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Economic Evaluation

Early Cost-Effectiveness of Onasemnogene Abeparvovec-xioi (Zolgensma) and Nusinersen (Spinraza) Treatment for Spinal Muscular Atrophy I in The Netherlands With Relapse Scenarios

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ABSTRACT

Objectives: Onasemnogene Abeparvovec-xioi (AVXS-101) is a gene therapy intended for curative treatment of spinal muscular atrophy (SMA) with an expected price of around €2 000 000. The goal of this study is to perform a cost-effectiveness analysis of treatment of SMA I patients with AVXS-101 in The Netherlands including relapse scenarios.

Methods: An individual-based state-transition model was used to model treatment effect and survival of SMA I patients treated with AVXS-101, nusinersen and best supportive care (BSC). The model included five health states: three health states according to SMA types, one for permanent ventilation and one for death. Deterministic and probabilistic sensitivity analyses were performed. Effects of relapsing to lower health states in the years following treatment was explored.

Results: The base-case incremental cost-effectiveness ratio (ICER) for AVXS-101 versus BSC is €138 875/QALY, and €53 447/QALY for AVXS-101 versus nusinersen. If patients relapse within 10 years after treatment with AVXS-101, the ICER can increase up to 6-fold, with effects diminishing thereafter. Only relapses occurring later than 50 years after treatment have a negligible effect on the ICER. To comply with Dutch willingness-to-pay reference values, the price of AVXS-101 must decrease to €680 000.

Conclusions: Based on this model, treatment with AVXS-101 is unlikely to be cost-effective under Dutch willingness-to-pay reference values. Uncertainty regarding the long-term curative properties of AVXS-101 can result in multiplication of the ICER. Decision-makers are advised to appropriately balance these uncertainties against the price they are willing to pay now.

Keywords: advanced therapy medicinal product, AVXS-101, cost-effectiveness, gene therapy, health technology assessment, microsimulation, relapse, spinal
muscular atrophy, Zolgensma

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Introduction

Spinal muscular atrophy (SMA) is a hereditary neurodegenerative disease that severely debilitates patients. SMA is caused by a mutation in the survival motor neuron 1 (*SMN1*) gene, turning it into the *SMN2* gene. *SMN2* undergoes alternative splicing, leading to insufficient production of functional SMN protein. The pathogenesis of SMA is caused by loss of *SMN1*, and severity is related to the number of copies of *SMN2*.[1] Symptoms of SMA include degeneration and loss of motor neurons resulting in muscle weakness, atrophy, and paralysis. SMA is classified in 4 phenotypes, with type I being the most severe and incident, accounting for about 50% of SMA cases. Overall, 1:6000 to 1:10 000 babies born in The Netherlands are diagnosed with SMA.[2] Patients with SMA I typically have 2 copies of *SMN2* and onset of clinical symptoms before 6 months of age. These infants never learn to sit unsupported and generally do not survive beyond 2 years.[1] In a study of survival of patients with SMA I, 93.3% of the 113 included patients had died at a median age of 6.95 months.[3] Patients with SMA II generally have 3 copies of *SMN2* and show signs of disease between 7 and 18 months and learn to sit unsupported. SMA III is clinically more heterogeneous, typically with 3 or 4 *SMN2* copies. Symptoms start after 20-30 years, when some patients lose the ability to walk unsupported.[1]

Until recently, patients in The Netherlands with SMA were treated with best supportive care (BSC) consisting of, among other measures, ventilatory and nutritional assistance.[2] Nusinersen, a treatment for SMA, is gradually made available to patients in The Netherlands with a confidential price reduction off the list price of €83 300 per vial. Nusinersen targets the splicing of *SMN2*, effectively turning the gene into the functional *SMN1*.[4,5] In 2018 the Dutch National Health Care Institute (ZIN) assessed the cost-

effectiveness of nusinersen for reimbursement in The Netherlands using the list price. The reported incremental cost-effectiveness ratio (ICER) was €502 289.[2] Despite this ICER being above the Dutch willingness-to-pay (WTP) threshold, nusinersen is conditionally approved for reimbursement in selected patient groups.[6] In reports by ZIN and the Institute for Clinical and Economical Review (CER Institute),[7,8] the cost-effectiveness of nusinersen for the treatment of SMA II and III was also studied. The reports showed costs per quality-adjusted life-year (QALY) of €3 739 196 and $8 156 000, respectively.

In 2019, onasemnogene abeparvovec-xioi (brand name Zolgensma) was granted market access in the United States by the Food and Drug Administration.[9] Onasemnogene abeparvovec has recently been granted market authorization by the European Commission.[10] Onasemnogene abeparvovec is a gene therapy that delivers a functional copy of the *SMN* gene to motor neuron cells in patients with SMA. The treatment effects range from symptoms stabilizing in some patients to patients improving up to the point where they can walk unsupported. Onasemnogene abeparvovec is delivered as a one-time intravenous injection.[11,12] The main advantage of gene therapies is that only 1 dose is needed during treatment, reducing patient burden compared to conventional therapies.[13] In the United States, onasemnogene abeparvovec is currently listed at $2.125 million per treatment.[14] Another therapy for SMA, RO7034067, is currently undergoing clinical trials.[15]

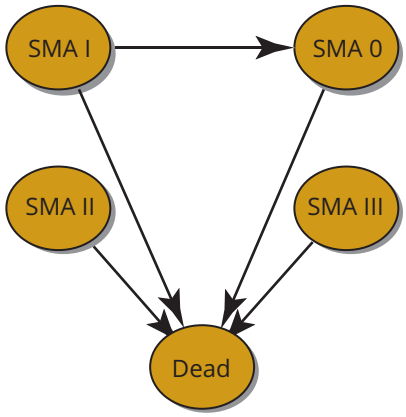
For onasemnogene abeparvovec, 2 cost-effectiveness analyses in the United States have been performed: 1 manufacturer sponsored[16] and 1 by the CER Institute.[7] The manufacturer-sponsored analysis compared onasemnogene abeparvovec with nusinersen, where onasemnogene abeparvovec is shown to dominate nusinersen.[16] The CER Institute study compared onasemnogene abeparvovec with BSC and nusinersen, reporting ICERs of $243 000 and $139 000, respectively.[7] The different outcomes of these studies can be attributed mainly to differences in quality-of-life measurements and estimated treatment effectivity.

