Beneluxa Review Group Assessment Summary

Onasemnogene abeparvovec

for the treatment of patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene

April 2021

Key Points for the Decision Maker

- Onasemnogene abeparvovec (OA) is a gene therapy for spinal muscular atrophy which is delivered into cells via a viral vector and administered as a once off intravenous infusion.

- Novartis Gene Therapies applied for reimbursement for OA in three countries Belgium, Ireland and the Netherlands for a subgroup of the licensed population; *treatment of all symptomatic SMA type 1 patients, and pre-symptomatic SMA patients with up to three copies of the SMN2 gene.*

- The clinical effectiveness is informed by four single armed studies of which three are complete, and two long term follow-up studies.

- Nusinersen and best supportive care are the main comparators. Nusinersen is considered standard of care in Ireland, the Netherlands and Belgium.

- The comparative benefit of OA over nusinersen is not currently known. The benefit of OA over best supportive care is likely to be greater although there is some uncertainty associated with the data due to the nature of the trials conducted.

- Of the adverse effects experienced in patients on OA, approximately half were serious adverse events. Rare side effects have been observed including thrombotic microangiopathy.

- The cost effectiveness of the OA was informed by a cost utility model constructed around three aspects of the disease; functional motor milestones, need for permanent ventilation and mortality. The model assumes that the benefit of OA is maintained for life whereas the benefit of nusinersen (an ongoing treatment) is only for the duration of the treatment.

- The Applicant modelled a subpopulation of the reimbursement claim which included patients with SMA type 1 with 2 copies of SMN2 gene who had onset of symptoms before 6 months. There were considerable limitations to the health related quality of life data and costs used in the model.

- The Review Group considered that the uncertainties in both the model and inputs were significant and therefore made adjustments to account for some of this uncertainty. The ICER for Ireland for patients with SMA type 1 with 2 copies of SMN2 gene versus nusinersen was €298,469 per QALY and €387,717 per QALY versus best supportive care. The probabilistic sensitivity analysis was of insufficient robustness to estimate the probability of cost effectiveness.

- It is estimated that approximately four patients will be treated in Ireland each year if used for the subpopulation sought for reimbursement; if used for the licensed population this estimate would increase to 21 patients. The 5 year cumulative net budget impact for Ireland for this sub population is €26.2 million and for the full licensed indication is €55.8 million.

Summary

In April 2021 the NCPE completed a joint assessment as part of the Beneluxa collaboration for onasemnogene abeparvovec (OA) (Zolgensma®) for the treatment of patients with spinal muscular atrophy (SMA). Assessment was undertaken between the Netherlands, Belgium and Ireland and was the first Beneluxa assessment including Ireland. Below is a summary of the two reports completed on relative effectiveness and the pharmacoeconomic assessment.

Description of Onasemnogene Abeparvovec

International non-proprietary name	Onasemnogene Abeparvovec (OA)
Proprietary Name	Zolgensma®
Pharmacotherapeutic Group	Other drugs for disorders of the musculoskeletal system
ATC code	M09AX09
Licensed indication	Conditional: Treatment of patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.
Mechanism of action	OA is a gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells to address the monogenic root cause of the disease. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons.
Formulation	Solution for infusion. Each mL contains OA with a nominal concentration of 2×10^{13} vector genomes (vg). Vials available in two volumes, containing an extractable volume of not less than either 5.5 mL or 8.3 mL.
Dose	Patients will receive a dose of nominal 1.1×10^{14} vg/kg OA. The total volume is determined by patient body weight.
Administration	Single-dose intravenous infusion preceded by corticosteroid-based immunomodulatory regimen 24 hours prior to and 30 days after administration. Precautions associated with preparation, handling, accidental exposure to and disposal handling and administering genetically-modified organism must be followed.
Duration of treatment	Once only
Other aspects	An antibody test for AAV9 using an appropriately validated assay is required in advance of treatment; treatment is not recommended if the titre is greater than 1.50. OA is an orphan medicinal product. OA is a hospital only treatment.
Price to wholesaler (*VAT is applied in Belgium and Ireland)*	€1,945,000 Ireland €2,285,375 (inc. 23% VAT) Belgium €2,061,700 (inc. 6% VAT)
Strength	2×10^{13} vg/mL
Pack size	1 vial

