The European Journal of Health Economics (2025) 26:1101–1110
https://doi.org/10.1007/s10198-024-01754-3

ORIGINAL PAPER

Cost comparison analysis of onasemnogene abeparvovec and nusinersen for treatment of patients with spinal muscular atrophy type 1 in the Netherlands

Simon van der Schans[1,2] · Rimma Velikanova[2,3] · Diana Weidlich[4] · Ruth Howells[5] · Anish Patel[6] · Matthias Bischof[7] · Maarten J. Postma[1,2,8] · Cornelis Boersma[1,2,9]

Received: 9 November 2023 / Accepted: 16 December 2024 / Published online: 21 February 2025

Abstract

Background Spinal muscular atrophy (SMA) is a rare genetic disease resulting in loss of motor function and, in severe cases (e.g., SMA type 1), infantile death. While treatments like nusinersen and onasemnogene abeparvovec improve prognosis for patients with SMA, costs for these medications can contribute to economic burden.

Objective Direct costs were compared for onasemnogene abeparvovec, a one-time gene replacement therapy, versus nusinersen, a lifelong therapy, for patients with SMA type 1 and/or three or more *survival motor neuron 2* (*SMN2*) gene copies in the Netherlands.

Methods A cost comparison analysis model of 1-year incident patient population from the Netherlands was used to compare costs of onasemnogene abeparvovec versus nusinersen for patients eligible for onasemnogene abeparvovec immediately after diagnosis. Multiple analyses were conducted for economic outcomes (e.g., base-case, break-even, deterministic sensitivity, probabilistic sensitivity, scenario analyses).

Results Cost differences of –€2.9 million (undiscounted) and –€1.5 million (discounted) per patient with SMA type 1 treated with onasemnogene abeparvovec versus nusinersen over a 20-year time horizon were identified (base-case). Reduced costs with onasemnogene abeparvovec versus nusinersen were evident after 8.25 years.

Conclusion Onasemnogene abeparvovec was less costly than nusinersen after 8.25 years of treatment of patients with SMA type 1 in the Netherlands.

Keywords Cost comparison analysis · Gene therapy · The Netherlands · Nusinersen · Onasemnogene abeparvovec · Spinal muscular atrophy

✉ Simon van der Schans
S.van.der.schans@umcg.nl

[1] Health-Ecore, Zeist, The Netherlands

[2] Unit of Global Health, Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen 9173 GZ, The Netherlands

[3] Asc Academics, Groningen, The Netherlands

[4] Clarivate, Munich, Germany

[5] Clarivate, Manchester, UK

[6] Novartis Gene Therapies, Inc., Bannockburn, IL, USA

[7] Novartis Gene Therapies Switzerland GmbH, Rotkreuz, Switzerland

[8] Department of Economics, Econometrics and Finance, Faculty of Economics and Business, University of Groningen, Groningen, The Netherlands

[9] Department of Management Sciences, Open University, Heerlen, The Netherlands

Introduction

Spinal muscular atrophy (SMA) is an autosomal-recessive inherited genetic disease that occurs due to deletion or mutation of the 5q13 *survival motor neuron 1* (*SMN1*) gene, impacting motor neuron activity, and thus muscle function [1]. There are four SMA types based on age at disease onset and maximum motor function achieved [1]. SMA type 1, the most severe and common type, accounting for approximately 60% of all reported cases, is characterised by early disease onset (age < 6 months) and a rapid decline in motor and respiratory functions [1, 2]. SMA types 2 and 3 have a milder disease course, demonstrating a later onset of motor and respiratory function deterioration [1]. The mildest and rarest form is SMA type 4, which usually presents in adulthood (age > 21 years) [1].

Without treatment, patients with SMA type 1 may experience rapid disease progression and early death, while patients with SMA type 2 have reduced survival, and patients with SMA types 3 or 4 survive into adulthood with slower disease progression [3–5]. Though treatment strategies are crucial for survival, health care and drug costs for patients with SMA contribute to substantial economic burden. The estimated annual health care costs per SMA patient in the Netherlands are €65,277, €18,538, and €11,003 [6], while estimated annual non-medical costs (e.g., caregiver costs, food, travel, dietary supplements, and transportation assistance) are €69,032, €39,352, and €32,930 for patients with SMA types 1, 2 and 3, respectively [6].

It is difficult to assess direct cost differences of available treatments because of variations in dosage regimens. Onasemnogene abeparvovec, a one-time administration gene replacement therapy, directly replaces the defective *SMN1* gene, thereby restoring SMN protein expression [6]. Onasemnogene abeparvovec was approved by the Healthcare Institute of the Netherlands (2021) for patients with SMA type 1 and/or up to three copies of the *SMN2* gene [6]. One-time administration costs for onasemnogene abeparvovec equal €1,945,000 [7]. Nusinersen, the first available treatment made reimbursable for patients with SMA younger than 9.5 years of age in the Netherlands (2018) [8, 9], involves a series of lifelong intrathecal injections (administered via lumbar puncture six times in the first year, then three times per year for the remainder of the patient's life) [8, 9]. Nusinersen improves the expression of the *SMN2* gene, which is the backup of the *SMN1* gene that is nonfunctional in patients with SMA [8, 9]. Nusinersen costs €514,395 in the first year and €257,198 in subsequent years for the remainder of the patient's life [7, 8]. A third treatment, risdiplam, an *SMN2* splicing modifier, also requires lifelong administration and has comparable costs to that of nusinersen, though risdiplam is administered orally, which may reduce costs slightly [10, 11].

Though treatment with onasemnogene abeparvovec requires greater upfront costs than nusinersen, direct cost comparisons remain unclear, considering additional lifelong non-drug related costs. Potential long-term advantages such as improved motor capabilities and overall survival could contribute to overall affordability and reduced costs. Cost-utility analyses have assessed added value and reduced costs with onasemnogene abeparvovec versus nusinersen over a lifetime time horizon [12, 13]. A cost comparison is valuable to inform treatment care options from a heath care payer cost perspective. This cost comparison analysis is the first to assess treatment and health care cost implications with onasemnogene abeparvovec versus nusinersen. We performed a model-based cost comparison of onasemnogene abeparvovec versus nusinersen treatment for patients with SMA type 1 with up to three *SMN2* gene copies in the Netherlands using multiple analyses (i.e., base-case, break-even, deterministic sensitivity, probabilistic sensitivity, scenario analyses). These analyses investigated initial costs and cost offsets for a one-time treatment compared with a lifelong treatment.