Gene therapies are relatively new, and little is known about their long-term effectiveness. A clinical trial studying a gene therapy for the treatment of hemophilia A showed a decline in effect 3 years after treatment.[17] The manufacturer stated that the treatment effects were expected to last for a maximum of 8 years.[18] Although it cannot be assumed that the effects of onasemnogene abeparvovec will show similar sustainability, these results do stress the importance of assessing the effects of relapses on the ICER. A relapse scenario analysis in the CER Institute study where fixed proportions (10%, 20%, or 30%) of patients able to sit lost treatment effects directly after treatment resulted in slightly higher ICERs. The study presented here evaluated a wide range of possible levels of treatment sustainability to assess the effect of relapses on the ICER.

For accurate reimbursement decisions, early modeling is necessary to inform decision makers on the cost-effectiveness of the new therapy. Although reimbursement decisions are made on a country-level basis, the effectiveness of the therapy and effects of relapses on the ICER will be comparable in all countries. In this study, the Dutch setting will be studied. Since only results of a study on onasemnogene abeparvovec treatment with SMA I is currently published, only SMA I will be included in this study.

Based on literature and the health technology assessment reports provided by ZIN and the CER Institute, the goal of this study was to compare the cost-effectiveness of onasemnogene abeparvovec to BSC and nusinersen for the treatment of SMA I. In addition, the effect of a lack of sustained curative properties of onasemnogene abeparvovec on cost-effectiveness estimates was explored.

Figure 1. Structure of the model used. SMA 0, SMA I, SMA II, SMA III, and death depict the health states in the model. Arrows represent possible state transitions. Transition from SMA I to SMA 0 is only modelled in the best supportive care arm.



SMA indicates spinal muscular atrophy.

Methods

General

To model the lifespan of patients with SMA I and take into account the possibilities of relapse after treatment, a microsimulation model was built in R version 3.6.1.[19] The model code was adapted from the microsimulation tutorial published by the Decision Analysis in R for Technologies in Health (DARTH) workgroup.[20] Information from previously published cost-effectiveness studies of onasemnogene abeparvovec and nusinersen[2,7,16] was used to construct the model. A graphical overview of the model structure can be found in Figure 1. The model contains 5 health states, including death as an absorbing state. Health states 1-3 reflected health states corresponding to SMA I-III, with an additional health state 0 for patients with SMA I in need of permanent ventilation, defined as need of ventilatory assistance for at least 16 hours for 14 or more days.[7] The possibility for relapse based on individual patient survival time required the construction of a microsimulation, whereas transition probabilities are retrieved from published survival curves. The base-case model (without relapse possibilities) therefore functions similarly to a partitioned survival model.

The base-case model presented in this article does not behave as a classical microsimulation where all individuals in the model have unique characteristics. The basis of the survival estimates are parametric survival curves obtained from published Kaplan-Meier curves, similar to a partitioned survival model. These parametric functions are translated to transition probabilities per cycle in the model. This approach was taken because to implement survival adequately in the relapse analysis the moment of relapse needed to be traced.

Clinical Trials

Treatment of patients with SMA I with nusinersen has been studied in the ENDEAR (NCT02193074) clinical trial.[5] This is a phase III randomized, placebo-controlled clinical trial including 122 patients, with a median follow-up of 394 days. At the start of the trials, all patients were diagnosed with SMA I, corresponding to health state 1. At the end of the trial, 69 (56.41%) patients in the treated arm remained in health state 1, 23 (18.59%) patients in

Table 1. Input parameters for the base-case analysis.

Variable	Base	Min	Max	Distribution	Source
Mean age (months)	3.4			Fixed	[12]
Mean weight (kg)	5.7			Fixed	[12]
Sex: male (%)	42			Fixed	[12]
Time horizon (years)	100			Fixed	NA
Discount rate costs	0.04	0	0.08	Fixed	[21]
Discount rate effects	0.015	0	0.03	Fixed	[21]
Utility values					
SMA I	0.733	0.714	0.753	Beta	[2]
SMA II	0.752	0.721	0.783	Beta	[2]
SMA III	0.878	0.821	0.993	Beta	[2]
Permanent ventilation	0.733	0.714	0.753	Beta	[2]
Costs treatment arms					
SMA I	€ 9,936	€ 6,240	€ 11,086	Gamma	[2], [22]
SMA II	€ 10,526	€ 7,894	€ 13,158	Gamma	[2], [22]
SMA III	€ 5,863	€ 4,397	€ 7,329	Gamma	[2], [22]
Permanent ventilation	€ 15,201	€ 14,331	€ 17,023	Gamma	[2], [22]
Drug costs					
Onasemnogene abeparvovec	€ 2,000,000	€ 1,500,000	€2,500,000	Gamma	Placeholder price
Administration costs	€ 1,336.11			Fixed	[23]
Nusinersen	€ 83,300	€ 62475	€ 104,125	Gamma	[2]
Administration costs	€ 1,004			Fixed	[2]
Costs BSC arm					
SMA I	€ 11,047	€ 10,378	€ 12,334	Gamma	[2], [22]
SMA II	€ 10,526	€ 7,894	€ 13,158	Gamma	[2], [22]
SMA III	€ 5,863	€ 4,397	€ 7,329	Gamma	[2], [22]
Permanent ventilation	€ 15,201	€ 14,331	€ 17,023	Gamma	[2], [22]
Transition parameters					
SMA I -> Death (Treatment)				Weibull	[3]
Intercept	4.167065	3.526969	4.784291		
Scale	1.37909	0.9402944	2.0038042		
SMA I -> EFS (BSC)				Exponential	[5]
Intercept	2.922773	2.544759	3.295987		
SMA I -> OS (BSC)				Weibull	[5]
Intercept	4.248068	3.160661	5.296624		
Scale	0.5290965	0.3363636	0.8147468		
SMA II -> Death				Weibull	[24]
Intercept	3.83344	3.645634	4.014528		
Scale	0.5028791	0.4037954	0.6200652		
SMA III -> Death				-	[25]
Derived from Dutch general population survival					
Treatment effects (starting health states)					
Onasemnogene abeparvovec					
1	0.08			Dirichlet	[12]
2	0.59			Dirichlet	[12]
3	0.33			Dirichlet	[12]
0	0			Dirichlet	[12]

