Cost Effectiveness of Onasemnogene Abeparvovec in Infants with Presymptomatic Spinal Muscular Atrophy in Italy

RWD129

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Introduction

- SMA is a devastating rare disease and the most common genetic cause of infant death,[1] with worldwide prevalence of 1 to 2 per 100,000 persons[2]
- Patients with SMA lack the *SMN1* gene, leading to reduced SMN protein, loss of functional motor neurons, and progressive, debilitating and often fatal muscle weakness[3,4]
- Treatments approved for patients with SMA include onasemnogene abeparvovec, a one-time intravenous infusion gene therapy targeting *SMN1*, and nusinersen and risdiplam, which are *SMN2* gene-targeting treatments that require multiple doses via intrathecal or oral administration, respectively[5]
- While treatments allow patients with SMA to achieve motor milestones and longer survival, the costs associated with treatment can contribute to other SMA-related costs and add to financial strain[6]

Objective

- We sought to assess the cost effectiveness of treatment with onasemnogene abeparvovec versus other disease-modifying therapies or BSC for infants in Italy with genetically confirmed, presymptomatic SMA

Methods

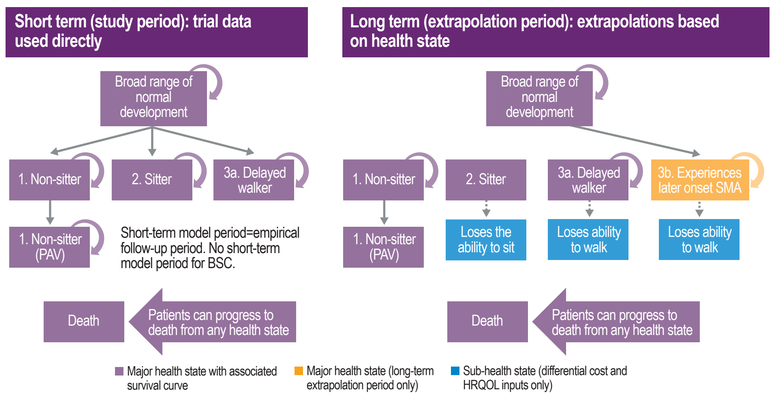
Population cohort and patient distribution

- This cost-utility analysis included a hypothetical cohort of 1,000 infants with genetically confirmed, presymptomatic SMA who were ≤6 weeks (≤42 days) of age at the time of treatment[7,8]
- Patients were stratified as two-copy and three-copy *SMN2* gene cohorts (66.7% and 33.3% of patients, respectively)[9-11] and observed from treatment initiation until death

Model structure and assumptions

- A Markov model based on the Italian National Health Service perspective and a lifetime time horizon was developed to assess the cost effectiveness of onasemnogene abeparvovec compared with nusinersen, risdiplam, or BSC (e.g., routine vaccinations, nutritional support, airway clearance, respiratory support, physiotherapy, postural support)[12-15] (**Figure 1**)
  - All characteristics, assumptions, and justifications used to develop the model can be found in **Table 1**
  - Health state transitions were assessed for eight main health states aside from BRND and death: non-sitter (no PAV), non-sitter (PAV), sitter, sitter (loses ability to sit), delayed walker, delayed walker (loses ability to walk), experiences later onset SMA, and experiences later onset SMA (loses ability to walk) (**Table 2**). Each of the health states was assigned a specific utility score derived from the literature.[16–18]

Figure 1. Model structure



BSC, best supportive care; HRQOL, health-related quality of life; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

Table 1. Key assumptions used in the model

Assumption	Rationale				
	Highest milestone	Similar to:	Survival	HRQOL	Monthly medical costs
Infant milestone achievement is a proxy for SMA severity and prognosis	Walking	SMA type 3	Full lifespan	Full (general population)	Minimal
	Sitting	SMA type 2	Into adulthood	Moderate	Moderate
	Not sitting	SMA type 1	Death in early childhood	Low	High
Disease-modifying treatment permanently halts disease progression without regression					
The model follows patients for a full lifespan (lifetime time horizon)					
Without disease-modifying treatments	• SMA severity is driven by *SMN2* copy number: the model analyzes two- and three-copy patients separately[19,20] • Patients with SMA types 2 or 3 may lose motor milestones over time • Patients may progress more quickly to symptomatic SMA and develop a more severe form of SMA without treatment				
Survival estimates	• Moving into a different health state results in improved survival • Patients are expected to experience significant survival gains due to improved respiratory and nutritional function and independence from support • In the absence of lifetime follow-up data, the model uses survival data for patients with SMA who can sit and walk to predict survival for treated patients in sitting and walking health states • Survival in each health state is based on observed and extrapolated survival curves from clinical trials and natural history studies using published methods[21]				

HRQOL, health-related quality of life; SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene.