Methods

Patient population and cost assumptions for SMA-related health care and drug and administration costs

Patient population

Based on an average SMA type 1 incidence of 5.4 patients per year (the Netherlands population, 2015–2019), along with expert opinion (personal communication, L. van der Pol and F. Asselman) estimating onasemnogene abeparvovec initiation in 94% of patients, 5.1 patients were eligible for SMA treatment in a 1-year model (validated by personal communication, University Medical Centre Utrecht; SMA patient data in the Netherlands; 2015–2019) [14]. Thus, patients were excluded if not immediately eligible for onasemnogene abeparvovec treatment (i.e., those with elevated anti–adeno-associated virus serotype 9 antibody [AAV9-Ab] titers > 1:50, including those with elevated AAV9-Ab titers who started nusinersen, or those with caregiver hesitancy due to religious or personal reasons) [9, 15, 16]. Only newly diagnosed patients were included based on the wide acceptance that prompt treatment initiation after diagnosis results in the best health outcomes [17–19]. Eligible patients were grouped into two cohorts: onasemnogene abeparvovec or nusinersen ($n = 5.1$ per group). Data were from published

sources, as well as health technology assessments and local expert opinion.

SMA-related health care costs

Annual SMA-related health care costs and survival rates for patients with SMA type 1 were from the publicly available Netherlands nusinersen reimbursement report and assumed to be the same per cohort. SMA-related health care costs were calculated by category of care (i.e., respiratory, gastrointestinal, nutritional, orthopaedic) (Table 1, Fig. S1A, Fig. S1B) [6, 20]. It was assumed that adverse events were equal between the treatments; therefore, costs related to the management of adverse events were not included. Likewise, because of the nature of SMA, it was difficult to separate treatment-related adverse events from SMA-related complications, which were already accounted for in health state costs [2, 3]. Real-world care costs were included to estimate the health care costs for patients who were non-adherent to nusinersen therapy (Netherlands nusinersen reimbursement report [20]). Patients who discontinued nusinersen (i.e., non-persistent patients) were not included in health care costs analyses.

Drug and administration costs

Drug costs for each treatment were derived from the G-standard databank; annual drug costs were calculated based on label administration instructions (Fig. S1A and S1B) [6–8]. Respective prices for onasemnogene abeparvovec and nusinersen were €1,945,000 and €85,733 per vial, respectively, with estimated costs of €3,800 per one administration for both [7, 20]. As onasemnogene abeparvovec is only administered once, there are no annual treatment acquisition costs. With nusinersen treatment, four loading doses are administered at initiation (within the first 63 days), then a maintenance dose every 4 months thereafter [8, 9] (i.e., six doses in the first year after treatment initiation (€514,395 drug cost; €22,800 administration cost), and three doses per year in subsequent years (€257,198 drug cost; €11,400 administration cost) [6–8].

Table 1 Average SMA type 1-related health care costs per category, derived from the Netherlands nusinersen reimbursement report for nusinersen- and onasemnogene abeparvovec-treated patients (€2023) [20]

SMA-related health care costs	Costs per year
Respiratory care	€43,782
Gastrointestinal care	€4,281
Nutritional care	€4,640
Orthopedic care	€5,053
Total costs	€57,756

SMA, spinal muscular atrophy

To incorporate a measure of adherence in the model, we included the average number of doses (2.499) for nusinersen-treated patients after the loading doses [4]. It was assumed that all patients treated with nusinersen would adhere to the first four loading doses. Price discounts for nusinersen are subject to commercial in confidence arrangements; therefore, no data are available in the public domain. No price discounts or price dynamics were included in our analysis.

Model structure and specifications

The cost comparison model was built using Microsoft Excel 2016© (Microsoft Inc, Richmond, VA, USA) (Fig. 1). The primary model outputs were total costs per treatment and cost differences between onasemnogene abeparvovec- and nusinersen-treated patients. Separate drug costs, administration costs, and SMA-related health care costs per patient are presented in addition to the total costs per treatment.

Base-case analysis

The base-case analysis used a 20-year time horizon, in line with long-term investment time horizons and selected to capture relevant cost implications for decision-makers within a limited length of the time to reduce uncertainty. No background mortality was included. The average age at clinical diagnosis was 4.8 months, as observed in clinical practice in the Netherlands (personal communication, University Medical Centre Utrecht; SMA patient data in the Netherlands; 2015–2019). Only drug and health care costs were evaluated as per the payer perspective. Societal costs such as those for travel, informal care, and loss of productivity were not included [21]. All cost outcomes were discounted at a rate of 4% annually as required by the Netherlands pharmacoeconomic guidelines and were indexed to the 2023 Euro value [21, 22].

Break-even analysis

A break-even analysis of total costs was conducted to assess the length of time a patient would need to undergo treatment with nusinersen to incur costs equal to the onasemnogene abeparvovec upfront cost.

Deterministic sensitivity analysis

A deterministic sensitivity analysis (DSA) was performed to analyse the effect of changes in key parameters on cost differences. Key parameters included discount rate, drug costs, health care costs, incidence, time horizon, percentage of patients eligible for onasemnogene abeparvovec treatment, and administration costs. The parameter values were varied by ± 20%.