continued on next page

Table 1. Continued

Variable	Base	Min	Max	Distribution	Source
Nusinersen					
1	0.5641			Dirichlet	[5]
2	0.1859			Dirichlet	[5]
3	0			Dirichlet	[5]
0	0.25			Dirichlet	[5]
BSC					
1	0.68			Dirichlet	[7]
2	0			Dirichlet	[7]
3	0			Dirichlet	[7]
0	0.32			Dirichlet	[7]

health state 2, and 30 (25%) needed permanent ventilation, corresponding to health state 0. No patients reached health state 3. The placebo group showed no improvement; that is, all remained in the health state they were in at the start of the study, with 28 patients (68%) in health state 1, and 13 (32%) in health state 0 in need of permanent ventilation. Onasemnogene abeparvovec was studied in the STRIVE (NCT03461289) clinical trial, a 1-arm trial with historical control.[11,12] Twelve patients were enrolled in the study and followed up for 2 years. At the end of the trial, 1 patient (8%) was in a condition corresponding to health state 1, 7 (59%) in health state 2, and 4 (33%) in health state 3. No patients needed permanent ventilation.

Target Population and Model Setting

The target population is infants born with SMA I, as included in the STRIVE clinical trial.[12] Since only the high-dose cohort was continued in further trials,[12] results from these patients were used to build the model population. This cost-effectiveness analysis was performed for The Netherlands, with a societal perspective. As comparators, both BSC and treatment with nusinersen were used.

Treatment Effect

Patients with SMA I who get treated enrolled in the model in one of the health states (reflecting SMA I-III) proportional to the outcomes of the ENDEAR[5] or STRIVE[12] clinical trials after treatment with nusinersen or onasemnogene abeparvovec, respectively. Because all patients at baseline had SMA I, patients in the BSC arm enrolled in health state 1. The proportion of patients in each health state in the BSC scenario is derived from ENDEAR,[5] since in this trial a placebo group was included, whereas the STRIVE trial used a historical comparison.[12] At the end of the ENDEAR clinical trial, 25% of patients in the nusinersen arm needed permanent ventilation. Based on the report by the CER Institute, patients in the treatment arms were assumed not to regress health state 0 after the clinical trial ended, as deemed reasonable by clinical experts in the study.[7] In the BSC arm, 32% needed permanent ventilation at the end of the ENDEAR trial,[5] which is reflected in the starting health states of the model. Distribution of patients among starting health states can be found in Table 1.

No information is known on long-term effectiveness of onasemnogene abeparvovec and nusinersen. Therefore, in the base-case analysis, patients were assumed to stay in their respective health states until they die. In a scenario analysis, the effect of relapsing to a lower health state was explored. For an overview of assumptions made in this model, see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021. Reporting of this model is done according to the Consolidated Health Economic Evaluation Reporting Standards statement.[25] All the R codes can be found at https://github.com/TFBroekhoff/SMACostEff.

Time Horizon and Cycle Length

For this model, a lifetime horizon of 100 years was chosen, with monthly cycles. Because patients in the health states 1 and permanent ventilation have a general survival of up to 2 years, monthly cycles give the necessary detail to accurately model survival. A lifetime horizon is needed because survival with SMA III equals survival of the general population.[1,21]

Discount Rate

Costs were discounted at a yearly rate of 4%, and utilities at a yearly rate of 1.5%, as per HTA guidelines provided by the Dutch National Health Care Institute.[26]

Treatment Structure

Onasemnogene abeparvovec is a gene therapy, administered once early in the lifespan of patients via intravenous injection. Nusinersen is given intrathecally. Treatment starts with 4 loading doses in the first 2 months of treatment, with an additional dose every 4 months thereafter until death. BSC in The Netherlands entails ventilatory and nutritional assistance and physiotherapy.[27]

Health Outcomes

In the STRIVE clinical trial, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score was used to assess the improvement of patients treated with onasemnogene abeparvovec. This same score is used in the ENDEAR trial studying nusinersen.[5] This score is used to report health outcomes in the clinical trials. In this study, the scores were converted to place patients in 1 of the 3 included SMA types in the model. In the base-case analysis, patients remained in their assigned health state until death.

Health State Utilities

Each health state was assigned a utility value. The health state utilities in the base-case model were taken from the ZIN model.[2] Another published cost-effectiveness study comparing onasemnogene abeparvovec with nusinersen in the United States used the same values.[15] The CER Institute Model used different utility values, taken from Thompson et al[28] and Tappenden et al[23]

Table 2. Results of the base-case analysis.

	Costs	MCSE (%)	QALYs	MCSE (%)	Incremental Costs	MCSE (%)	QALYs Gained	MCSE (%)	ICER
BSC	922130	9365 (1.02)	4.415	0.052 (1.18)					
Onasemnogene abeparvovec	4024879	7424 (0.18)	26.757	0.136 (0.51)	3102749	12021 (0.39)	22.342	0.146 (0.65)	138875
BSC	922130	9365 (1.02)	4.415	0.052 (1.18)					
Nusinersen	3002379	28279 (0.94)	7.625	0.089 (1.17)	2080249	29831 (1.43)	3.211	0.104 (3.24)	647850
Nusinersen	3002379	28279 (0.94)	7.625	0.089 (1.17)					
Onasemnogene abeparvovec	4024879	7424 (0.18)	26.757	0.136 (0.51)	1022499	28804 (2.82)	19.131	0.156 (0.82)	53447

BSC indicates best supportive care; ICER, incremental cost-effectiveness ratio; MCSE, MoneteMonte Carlo Squared Error; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy.

and US general population utility. Also, in the CER Institute model, assumptions were made on improved utility after treatment, regardless of health state, based on assumed improvement on unmeasured treatment milestones. The utilities used by CER Institute were used in a scenario analysis. Input parameters for the base-case analysis can be found in Table 1. The scenario input values are listed in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021.

