Cost-Effectiveness of Onasemnogene Abeparvovec for Spinal Muscular Atrophy Type 1 (SMA1) Against Nusinersen in Japan

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BACKGROUND

- SMA is a rare autosomal recessive disorder characterized by degeneration of lower motor neurons in the spinal cord and brainstem, leading to weakness and muscle atrophy, loss of independent breathing and swallowing, and early death.[1] SMA is most commonly caused by a deletion or mutation in *SMN1*, which leads to insufficient levels of SMN protein
- Patients with the most severe form of SMA, type 1 (SMA1), will typically be diagnosed before 6 months of age when they fail to reach gross motor milestones such as rolling or ability to sit without assistance[2]
- On Shinoku Island, Japan, the estimated incidence of SMA is 2.7 per 100,000 live births.[3] Treatment was limited to symptom management and supportive care until 2017, when the Japan MHLW approved nusinersen (Spinraza®), a modified ASO with 4 loading doses and a once-every-4 months maintenance dose thereafter. Nusinersen increases production of SMN protein via a complementary gene *(SMN2)*[4]
- A new therapy, onasemnogene abeparvovec (Zolgensma®, formerly AVXS-101), an AAV9-based gene-replacement therapy containing a copy of the human *SMN* transgene, crosses the blood-brain barrier to treat the root cause of SMA. Onasemnogene abeparvovec was approved in the USA and Japan for children <2 years of age in 2019 and 2020, respectively.[5] Onasemnogene abeparvovec is designed for immediate, sustained SMN protein expression, allowing for rapid onset and durable therapeutic effect with a one-time dose[6]
- In a phase 1 study (NCT02122952), treatment with proposed therapeutic dose of onasemnogene abeparvovec improved survival, motor function, and motor milestone achievement in patients with SMA1[6]
  - All 12 patients in the proposed therapeutic dose cohort reached 24 months of age alive without need for permanent ventilation
  - Eleven of 12 patients treated with the proposed therapeutic dose achieved motor milestones rarely or never achieved in the untreated SMA1 population

OBJECTIVE

This study evaluated the cost-effectiveness of onasemnogene abeparvovec against nusinersen for SMA1 patients aged <2 years in Japan

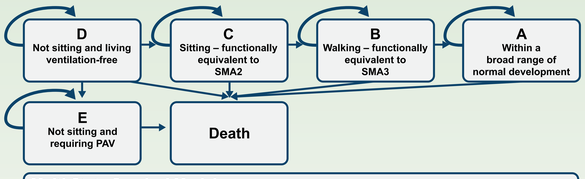
METHODS

Model Overview

- We adapted a previously published cost-effectiveness model for onasemnogene abeparvovec[7] versus nusinersen for SMA1 over a lifetime from the US setting to the Japan setting, from a healthcare payer perspective
- The early period of the model uses motor milestone data directly from published clinical studies (onasemnogene abeparvovec: AVXS-101-CL-101 [NCT02122952][6], and nusinersen: ENDEAR [NCT02193074][8]; SHINE [NCT02594124][9])

Model Health States

Figure 1. Multi-State Survival Model of SMA1



Multi-State Survival Model

- Patients who achieved sitting were assumed to have survival, costs, and QOL that aligned with SMA2 patients who sit but never walk[10]
- Patients who achieved walking were assumed to have survival, costs, and QOL that aligned with SMA3 patients with a normal life expectancy[10,11]
- Survival for patients who did not achieve motor milestones was derived from the clinical trials and extrapolated beyond the trial period using the NeuroNext natural history trial [NCT01736553][12]

Proportion of Patients Entering Sitting and Walking Health States

Table 1. Motor Milestone Data Used for Model Health State Transitions

	Time Point (number of patients still alive)	% Achieving Independent Sitting (but not walking)	% Achieving Walking
Nusinersen ENDEAR [NCT02193074][8] and SHINE [NCT02594124][9]	Baseline (N=81)	0	0
	Day 64 (N=70)	1	0
	Day 183 (N=65)	5	0
	Day 302 (N=51)	10	0
	Day 394 (N=48)	15	0
	Day 578 (N=31)	29	0
	Day 689 (N=17)	24	0
Onasemnogene abeparvovec AVXS-101-CL-101 [NCT02122952][6]	Age 0-6 mo (N=12)	0	0
	Age 6-12 mo (N=12)	0	0
	Age 12-18 mo (N=12)	17	0
	Age 18-24 mo (N=12)	50	0
	Age 24-30 mo (N=12)	58	17
	Age 30-36 mo (N=12)	75	17

