COST-EFFECTIVENESS OF ORPHAN MEDICINES FOR THE MANAGEMENT OF SPINAL MUSCULAR ATROPHY: THINKING OUTSIDE THE BOX

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INTRODUCTION

- Most of the medicines for rare diseases, due to their high costs, pose incremental cost-effectiveness ratio (ICER) values far beyond the conventional cost-effectiveness threshold for reimbursement. The hypothesis is that we have to think outside the box when it comes to cost-effectiveness of orphan medicines in general and for the management of spinal muscular atrophy (SMA) as an specific example.

OBSERVATONS AND CONCLUSIONS

- According to our previous research within the field, observations we identified through our systematic review (https://doi.org/10.1111/bcp.16267) of economic evaluations of orphan medicines for SMA (which included eight CEAs and six CUAs),as well as raising concerns about the accessibility of orphan medicines in general, there is a high need for pharmacoeconomic analyses also in cases when the cost of treatment is very high and the ICER values exceed the usual, acceptable values for standard therapy. Specific willingness to pay thresholds for orphan medicines are of the utmost importance, to allow patients with SMA to have access to safe and effective treatments. The present topic is important since with such economic evaluations, we get the possibility to compare the value of medications in the same indication; however, we should emphasize that in the interpretation of data and in making decisions about the use of medicines, the impact of new knowledge should be considered.
- Last but not least, in the process of decision-making regarding orphan medicines for SMA, pharmacoeconomics is just one domain of health technology assessment evaluation. For orphan medicines other domains are also notably important; thus, policy makers should not only take the pharmacoeconomic aspect into consideration, but the safety, efficacy, social and ethical aspects, and quality of life as well.

