosus, *SLEDAI-2K* SLE Disease Activity Index 2000, *SoC* standard of care, *SRI-4* SLE Responder Index, *USD* United States dollar

[a]For the base case scenario, moderate-to-severe SLE was defined as BILAG-2004 $\geq$ 20 or SLEDAI-2K $\geq$ 10. Clinical response was based on the SRI-4

Sensitivity Analyses

The base case assumptions and alternative values for these assumptions were tested and fully explored in the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The full range of uncertainty is tested for each variable with anticipated uncertainty. A PSA combined bootstrapping with random draws from uncertainty distributions. By bootstrapping the data from the randomized clinical trial using normal and Poisson distributions, we obtained uncertainty margins surrounding the parameters. The full range of uncertainty is tested for each variable with anticipated uncertainty.

Table 4 Base case per patient-year costs among patients with moderate-to-severe SLE from the payer perspective (2022 USD)

Cost component[a]	Acthar Gel	SoC
Treatment	$77,228	–
Direct medical costs		
Concomitant medication	$1533	$7033
Inpatient	$5139	$10,378
Outpatient	$13,230	$19,431
Emergency department	$516	$804
Physician visit	$2605	$3491
Surgery	$2380	$9902
Organ damage	$3153	$9022
Pain-related costs	$1455	$4162
Total direct medical	**$30,011**	**$64,223**
Indirect costs		
Pain-related	$5667	$16,168
Productivity loss	$4596	$13,103
Activity impairment	$2428	$11,681
Total indirect	**$12,691**	**$40,951**

Bold is used to differentiate between "total of all individual costs" from "individual costs" listed under direct and indirect cost categories.

BILAG British Isles Lupus Assessment Group, *BICLA* BILAG-based Composite Lupus Assessment, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years, *SLE* systemic lupus erythematosus, *SLEDAI-2K* SLE Disease Activity Index 2000, *SoC* standard of care, *SRI-4* SLE Responder Index, *USD* United States dollar

[a]For the base case scenario, moderate-to-severe SLE was defined as BILAG-2004 $\geq$ 20 or SLEDAI-2K $\geq$ 10. Clinical response was based on the SRI-4

Scenario Analyses

Four scenario analyses were conducted varying the definition of moderate-to-severe SLE (BILAG-2004 $\geq$ 20 or SLEDAI-2K $\geq$ 10) and a clinical measure of response (SRI-4 or BICLA) in each scenario. BICLA was assessed as a secondary outcome in the Phase 4 SLE trial [20].

RESULTS

Base Case Analyses

The use of Acthar Gel in moderate-to-severe SLE (defined as BILAG-2004 $\geq$ 20 or SLEDAI-2K $\geq$ 10) results in an incremental cost of $117,270 and an incremental QALY gain of 0.881, resulting in an ICER of $133,110 per QALY compared to that of SoC from the payer perspective over 2 years. From the societal perspective over 2 years, Acthar Gel has an incremental cost of $62,399 and an incremental QALY gain of 0.881, resulting in an ICER of $70,827 per QALY compared to that of SoC. The ICER was lower from the payer ($94,818 per QALY) and societal ($32,525 per QALY) perspective over 3 years (Table 3).

From the payer perspective, the incremental cost per SRI-4 response achieved was $30,750 and $21,452 compared to SoC over 2 and 3 years, respectively. From the societal perspective, the incremental cost per SRI-4 response achieved was $16,362 and $7358 compared to SoC over 2 and 3 years, respectively. The breakdown of costs over 3 years by each cost component is provided in Table 4.

Sensitivity Analyses

DSA findings are consistent with the base case analysis; Acthar Gel is a cost-effective strategy over SoC at a threshold of $150,000 per QALY.