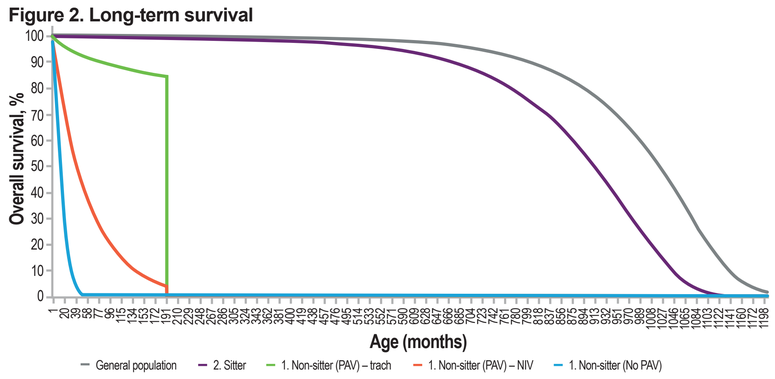
Table 2. Health states based on highest achieved motor milestones representing possible disease trajectory

Health state	Criteria
BRND	Infants must meet all the following criteria during the clinical trial period: meet WHO motor milestones at the 99th percentile (sitting by 9 months of age, walking by 18 months age; threshold can be amended by user input), no PAV, no gastrostomy
1. Non-sitter (no PAV)	Individual does not sit independently
1. Non-sitter (PAV)	Individual does not sit independently and requires PAV (tracheostomy or 16 hours/day noninvasive ventilation)
2. Sitter	Individual sits independently but does not walk independently during clinical trial period
2. Sitter (loses ability to sit)	Individual sits independently but does not walk independently during clinical trial period and is likely to lose the ability to sit independently (user-input proportion)
3a. Delayed walker	Individual sits and walks independently but is outside the WHO 99th percentile for normal motor development (or, for untreated patients, was diagnosed with SMA type 3a) (i.e., motor symptoms presenting as delayed milestones between 18 and 36 months of age)
3a. Delayed walker (loses ability to walk)	Individual sits and walks independently but is outside WHO 99th percentile for normal motor development (or, for untreated patients, was diagnosed with SMA type 3a) and is likely to lose the ability to walk independently (user-input proportion)
3b. Experiences later onset SMA	Individual meets criteria for BRND during the clinical trial period but is expected to experience SMA symptom onset in the future extrapolation period (user-input proportion)
3b. Experiences later onset SMA (loses ability to walk)	Individual meets criteria for BRND during the clinical trial period but is predicted to experience SMA symptom onset in the future extrapolation period (user-input proportion) and is likely to lose the ability to walk independently

BRND, broad range of normal development; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; WHO, World Health Organization.

  - The survival curves used in the base-case analysis for long-term extrapolation are presented in **Figure 2**, with overall average survival estimates of 46 months (non-sitter [no PAV]), 196 months (both for non-sitter [PAV] and non-sitter [PAV/tracheostomy]), and 1,156 months (sitter)
  - Model outcomes included total lifetime costs per patient, LYs, and QALYs accumulated during the simulation, the results of which are presented as ICERs
  - The model was developed and contextually adapted using Microsoft Excel® per Microsoft 365 (Version 2210, Build 16.0.15726.20188)

Figure 2. Long-term survival



Data were based on literature: general population[17]; sitter (type 2a and type 2b pooled)[22]; non-sitter (no PAV)[23]; non-sitter (PAV) and non-sitter (PAV and tracheostomy).[24]
NIV, noninvasive ventilation; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; trach, tracheostomy.

Clinical inputs

- Treatment effects were estimated using data from SPR1NT (onasemnogene abeparvovec; NCT03505099),[7,8] NURTURE (nusinersen; NCT02386553),[25] and RAINBOWFISH (risdiplam; NCT03779334),[26] with each health state assigned a health utility score derived from the US Institute for Clinical and Economic Review assessment, the UK Evidence Review Group, and the literature, and ranging from 0.0 (non-sitter [PAV]) to 0.95 (delayed walker, later onset SMA, BRND)[16,18]

Resource use and costs

- Costs were extrapolated from Italian national tariffs, with a willingness-to-pay threshold of approximately €80,000/QALY[27] and a discount rate of 3%
- Treatment costs were based on pricing standards of the Italian Medicines Agency (AIFA) and national or regional tariffs (**Table 3**)
- SMA care–related costs were based on the literature and expert opinion: €641/month (delayed walker, later onset SMA, BRND); €1,723/month (sitter, later onset SMA [loses ability to walk]); €4,470/month (sitter [loses ability to sit] and non-sitter [no PAV]); €6,385/month (non-sitter [PAV])[28]