Description and Epidemiology of the disease

SMA is a serious, progressive muscle disease that leads to reduced mobility, curvature of the spine, loss of the arm and hand functions and paralysis of the respiratory muscles. It is a rare disease caused by a homozygous deletion of the survival motor neuron (SMN) 1 gene on chromosome 5q. The SMN protein is encoded by two genes, SMN1 and SMN2. In all patients with SMA there is no functional SMN1 gene.

The current classification of the type of SMA is based on clinical criteria. The number of SMN2 copies correlates (but not perfectly) with the SMA types. In general, patients with 3 or more copies of SMN2 have a relatively milder course of the disease (types 3, 4).

Type 1 SMA is characterized by onset before 6 months of age, failure to achieve sitting without support, and a life expectancy of 2 years or less. When treated with best supportive care, life expectancy improves a little with a median survival of 2 years. About half of children diagnosed have the most severe form of SMA (type 1). Type 2 usually becomes symptomatic between ages 6 and 18 months, but may start earlier. These patients ultimately attain independent sitting and may live into adolescence or longer. SMA type 3 (juvenile SMA or Kugelberg-Welander disease) becomes symptomatic after 18 months, and all patients walk independently at some time. Patients with SMA type 3 may survive longer than 60 years.

In symptomatic patients, age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict the severity of the disease. In pre-symptomatic patients SMN2 copy number is the most important predictor of clinical severity and age of onset. Patients with two or three copies of the SMN2 gene may go on to develop as type 2 or 3 SMA.

Proposed place in treatment

The current treatment options for SMA include nusinersen and supportive care. Nusinersen (Spinraza®) is reimbursed in all BeneLuxa countries. Nusinersen is administered by intrathecal injection, once every 4 months, after the initial loading phase.

The Applicant requests reimbursement for OA in pre-symptomatic patients and untreated symptomatic patients with type 1 SMA; however, the full licensed indication includes all

patients with up to 3 copies of the SMN2 gene. The license does not preclude the use of OA in patients who have been previously treated with other SMA therapies, nor does it preclude the subsequent use of other SMA therapies following OA treatment. Subsequent nusinersen use has been reported in the extension studies LT-001, LT-002 and in RESTORE.

Clinical and Comparative effectiveness

Clinical Effectiveness

Four studies (START, STR1VE-EU, STR1VE-US and SPR1NT) and the two long-term follow-up studies (LT-001 and LT-002) are included in the clinical study program (Table 1). To date only open label, single arm studies are available. Marketing authorisation of OA was based on two clinical trials in 22 and 12 patients with symptomatic SMA type 1 (STR1VE-US and START respectively) who received a therapeutic dose of the product. One similar trial with 33 patients (STR1VE-EU) is complete (Sept 2020) (however only interim data was available) and one other trial investigating 29 pre-symptomatic SMA patients with two or three copies of SMN2 (SPR1NT) is ongoing (SPR1NT also included one patient with four copies of SMN2). Survival, ventilation-free survival and mobility outcomes such as CHOP-INTEND and motor milestones were evaluated. Only patients younger than 6 months of age at the time of gene infusion were included in these trials.

The quality of the evidence is low mainly due to single arm, uncontrolled trial designs, and the very small number of patients. Data are available primarily on only two of the four studies (one still ongoing) and the follow-up time is limited. Interim data was provided for the STR1VE-EU from the Applicant following request by the Review Group. Data from historical controls are available, but there are differences in outcome definition and baseline characteristics e.g. mobility scores, ventilation and nutritional support, which affect the comparability with the OA trials.