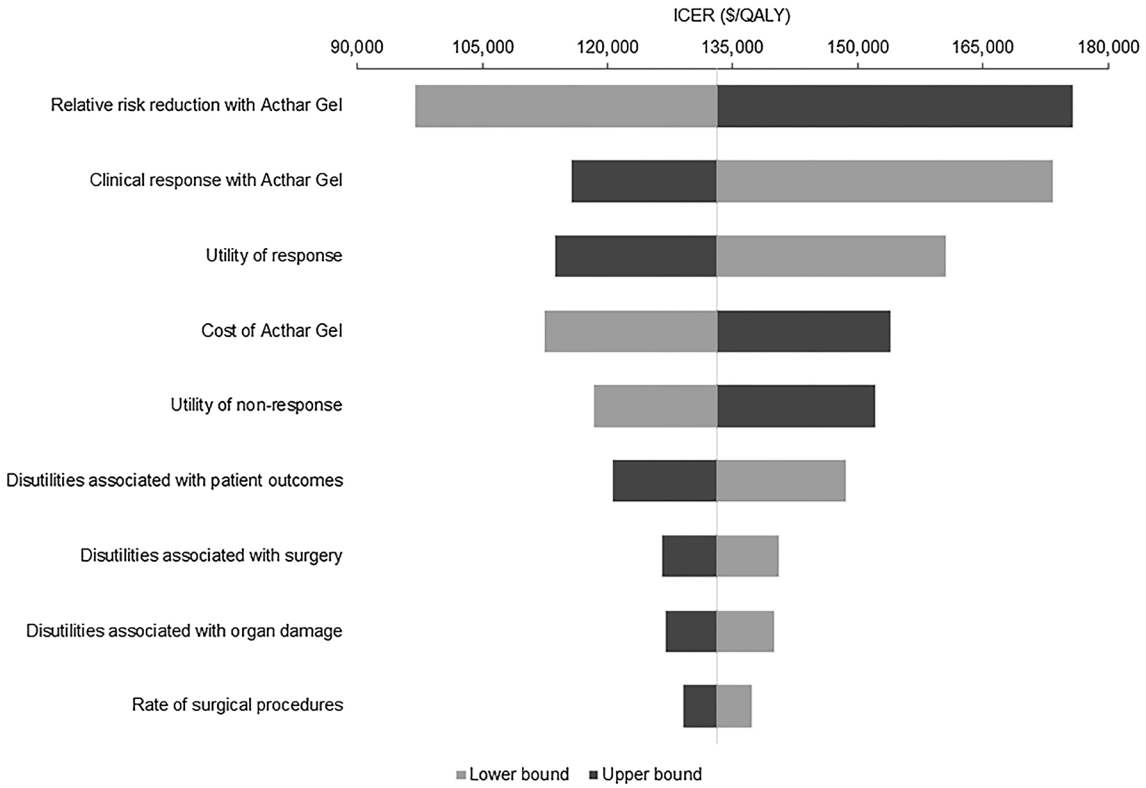

Fig. 2 Deterministic sensitivity analyses. Base case: Moderate-to-severe SLE was defined as BILAG-2004 ≥ 20 or SLEDAI-2K ≥ 10; Clinical response was based on the SRI-4; 2-year payer perspective. *BILAG* British Isles Lupus Assessment Group, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years, *SLE* systemic lupus erythematosus, *SLEDAI-2K* SLE Disease Activity Index 2000, *SoC* standard of care, *SRI-4* SLE Responder Index

The relative risk reduction with Acthar Gel, clinical response with Acthar Gel, the utility of response and non-response, and the cost of Acthar Gel are major influencers of the ICER (Fig. 2).

PSA randomly sampled parameters from within chosen distributions over 1000 iterations. The PSA shows that Acthar Gel is cost-effective for 63.1% of the iterations at a willingness-to-pay threshold of $150,000 per QALY over 3 years from a payer perspective. The findings from the PSA are consistent with the base case analysis; Acthar Gel is cost-effective compared to the SoC (ICER: $129,677 per QALY; 95% confidence interval [CI]: $121,476, $137,878 per QALY) at a willingness-to-pay threshold of $150,000 per QALY.