Table 1: Basic characteristics of studies included in systematic review

First author	Year of publication	Country	Perspective	Study type	Time horizon	Model type	Industry funding	Population	Intervention/comparator
Broekhoff	2021	Netherlands	• Societal perspective	CEA	Lifetime horizon of 100 years	Individual-based state transition model	No	• SMA 1	• onasemnogene abeparvovec-xioi *vs.* BSC • nusinersen *vs.* BSC • onasemnogene abeparvovec-xioi *vs.* nusinersen
CADTH	2019	Canada	• Publicly funded health care payer perspective	CUA	• SMA 1: 25 years • SMA 2: 50 years • SMA 3: 80 years	Three Markov models: • for SMA 1 • for SMA 2 • for SMA 3	No	• SMA 1 • SMA 2 • SMA 3	• nusinersen *vs.* real-world care in SMA 1 • nusinersen *vs.* real-world care in SMA 2 • nusinersen *vs.* real-world care in SMA 3
CADTH	2021	Canada	• Publicly funded health care payer perspective	CUA	Lifetime horizon of 80 years	Markov model	No	• SMA 1	• onasemnogene abeparvovec-xioi *vs.* BSC • onasemnogene abeparvovec-xioi *vs.* nusinersen
CADTH	2021	Canada	• Publicly funded health care payer perspective	CUA	• SMA 1: 25 years • SMA 2 or 3: 80 years	Two Markov models: • for SMA 1 • for SMA 2 or 3	No	• SMA 1 • SMA 2 • SMA 3	SMA Type 1: • risdiplam *vs.* BSC • risdiplam *vs.* nusinersen SMA Type 2 or 3: • risdiplam *vs.* BSC • risdiplam *vs.* nusinersen
Dean	2021	USA	• Commercial payer perspective • Modified societal perspective	CUA	Lifetime horizon[a]	Updated model based on Studies [28] and [30]	Yes, Novartis Gene Therapies	• SMA 1	• onasemnogene abeparvovec-xioi *vs.* BSC • onasemnogene abeparvovec-xioi *vs.* nusinersen
ICER	2019	USA	• Health care sector perspective • Modified societal perspective	CEA	Lifetime horizon	Three de novo models: • for symptomatic patients with infantile-onset SMA • for symptomatic patients with later-onset SMA • for presymptomatic SMA patients	No	• SMA 1 • SMA 2 • SMA 3	• nusinersen *vs.* BSC in presymptomatic SMA • hypothetical drug X for presymptomatic SMA *vs.* BSC • nusinersen *vs.* BSC in infantile-onset (Type 1) SMA • onasemnogene abeparvovec-xioi *vs.* BSC in infantile-onset (Type 1) SMA • onasemnogene abeparvovec-xioi *vs.* nusinersen in infantile-onset SMA 1) • nusinersen *vs.* BSC in later-onset SMA
Jalali	2020	USA	• Societal perspective	CEA	30 months	Four Markov models	No	• SMA 1	• nusinersen with no NBS *vs.* no NBS with no treatment • nusinersen with NBS *vs.* no NBS with nusinersen • nusinersen with NBS *vs.* no NBS and no treatment
Malone	2019	USA	• Commercial insurer perspective[b]	CUA[c]	Lifetime horizon	Markov model	Yes, AveXis, a Novartis company	• SMA 1	• onasemnogene abeparvovec-xioi *vs.* nusinersen
NCPE	2017	Ireland	• Health Service Executive's (HSE) perspective • The model incorporates an option to include a wider societal perspective as a secondary analysis	CEA	Lifetime horizon	Two Markov models: • for infantile-onset SMA • for later-onset SMA	No	• Infantile-onset SMA • Later-onset SMA	• nusinersen *vs.* SOC for infantile-onset SMA • nusinersen *vs.* SOC for later-onset SMA
Shih	2021	Australia	• Societal perspective	CEA	• 5 years • 60 years	Markov models for each treatment option	No	• Infantile-onset SMA • Later-onset SMA	• early nusinersen treatment *vs.* gene therapy • early nusinersen treatment *vs.* late nusinersen treatment • early nusinersen treatment *vs.* supportive care • gene therapy *vs.* late nusinersen treatment • gene therapy *vs.* supportive care • late nusinersen treatment *vs.* supportive care • NBS and nusinersen treatment *vs.* NBS and gene therapy • NBS and nusinersen treatment *vs.* no NBS and nusinersen treatment • NBS and nusinersen treatment *vs.* no NBS and supportive care • NBS and gene therapy *vs.* no NBS and nusinersen treatment • NBS and gene therapy *vs.* no NBS and supportive care • no NBS and nusinersen treatment *vs.* supportive care
Tappenden	2018	UK	• NHS (National Health Service) perspective • PSS (Personal Social Services) perspective	CUA	• Early-onset: 60 years • Later-onset: 80 years	Two de novo models • For early-onset SMA • Later-onset SMA	No	• Early-onset (Type I) SMA • Later-onset (Type II/III) SMA	Early-onset SMA • nusinersen *vs.* usual care Later-onset SMA • nusinersen *vs.* usual care
Thokala	2020	USA	• Health care sector perspective • Modified societal perspective	CEA	• Lifetime horizon • 10 years (for societal perspective)	One de novo model	No	SMA 1	• nusinersen *vs.* BSC
Wang	2022	Australia	Healthcare system perspective	CEA	Lifetime horizon of 100 years	One Markov model	No	SMA 1	• nusinersen *vs.* SOC • onasemnogene abeparvovec-xioi *vs.* SOC • onasemnogene abeparvovec-xioi *vs.* nusinersen
Zuluaga-Sanchez	2019	Sweden	• Societal perspective • Payer perspective (in sensitivity analysis)	CEA	• Infantile-onset: 40 years • Later-onset: 80 years	Two de novo Markov cohort health transition models: • one for infantile-onset SMA • one for later-onset SMA	Yes, Biogen	• Infantile-onset SMA • Later-onset SMA	Infantile-onset SMA: • nusinersen plus SoC *vs.* SoC alone • nusinersen *vs.* SoC Later-onset SMA • nusinersen plus SoC *vs.* SoC alone • nusinersen *vs.* SoC

