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ORIGINAL RESEARCH

Assessing the impact of single or short-term administration on a therapy's cost-effectiveness: a hypothetical disease-agnostic model

Alexa C. Klimchak[a], Lauren E. Sedita[a], Katherine L. Gooch[a] and Daniel C. Malone[b]

[a]Sarepta Therapeutics, Inc, Cambridge, MA, USA; [b]College of Pharmacy, University of Utah, Salt Lake City, UT, USA

ABSTRACT

Aims: Assessing the value of single or short-term therapies (SSTs) within traditional cost-effectiveness analyses (CEAs) has been a topic of discussion as the number of SSTs increases, particularly regarding the effect of discounting on valuation. To quantify the impact of discounting in economic evaluations, a CEA of a hypothetical SST and equivalent chronic therapy was conducted using standard methods.

Materials and methods: A lifetime Markov model was developed for a hypothetical chronic, progressive disease that could be treated with an SST, chronic therapy, or no novel treatment, termed standard of care (SoC). Incremental cost-effectiveness ratios (ICERs) with quality-adjusted life years (QALYs) comparing SST vs. SoC and an equivalent chronic therapy vs. SoC were assessed from a payer perspective. Both treatments had equal benefits and undiscounted lifetime costs; 3% discounting was applied to costs/benefits in the base case, and the impact of discounting was assessed.

Results: In the base case example, both the SST and equivalent chronic therapy vs. SoC had ICERs of $86,000/QALY without discounting. With 3% discounting, the ICER for the SST increased by 116% ($186,000/QALY) while the ICER for the chronic therapy increased by 10% ($95,000/QALY) despite equal clinical benefit. In scenario analyses, the ICER of the SST was consistently higher than the equivalent chronic therapy across a range of assumptions/inputs. Varying the cost/benefit discount rates had a greater impact on the SST. Differences in the ICERs between the therapies increased with increasing life expectancy/time horizon.

Limitations: The simple model structure may not be reflective of acute or more complex diseases. Also, the scenario of perfect equivalency in efficacy and lifetime costs is hypothetical.

Conclusions: This quantitative assessment showed the extent to which SST CEAs are highly sensitive to discounting, resulting in worse value assessments for SSTs than equivalent chronic therapies.

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Introduction

Single or short-term therapies (SSTs), including gene therapies, may offer substantial health gains as they have the potential to provide lifetime benefits from a single treatment. By 2025, between 10 and 20 gene therapy products are estimated to be approved by the United States (US) Food and Drug Administration (FDA) each year[1]. In anticipation of the growing number of SSTs, efforts to comprehensively determine the value of these novel therapies are underway.

Cost-effectiveness analysis (CEA) is a commonly applied approach to estimate the value of a therapy in terms of the incremental costs and health benefits compared to an alternative therapy or other standard of care (SoC). These assessments not only guide health policy, but also inform health resource allocation[2,3]. While CEAs can also evaluate health services and procedures, a substantial majority assess therapies, specifically chronic therapies[4], as there are not as many SSTs currently available. There are numerous challenges with using the traditional CEA framework to assess SSTs, including evaluation of clinical effectiveness, uncertainties around long term durability, accommodation of up-front treatment costs, and the potential application of additional aspects of value[5–9]. Previous studies have also suggested that the application of equivalent discount rates to both costs and benefits, as recommended by most guidelines and typical of the majority of CEAs[10], is a potential bias against SSTs given their up-front costs and potential long-term benefits[11–13]. As a result, there is ongoing discussion regarding whether traditional CEA methods, including standard discounting, should be adapted for SSTs[5,14,15].

Although the potential impact of discounting on the economic evaluation of SSTs has been described[11,12], it has yet to be quantified and compared to that of chronic therapies because of complexities in typical disease-specific models, the few SSTs currently available, and the underlying differences in treatment costs and benefits for those few diseases in which both SSTs and chronic therapies are approved. Thus, a

CONTACT Alexa C. Klimchak AKlimchak@Sarepta.com Sarepta Therapeutics, Inc., Cambridge, MA 02142, USA

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disease-agnostic model was constructed to quantitatively assess the potential impact of discounting on an SST vs. a theoretically equivalent chronic therapy with the same clinical benefit using a traditional CEA. The model offers the opportunity to isolate the impact of discounting without potential confounding factors, such as unequal treatment benefits, differing costs/utilities, and varying health states across different diseases.