Table 3. Treatment costs for patients with SMA type 1

Treatment arm	Drug	Value
Onasemnogene abeparvovec	Onasemnogene abeparvovec treatment cost (per dose): single dose, Day 1	€1,945,000[29a]
	Onasemnogene abeparvovec administration cost	
	Inpatient: single-dose intravenous infusion	€2,850[30]
Nusinersen	Nusinersen treatment cost (per dose): loading dose on Days 1, 15, 29, 59, then maintenance dose once every 4 months	€63,175[29a]
	Nusinersen administration costs (by age)	
	Up to 5 years of age	
	Inpatient	€2,850[30]
	Outpatient	€219[31]
	6–18 years of age	
	Inpatient	€2,850[30]
	Outpatient	€219[31]
	19 years of age and older	
	Inpatient	€2,850[30]
	Outpatient	€219[31]
Risdiplam	Treatment cost (per-pack price) used to calculate monthly weight-based dose	€7,477[29a]

SMA, spinal muscular atrophy.
[a]Ex-factory price.

Sensitivity analyses

- The deterministic sensitivity analysis (DSA) was conducted to evaluate the variation of a single parameter on the ICER achieved in the base-case analysis
- The probabilistic sensitivity analysis (PSA) was conducted through a Monte Carlo simulation, and results are presented across a cost-effectiveness plane

Results

- The DSA results indicated that in most scenarios, onasemnogene abeparvovec was dominant (less costly, more effective) when compared with nusinersen or risdiplam and cost-effective (more costly, more effective) when compared with BSC (exceptions described in **Table 4**)
- For example, in the full cohort scenario, onasemnogene abeparvovec was dominant when compared with nusinersen or risdiplam (ICERs, –€8,899,270 and –€882,772, respectively) and cost-effective when compared with BSC (€90,539 per QALY gained)

Table 4. Model results: lifetime time horizon

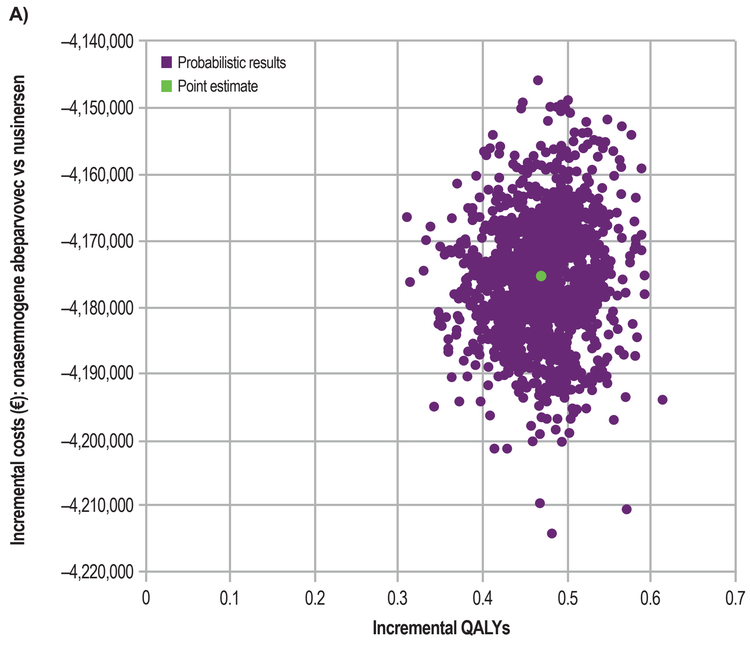
Full cohort: two or three *SMN2* copies					
Characteristic	**Incremental costs**	**Incremental LYs**	**Incremental QALYs**	**ICER – payer perspective**	**Conclusion**
Full cohort					
Onasemnogene abeparvovec vs. nusinersen	–€4,175,460	0.04	0.469	–€8,899,270	Dominant
Onasemnogene abeparvovec vs. risdiplam	–€4,601,976	0.47	5.213	–€882,772	Dominant
Onasemnogene abeparvovec vs. BSC	€1,838,666	16.48	20.308	€90,539	Cost effective
Patients with two *SMN2* copies					
Onasemnogene abeparvovec vs. nusinersen	–€4,174,487	0.05633	0.707	–€5,905,754	Dominant
Onasemnogene abeparvovec vs. risdiplam	–€4,627,376	0.70	7.818	–€591,885	Dominant
Onasemnogene abeparvovec vs. BSC	€1,996,386	23.35	24.554	€81,307	Cost effective
Patients with three *SMN2* copies					
Onasemnogene abeparvovec vs. nusinersen	–€4,177,407	–0.00654	–0.0062	€673,883,386	Less costly but less effective
Onasemnogene abeparvovec vs. risdiplam	–€4,551,169	0.00	0.0024	–€1,863,578,556	Dominant
Onasemnogene abeparvovec vs. BSC	€1,523,189	2.74	11.815	€128,919	Exceeds WTP

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene; WTP, willingness-to-pay.