Table 2: Economic outcomes of studies included in systematic review

Broekhoff, 2021	• **onasemnogene abeparvovec-xioi *vs.* BSC:** Incremental costs €3 102 749, incremental QALYs of 22.342, resulting in an ICER of €138 875 per QALY gained • **nusinersen *vs.* BSC:** Incremental costs €2 080 249, incremental QALYs of 3.211, resulting in an ICER of €647 850 per QALY gained, thus being extendedly dominated by onasemnogene abeparvovec-xioi• **onasemnogene abeparvovec-xioi *vs.* nusinersen:** Incremental costs of €1 022 499 and incremental QALYs of 19.131, resulting in an ICER of €53 477 per QALY gained
CADTH, 2019	• **nusinersen *vs.* real-world care in SMA Type 1:** An ICER of CAD$9161397 per QALY • **nusinersen *vs.* real-world care in SMA Type 2:** An ICER of CAD$24387422 per QALY • **nusinersen *vs.* real-world care in SMA Type 3:** An ICER of CAD$7429834 per QALY
CADTH, 2021	• **onasemnogene abeparvovec-xioi *vs.* BSC:** An ICER of CAD$334090 per QALY • **onasemnogene abeparvovec-xioi *vs.* nusinersen:** Onasemnogene abeparvovec-xioi appeared to dominate nusinersen
CADTH, 2021	**SMA Type 1:** • **risdiplam *vs.* BSC:** An ICER of CAD$1203108 per QALY • **risdiplam *vs.* nusinersen:** Risdiplam was dominant **SMA Type 2 or 3:** • **risdiplam *vs.* BSC:** An ICER of CAD$37378163 per QALY • **risdiplam *vs.* nusinersen:** Risdiplam was dominant
Dean, 2021	**Commercial Payer Perspective:** • **onasemnogene abeparvovec-xioi *vs.* BSC:** Incremental cost per QALY gained was USD$161648 • **onasemnogene abeparvovec-xioi *vs.* nusinersen (scenario analysis):** Incremental cost per QALY gained will be USD $-64 121; therefore, onasemnogene abeparvovec-xioi will be dominant **Modified Societal Perspective:** • **onasemnogene abeparvovec-xioi *vs.* nusinersen:** Cost per QALY gained will be $-53 815; therefore, onasemnogene abeparvovec-xioi will be dominant
ICER, 2019	**Health Care Sector Perspective:** • **nusinersen vs BSC in pre-symptomatic SMA:** An ICER of $709 000 per QALY gained and cost per LY gained was $652 000. (No published data on onasemnogene abeparvovec-xioi's effectiveness in this population exists.) • **hypothetical drug X for pre-symptomatic SMA *vs.* BSC:** An ICER $157 000 per QALY gained and cost per LY gained was $144 000 • **nusinersen *vs.* BSC in infantile-onset (Type 1 SMA):** An ICER of $1 112 000 per QALY and cost per LY gained was $590 000 • **onasemnogene abeparvovec-xioi vs BSC in infantile-onset (Type 1) SMA:** An ICER of $243 000 per QALY gained and cost per LY gained was $182 000 • **onasemnogene abeparvovec-xioi *vs.* nusinersen in infantile-onset (Type 1) SMA:** An ICER of $139 000 per QALY gained and cost per LY gained of $117 000 • **nusinersen *vs.* BSC in later-onset SMA:** An ICER of $8 156 000 per QALY gained and an incremental cost per LY gained was dominated **Modified Societal Perspective:** • **nusinersen *vs.* BSC in pre-symptomatic SMA:** An ICER of $687 000 per QALY gained and cost per LY gained was $632 000 • **hypothetical drug X for pre-symptomatic SMA *vs.* BSC**: An ICER of $161 000 per QALY and an incremental cost per LY gained of $145 000• **nusinersen *vs.* BSC in infantile-onset (Type 1 SMA):** An ICER of $1 124 000 per QALY gained and an incremental cost per LY gained of $596 000 • **onasemnogene abeparvovec-xioi *vs.* BSC in infantile-onset (Type 1 SMA):** An ICER of $238 000 per QALY gained and an incremental cost per LY gained of $178 000 • **onasemnogene abeparvovec-xioi *vs.* nusinersen in infantile-onset (Type 1) SMA**: An ICER of $129 000 per QALY gained and an incremental cost per LY gained of $109 000 • **nusinersen *vs.* BSC in later-onset SMA:** An ICER of $8 156 000 per QALY gained and an incremental cost per LY gained was dominated