Methods

This study assessed the long-term costs and clinical benefits of two hypothetical treatments vs. SoC for a long-term chronic, progressive disease. The primary outcome was the incremental cost per QALY (ICER).

Model structure

This study used a *de novo* disease-agnostic Markov model developed in Microsoft Excel to simulate the effect of SSTs and chronic therapies for a homogenous cohort. The model assessed a hypothetical chronic, progressive disease using three health states: baseline, progression, and death (Figure 1). With treatment, patients could transition from progression to baseline, reflecting one benefit of treatment. While a three-state model is relatively simple, it has been used in CEAs for numerous treatments, including those for COVID-19, HIV, obesity, and cancer[16–24].

Treatment costs and efficacy

Two hypothetical treatments were assessed: an SST and a clinically-equivalent chronic therapy. The SST treatment cost was the average wholesale acquisition cost of FDA-approved gene-based therapies at the time of the analysis ($1,500,000)[25,26]. It was assumed the SST was given one time at the start of the analysis. The cost of chronic therapy, administered continuously in the baseline and progression states, amortized the undiscounted SST treatment costs over the patients' lifetime ($54,000/year in the base case).

Both hypothetical treatments increased survival and improved utility by slowing disease progression and permitting a return to the baseline state. Hazard ratios (HRs) for nonfatal events ranged from 0.45 to 0.85, with a base case value of 0.65 (Table 1). For context, a meta-analysis of statin clinical trials showed a range of HRs from 0.52 to 0.94 for nonfatal myocardial infarction, with an overall value of 0.71[27]. HRs for fatal events ranged from 0.60 to 0.98. This is similar to all-cause mortality HRs for neoadjuvant chemoradiotherapy and surgery for esophageal carcinoma (range, 0.40 to 0.96; overall, 0.81)[28].

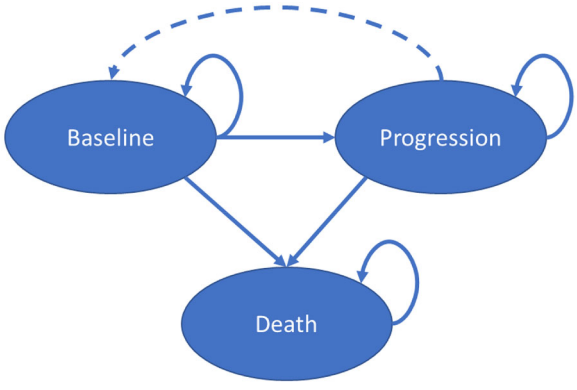

Figure 1. Model structure. Patients can only transition from progression back to baseline with treatment.

Transition probabilities, direct medical costs, and utilities

Annual transition probabilities, direct medical costs, and utilities were selected from appropriate ranges (intentionally chosen not to represent any specific disease) based on expert opinion (Table 1). Specifically, annual transition probabilities ranged from 2% to 25% in the base case. For context, these transition probabilities were similar to those reported for secondary, progressive multiple sclerosis (range, 0.2% to 35%)[29] and Alzheimer's disease (range, 2% to 42%)[30]. All-cause mortality risk was estimated based on US Center for Disease Control and Prevention life tables[31].

The direct medical costs for the progression state in the base case analysis was $100,000/year. This is similar to patients diagnosed with spinal muscular atrophy (SMA) by their first birthday ($112,644/year)[32]. The direct medical costs ranged up to $200,000/year in scenario analyses, which is between the direct medical costs of urea cycle disorder ($140,044/year)[33] and hemophilia A ($614,886/year)[34].

Utility values ranged from 1.0 (perfect health) to 0.05. For context, a review of 1,000 published utility values showed a wide range of estimates across health states, with an overall range from 1.0 to −0.12[35]. Specifically, health state utilities for breast cancer ranged from 0.16 to 0.99 while those for severe angina ranged from 0.354 to 0.707. The wide range of estimates reflect variations in disease severity, country, instrument, tariffs, and rater (proxy vs. self).