Costs

Because no price for onasemnogene abeparvovec in The Netherlands is known, a placeholder price of €2 000 000 was used. This placeholder price is based on the list price of onasemnogene abeparvovec in the United States of $2.125 million.[13] Onasemnogene abeparvovec is administered via intravenous infusion. In The Netherlands, the expertise center for patients with SMA is the University Medical Center Utrecht. The mean price listed for an intravenous treatment for patients who do not stay longer than 1 day in the University Medical Center Utrecht tariff list[22] was used for administration costs. For nusinersen, treatment costs per infusion according to the ZIN model[2] was used (€83 300).

The health state costs, including costs for additional care apart from treatment and non-healthcare costs, such as informal care and lost productivity, are derived from the ZIN report, which uses cost calculations by Klug et al.[29] Additional detailed information regarding costs implemented to adhere to the societal perspective can be found in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021. Costs were inflated to 2019 cost levels using inflation data.[30] For patients with SMA I, death usually comes after a period of increased pulmonary symptoms.[1] To account for the extra needed health care costs in this period, the equivalent of 3 months' worth of health expenses for permanent ventilation were added when a patient dies. Input parameters for costs can be found in Table 1.

Transition Probabilities

State transitions probabilities were estimated using parametric survival modeling. Published Kaplan-Meier curves were converted to parametric survival functions using the algorithm published by Hoyle and Henley.[31] Final survival curves were chosen based on the Akaike information criterion, the Bayesian information criterion, and a visual inspection of fit. Transition probabilities per cycle were obtained by dividing the proportion of patients alive at timepoint t by the proportion alive at $t - 1$. At each cycle, a multivariate normal distribution was used to place individuals in health states for the next cycle according to the respective transition probabilities. For states 2, 3, and permanent ventilation, possibilities were to remain in the same health state or to die, with different probabilities per health state. In health state 1, individuals could additionally transition into permanent ventilation. A detailed description of the mechanism distributing patients among health states at each cycle is given in the tutorial paper by Decision Analysis in R for Technologies in Health.[20] SMA I survival and transition to need of permanent ventilation were based on the overall survival (OS) and event-free survival (EFS) curves of the sham control arm in the ENDEAR clinical trial, with events being need of permanent ventilation.[5] The EFS and OS in this study were used to calculate the probability of needing permanent ventilation for the BSC arm by calculating the difference in the proportion of patients remaining in the EFS curve from the OS curve for each timepoint. Survival on permanent ventilation, and SMA I after treatment, was obtained from the noninvasive respiratory aid arm in the study by Gregoretti et al.[3] This survival curve shows longer survival than the SMA I BSC arm in the ENDEAR trial, and it is used for the treatment arm to incorporate assumed treatment benefits. A more detailed explanation of this assumption is given in the CER Institute report.[7] SMA II survival was modeled after Zerres et al.[31] SMA III survival was based on general survival of the Dutch population,[21] based on previous research.[7] It is not yet known whether patients will improve or relapse later in life. Therefore, all patients were assumed to remain in their respective health states until death, except patients in the BSC arm deteriorating to need of permanent ventilation. All survival parameters can be found in Table 1. Further explanation of parametric survival estimation with survival curves and probabilities overlaid with published Kaplan-Meier curves can be found in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021.

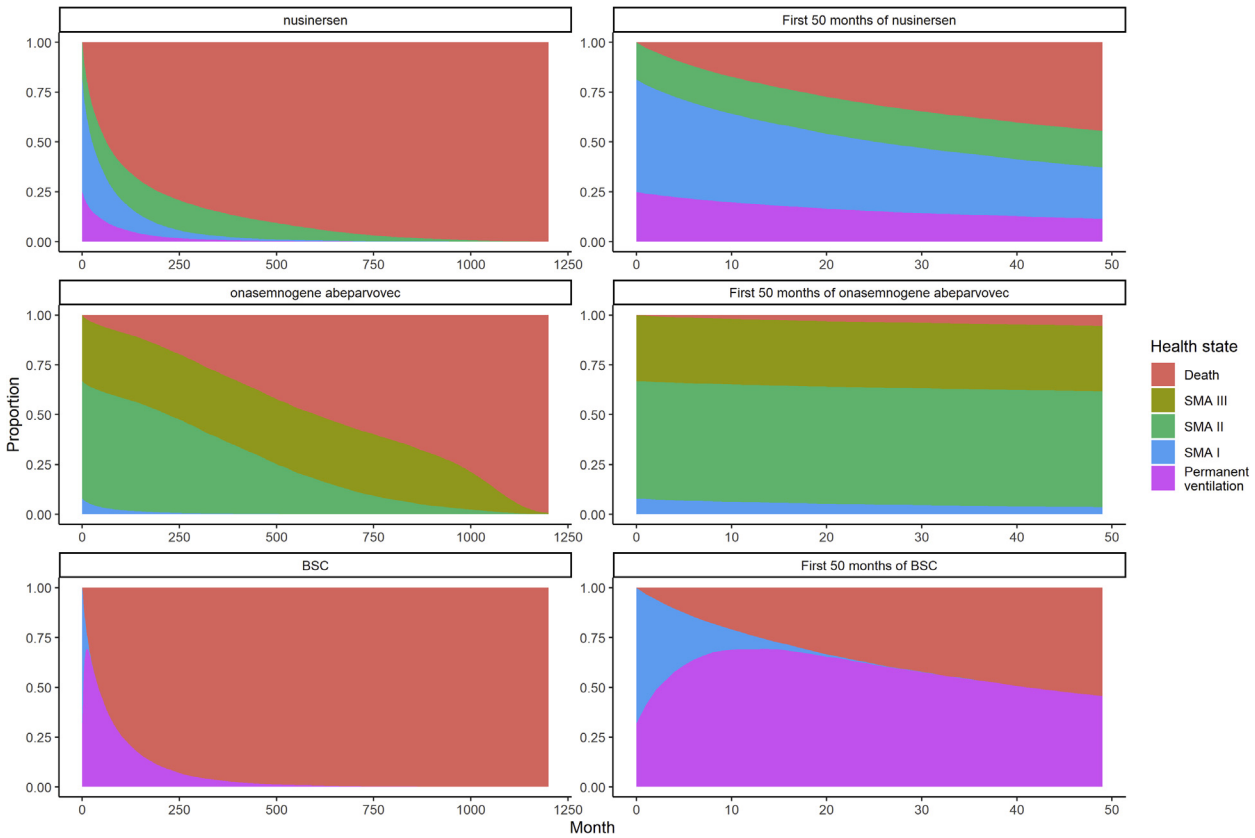
Analysis

Using this model, the costs and QALYs were calculated for patients undergoing treatment with onasemnogene abeparvovec or nusinersen or receiving BSC. The results from the simulations were combined to calculate the ICER in €/QALY for all possible combinations.[32]