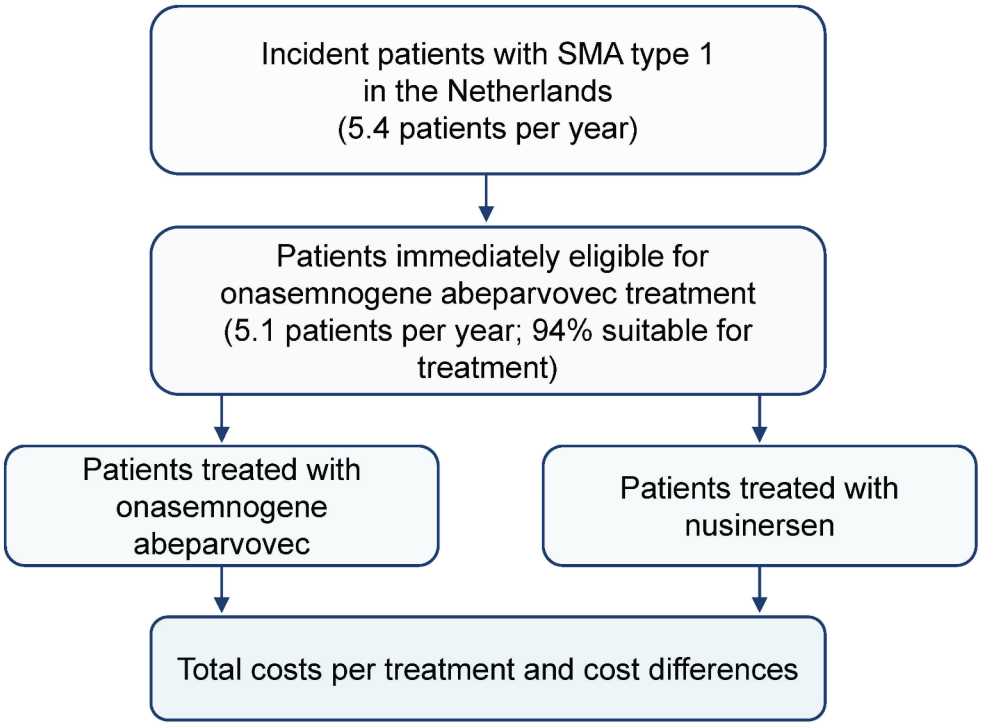

Fig. 1 Cost comparison analysis model structure. Reasons for not immediately being eligible for treatment with onasemnogene abeparvovec are high anti-AAV9-Ab titers and parental hesitancy to initiate gene replacement therapy. AAV9-Ab, adeno-associated virus serotype 9 antibody; SMA, spinal muscular atrophy

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) with 1,000 iterations was performed for economic and epidemiologic parameters (Table S1). Economic parameters included costs related to treatment and administration of nusinersen or onasemnogene abeparvovec as well as SMA-related health care costs, while epidemiologic parameters included SMA type 1 incidence.

Scenario analysis

Scenario analyses were informed by literature-based variations of model input assumptions, as well as alternative assumptions of drug costs and time horizon. Analyses were performed by varying the time horizon, percentage of patients for which onasemnogene abeparvovec treatment was initiated, incidence of SMA type 1 patients, drug costs, health care costs, administration costs, and discount rate (Table 2). A scenario analysis was also performed to assess the cumulative effect of combined assumptions on cost differences. Lastly, a persistence scenario analysis was performed to account for changes in the number of patients who remained on nusinersen treatment over time. Persistence input was used to assess the implications of patients discontinuing nusinersen treatment in the first two years after treatment initiation.

Results

Base-case analysis

The undiscounted and discounted cost differences over 20 years for onasemnogene abeparvovec compared with nusinersen were –€14.7 million and –€7.9 million, respectively, per 5.1 SMA type 1 patients (Table 3), corresponding to –€2.9 million (undiscounted) and –€1.5 million (discounted) cost differences with onasemnogene abeparvovec versus nusinersen per patient treated.

Break-even analysis

Onasemnogene abeparvovec demonstrated overall lower discounted costs versus nusinersen (Fig. 2). Break-even points between the two treatments were at 7.6 years (undiscounted, not shown) and 8.25 years (discounted) after treatment initiation (Fig. 2). Beyond 8.25 years, onasemnogene abeparvovec was less costly than nusinersen for the remainder of time assessed, totalling 20 years.

Deterministic sensitivity analysis

The greatest DSA impact was with nusinersen drug costs (–€4.6 million [low]/–€11.3 million [high]) compared with the base-case estimate of –€7.9 million [Fig. 3]). The following are ordered from the second greatest to the lowest DSA impact: variations in the time horizon (–€5.6 million

Table 2 Base-case parameters and scenario analyses inputs

Parameter	Base-case parameter	Scenario input(s)	Reasoning
Time horizon	20 years	10, 30, 50 years, and lifetime [assumptions]	Alternative assumptions were used to assess outcomes using a 20-year time horizon for the base-case parameter, and 10, 30, 50 years, and lifetime time horizons for scenario inputs.
Percentage of patients for whom onasemnogene abeparvovec treatment was initiated	94%[a]	100% [assumption] and 85.7% [16]	This percentage may change in the future depending on multiple factors. These alternative assumptions were applied to present potential effects • Re-evaluation of anti-AAV9-Ab titers, resulting in 100% of patients initiating onasemnogene abeparvovec treatment • The lowest estimate of patients with high titers (85.7%) from Day et al. [16]
SMA type 1 incidence	5.4 patients per year[a]	3 and 9 patients per year[a]	These are the highest and lowest incidence among all patients with SMA in the Netherlands supplied by the UMC Utrecht.
Drug costs	Onasemnogene abeparvovec: €1,945,000 per vial [6] Nusinersen: €85,733 per vial [7]	20% reduction [assumption]	In absence of insight into the potential discount, a 20% decrease was assumed to be reasonable for the purpose of the scenario analysis.
Discount rate	4% [29]	2.5% and 5.5% [30]	Alternative inputs for the discount rate were recommended for societal cost-benefit analysis.
Health care costs (onasemnogene abeparvovec-treated patients)	Respiratory care: €43,782 Gastrointestinal care: €4,281 Nutritional care: €4,640 Orthopedic care: €5,053	20% increased	To determine the effect of changing health care costs, a 20% increase was included.
Health care costs (nusinersen-treated patients)	Respiratory care: €43,782 Gastrointestinal care: €4,281 Nutritional care: €4,640 Orthopedic care: €5,053	20% increased	To determine the effect of changing health care costs, a 20% increase was included.
Administration costs for each administration (nusinersen and onasemnogene abeparvovec)	€3,800	€1,532 [6]	Input from the onasemnogene abeparvovec reimbursement dossier, and administration input for Belgian costs.
Persistence	Persistence was not part of the base case. Assuming 100% of patients starting nusinersen treatment would continue.	Average estimate on persistence over time derived from Gauthier-Loiselle et al. [31]	Persistence input was used to assess the implications of patients discontinuing nusinersen treatment [31].