Jalali, 2020	• **nusinersen with no NBS *vs.* no NBS with no treatment:** An ICER was $508 481 per event-free LY saved and $522 118 per event-free QALY saved. The nusinersen with no NBS strategy was subsequently eliminated by extended dominance of the combined strategies of no NBS and no nusinersen and NBS with nusinersen • **nusinersen with NBS *vs.* no NBS with nusinersen:** The ICERS were $193 867 per event-free LY saved and $199 510 per event-free QALY saved • **nusinersen with NBS *vs.* no NBS and no treatment:** An ICER was $330 558 per event-free LY saved
Malone, 2019	• **onasemnogene abeparvovec-xioi $2.5 M *vs.* nusinersen:** The ICER was USD$-203 072 per QALY • **onasemnogene abeparvovec-xioi $3 M *vs.* nusinersen:** The ICER was USD$-156 182 per QALY (dominant)• **onasemnogene abeparvovec-xioi $4 M *vs.* nusinersen:** The ICER was USD$-62 402 per QALY• **onasemnogene abeparvovec-xioi $5 M vs nusinersen:** The ICER was USD$31379 per QALY
NCPE, 2017	• **nusinersen *vs.* SOC for infantile-onset SMA:** An ICER of €501 069 per QALY gained or €453 079 per LY gained; subgroup analysis indicated improved cost-effectiveness when treatment was started earlier, i.e. disease duration less than 12 weeks (€476 596 per QALY) and where age at symptom onset was less than 12 weeks • **nusinersen *vs.* SOC for later-onset SMA:** An ICER of €2 107 108 per QALY gained or €3 906 818 per LY gained
Shih, 2021	**SMA treatment strategies: 5 years:** • **early nusinersen treatment *vs.* gene therapy:** The ICER was dominant • **early nusinersen treatment *vs.* late nusinersen treatment:** An incremental QALY of 0.78; the ICER was $416 000 per QALY • **early nusinersen treatment *vs.* supportive care:** An incremental QALY of 1.37; the ICER was $1 168 000 per QALY • **gene therapy *vs.* late nusinersen treatment:** An incremental QALY of 0.78; the ICER was $637 000 per QALY • **gene therapy *vs.* supportive care:** An incremental QALY of 1.37; the ICER was $1 294 000 per QALY • **late nusinersen treatment *vs.* supportive care:** An incremental QALY of 0.58; the ICER was $2 179 000 per QALY **NBS and treatment strategies: 5 years:** • **NBS and nusinersen treatment *vs.* NBS and gene therapy:** The ICER was dominant (nusinersen was less costly but equivalently effective) • **NBS and nusinersen treatment *vs.* no NBS and nusinersen treatment:** An ICER of $494 000 per QALY (dominant to $5321000) • **NBS and nusinersen treatment *vs.* no NBS and supportive care:** An ICER of $1 237 000 per QALY • **NBS and gene therapy *vs.* no NBS and nusinersen treatment:** An ICER of $714 000 per QALY • **NBS and gene therapy *vs.* no NBS and supportive care:** An ICER of $1 360 000 per QALY • **no NBS and nusinersen treatment *vs.* supportive care:** An ICER of $2 179 000 per QALY **SMA treatment strategies: 60 years:** • **early nusinersen treatment *vs.* gene therapy:** The ICER was dominated • **early nusinersen treatment *vs.* late nusinersen treatment:** An incremental QALY of 9.93; the ICER was $507 000 per QALY • **early nusinersen treatment *vs.* supportive care:** An incremental QALY of 14.61; the ICER was $570 000 per QALY • **gene therapy *vs.* late nusinersen treatment:** An incremental QALY of 9.93; the ICER was dominant • **gene therapy *vs.