Sensitivity Analyses

To examine the impact of specific parameters on the outcome, a stepwise deterministic sensitivity analysis was conducted with 7 steps for the lower and upper bound. Used parameters, with associated uncertainty distributions, can be found in Table 1. To evaluate the parameter uncertainty in the model, a probabilistic

Figure 2. Trace plots of the microsimulation. The y-axis shows the proportion of individuals in a health state. The x-axis represents time in months. Left hand side: trace plots for the full time horizon. Right hand side: zoomed in on the first 50 months. BSC indicates best supportive care; SMA, spinal muscular atrophy.



sensitivity analysis (PSA) was conducted using 10 000 Monte Carlo simulations. Input parameter values were simultaneously sampled according to their uncertainty distributions. For the state transitions, Cholesky decomposition matrices were used to account for correlation between survival function parameters in calculating random survival probabilities. In some of the iterations, survival in health state 2 surpassed health state 3, which is based on general survival. Since living longer in health state 2 with higher disability compared to health state 3 is unlikely in this setting, health state 2 survival was modeled to always be equal to or lower than health state 3 survival. The results from the PSA were used to construct a cost-effectiveness acceptability curve (CEAC) to assess the uncertainty around the cost-effectiveness at different WTP thresholds.

Scenario Analyses

Because the long-term effectiveness of gene therapies is not yet known, the possibility of relapsing after treatment with onasemnogene abeparvovec was explored in a scenario analysis. Used probabilities per cycle were 0.001, 0.0025, 0.005, 0.01, 0.025, and 0.05. The period after which a relapse could occur was also varied, starting from 1 year after treatment until 99 years using intervals of 1 year. Because survival data after relapse were not available, survival probabilities in the health state after a relapse were assumed equal to being assigned this health state at the start of the model. In another scenario analysis, the health state utility values as used by CER Institute[7] were used in the model. Given the large time horizon and the fact that different HTA organizations recommend different discount rates, a third scenario analysis includes an annual discount value of 3.5% for both costs and utilities, based on guidelines provided by the National Institute of Health and Care Excellence.[33]

Results

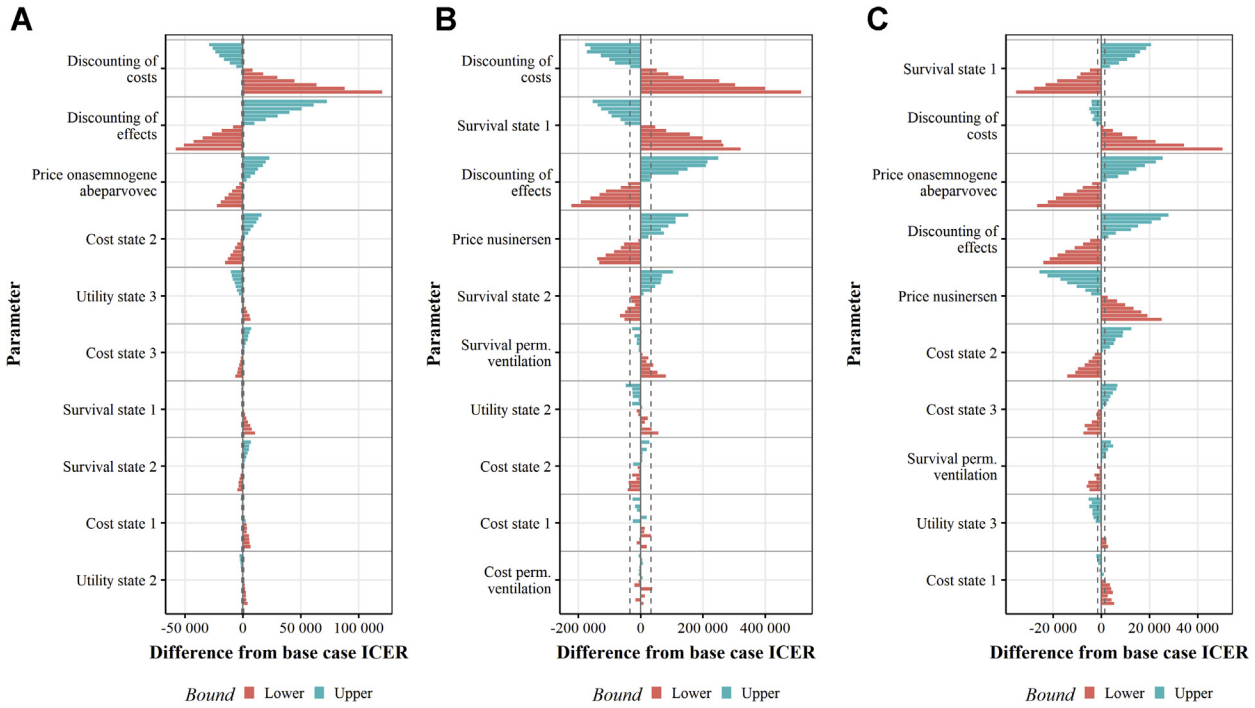
Incremental Costs and Outcomes

Base-case results of the models can be found in Table 2. For onasemnogene abeparvovec compared with BSC, incremental costs were €3 102 749, and incremental QALYs 22.342, resulting in an ICER of €138 875/QALY. For nusinersen compared with BSC, incremental costs were €2 080 249, and incremental QALYs 3.211, which gave an ICER of €647 850/QALY, thus being extendedly dominated by onasemnogene abeparvovec. Onasemnogene abeparvovec compared to nusinersen resulted in incremental costs of €1 022 499 and 19.131 incremental QALYs, leading to an ICER of €53 477/QALY. Trace plots of distribution of patients over health states for the base-case model can be found in Figure 2.