AAV9-Ab, adeno-associated virus serotype 9 antibody; SMA, spinal muscular atrophy; UMC, University Medical Centre

[a]Personal communication (L. van der Pol and F. Asselman), University Medical Centre Utrecht, the Netherlands; patient data spinal muscular atrophy in the Netherlands; 2015–2019

Table 3 Undiscounted and discounted costs for onasemnogene abeparvovec- and nusinersen-treated annual incident patients with SMA type 1 immediately eligible for gene replacement therapy treatment (5.1 patients), €2023

	Onasemnogene abeparvovec		Nusinersen
Undiscounted costs, €			
20-year time horizon	15.8 million		30.5 million
Cost difference[a]		–14.7 million	
Discounted costs, €			
20-year time horizon	14.0 million		22.0 million
Cost difference[a]		–7.9 million[b]	

[a]Negative cost differences indicate lower treatment costs for onasemnogene abeparvovec therapy

[b]Sum of costs does not add up because of rounding

SMA, spinal muscular atrophy

[low]/–€9.9 million [high]); onasemnogene abeparvovec drug costs (–€9.9 million [low]/–€6.0 million [high]); SMA type 1 incidence (–€6.4 million [low]/–€9.5 million[high]); discount rate (–€9.0 million [low]/–€7.0 million [high]); health care costs of nusinersen-treated patients (–€7.3 million [low] /–€8.6 million [high]); health care costs of onasemnogene abeparvovec-treated patients (–€8.6 million [low]/–€7.3 million [high]); nusinersen administration costs (–€7.8 million [low]/–€8.1 million [high]); percentage of patients with SMA who were eligible for onasemnogene abeparvovec (–€8.0 million [low]/–€7.8 million [high]); onasemnogene abeparvovec administration costs (limited DSA effect, €7.7 thousand between low and high input).

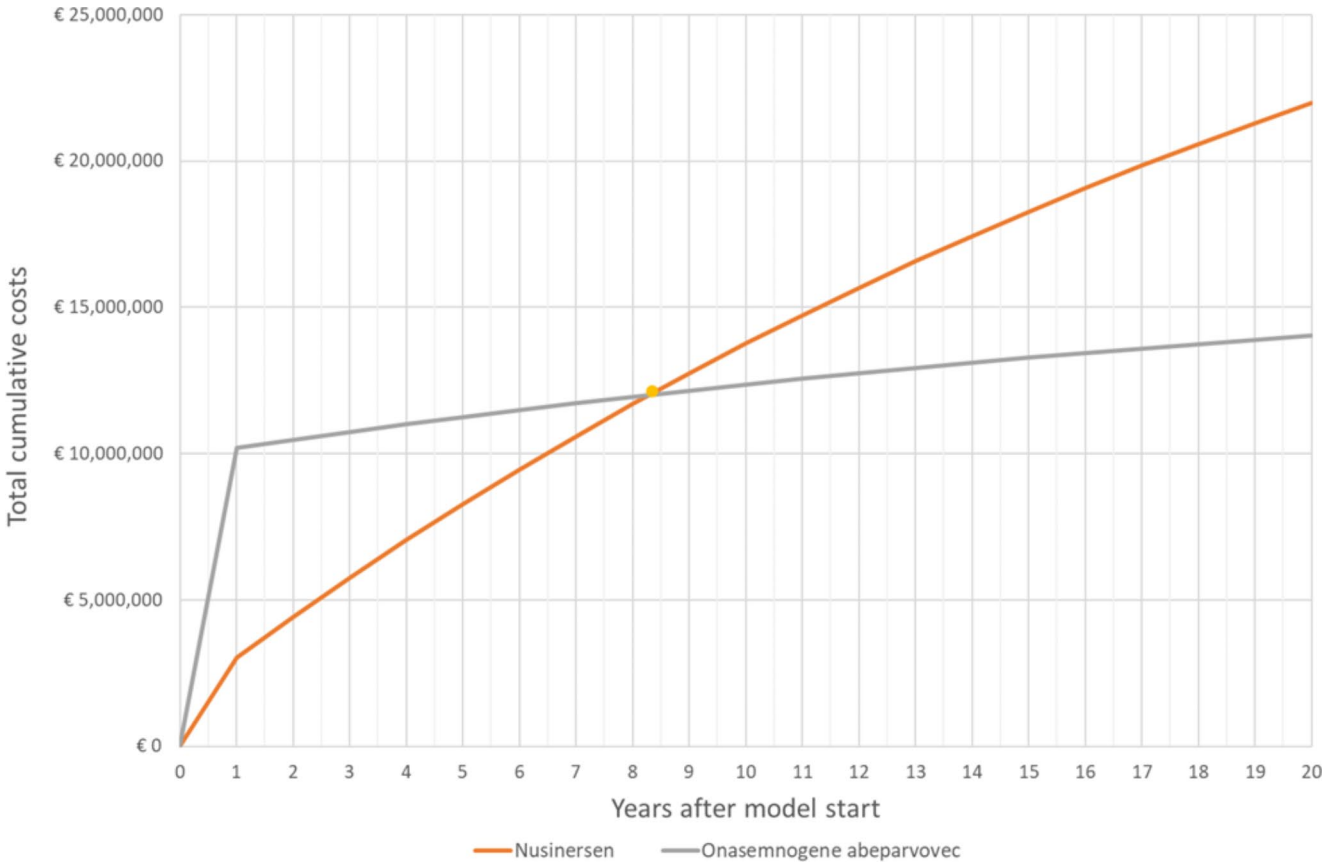

Fig. 2 Break-even analysis between nusinersen and onasemnogene abeparvovec, 4% discount rate (€2023, discounted). The horizontal axis only includes the first 20 years of treatment. It was assumed that all costs occurred at the end of each calendar year. The orange circle depicts the break-even point, at which time onasemnogene abeparvovec costed the same as nusinersen, and thereafter became less costly