Other inputs and assumptions

The study assessed a 5-year-old over a lifetime horizon, reflecting a disease with pediatric onset and allowing for substantial health gains. The model used annual cycles with half-cycle corrections. A discount rate of 3% per annum was applied to costs and benefits in the base case. This discounting rate was based on the standard practice in the US[36] and reflects the economic concept that current costs (and health benefits) have greater value than those in the future. A US payer perspective was adopted. Results were rounded to the nearest $1,000.

Sensitivity and scenario analyses

Numerous sensitivity and scenario analyses were performed to evaluate the impact of the inputs on the results. To account for model uncertainty, probabilistic sensitivity analysis (PSA) was conducted. Input values were sampled from uniform distributions (Table 1). Although uniform distributions

Table 1. Input values.

Parameter	Base case value	Lower bound	Upper bound	Assumption
Utilities				
Baseline	1	0.1	1	
Progression	0.5	Calculated	Calculated	50% of baseline utility to ensure disease progression lowers utility
Death	0			By definition
Transition probability (annual)				
Baseline to progression	15%	1%	30%	
Baseline to death	2%	0%	Minimum of {5%, risk of progression to death − 1%}	Risk of mortality is worse in progression than baseline
Progression to death	10%	1%	20%	
Progression to baseline[a]	25%	10%	50%	
Hazard ratios				
Baseline to progression	0.65	0.45	0.85	
Baseline to death	0.9	0.82	0.98	
Progression to death	0.75	0.6	Minimum of {0.9, (HR of baseline to death − 0.05)}	Treatment benefit in reducing mortality is better in progression
Costs				
Baseline (annual)	$0	$0	Minimum of {$100,000, progression costs – $10,000}	Direct medical costs must be lower in baseline than progression
Progression (annual)	$100,000	$10,000	$200,000	
SST therapy	$1,500,000	$100,000	$5,000,000	
Chronic therapy (annual)	$54,000	Calculated	Calculated	Based on amortizing SST costs over patients' lifetime

[a]Only with hypothetical treatment.

Table 2. Impact of discounting and timing of treatment for the base case.

	Chronic therapy vs. SoC			SST vs. SoC		
	3% Discounting	No discounting	% Difference with discounting	3% Discounting	No discounting	% Difference with discounting
Incremental Costs	$647,000	$1,289,000	−50%	$1,270,000	$1,289,000	−2%
QALYs Gained	6.8	14.9	−54%	6.8	14.9	−54%
ICER per QALY	$95,000	$86,000	10%	$186,000	$86,000	116%

Notes: Results rounded to nearest $1,000. Equal discounting was applied to costs and health benefits.
Abbreviations. SoC, standard of care; SST, single or short-term therapy.

are atypical in a disease-specific CEA, a uniform distribution was used to ensure the analyses covered a wide range of inputs and did not over-sample values closer to the base case assumptions. SST treatment costs, HRs, transition probabilities, direct medical costs, and utilities were varied in 1,000 scenarios. For each SST cost, the equivalent chronic treatment's annual costs were calculated by amortizing the undiscounted SST cost over the patients' lifetime.

In scenario analyses, the values used for discount rates for costs and benefits were disassociated to examine the impact of differential discounting. Discount values ranged from 0% to 5%, where the benefit discount rate was never higher than that for costs. HRs were also varied to see how the ICERs changed with varying health gains. To ensure consistency, the relationship between the HRs was maintained and the SST cost remained at $1,500,000. The chronic costs varied based on the patients' overall survival by amortizing the undiscounted SST cost over the patients' lifetime.