Comparative Effectiveness

The effectiveness of nusinersen in symptomatic type 1 SMA patients was examined in a randomised control trial (ENDEAR) and associated long term follow up study (SHINE). The Applicant presented an unanchored indirect treatment comparison of OA (START and STR1VE-US) with nusinersen (ENDEAR/SHINE) for symptomatic Type 1 SMA patients.

Differences between study populations may bias estimates from naïve comparisons of outcomes between separate clinical trials. The Applicant also presented unanchored matching adjusted indirect comparison (MAIC) with nusinersen to attempt to adjust for some of these differences. The Review Group consider the MAIC did not fully account for differences between OA and nusinersen study populations. Therefore, results of the comparisons between OA and nusinersen in symptomatic SMA Type 1 are likely subject to bias and are highly uncertain. An added benefit of OA versus nusinersen cannot be concluded.

Safety

The most frequent adverse events encountered were increased transaminases, thrombocytopenia, vomiting, pyrexia, aspartate aminotransferase increased, increased alanine aminotransferase, and increased troponin-I. Thrombotic microangiopathy (TMA) has been reported in five patients treated with OA, among approximately 800 treated patients. Four of these patients recovered and one patient died following haemofiltration.

Safety data from the EPAR of OA were derived from the four studies in which, at the cut-off date of 31 December 2019, 100 patients received OA; 97 patients received the proposed dose of 1.1 x 10^{14} vg/kg (referred to as 2.0 x 10^{14} vg/kg in study in START) and 3 received a lower dose. 99% (96/97) of patients in the trial experienced at least one adverse event and 46% (45/96) were considered to have at least one serious adverse event. These adverse events resulted in death or study discontinuation in 2 and 3 treated patients, respectively.

Cost-effectiveness

The Applicant submitted a cost-utility analysis to assess the cost-effectiveness of OA compared to best supportive care (BSC) and to nusinersen.

Model structure

A cohort Markov state-transition model was constructed around three aspects of the disease; functional motor milestones, ventilation status (need for permanent ventilation) and survival (time to death). The model incorporates five health states, defined by motor status: A state (within a broad range of normal development), B state (walks unassisted), C

state (sits unassisted), D state (not sitting) and E state (permanent assisted ventilation). The base case only incorporates four of these states (B to E). The model assumes that the benefit of OA is maintained for life whereas the benefit of nusinersen (an ongoing treatment) is only maintained for the duration of the treatment.

Decision problem and model structure

Population	Modelled population: Patients with symptomatic type 1 SMA who are diagnosed and treated before 6 months of age. A scenario analysis is included for patients with pre-symptomatic SMA.
Intervention	OA as an adjunct to best supportive care, single- dose intravenous infusion.
Comparators	Nusinersen (Spinraza®) 12 mg intrathecal injection on Days 0, 14, 28 and 63, followed by a maintenance dose once every 4 months thereafter. Best Supportive Care (BSC)
Outcome(s)	Quality adjusted life years (QALYs) and costs
Time horizon	Lifetime
Discount rate	Ireland: 4% for costs and benefits Belgium: 3% for costs and 1.5% for benefits. Netherlands: 4% for costs and 1.5% for benefits.
Perspective	Ireland: Payer Belgium: Payer Netherlands: Societal

The Review Group identified a number of structural limitations with the model submitted by the Applicant including the length of model cycle, inappropriate application of the half cycle correction and lack of sequential treatment options after either OA or nusinersen. The modelled population is a subset of the licensed population and a subset of the population sought for reimbursement by the Applicant.