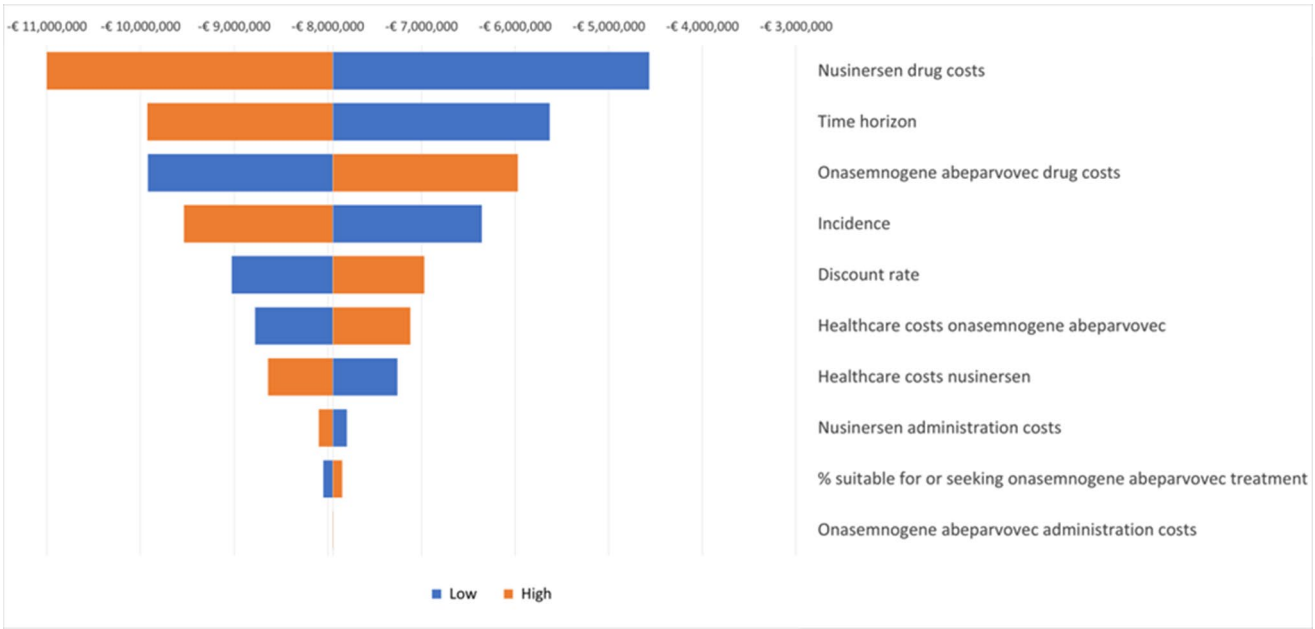

Fig. 3 Deterministic sensitivity analysis (Tornado diagram). Input parameters varied by ± 20% from the base-case scenario. SMA, spinal muscular atrophy

Probabilistic sensitivity analysis

The probability of lower costs with onasemnogene abeparvovec versus nusinersen increased with each 5-year period after treatment initiation, indicating 15.4% probability at 5 years, 64.8% probability at 10 years, and 86.1% probability after 15 years (Fig. 4). The probability of onasemnogene abeparvovec being less costly than nusinersen continued to slightly increase with time at 20 years (95.7% probability), 25 years (97.7% probability), and 30 years (98.4% probability).

Scenario analyses

Total costs were lower for onasemnogene abeparvovec-treated patients versus nusinersen-treated patients in all scenarios analysed, with cost differences ranging from –€0.4 million (persistence) to –€20.4 million (lifetime time horizon) (Table 4). The combination scenario analysis indicated a –€0.5 million cost difference between onasemnogene abeparvovec and nusinersen treatment.

Costs were €3.4 million greater with onasemnogene abeparvovec versus nusinersen in the low persistence scenario, and €3.4 million lower with onasemnogene abeparvovec versus nusinersen in the high persistence scenario. Health care costs were €2.1 million greater with onasemnogene abeparvovec versus nusinersen. Discounted annual costs were lower with onasemnogene abeparvovec versus nusinersen (€40,579 vs. €201,287 [10 years] and €27,413 vs. €135,982 [20 years]).

Discussion

Overall, onasemnogene abeparvovec was less costly than nusinersen for patients from the Netherlands with SMA type 1 (over 20-year time horizon), despite greater treatment costs in the first year of treatment. In a real-world setting, these reduced costs were expected to continue over a lifetime time horizon. There was a discounted cost reduction of €1.5 million per patient with onasemnogene abeparvovec versus nusinersen, which was evident after 8.25 years and beyond.

The DSA demonstrated that the parameters with the largest effect on the cost differences were nusinersen costs, time horizon, onasemnogene abeparvovec costs, and the discount rate. The probability of onasemnogene abeparvovec being less costly when compared with nusinersen was 86.1% when using a 15-year time horizon, which demonstrated the robustness of the cost difference estimate. Furthermore, in all scenario analyses, onasemnogene abeparvovec was found to be less costly compared with nusinersen. In a worst-case scenario with conservative assumptions used jointly, onasemnogene abeparvovec resulted in reduced costs compared with nusinersen treatment.