Additional scenarios were performed to evaluate those assessed in a study by Pearson et al.[15], which examined the maximum "value-based" price of hypothetical potential cures for hypothetical diseases of varying severity. In that analysis, the "value-based" price was determined without discounting, simply stating the hypothetical treatment benefits (QALYs gained and annual cost offsets by replacing SoC). The first scenario analyzed a fatal disease in a 5-year-old, who would have died in 10 years with SoC. The hypothetical cure would add 50 undiscounted QALYs through increased survival. The second scenario evaluated a hypothetical cure for a nonfatal disease in a 15-year-old who would gain 0.2 QALYs per year in improved utility over 50 years[15]. The inputs in this study's disease-agnostic model were adjusted to recreate the undiscounted results (Supplemental Table 1). Using the disease-agnostic model and standard 3% discounting, the maximum "value-based" price of the SST and an equivalent chronic therapy were calculated, assuming the same $100,000/QALY cost-effectiveness threshold as in the original analysis.

Results

Base case analysis

The results for the base case scenario comparing SST vs. SoC and the equivalent chronic therapy vs. SoC are shown in Table 2. By design, clinical benefits gained due to treatment were equal for both therapies, as were lifetime undiscounted incremental costs. Without discounting, the ICER was $86,000/QALY for both the SST and chronic therapy vs. SoC. When a 3% discount rate was applied to both costs and benefits, chronic therapy had an ICER of $95,000/QALY, 10% higher than when no discounting was applied. For the chronic therapy, discounting substantially reduced the incremental costs by 50% and QALYs gained by 54%. Overall, discounting costs and benefits resulted in a relatively small impact on the ICER for the chronic therapy.

In contrast to a chronic therapy, the treatment cost of an SST is incurred up-front whereby discounting has no effect on the value included in the analysis. Indeed, discounting had a nominal impact on total incremental costs of the SST vs. SoC (−2%; Table 2). On the other hand, QALYs gained were reduced by 54% when 3% discounting was applied (by definition equivalent to the chronic therapy analysis). Thus, the net impact of discounting both costs and benefits for the SST resulted in a much higher ICER than the chronic therapy. In the base case, the ICER of an equivalent SST vs. SoC was $186,000/QALY, above standard cost-effectiveness thresholds and almost double that of the equivalent chronic therapy. The ICER with 3% discounting was 116% higher than without discounting.

Probabilistic sensitivity analysis

Of the 1,000 PSA scenarios analyzed, the ICER for the SST was always higher than that for the equivalent chronic therapy, although the magnitude of the difference varied. When the chronic therapy was within the standard cost-effectiveness threshold of $150,000/QALY, the equivalent SST was above the threshold in 52% of the iterations.

Table 3. Impact of varying discount rates on ICER per QALY.

			Costs			
			0.0%	1.5%	3.0%	5.0%
Chronic therapy vs. SoC	Benefits	0.0%	$86,000	$59,000	$43,000	$32,000
		1.5%		$90,000	$66,000	$49,000
		3.0%			$95,000	$70,000
		5.0%				$104,000
SST vs. SoC	Benefits	0.0%	$86,000	$85,000	$85,000	$87,000
		1.5%		$130,000	$130,000	$133,000
		3.0%			$186,000	$190,000
		5.0%				$282,000

Note: Results rounded to nearest $1,000.
Abbreviations. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care; SST, single or short-term therapy.

Impact of varying discount rates on ICER per QALY

The ICER of the chronic therapy ranged from $86,000 to $104,000 when applying equal discount rates for costs and health benefits (Table 3). Use of the same discount rate for costs and benefits had a much larger impact on the ICER of the SST, ranging from $86,000 to $282,000. Furthermore, the ICERs of both the SST and the equivalent chronic therapy were noticeably impacted by variations in only the benefit discount rate. However, increasing the cost discount rate noticeably improved the ICER of the chronic therapy, but had a negligible impact on the ICER result for the SST.

Impact of varying treatment efficacy

Figure 2 shows the impact of varying treatment efficacy on the ICER of each therapy. Variation in HRs yielded 8 to 23 undiscounted life years gained. With an increased survival of 8 and 23 years, the ICER of the SST was $289,000 and $109,000, respectively, and the ICER of the chronic therapy was $167,000 and $41,000, respectively. For every treatment efficacy analyzed, the ICER of the SST was higher than that for the equivalent chronic therapy. As treatment benefits increased, the ratio between the ICERs also increased, ranging from 1.73:1 to 2.63:1 with 8 to 23 life years gained, respectively.