Sensitivity Analysis

In the stepwise deterministic sensitivity analysis, for all comparisons, discounting of costs and effects had the strongest influence on the ICER, as can be seen in Figure 3. In both comparisons with nusinersen, survival in health state 1 was also

Figure 3. Results of the stepwise deterministic sensitivity analysis showing the influence of varying separate parameters in the model on the base-case incremental cost-effectiveness ratio as described in Table 2. Gray dotted line: uncertainty around the base-case estimate, as Monte Carlo squared error. (A) Onasemnogene abeparvovec vs BSC. (B) Nusinersen vs BSC. (C) Onasenmogene abeparvovec vs nusinersen. BSC, best supportive care; ICER, incremental cost-effectiveness; rob, probability; perm. ventilation, need of permanent ventilatory assistance.



an important driver of the ICER. Price of treatment had a notable influence in all comparisons.

Results of the PSA can be found in Figure 4. The CEACs can be found in Appendix 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021. In a small number of cases (1.12%), nusinersen was dominated by BSC, and in a larger number of cases (11.1%), onasemnogene abeparvovec dominated nusinersen. This caused the CEACs with nusinersen never to reach 0 or 100%.

At a WTP of €80 000/QALY, as is applicable for diseases with high burden in The Netherlands,[34] onasemnogene abeparvovec had 0.0002% chance of being cost-effective and nusinersen 0.01%, both compared with BSC. To comply with a WTP of €80 000/QALY, the price of onasemnogene abeparvovec should not exceed €680 000.

Scenario Analyses

Higher probability and earlier start of relapse both increased the ICER (see Figure 5A). As seen in Figure 5B, all relapse probabilities showed similar relations of the ICER with relapse start time, with differing levels of magnitude up to a factor 6.

Using the utility values from the CER Institute report, which are lower than the ZIN values, the incremental QALYs for onasemnogene abeparvovec versus BSC were 23.572, for nusinersen/BSC 2.979, and for onasemnogene abeparvovec versus nusinersen 20.773, resulting in ICERs for onasemnogene abeparvovec versus BSC of €130 630/QALY, for nusinersen/BSC of €698 281/QALY, and for onasemnogene abeparvovec/nusinersen of €49 222/QALY. More detailed results can be found in Appendix 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021.

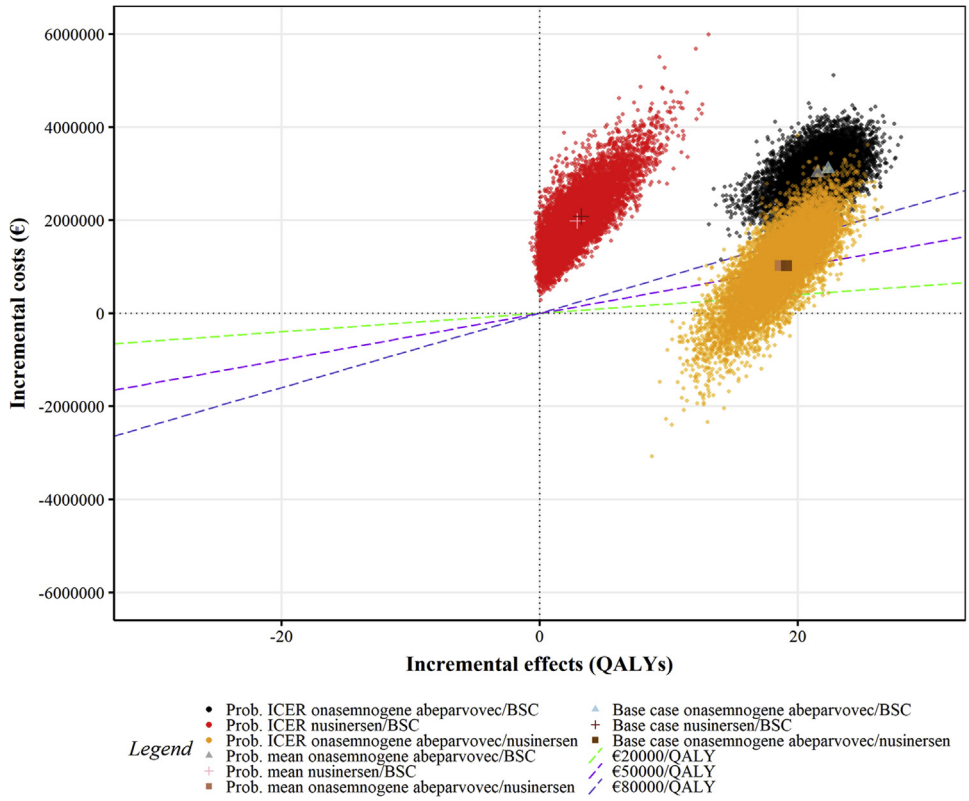
With an equal discount value of 3.5% for both costs and utilities, the ICERs are higher than with the discount values 4% for costs and 1.5% for utilities. The ICER for onasemnogene abeparvovec versus BSC is €227 690/QALY, for nusinersen versus BSC €994 192/QALY, and for onasemnogene abeparvovec versus nusinersen €863 70/QALY. A table with more detailed results is listed in Appendix 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.09.021.

Discussion

Based on this cost-effectiveness model for the treatment of patients with SMA I, onasemnogene abeparvovec has an ICER compared with BSC of €138 875/QALY. Both therapies are not cost-effective under Dutch WTP standards. Compared with nusinersen, onasemnogene abeparvovec has an ICER of €53 447/QALY. When relapses occur early after treatment, the ICER can increase up to 6-fold.

The ICER of onasemnogene abeparvovec compared with nusinersen was €53 447/QALY, similar to findings from in the United States.[7] This cost-effective ICER can be partially explained by the higher effectivity of onasemnogene abeparvovec, but also by the different cost distribution of both treatments. Where onasemnogene abeparvovec is administered once, total treatment costs of nusinersen increase as patients live longer. Not accounting for discounting, with a price of €83 300 per vial, 6.6 years of survival would be needed for nusinersen to surpass the estimated onasemnogene abeparvovec treatment cost of €2 million. This calculation does not include additional costs associated with SMA treatment.

Figure 4. Cost-effectiveness plane for the three simulated scenarios. BSC indicates best supportive care; prob, probalistic; QALY, quality-adjusted life-year.