This analysis adds to the existing literature on cost-utility analyses comparing onasemnogene abeparvovec versus nusinersen in the Netherlands [12, 13]. With our cost comparison analysis, we have highlighted the cost differences of one-time versus lifelong therapy. In turn, this analysis was from the payer perspective, thus it may benefit those making decisions for the Netherlands health care system. We took a conservative approach in omitting societal costs such

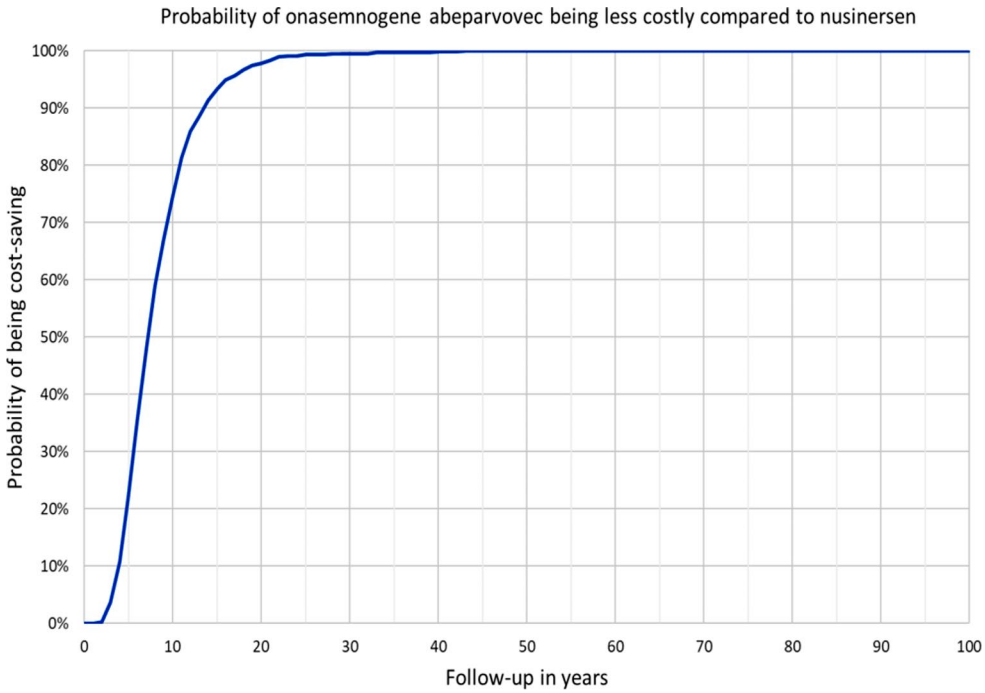

Fig. 4 Probability of onasemnogene abeparvovec costing less than nusinersen

Table 4 Scenario-analyses: parameters and outcomes (€2023, discounted)

Scenario	Cost of onasemnogene abeparvovec-treated patients, €	Cost of nusinersen-treated patients, €	Cost differences, €[a]
Base case	14.0 million	22.0 million	–7.9 million[b]
2.5% discount rate for costs [31]	14.6 million	24.6 million	–10.1 million[b]
5.5% discount rate for costs [31]	13.6 million	19.8 million	–6.2 million
Time horizon			
10 years	12.4 million	13.8 million	–1.4 million
30 years	15.2 million	27.5 million	–12.4 million[b]
50 years	16.4 million	33.8 million	–17.4 million
Lifetime	17.2 million	37.6 million	–20.4 million
Incidence			
Three patients with SMA type 1 per year (1:56,666 per year)[c]	7.8 million	12.2 million	–4.4 million[b]
Nine patients with SMA type 1 per year (1:18,888 per year)[c]	23.4 million	36.6 million	–13.2 million
Percentage of patients initiating onasemnogene abeparvovec treatment			
100%	14.9 million	23.4 million	–8.5 million
85.7% [18]	12.8 million	20.0 million	–7.2 million
Drug costs reduced by 20%	12.1 million	18.6 million	–6.5 million
Health care costs increased by 20%			
Onasemnogene abeparvovec-treated patients	14.9 million	22.0 million	–7.1 million
Nusinersen-treated patients	14.0 million	22.7 million	–8.6 million[b]
Administration costs nusinersen	14.0 million	21.5 million	–7.5 million
Persistence	14.0 million	14.4 million	–0.4 million
Combination scenario			
Time horizon: 10 years Incidence: 1:56,666 per year SMA type 1 Onasemnogene abeparvovec treatment initiation: 85.7% Health care costs (Onasemnogene abeparvovec-treated patients) increased	6.5 million	7.0 million	–0.5 million

[a]Negative cost differences indicate onasemnogene abeparvovec-treated patients being less costly than nusinersen-treated patients

[b]Sum of costs does not add up because of rounding

[c]Personal communication (L. van der Pol and F. Asselman), University Medical Centre Utrecht, the Netherlands; patient data spinal muscular atrophy in the Netherlands; 2015–2019

SMA, spinal muscular atrophy

as those for travel, informal care, and loss of productivity, which would be expected to be greater with nusinersen than onasemnogene abeparvovec due to the greater number of administrations required.

Although this cost comparison model allowed for the analysis of multiple scenarios, it has some limitations. This analysis focused on comparing onasemnogene abeparvovec versus nusinersen, but did not include risdiplam, which is expected to have similar costs compared with nusinersen. In accounting for health care costs, non-persistent nusinersen patients were omitted. These patients may potentially incur greater health care costs after stopping treatment; however, since this exact impact is unknown, we used a conservative approach by omitting them. Also, this analysis focused only on economic outcomes owing to the nature of the analysis and assumed comparable health care costs based on long-term clinical trials. Thus, clinical and patient-level data were not evaluated. When paired with appropriate willingness-to-pay thresholds, clinical and patient-level data are critical for decision-making on reimbursement policies in the treatment of rare diseases like SMA. Though comparative effectiveness data are lacking in this analysis and in the literature, one matching-adjusted indirect comparison demonstrated longer event-free survival and favourable overall survival with onasemnogene abeparvovec versus nusinersen within a 24-month follow-up [23]. Currently, registry data supplement clinical trial data on efficacy and durability [24, 25]. Future studies may further evaluate treatment comparisons in terms of effectiveness within the SMA treatment landscape.

SMA-related health care costs (i.e., respiratory, gastrointestinal, nutritional, orthopaedic care) used in this analysis were taken from onasemnogene abeparvovec and nusinersen reimbursement dossiers and original data from Klug and colleagues [20, 26]. These were deemed the most appropriate cost inputs because of the similarities between health

care systems of Germany and the Netherlands [7, 20]. There are also alternative greater estimates for SMA-related health care costs available from a health care resource utilisation study from the United Kingdom [6]. Since changes to non-drug costs (e.g., using the greater UK SMA-related health care costs) in the analysis will apply equally for both treatments, they will not affect the cost difference estimate [27].