Impact of discounting on "value-based" price

Additional scenarios were performed using the disease-agnostic model to evaluate two previously described hypothetical SSTs for diseases of varying severity[15]. In the first scenario (a hypothetical cure that increased survival for a fatal disease), Pearson et al.[15] showed a maximum "value-based" price of $7,000,000. In contrast, using the disease-agnostic model and 3% discounting of costs and benefits, the maximum "value-based" price for the SST was $3,300,000 (Table 4). The price for the equivalent chronic therapy was

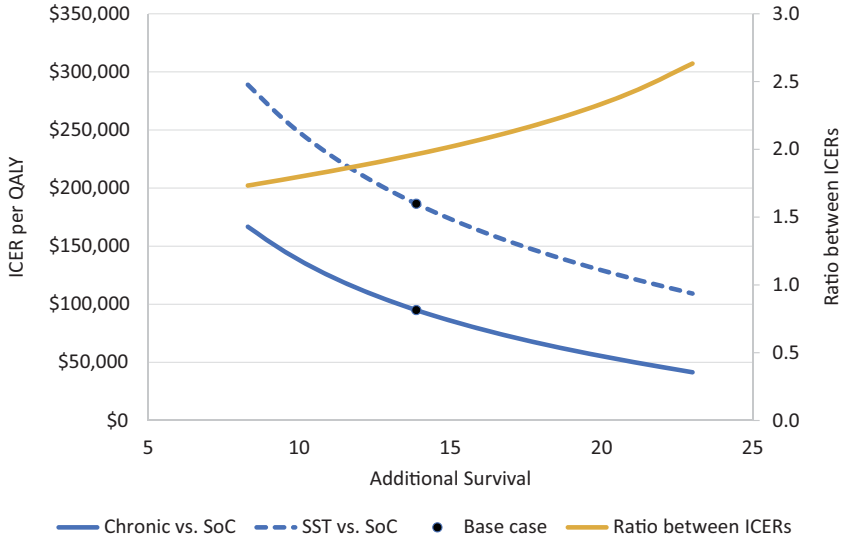

Figure 2. ICER per QALY for both hypothetical therapies with varying survival gains. Gold line represents the difference in value. Abbreviations. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care; SST, single or short-term therapy.

Table 4. Impact of discounting on "value-based" pricing.

	Scenario	Annual cost of current treatment	QALYs gained	QALY gain price component	Cost-offset price component	Cumulative "value-based" price
Scenario 1[a]	Pearson et al.[15] (no discounting) – recreated	$200,000	50.0	$5.00 million	$2.00 million	$7.00 million
	SST with discounting[c]	$200,000	17.6	$1.76 million	$1.57 million	$3.33 million
	Equivalent chronic therapy[c]	$200,000	17.6	$1.76 million	$1.57 million	$120,000/year
Scenario 2[b]	Pearson et al.[15] (no discounting) – recreated	$200,000	10.0	$1.00 million	$10.00 million	$11.00 million
	SST with discounting[c]	$200,000	4.8	$0.48 million	$4.83 million	$5.31 million
	Equivalent chronic therapy[c]	$200,000	4.8	$0.48 million	$4.83 million	$220,000/year

Notes: Results rounded to the nearest $10,000. Each QALY gained was valued at $100,000.
Abbreviations. QALY, quality-adjusted life-year; SST, single or short-term therapy.
[a]Scenario 1 assesses a new cure for a fatal disease in a 5-year-old patient, who would have died in 10 years with current treatment. With the novel treatment, the patient gains 50 QALYs[15]. A baseline utility of 0.851 was assumed, aligning with the age- and gender-adjusted utility of the general US population, a value used by the Institute for Clinical and Economic Review in their studies when calculating equivalent life years[41,72,73].
[b]Scenario 2 assesses a new cure for a nonfatal disease in a 15-year-old, who would have lived for 50 more years with current treatment. With the novel treatment, the patient gains 0.2 QALYs per year in improved quality of life over the 50 years[15].
[c]Costs and health benefits discounted at 3% per annum.