Scenario Analyses

For all scenarios, ICER for Acthar Gel versus SoC was within the willingness-to-pay threshold of $150,000 per QALY over 3 years from both payer and societal perspectives (Table 5).

DISCUSSION

Effective management of chronically active SLE is crucial to reducing the associated clinical and economic burden on patients as well as improving patient QoL [2, 13–16]. Acthar Gel has been shown to be safe and effective treatment among patients with moderate-to-severe SLE who have persistently active SLE despite aggressive treatment [2, 18–20]. It is important to assess both economic and health outcomes

Table 5 Scenario analyses results for incremental cost-effectiveness among patients with moderate-to-severe SLE (2022 USD)

Acthar Gel versus SoC	Incremental costs	Incremental QALYs	ICER (cost/QALY)	Cost/response
Scenario 1: Moderate-to-severe SLE: BILAG-2004 ≥ 20; clinical response: SRI-4				
Payer				
2 years	$112,213	0.919	$122,103	$28,060
3 years	$114,639	1.456	$78,736	$17,896
Societal				
2 years	$54,664	0.919	$59,482	$13,669
3 years	$24,710	1.456	$16,971	$3857
Scenario 2: Moderate-to-severe SLE: SLEDAI-2K ≥ 10; clinical response: SRI-4				
Payer				
2 years	$128,389	0.833	$154,128	$35,143
3 years	$145,271	1.292	$112,439	$25,116
Societal				
2 years	$75,229	0.833	$90,311	$20,592
3 years	$62,929	1.292	$48,707	$10,880
Scenario 3: Moderate-to-severe SLE: BILAG-2004 ≥ 20; clinical response: BICLA				
Payer				
2 years	$75,456	1.021	$73,904	$16,954
3 years	$65,656	1.568	$41,872	$9513
Societal				
2 years	$13,162	1.021	$12,891	$2957
3 years	− $29,113	1.568	Dominant	−$4,219
Scenario 4: Moderate-to-severe SLE: SLEDAI-2K ≥ 10; clinical response: BICLA				
Payer				
2 years	$123,693	0.869	$142,339	$30,713
3 years	$142,428	1.316	$108,228	$23,051
Societal				
2 years	$65,416	0.869	$75,277	$16,243
3 years	$54,591	1.316	$41,483	$8835
Scenario 5: Moderate-to-severe SLE: BILAG-2004 ≥ 20 or SLEDAI-2K ≥ 10; clinical response: BICLA				
Payer				
2 years	$109,030	0.849	$128,422	$28,166
3 years	$121,222	1.282	$94,557	$20,495

Table 5 continued

Acthar Gel versus SoC	Incremental costs	Incremental QALYs	ICER (cost/QALY)	Cost/response
Societal				
2 years	$53,752	0.849	$63,312	$13,886
3 years	$38,184	1.282	$29,785	$6456

BILAG British Isles Lupus Assessment Group, *BICLA* BILAG-based Composite Lupus Assessment, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years, *SLE* systemic lupus erythematosus, *SLEDAI-2K* SLE Disease Activity Index 2000, *SoC* standard of care, *SRI-4* SLE Responder Index, *USD* United States dollar

to understand the value of the interventions. The current analysis was conducted to understand the potential health-economic implications of using Acthar Gel for the short-term treatment of patients with persistently active moderate-to-severe SLE. To the best of our knowledge, this is the first economic analysis to compare the cost-effectiveness of Acthar Gel versus SoC for persistently active moderate-to-severe SLE despite aggressive treatment with conventional medications.

The findings from the current base case analysis indicate that Acthar Gel is cost-effective compared to SoC at a willingness-to-pay threshold of USD 150,000 per QALY over 2 years from both payer and societal perspectives. The findings were consistent in the sensitivity analysis. The use of Acthar Gel results in reduced direct medical (excluding treatment) and indirect costs with gain in QALYs. The relative risk reduction and clinical response with Acthar Gel primarily influenced variation in ICER estimates. The probable reason could be that achievement of the clinical response is important for reducing organ damage and improving patient QoL. The cost-effectiveness of Acthar Gel may further improve with rebates and drug price discounts.