Gene replacement therapy represents an important innovation in drug development and provides an opportunity to fundamentally change the standard of care and clinical outcomes for patients with SMA [28]. In the broad discussion of gene therapies, the focus should not only be tied to greater upfront costs in the short-term but should also emphasise the potential for overall lower costs versus other therapies. To our knowledge, this is the first published cost comparison for a novel gene replacement therapy, and we believe this analysis can help inform health care decision-making. In our analysis, higher upfront costs for onasemnogene abeparvovec were substantially offset by the costs of nusinersen treatment. This did not include spreading of upfront costs of onasemnogene abeparvovec, which could also negate some of the impact of these upfront costs. In markets where reimbursement decisions are largely based on evaluating cost differences between therapies, this existing analysis will be highly relevant.

Conclusion

Onasemnogene abeparvovec was less costly over a 20-year time horizon for the treatment of SMA type 1 patients in the Netherlands when compared with nusinersen. The initial treatment costs of onasemnogene abeparvovec were offset, and thus reduced costs were observed with onasemnogene abeparvovec after 8.25 years. Providing one-time treatment with an upfront cost that provides a lifetime treatment effect can save substantial health care costs when replacing a chronic lifelong treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10198-024-01754-3.

Acknowledgements The authors would like to acknowledge Fay-Lynn Asselman, MSc (University Medical Center Utrecht), and Ludo van der Pol, MD, PhD (University Medical Center Utrecht) for their contributions in the development of this manuscript, which included validation of model assumptions, parameter inputs, and results. Editorial support and medical writing assistance was provided by Caryne Craige, PhD (Kay Square Scientific). This support was funded by Novartis Gene Therapies, Inc.

Author contributions *Study concept and design*: Cornelis Boersma, Simon van der Schans. *Material preparation*, *data collection*: Cornelis Boersma, Simon van der Schans. *Analysis and interpretation of data*: Cornelis Boersma, Simon van der Schans. *Drafting of the manuscript*: Cornelis Boersma, Simon van der Schans. *Review and editing*: Simon van der Schans, Rimma Velikanova, Diana Weidlich, Ruth Howells, Anish Patel, Matthias Bischof, Maarten Postma, Cornelis Boersma. All authors read and approved the final manuscript for submission.

Funding This analysis was financially supported by Novartis Gene Therapies, Inc.

Data availability All data generated or analyzed during this study are included in this published article/as supplementary information files.

Declarations

Ethical approval This article is a cost comparison analysis and does not contain any new studies with human participants or animals performed by any of the authors.

Competing interests Matthias Bischof and Anish Patel are employees of Novartis Gene Therapies, Inc., and own Novartis stock or other equities. Cornelis Boersma and Maarten Postma have received grants from Novartis Gene Therapies, Inc. Diana Weidlich and Ruth Howells are employees of Clarivate, which received funding for this analysis from Novartis Gene Therapies. Simon van der Schans and Rimma Velikanova report no conflicts of interest.

References

1. Kolb, J.T., Kissel, S.J.: Spinal muscular atrophy. Neurol. Clin. **33**(4), 1–16 (2015). https://doi.org/10.1016/j.ncl.2015.07.004
2. Gezondheidsraad: Neonatale screening op spinale spieratrofie [Neonatal screening for spinal muscular atrophy] [Website in Dutch]. Accessed 20 December 2024. https://www.gezondheidsraad.nl/documenten/adviezen/2019/07/23/neonatale-screening-op-spinale-spieratrofie
3. Gregoretti, C., Ottonello, G., Chiarini Testa, M.B., et al.: Survival of patients with spinal muscular atrophy type 1. Pediatrics. **131**(5), e1509–e1514 (2013). https://doi.org/10.1542/peds.2012-2278
4. Kolb, S.J., Coffey, C.S., Yankey, J.W., et al.: Natural history of infantile-onset spinal muscular atrophy. Ann. Neurol. **82**(6), 883–891 (2017). https://doi.org/10.1002/ana.25101
5. Zerres, K., Rudnik-Schöneborn, S., Forrest, E., et al.: A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA):