$120,000/year, which is lower than the SoC cost due to the increase in survival and the relatively short period for cost offsets.

In the second scenario (a hypothetical cure that increased utility for a nonfatal disease), the maximum "value-based" price was $11,000,000 in Pearson et al.[15]. Using the disease-agnostic model and 3% discounting of costs and benefit, the maximum "value-based" price was $5,300,000 for the SST and $220,000/year for the equivalent chronic therapy (Table 4). Thus, discounting has a substantial impact on the overall value assessments of the SSTs, reducing the "value-based" price by more than 50% in both scenarios.

Discussion

As the number of SSTs under development continues to increase, it is important to understand how these therapies fit within a traditional CEA framework, historically designed to evaluate chronic therapies[4]. The present study demonstrated that the ICER of an SST is consistently higher than that of an equivalent chronic therapy, which aligns with a recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) panel report[7]. In the base case analysis, the ICER of the SST was nearly double the ICER of the equivalent chronic therapy. This discrepancy is noteworthy as the ICERs of the two therapies without discounting were equivalent by design. Furthermore, although the ICER of the chronic therapy was within the standard cost-effectiveness threshold, the equivalent ICER of the SST noticeably exceeded the threshold. The ICER of the SST was consistently higher than that of the equivalent chronic therapy across a range of inputs (costs, risks, utilities, and hazard ratios), with many scenarios where the chronic therapy was within standard cost-effectiveness thresholds, but the equivalent SST was not. Moreover, the discrepancy between the ICERs increased with greater health benefits. Thus, although the SST and chronic therapy had projected exactly the same treatment benefits, the CEA results suggest that the two treatments have different values. This inadvertently suggests that chronic therapies provide greater value than SSTs despite equivalent benefits and costs.

The model developed in this study allowed for the direct comparison of ICERs of equivalent SSTs and chronic therapies to quantify the impact of discounting on SST valuations compared to those of chronic therapies offering the same benefits. This study has quantified the impact of discounting on the valuation of treatments with one-time administration. With the increasing number of SSTs available, a few CEAs have considered the incremental value of the SST over an available chronic therapy[37–39] although these therapies were inherently different in the benefits provided and the lifetime treatment costs[37–39]. The model used a hypothetical pediatric patient over a lifetime horizon; therefore, further studies are necessary to evaluate the impact of these treatments as a function of age.

The sensitivity of SSTs to discounting described in this study is supported by real-world examples. For example, in an assessment of onasemnogene abeparvovec (a gene therapy for SMA) vs. best supportive care, the base case ICER was £177,061/QALY with 3.5% discounting of costs and benefits, compared to £99,423/QALY (45% lower) without discounting[40]. In contrast, the ICER for nusinersen (a chronic SMA therapy) vs. best supportive care was only improved by 15% without discounting[40]. In another assessment of betibeglogene autotemcel (a gene therapy for beta-thalassemia), removing the 3% discount rate improved the ICER from $95,000/QALY to dominating SoC[41]. Similarly, reducing the discount rate from 3% to 1.5% for tisagenlecleucel, a chimeric antigen receptor T-cell (CAR-T) therapy, improved the ICER by approximately 20%[42]. The impact of discounting on SSTs is also similar to that observed with preventative interventions, where costs are incurred upfront but benefits may be obtained in the future[43]. Analysis of the human papillomavirus 16/18 vaccine, used to prevent cervical cancer, showed a five-fold increase in QALYs gained without the 3% discount rate[44]. It should be noted that some SSTs provide value due to cost offsets and have limited, if any, QALYs gained, such as valoctocogene roxaparvovec, a gene therapy approved to treat hemophilia A[45]. The evaluations of these SSTs will be negligibly influenced by the selected benefit discount rate.