Survival Inputs

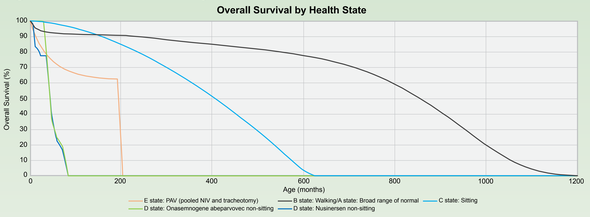
- Mortality and probability of permanent ventilation for the first phase of the model (aligning with the clinical trial follow-up periods) for patients remaining in the D state (not sitting) is based on observed OS and event-free survival. For patients who transition to other health states, and for D state survival beyond the observed trial period, survival is extrapolated using parametric curves fitted to survival curves using published methods[13]

Survival by Health State

Table 2. Summary of Survival Sources

Transition	Onasemnogene abeparvovec	Nusinersen
D to death D to E	Short-term model: AVXS-101-CL-101 [NCT02122952][6]	Short-term model: ENDEAR [NCT02193074][8] and SHINE [NCT02594124][9]
D to C C to B	Long-term: Projected OS using NEURONEXT [NCT01736553][11] Gross motor milestones achieved during short term are assumed to be sustained until death	Long-term: Projected OS using NEURONEXT [NCT01736553][11] Gross motor milestones achieved during short term are assumed to be sustained until death
E to death	Based on a retrospective chart review of tracheotomy and noninvasive ventilation[14], projected using parametric estimation	
C to death	Parametric curve fitted to SMA2 longitudinal survival study[10]	
B to death A to death	Japan mortality tables[11]	

Figure 2. Survival Estimates by Health State



Cost Inputs

- Onasemnogene abeparvovec placeholder price was JPY232.0M, which was the US price converted into Japanese currency (USD1=JPY109). For nusinersen, we used a list price of JPY9,320,424. In Japan there are no stopping rules for nusinersen, so we modeled all patients in that arm continuing to receive treatment. For SMA-related care costs, we conducted a study of Japan-specific HCRU and applied this to reference costs from Japan. The cost of outpatient treatment for SMA was based on claims database analysis and supplemented by interviews with 2 SMA clinical experts to categorize data by health state and distinguish between related and unrelated SMA medical costs. We used a 2% discount rate for costs and outcomes per guidelines for the economic evaluation of drugs in Japan[15]

Table 3. SMA-Related Cost Inputs Used in Model (JPY)

SMA-Related Medical Costs (annual)	E: Permanent Assisted Ventilation	D: Not Sitting and Living Ventilation-Free	C: Sitting Independently	B: Walking Independently	A: Within a Broad Range of Normal
Drugs	847,653	715,476	9,321	8,057	0
Medical tests	34,023	34,023	17,038	7,828	0
Medical visits (including emergency room)	1,286,044	1,287,412	270,276	42,240	0
Hospitalizations	6,586,498	4,559,883	952,472	139,042	0
Equipment	216,000	216,000	0	0	0
Ventilator-related costs	1,819,200	1,819,200	0	0	0

Table 4. Treatment-Related Cost Inputs Used in Model

Treatment-Related Costs	Value (JPY)	Source
Onasemnogene abeparvovec		
Onasemnogene abeparvovec, IV infusion, 2.0×10[14] vg/kg	Placeholder price of 232M	Placeholder
IV infusion (up to 1 hour)	770	G001 IV injection and infant addition
Anti-AAV9 diagnostic test	790	Not available in Japan, and assumed similar testing; D012-11 virus antibody test
Prednisolone 1mg/kg/day, 30 days	166	Calculated with body weight 7 kg
Liver function test	560	D007 Blood chemistry test (Total bilirubin, ALP, AST, ALT)
Cardiac troponin	1,170	D007 Blood chemistry test (Myocardial troponin I)
Nusinersen		
Nusinersen, injection for intrathecal use, 12mg (5mL) per administration	9,320,424	Determined with reference to the "Method of Spinraza Administration – Intrathecal administration by lumbar puncture (Sep 2017)"[16] and "Guidelines for the use of anesthetics ver.3 Pediatric Anesthetics (Mar.2016)"[17]
Inpatient intrathecal injection	68,060 (≤5 yrs) 57,870 (≥6 yrs)	
Anesthesia	1,611 (≤5 yrs) 1,161 (≥6 yrs)	
Imaging (ultrasound or fluoroscopy)	22,070 (≤5 yrs) 18,020 (≥6 yrs)	