* supportive care:** An incremental QALY of 14.61; the ICER was $202 000 per QALY • **late nusinersen treatment *vs.* supportive care:** An incremental QALY of 4.68; the ICER was $706 000 per QALY **NBS and treatment strategies:: 60 years:** • **NBS and nusinersen treatment *vs.* NBS and gene therapy:** The ICER was dominated (nusinersen was more costly but equivalently effective) • **NBS and nusinersen treatment *vs.* no NBS and nusinersen treatment:** An ICER of $513 000 per QALY • **NBS and nusinersen treatment *vs.* no NBS and supportive care:** An ICER of $577 000 per QALY • **NBS and gene therapy *vs.* no NBS and nusinersen treatment:** Dominant (dominant to $239000) • **NBS and gene therapy *vs.* no NBS and supportive care:** An ICER of $216 000 per QALY • **no NBS and nusinersen treatment *vs.* supportive care:** An ICER of $706 000 per QALY
Tappenden, 2018	**ERG'S Preferred Analyses: Early-onset SMA:** • **nusinersen *vs.* usual care:** The ICER was estimated to be £421 303 per QALY gained (including patient health gains only). Additional exploratory analyses led to ICERs ranging from £366 289 per QALY gained to dominated. **ERG's Preferred Analyses: Later-onset SMA:** • **nusinersen *vs.* usual care:** The ICER was estimated to be £408 769 per QALY gained (including patient health gains only). Additional exploratory analyses led to ICERs ranging from £432 191 per QALY gained, to in excess of £18.4 million per QALY gained.
Thokala, 2020	**Health Care Sector Perspective:** • **nusinersen *vs.* BSC:** Nusinersen produced greater QALYs (3.24) and LYs (7.64) compared with BSC (0.46 QALYs and 2.40 LYs). Incremental costs per QALY gained of approximately USD$1112000 and an incremental cost per LY gained of USD$590000 **Modified Societal Perspective:** • **nusinersen *vs.* BSC:** Nusinersen produced greater QALYs (3.24) and LYs (7.64) compared with BSC (0.46 QALYs and 2.40 LYs). Incremental costs per QALY gained of approximately USD$1124000 and an incremental cost per LY gained of USD$596000
Wang, 2022	• **nusinersen *vs.* SOC:** Incremental QALYs of 0.301 leading to an ICER of AU$2772798 per QALY gained • **onasemnogene abeparvovec-xioi *vs.* SOC:** Incremental QALYs of 2.273, resulting in an ICER of AU$1808471 per QALY gained • **onasemnogene abeparvovec-xioi *vs.* nusinersen:** Incremental QALYs of 1.972, resulting in an ICER of AU$1238288 per QALY gained
Zuluaga-Sanchez, 2019	**Societal Perspective: Infantile-onset SMA:** • **nusinersen plus SoC *vs.* SoC alone:** Associated with 3.86 incremental QALYs (for patients) and 6.22 incremental LYs • **nusinersen *vs.* SoC:** An ICER (patients) of 5 664 875 SEK per QALY gained, in comparison to SoC **Later-onset SMA:** • **nusinersen plus SoC *vs.* SoC alone:** Associated with 9.54 incremental QALYs (for patients) and 1.84 incremental life-years gained • **nusinersen *vs.* SoC:** An ICER (patients) of 3 985 640 SEK per QALY gained, in comparison to SoC **Payer Perspective**: (LYs and QALYs are the same as reported for the societal perspective) **Infantile-onset SMA:** • **nusinersen *vs.* SoC:** Treatment with nusinersen was associated with an ICER (patients) of 5 562 027 SEK per QALY gained, in comparison to SoC **Later-onset SMA:** • **nusinersen *vs.* SoC:** Treatment with nusinersen was associated with an ICER (patients) of 4 079 635 SEK per QALY gained, in comparison to SoC

SCAN TO CHECK: A systematic review of economic evaluations of orphan medicines for the management of spinal muscular atrophy

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