While discounting future costs is largely accepted as a best practice in various economic modeling, discounting of health benefits is more controversial. Specific points of controversy include choice of discount model (e.g. constant vs. hyperbolic), discount rate height, and equal discounting of costs and benefits[46]. Furthermore, discounting treats both

delayed and prolonged benefits the same (e.g. an additional year of life 5 years from now is valued the same whether it was the first life year gained due to treatment or the fifth). Postma et al.[47] highlighted the dependence of future health gains on prior survival as support for changes to the constant and equal discounting of benefits over time. However, most current CEA guidelines in various countries recommend discounting costs and benefits equally with rates varying from 0% to 5%[46]. The use of equal discounting has been influenced by two arguments: the consistency argument proposed by Weinstein and Stason[48] and the postponement dilemma described by Keeler and Cretin[49]. Using differential discounting with a higher rate for costs than benefits, Keller and Cretin showed that a therapy's cost-effectiveness would improve each year that it is postponed and theorized that decision makers would ultimately postpone the intervention indefinitely[49]. However, indefinite postponing does not occur in practice[46,50,51].

Because equal discounting negatively impacts therapies with upfront costs and sustained health benefits[52], arguments in favor of differential discounting with lower rates for benefits are increasing in recent years[47,51–54]. For example, the Zorginstituut Nederland recommends discounting costs at 4% and benefits at 1.5%[43]. John et al.[52] suggest the benefit discount rate should be 0.3% to 1.5% lower than the cost discount rate in Germany. Nonetheless, the majority of CEAs performed in the US continue to use 3% discounting for both costs and benefits[2].

The growing pipeline of SSTs has prompted questions about their affordability. However, it is important that CEAs are undertaken without adjustments for budget impact concerns[55], to ensure that value and affordability are not conflated. Without discounting, the Pearson publication[15] estimated potential "value-based" prices of $7,000,000 for a hypothetical new cure for a fatal disease in a 5-year-old patient and $11,000,000 for a hypothetical new cure for a nonfatal disease in a 15-year-old. Acknowledging the hardship this might cause health care budgets from a budget impact perspective, numerous proposals were suggested to reduce the value assessment of SSTs[5,14,15]. Recent assessments by the Institute for Clinical and Economic Review for SSTs have included scenario analyses based on these proposals, including accrediting 50% of the shared savings back to the healthcare system and capping the annual cost offsets included in the analysis[41,45,56]. This study, however, shows the value assessment for both hypothetical SSTs are substantially impacted by discounting, which was not considered in the original analysis. Application of the proposed adjustments to the CEA in Pearson et al.[15] would further reduce the valuation of the SSTs. Therefore, any studies aimed at informing methodological or policy changes to address the valuation of SSTs should be performed in a manner similar to a traditional CEA, including discounting.

The purpose of CEA is to determine a therapy's value to inform resource allocation[57], and leveraging a standard approach allows for relative valuation across a range of diseases and treatments[58]. Thus, it is reasonable to consider modifying approaches when assessing SSTs[5,14,15] in a standardized manner[10] rather than ad hoc adjustments, which have been applied on a case-by-case basis, including for mifamurtide[59]. Mifamurtide is indicated for a rare type of osteosarcoma and administered over 36 weeks with potential benefits lasting a lifetime, making it SST-like[59]. NICE found the CEA was substantially sensitive to the benefit discount rate[60]. Specifically, all benefits would be discounted away after 22 years with the standard UK 3.5% discount rate compared to 49 years with a 1.5% rate[61]. Ultimately, the 1.5% benefit discount rate was used given the curative potential of the therapy and the expected sustained benefit[60].

SSTs may have other unique elements of value that should be considered but are not generally included in traditional CEAs. For example, CEAs do not consider potential patient or caregiver preference for the convenience of an SST. Current studies are underway to evaluate patient preferences for gene therapies and gain insight on other elements of potential value[62–64]. In patients with hemophilia A, dosing frequency/durability of treatment was viewed as the most important gene therapy attribute even over efficacy (i.e. effect on annual bleeding) and safety uncertainties[65]. In patients with SMA or their caregivers, preference was given to one-time administration over repeat intrathecal injections[63] although this burden did not get quantified in a recent CEA[65]. While some CEAs include non-adherence for chronic therapies, it is not considered consistently; therefore, the relative value of SSTs in terms of adherence will likely be muted. Additionally, CEAs omit other recurring costs associated with chronic therapies, such as continuous provider visits to refill prescriptions, travel for treatments, and processing prescription coverage and pre-authorizations. Not including these characteristics and costs can diminish the relative valuation of SSTs relative to chronic therapies. Furthermore, while discounting generally incorporates loss of exclusivity[66], this does not apply to SSTs and many chronic therapies have real price increases beyond inflation (e.g. price increases outpaced inflation for nearly half of Medicare-covered drugs in 2020)[67], which are not included in most CEAs.