Treatment effects for the cost-effectiveness model

Clinical trial data is used to inform the initial short term phase of the model up to approximately 36 months and inputs for the long term model are informed by assumptions and extrapolations of survival and functional milestones. Treatment effects are modelled for death, permanent assisted ventilation (E state), and the attainment of motor milestones of independent sitting (C state) and walking (B state). It is assumed that attainment of sitting and walking are associated with improvements in life expectancy. Data for BSC was informed by the natural history study NeuroNext. OA treatment effectiveness was informed

by START (n=12) and STR1VE-US (n=22). Nusinersen treatment effectiveness was informed by ENDEAR/SHINE (n=81).

The NCPE Review Group identified a number of limitations with the treatment effectiveness inputs submitted by the Applicant. The use of outcomes from separate studies with differences in patient populations at baseline, differing prognoses, and age at treatment initiation introduces considerable uncertainty to the economic model. The MAIC weighting approach applied in the nusinersen comparison is unlikely to fully account for differences between studies and the resulting nusinersen comparison is likely biased. The applicability of the selected natural history studies and method of incorporating this in the model is an additional source of uncertainty. Patients who discontinue from nusinersen are assumed to have a very poor prognosis i.e. 90% regress within one year; no disimprovement (for lifetime) is assumed for patients on OA.

Health-related quality of life

No health-related quality of life (HRQoL) outcomes were measured in the SMA type 1 clinical trials for OA or nusinersen. A number of studies measuring HRQoL across the spectrum of SMA types were identified by the Applicant, reporting a wide range of utilities for the same health states. Variation arose from the HRQoL instruments and measurement methods used, the population from which utilities were drawn (e.g. patients, or parent/clinician proxies) and the target patient population. In the model, the Applicant made extreme assumptions for the E state and B state utility (zero quality of life for the E state, and quality of life of the general population for the B state); used parent-proxy results from an SMA Type 1 patient cohort in the UK (n=7, mean utility 0.19) for the D state; and a UK clinical-expert elicited estimate of utility (0.6) in a general SMA cohort who can sit unassisted for the C state. The Applicant's approach to selecting utility values was inconsistent. Overall, the Review Group considers that there is significant uncertainty associated with the health state utility values used in the model. This is due to the scarcity of data in the population of interest, and the methodological challenges of utility valuation in young children.

Health care resource use and costs

The model included drug acquisition and administration costs for OA and nusinersen, and healthcare costs associated with BSC in SMA.

A UK healthcare resource use study (HCRU study), conducted by Novartis Gene Therapies to determine the HCRU costs associated with BSC for SMA patients in the UK, formed the basis for the healthcare costs used in the model. This was supplemented by data from a separate study reporting costs associated with the treatment of children who are ventilator-dependent in the UK. There is significant uncertainty associated with SMA healthcare costs in the model, due to a lack of available data on existing patients treated with BSC or nusinersen, uncertainty in the nature of future outcomes for patients treated with OA or nusinersen, and a general lack of transparency in the methods used by the Applicant to calculate costs. The Review Group adjusted these costs in the alternative base case analysis using an alternative data source (Klug et al) which was considered more appropriate. Costs based on the Klug et al study are closely aligned with Belgian base case costs and are significantly lower than Dutch and Irish base case costs.

Societal costs in the model included patients' potential income, lost family income and direct non-medical costs. As with the SMA healthcare costs, there is significant uncertainty associated with SMA societal costs in the model, largely due to the Applicant's methods of adapting data from the US to the Netherlands and Ireland. This approach was not justified by the Applicant and is not considered to be an appropriate method of calculating societal costs for these countries. The Review Group incorporated non-healthcare costs from the Dutch nusinersen reimbursement report in the alternative base case analysis.