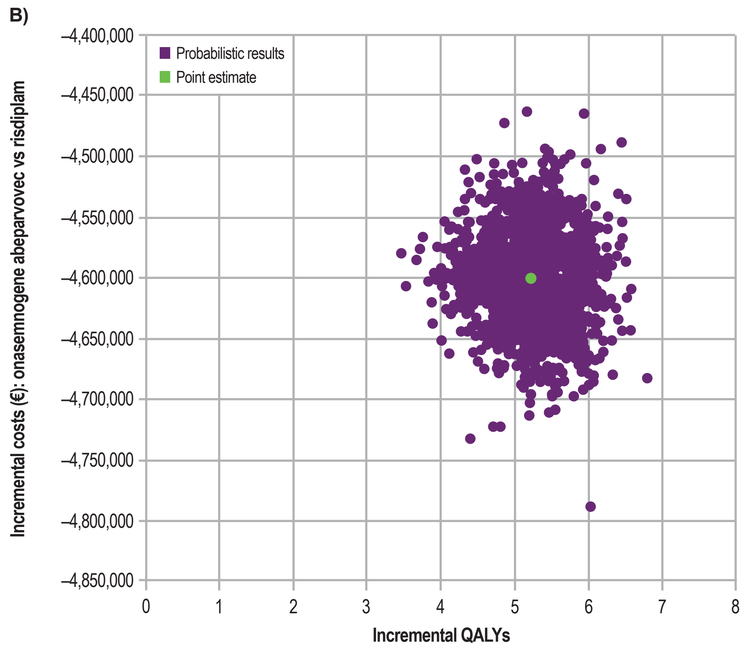
  - Results of the PSA are presented on cost-effectiveness planes (**Figure 3A**, **B**, and **C**). In line with the deterministic results, onasemnogene abeparvovec therapy is dominant over both nusinersen and risdiplam therapy, and cost effective when compared with BSC.

Figure 3. Probabilistic sensitivity analysis in the full cohort for onasemnogene abeparvovec versus nusinersen (A), risdiplam (B), and BSC (C)

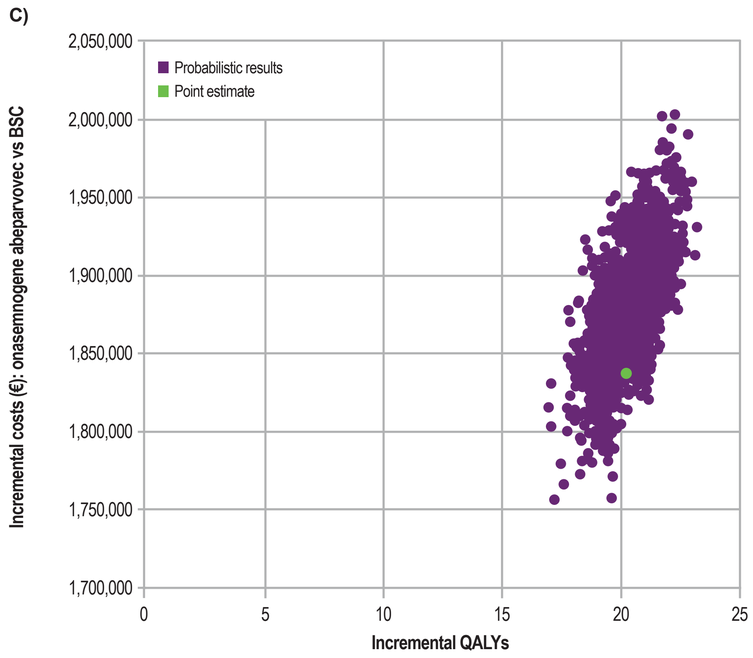
A)



B)



C)



BSC, best supportive care; QALY, quality-adjusted life-year.

Limitations

- This model did not account for discontinuations or switching or combining of treatments
- Study periods, including open label extension and follow-up periods, differed between studies.

Conclusions

- Onasemnogene abeparvovec was dominant (less costly and more effective) compared with other treatment options and cost-effective when compared with BSC
- Onasemnogene abeparvovec is a cost-effective treatment option for infants with genetically confirmed, presymptomatic SMA

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Abbreviations

BRND, broad range of normal development; BSC, best supportive care; DSA, deterministic sensitivity analysis; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio; LY, life-year; PAV, permanent assisted ventilation; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; SMN, survival motor neuron; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene; WHO, World Health Organization; WTP, willingness-to-pay.

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