QOL Inputs

- For health-related QOL for non-sitting, sitting, and permanent ventilation health states, we used values from ICER US for SMA1[18]

Table 5. Utility Scores Used in Model

Health State	Utility scores	Source
E (PAV)	0.19	ICER SMA1 review US[18]
D (aligns with SMA1)	0.19	
C (aligns with SMA2)	0.60	
B (aligns with SMA3)	Japan EQ-5D population norms	Shiroiwa 2016[19]
A (within a broad spectrum of normal development)		

RESULTS

- Patients in the onasemnogene abeparvovec arm survived for an average 22.63 discounted life-years, resulting in 14.51 discounted QALYs, against 8.22 discounted life-years and 2.55 QALYs for nusinersen
- Assuming a placeholder price of JPY232M, the estimated average total drug and medical cost over a lifetime for onasemnogene abeparvovec patients was JPY266.4M versus JPY331.5M for nusinersen
- As the lifetime cost of onasemnogene abeparvovec is lower than nusinersen and the benefits are higher, onasemnogene abeparvovec dominates nusinersen

Table 6. Model Results

Lifetime Average per Patient	Onasemnogene Abeparvovec	Nusinersen	Difference
Life-years (undiscounted)	34.52	10.06	24.47
Life-years (discounted*)	22.63	8.22	14.41
QALYs (undiscounted)	23.28	3.34	19.95
QALYs (discounted*)	14.51	2.55	11.96
Costs (undiscounted), JPY	280.2M	393.2M	(−113.0M)
Costs (discounted*), JPY	266.4M	331.5M	(−65.1M)
Cost/life-year gained	Onasemnogene abeparvovec vs nusinersen: dominant		
Cost/QALY gained	Onasemnogene abeparvovec vs nusinersen: dominant		

*2% discount rate applied

Figure 3. Tornado Diagram: Parameters With Greatest Impact on Costs (impact of ≥1%)

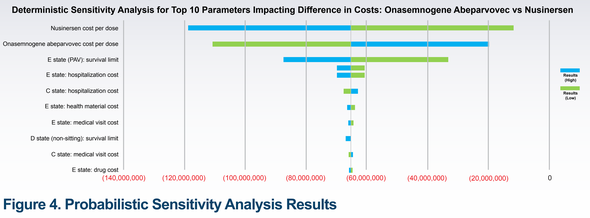
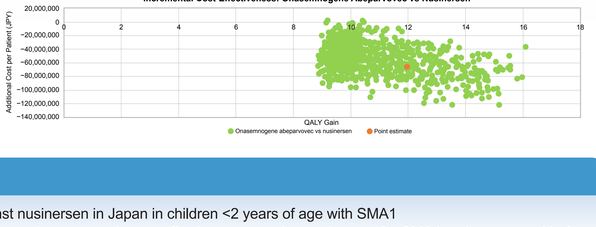


Figure 4. Probabilistic Sensitivity Analysis Results



CONCLUSIONS

- Based on these analyses, onasemnogene abeparvovec is cost-effective and dominant against nusinersen in Japan in children <2 years of age with SMA1
- This finding is similar to a US-based model, where at a list price of USD2.125M, onasemnogene abeparvovec is cost-effective compared to nusinersen for SMA1 patients treated before 2 years age

ABBREVIATIONS: AAV9, adeno-associated virus serotype 9; ASO, antisense oligonucleotide; EQ-5D, EuroQol five-dimension scale; HCRU, healthcare resource use; ICER, Institute for Clinical and Economic Review; IV, intravenous; MHLW, Minister for Health, Labour and Welfare; OS, overall survival; PAV, permanent assisted ventilation; QALY, quality-adjusted life-year; QOL, quality of life; SMA, spinal muscular atrophy; SMA1, SMA type 1; SMA2, SMA type 2; SMA3, SMA type 3; SMN survival motor neuron protein; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene; US, United States.

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