In the ZIN report,[2] the ICER of nusinersen versus BSC is €502 289/QALY, which is lower than the ICER of €647 850/QALY reported here. The difference in ICERs can be explained by the difference in model-building approaches. The ZIN model used a different model structure with more health states. The model structure in this study was adapted from the CER Institute report, where both nusinersen and onasemnogene abeparvovec were modeled. Also, in the ZIN model, an assumption was made where the health of 8% of patients worsened over time.

In this article, nusinersen is shown to be extendedly dominated by onasemnogene abeparvovec. However, it should be noted that the prices used in this study are the publicly available list prices. Confidential price negotiations have taken place in The Netherlands for nusinersen. Negotiations are also likely for onasemnogene abeparvovec. Whether onasemnogene abeparvovec will extendedly dominate nusinersen after these price negotiations remains unknown.

At the modeled price of €2 000 000, onasemnogene abeparvovec is not cost-effective under WTP thresholds in The Netherlands. To comply with the limit of €80 000/QALY, the price should not exceed €680 000. However, for orphan drugs the €80 000/QALY threshold is not necessarily an absolute limit in The Netherlands, since other therapies with very high ICERs, such as eculizumab or lumacaftor/ivacaftor, are also reimbursed after confidential price negotiations between the Ministry of Health and the manufacturer.[35,36]

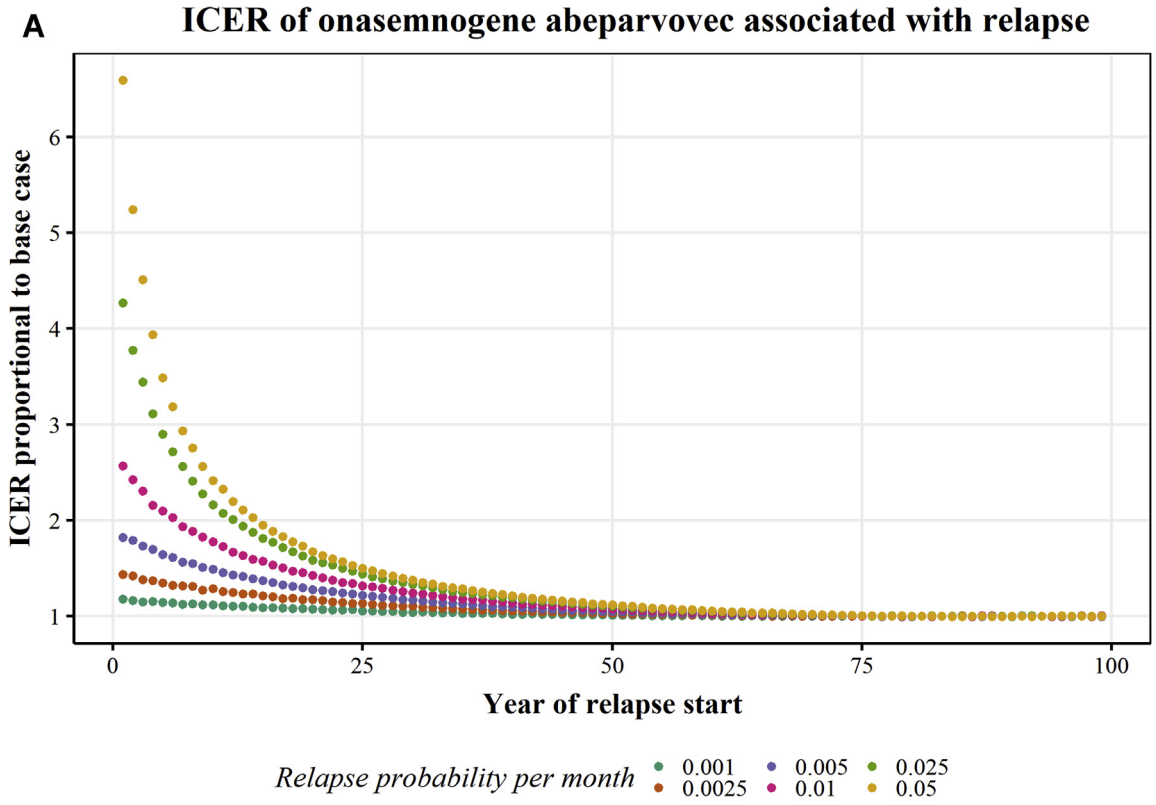
For another gene therapy, the manufacturer expected treatment effects to last up to 8 years.[17,18] Would this be the case for onasemnogene abeparvovec, the ICER could increase up to 2.76 times. Currently, the longest published follow-up is 2 years,[12] with longer studies underway.[37-39] Although the exact ICERs presented here are applicable only to the Dutch setting, the order of magnitude of the effect of relapses on the ICER are highly relevant for other countries that consider cost-effectiveness.