569 patients. J. Neurol. Sci. **146**(1), 67–72 (1997). https://doi.org/10.1016/s0022-510x(96)00284-5
6. Zorginstituut Nederland (ZIN): *Pakketadvies sluisgeneesmiddel onasemnogene abeparvovec (Zolgensma) bij de behandeling van spinale musculaire atrofie (SMA)* [Package advice for the lock medicine onasemnogene abeparvovec (Zolgensma®) in the treatment of spinal muscular atrophy (SMA)] [Website in Dutch]. (2021). https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/05/06/pakketadvies-sluisgeneesmiddel-onasemnogene-abeparvovec-zolgensma Accessed 5 June 2024
7. G-Standaard databank: Z-index [Z-index] [Website in Dutch]. (2023). https://www.z-index.nl/ Accessed 5 June 2024
8. Spinraza (nusinersen): Prescribing information. Biogen. (2024). https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf Accessed 5 June 2024
9. European Medicines Agency: Summary of product characteristics (Spinraza). (2024). https://www.ema.europa.eu/en/documents/product-information/spinraza-epar-product-information_en.pdf Accessed 5 June 2024
10. Horizonscan: *Minister Bruno Bruins bereikt akkoord over vergoeding Spinraza* [Minister Bruno Bruins reaches agreement on Spinraza compensation] [Website in Dutch]. (2018). https://www.horizonscangeneesmiddelen.nl/nieuws/spinraza-vergoed-voor-jonge-kinderen Accessed 5 June 2024
11. Zorginstituut Nederland (ZIN): Risdiplam [Website in Dutch]. (2020). https://www.horizonscangeneesmiddelen.nl/geneesmiddelen/risdiplam-neurologische-aandoeningen-sma/versie3?lang=nl Accessed 5 June 2024
12. Dean, R., Jensen, I., Cyr, P., et al.: An updated cost-utility model for onasemnogene abeparvovec (Zolgensma®) in spinal muscular atrophy type 1 patients and comparison with evaluation by the Institute for Clinical and Effectiveness Review (ICER). J. Mark. Access. Health Policy. **9**(1), 1889841 (2021). https://doi.org/10.1080/20016689.2021.1889841
13. Broekhoff, T.F., Sweegers, C.C.G., Krijkamp, E.M., et al.: Early cost-effectiveness of onasemnogene abeparvovec-xioi (Zolgensma) and nusinersen (spinraza) treatment for spinal muscular atrophy I in the Netherlands with relapse scenarios. Value Health. **24**(6), 759–769 (2021). https://doi.org/10.1016/j.jval.2020.09.021
14. Zolgensma (onasemnogene abeparvovec-xioi): Prescribing information. Novartis Gene Therapies, Inc. (2024). Accessed 20 December 2024. https://www.novartis.us/sites/www.novartis.us/files/zolgensma.pdf
15. Delhove, J., Osenk, I., Prichard, I., et al.: Public acceptability of gene therapy and gene editing for human use: A systematic review. Hum. Gene Ther. **31**(1–2), 20–46 (2020). https://doi.org/10.1089/hum.2019.197
16. Day, J.W., Finkel, R.S., Mercuri, E., et al.: Adeno-associated virus serotype 9 antibodies in patients screened for treatment with onasemnogene abeparvovec. Mol. Ther. Methods Clin. Dev. **21**, 76–82 (2021). https://doi.org/10.1016/j.omtm.2021.02.014
17. Lin, C.W., Kalb, S.J., Yeh, W.S.: Delay in diagnosis of spinal muscular atrophy: A systematic literature review. Pediatr. Neurol. **53**(4), 293–300 (2015). https://doi.org/10.1016/j.pediatrneurol.2015.06.002
18. Keinath, M.C., Prior, D.E., Prior, T.W.: Spinal muscular atrophy: Mutations, testing, and clinical relevance. Appl. Clin. Genet. **14**, 11–25 (2021). https://doi.org/10.2147/TACG.S239603
19. Dangouloff, T., Servais, L.: Clinical evidence supporting early treatment of patients with spinal muscular atrophy: Current perspectives. Ther. Clin. Risk Manag. **2**, 15:1153–1161 (2019). https://doi.org/10.2147/TCRM.S172291
20. Zorginstituut Nederland (ZIN): Pakketadvies sluisgeneesmiddel nusinersen (Spinraza®) voor de behandeling van spinale musculaire atrofie (SMA) [Package advice for lock medicine nusinersen (Spinraza®) for the treatment of spinal muscular atrophy (SMA)] [Website in Dutch]. (2018). https://www.zorginstituutnederland.nl/publicaties/adviezen/2018/02/07/pakketadvies-nusinersen-spinraza-voor-de-behandeling-van-spinale-musculaire-atrofie-sma Accessed 5 June 2024
21. Zorginstituut Nederland: Guideline for economic evaluations in healthcare. (2016). https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare Accessed 5 June 2024
22. StatLine: Jaarmutatie consumentenprijsindex; vanaf 1963 (cbs.nl) [Annual change in consumer price index; from 1963] [Website in Dutch]. (2023). https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70936NED/table?fromstatweb Accessed 5 June 2024
23. Bischof, M., Lorenzi, M., Lee, J., et al.: Matching-adjusted indirect treatment comparison of onasemnogene abeparvovec and nusinersen for the treatment of symptomatic patients with spinal muscular atrophy type 1. Curr. Med. Res. Opin. **37**(10), 1719–1730 (2021). https://doi.org/10.1080/03007995.2021.1947216
24. Pechmann, A., König, K., Bernert, G., et al.: SMArtCARE– a platform to collect real-life outcome data of patients with spinal muscular atrophy. Orphanet J. Rare Dis. **14**(1), 18 (2019). https://doi.org/10.1186/s13023-019-0998-4
25. Finkel, R.S., Day, J.W., De Vivo, D.C., et al.: RESTORE: A prospective multinational registry of patients with genetically confirmed spinal muscular atrophy– rationale and study design. J. Neuromuscul. Dis. **7**(2), 145–152 (2020). https://doi.org/10.3233/JND-190451
26. Klug, C., Schreiber-Katz, O., Thiele, S., et al.: Disease burden of spinal muscular atrophy in Germany. Orphanet J. Rare Dis. **11**(1), 58 (2016). https://doi.org/10.1186/s13023-016-0424-0
27. Duenas, A.: Cost-minimization analysis. In: Gellman, M. (ed.) Encyclopedia of Behavioral Medicine, 1st edn. Springer, New York (2013). https://doi.org/10.1007/978-1-4419-1005-9_1376
28. Gupta, Strategists: N = 1, a new paradigm. The value and challenges of precision medicine in the Netherlands. (2020). https://gupta-strategists.nl/storage/files/Gupta-Strategists-n1_a-new-paradigm.pdf Accessed 5 June 2024
29. Hakkaart-van Roijen, L., van der Linden, N., Bouwmans, C., et al.: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg [Cost guide: Methodology of cost research and reference prices for economic evaluations in health care] [PDF in Dutch]. (2016). https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn%2Bvoor%2Bhet%2Buitvoeren%2Bvan%2Beconomische%2Bevaluaties%2Bin%2Bde%2Bgezondheidszorg%2B%2528verdiepingsmodules%2529.pdf Accessed 5 June 2024
30. Pomp, M., Schoemaker, C.G., Polder, J.J.: Op weg naar maatschappelijke kosten-batenanalyses voor preventie en zorg: Themarapport Volksgezondheid Toekomst Verkenning 2014 [Towards social cost-benefit analyzes for prevention and care: Theme Report Public Health Future Outlook 2014] [Website in Dutch]. (2014). https://www.rivm.nl/publicaties/op-weg-naar-maatschappelijke-kosten-batenanalyses-voor-preventie-en-zorg-themarapport Accessed 5 June 2024
31. Gauthier-Loiselle, M., Cloutier, M., Toro, W., et al.: Nusinersen for spinal muscular atrophy in the United States: Findings from a retrospective claims database analysis. Adv. Ther. **38**(12), 5809–5828 (2021). https://doi.org/10.1007/s12325-021-01938-w