The findings from the current study on lower direct medical costs are consistent with published economic evaluation, where patients with SLE receiving Acthar Gel had lower healthcare resource utilization and costs for medical services; lower per person per member hospitalization costs ($3192 vs $799, $p = 0.04$) after initiating Acthar Gel [8]. Furthermore, these findings showed that these lower medical costs partially offset the increased prescription costs by 37% [8]. However, these prior economic evaluations only focused on the direct medical costs and did not consider indirect costs. Furthermore, this prior analysis did not examine the cost-effectiveness of Acthar Gel, integrating clinical, economic, and patient-related health outcomes. This study adds to the nascent literature on economic assessments in moderate-to-severe SLE.

The current analysis also assessed the cost-effectiveness of Acthar Gel from the societal perspective as patients with SLE experience functional impairment, reduced productivity, poor QoL, unemployment, and increased mortality [8], which may further add to the overall economic burden for the patient and caregivers. It is crucial to consider indirect costs due to productivity loss and caregiver burden in addition to the direct medical costs in an economic evaluation. The current cost-effectiveness analysis includes costs accrued because of increased disability, caregiver costs, and costs due to the lost productivity of patients. The findings indicate that Acthar Gel is a cost-effective strategy compared to SoC over 2 years from the societal perspective at a willingness-to-pay threshold of USD 150,000 per QALY.

Cost of treatment is central to issues of access and affordability; however, it is important to assess the value of treatment based on the clinical, economic, and humanistic components. Interventions that are intended for a special population or offer substantial other benefits are considered high "Care Value"

within the cost/QALYs range of USD 100,000–150,000 [55, 56]. Based on the recommendations of the World Health Organization's Choosing Interventions that are Cost-Effective (WHO-CHOICE), this ICER threshold range is estimated to be three times the nation's per capita income [57]. Acthar Gel may provide value for the patients with persistently active moderate-to-severe SLE at a willingness-to-pay threshold of USD 150,000 per QALY.

The findings in the present model should be interpreted considering the following limitations. First, the efficacy, work productivity, and QoL data for the model were based on the data from a single Phase 4 SLE clinical trial, which may not reflect real-world outcomes. In addition, the sample size considered for the model was small and may have introduced bias to the findings to some extent. However, we conducted sensitivity analysis to account for uncertainty in the data used. Furthermore, the analysis was considered for patients with moderate-to-severe SLE and may not be generalizable to patients with mild SLE. Second, the presence of heterogeneity in the SLE population and other inflammatory comorbidities may further exacerbate SLE and enhance the value of Acthar Gel. Third, a simplified care paradigm was implemented for the model, which may not capture the complexity of SLE. Real-world treatment pathways in SLE are complex, dependent on multiple factors, and highly individualized. Fourth, the clinical measures used to define active, moderate-to-severe SLE have their strengths and limitations; thus, this might result in variation in cost-effectiveness estimates considering other cut-offs for the definition. Fifth, Phase 4 SLE clinical trial examined short-term outcomes, i.e., at 24 weeks in the RCT; the model assessed the cost-effectiveness of Acthar Gel versus SoC in a longer term (1–3 years). Lastly, the data on healthcare utilization and costs as well as health disutility were obtained from various published sources and may result in under- or over-estimation. However, a PSA was conducted to account for uncertainty in the parameters, and the findings were consistent with base-case analyses.

CONCLUSIONS

Acthar Gel is a cost-effective, value-based treatment option for appropriate patients with moderate-to-severe SLE at a willingness-to-pay threshold of $150,000 over 2–3 years from the US payer and societal perspectives. Further research is required to examine the long-term clinical effectiveness and cost-effectiveness of Acthar Gel for active SLE.

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