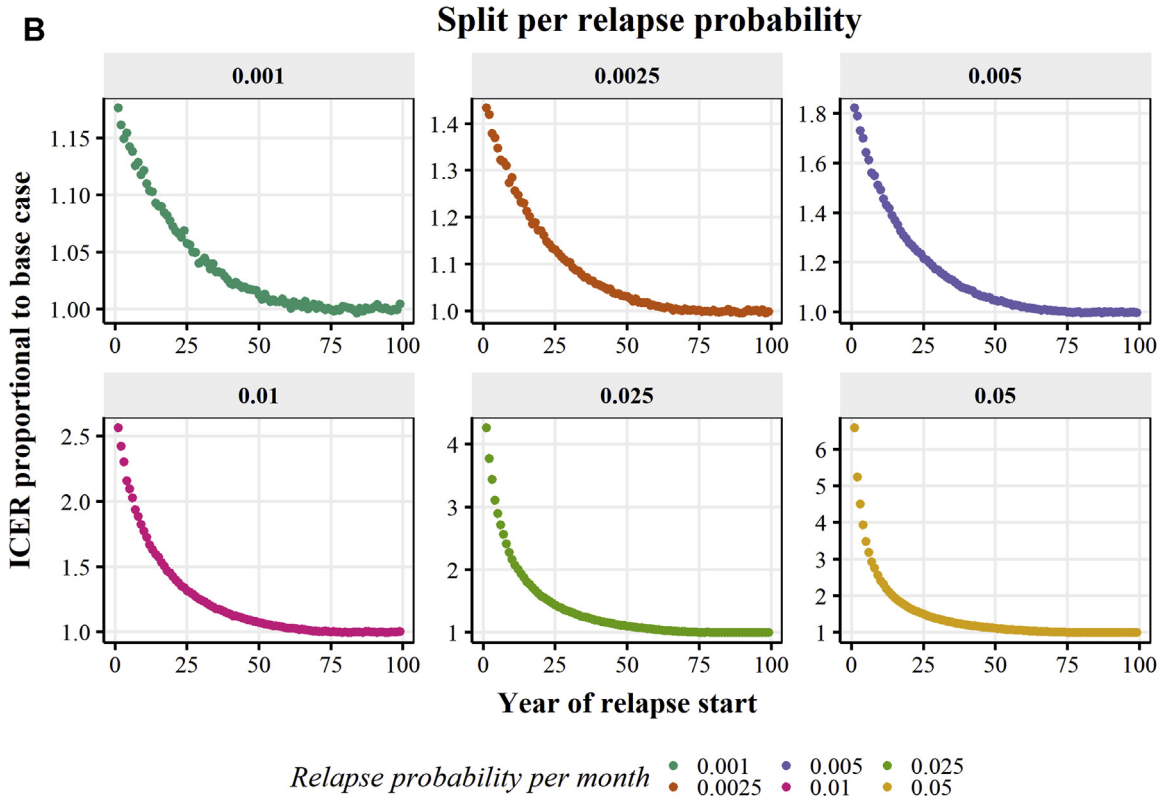
When evaluating therapies for reimbursement, the budget impact must also be considered. In The Netherlands, around 10 patients with SMA I are born per year,[2] leading to a budget impact of €20 million per year. With the cost-effective price of €680 000, the budget impact will be €6.8 million per year. In The Netherlands, cost-effectiveness analyses are not obligatory when the budget impact is smaller than 10 million euros.

Although the ICER of onasemnogene abeparvovec/nusinersen lies below the €80 000/QALY threshold, it should be noted that these 2 treatments both are not cost-effective compared to current standard of care, being BSC. Basing reimbursement on a comparison with a cost-ineffective therapy will lead to cost-ineffective care compared to BSC. Additionally, nusinersen has been subject to confidential price negotiations in The Netherlands, further complicating the comparison of onasemnogene abeparvovec with nusinersen, as a lower price for nusinersen would result in a larger ICER, possibly above the threshold.

Because no data are available on relapse of gene therapies, analyses like these are needed to gain insight in the effects of relapsing on cost-effectiveness. Although this analysis is done on treatment with onasemnogene abeparvovec, it can be assumed that the association between ICER and relapse for other one-time treatments will follow a similar pattern (but not necessarily a similar magnitude), with the effect of relapses on the ICER decreasing when relapses occur later.

Figure 5. (A) Association between year after which relapses can occur, and incremental cost-effectiveness ratios proportional to the base-case estimate of €138 875/quality-adjusted life-year. (B) Plotting the relapse probabilities on separate axes illustrates the similar pattern through which the ICER decreases as relapses occur later after treatment. ICER indicates incremental cost-effectiveness ratio.





To reimburse high-cost therapies, various strategies can be used.[40] The microsimulation presented here can be expanded to assess the ability of reimbursement mechanisms such as annuity payments[41] and pay-for-performance[42] to control healthcare spending. A pay-for-performance component in an annuity payment scheme, where payments cease or lower when the treatment effect diminishes, can help in lowering expenses and spreading budget impact.

The EMA recently published a positive opinion regarding onasemnogene abeparvovec.[9] This means that a reimbursement decision on onasemnogene abeparvovec will soon have to be made, requiring cost-effectiveness models to be developed. Although these models are built on limited information, they do provide important insights in the cost-effectiveness of a therapy and can expose caveats in current knowledge about the studied treatment.

Possibly, patients may be treated with both onasemnogene abeparvovec and nusinersen.[7] No studies have been done on this treatment combination, so it could not be included in this analysis. Since this would greatly increase treatment costs, decision makers should be mindful of this possibility.

Limitations

Information on the clinical efficacy of onasemnogene abeparvovec was limited. Only 1 phase I clinical trial was published at the time of model development,[11] conducted with 2 years of follow-up in 12 patients with historical control. Therefore, many assumptions on survival and long-term effectiveness had to be made. Owing to this uncertainty, survival in health state 2 could turn out higher than in health state 3 in the PSA without adjustment. This substantial uncertainty also leads to a small number of unlikely cases where BSC dominates nusinersen. Different levels of long-term effectiveness have been analyzed in the relapse scenario analysis. Results of ongoing phase 3 and long-term trials[36-38] may provide data for more accurate cost-effectiveness estimation. However, reimbursement decisions will soon have to be made based on the same limited information. This study provides an early insight in the potential cost-effectiveness of onasemnogene abeparvovec in different scenarios.

No direct data on a comparison of onasemnogene abeparvovec and BSC were available; hence a naïve comparison derived from BSC data of the ENDEAR trial was used. Because in these trials different patient populations were included, and treatment was administered at different times, a direct comparison cannot be made. However, it is still informative to assess the differences between onasemnogene abeparvovec and BSC for decision makers. This approach was adapted from the model used by CER Institute, where it is explained in more detail.[7,8]

In the base-case model, patients were assumed to stay in their respective health states until death. The treatment cost of onasemnogene abeparvovec is currently a placeholder price, derived from the CER Institute study,[7] since the actual price in The Netherlands is still unknown. When the price becomes available, the analysis can easily be redone by adjusting the treatment cost. Performing this analysis is important, since treatment price is the most influential variable on the ICER of onasemnogene abeparvovec versus BSC, apart from discounting of costs and effects, as seen in the deterministic sensitivity analysis.

Conclusion

Under Dutch WTP thresholds, treatment of SMA I with onasemnogene abeparvovec is not cost-effective compared to BSC. Compared to nusinersen, onasemnogene abeparvovec is cost-effective. This modeling study, based on preliminary effectiveness results, gives an early insight in the potential cost-effectiveness of onasemnogene abeparvovec in different scenarios. Decision makers should be aware of these scenarios and the potential consequences of these scenarios when making reimbursement decisions about SMA treatments. When relapses would occur within 10 years after treatment, the ICER will increase 1.5-6-fold, depending on the probability of relapse.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.09.021.

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