Universal adjustments to CEAs ideally would allow for comparisons to those that have been previously completed, as updating prior CEAs would be prohibitively time-consuming. Instead of ad hoc adjustments for some SSTs, it is worth discussing a few modifications to the traditional CEA framework to ensure fair assessments of SSTs. First, payment-over-time options, which are aimed at addressing affordability[67], would reduce the discrepancy between SSTs and chronic therapies observed in this study. Most options currently under consideration in the US consider a 3- or 5-year horizon, given approximately 20% of patients switch health plans annually[68]. Thus, most pay-over-time options would have a nominal effect on the valuation of an SST as this is a transient period of time within most lifetime models. Second, a lower discount rate for benefits could be applied, which would partially mitigate the discrepancies seen between SSTs and chronic therapies. Third, a normalization factor (i.e. ratio of discounted life years to undiscounted life years for treated patients over the full model horizon) may be applied to

SSTs, which would effectively assess an SST like an equivalent chronic therapy; however, such an approach has yet to be established. Finally, assessing broader elements of value not generally captured within most CEAs, including those described in the ISPOR value flower[69], may be even more important for capturing the full value obtained with SSTs. Ultimately, further research is needed to fully understand the CEA of SSTs within the traditional framework and to examine the impact of potential modifications. Based on the findings of this study, it is recommended that any modifications to the CEA framework for SSTs be universal rather than case-by-case adjustments based on the results of a particular therapy's CEA.

The present study is limited by the model structure may not be reflective of acute or more complex diseases. However, three-state Markov models have been used in a variety of diseases[16–24]. In addition, inputs were selected without regards to specific diseases or treatments. While this strengthens the generalizability, application of these insights to a particular therapy or disease would require the development of a disease-specific model. Also, the hypothetical scenario of perfectly equivalent SST and chronic therapies is unrealistic as there are no known examples of two therapies (one SST and one chronic therapy) with the same efficacy and lifetime costs. Furthermore, as with all therapies, there are uncertainties around durability of treatment effect that necessitate extrapolation to a lifetime horizon; however, currently approved gene therapies have shown long-term durability up to 7.5 years[70,71]. Finally, the model assumed that chronic therapy costs do not decline due to going off-patent.

Conclusions

Although there has been previous discussion on the appropriate use of discounting in evaluations of SSTs[11–13], this study is the first, to the authors' knowledge, that quantitatively demonstrates the impact of discounting of SSTs due solely to one-time administration without the idiosyncrasies of disease or treatment-specific inputs. Compared with chronic therapies with equal treatment costs and benefits, SSTs consistently had higher ICERs vs. SoC due to discounting of treatment benefits and these differences increased with increasing health benefits. This study suggests that value frameworks may need to be adapted for the evaluation of SSTs to ensure equitable assessments relative to chronic therapies.

Transparency

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Declaration of financial/other relationships

ACK, LES, KLG are employees of Sarepta Therapeutics, Inc. and may own stock/options in the company. DCM has served as a consultant to Sarepta Therapeutics, Inc. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors had full access to the data and analyzed and interpreted the data. ACK and LES wrote the original draft. All authors edited, reviewed, and approved the final manuscript for submission.

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Data availability statement

Qualified researchers may request access to the data that support the findings of this study from Sarepta Therapeutics Inc., by contacting medinfo@sarepta.com.

ORCID

Alexa C. Klimchak http://orcid.org/0000-0001-8196-7093
Lauren E. Sedita http://orcid.org/0000-0003-0899-1585
Daniel C. Malone http://orcid.org/0000-0002-5006-9394

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