Results

Results of the cost-utility analysis

Results of the cost-utility analyses only refer to the subgroup of the population addressed by the Applicant i.e. patients who are symptomatic with type 1 SMA who are assumed to be diagnosed and treated before 6 months of age. Importantly this is also a smaller population than the Applicant submitted in their reimbursement application. Cost-effectiveness results for the remaining licensed population were not included by the Applicant in the base case i.e. pre-symptomatic patients with SMA type 1, patients with SMA type 1 who are treated

after 6 months of age, patients with SMA Type 2 or SMA type 3 with up to 3 copies of the SMN2 gene, and patients who are already on nusinersen who may subsequently switch to OA. Given the limitations of the model and inputs highlighted previously, an alternative base-base analysis was conducted by the Review Group. This incorporated alternative plausible assumptions to more fully explore the potential cost effectiveness of OA in the modelled population (Table 2 and Table 3). The alternative analysis differs from the Applicant's model through the inclusion of the subsequent use of nusinersen in a proportion of OA patients reflecting real world usage observed in the LT-001 study. Subsequent usage is included for 40% patients in the C and D states at the age of 2 years onwards. Other changes were inclusion of costs based on Klug et al. and societal costs for the Dutch model based on the Dutch nusinersen reimbursement report. The base case results refer to list prices of OA and nusinersen. Confidential price agreements or patient access schemes are in place for nusinersen in all three countries. The impact of potential nusinersen price discounts was also explored in scenario analyses.

The incremental cost effectiveness ratio (ICER) for OA in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment at age before 6 months (estimated for Ireland based on the review group alternative base case using payer perspective) is €298,469 per QALY versus nusinersen and €387,717 per QALY versus BSC (Table 2 and Table 3). The Applicant estimated OA to be less costly and more effective versus nusinersen: ICER -€13,300 per QALY; and more costly and more effective versus BSC: ICER €345,554 per QALY (Table 4 and Table 5).

Uncertainty

A key driver of cost-effectiveness is the price of both treatments, in all country models. Reductions in the list price of nusinersen worsen the cost-effectiveness estimates of OA. The proportion of patients who discontinue nusinersen and survival in D state also has a significant impact. The cost of ventilation (hospitalisations and social services) in the C and E states has a significant impact on the Applicant's analysis in the Irish and Dutch models. Other variables have limited influence on the ICER estimates due to the manner in which they were implemented.

Treatment effectiveness inputs from OA and nusinersen studies are not varied in the probabilistic sensitivity analysis (PSA) and uncertainty associated with treatment effects is therefore not captured. The Review Group considers the exclusion of treatment effects from the PSA to be inappropriate, particularly given the very small number of patients used to inform OA treatment outcomes.

Budget impact

The budget impact of OA across all three countries is presented in Table 7. The Applicant correctly included all incident patients and prevalent type 1 patients in the Belgian estimate of patient numbers whereas only the incident type 1 patients were included for Ireland and Netherlands. The Review Group estimates included all type 1 patients for all countries (Table 6). For Ireland, four patients are estimated to be eligible in year 1. In the full licensed population (including type 2 and 3) the year 1 estimate increases to 21. The five year cumulative net drug budget impact, using the Review Group's eligible population estimates for the reimbursed population sought by the applicant, was €26.2 million for Ireland; if the full licensed population is considered this would increase to €55.8m (Table 7) Costs are highest in years one and two given the number of prevalent patients potentially eligible for treatment. When subsequent nusinersen use and its reduced cost are taken into account the cost offsets reduce considerably and the budget impact increases.

Conclusion

The clinical evidence in relation to OA suggests benefit in some patients however the design and follow-up of the clinical trials are such that there remains significant uncertainty as to the medium to long term outcomes both in terms of safety and efficacy. Evidence from the follow-up studies available indicate that subsequent treatment with nusinersen is used in a proportion of patients who have received OA. The comparative benefit of OA compared to nusinersen is not yet known. There are considerable limitations to the modelling approach and the data used to inform the model.

Formal recommendation for Ireland:

The NCPE recommends that OA not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments.

Tables

Table 1 Overview of clinical trials and outcomes with intravenous OA

Name	Study design*	Status	Patients	Survival‡	Motor milestones§
START (CL-101) Phase 1/2	Open-label dose-escalation *process A*	Completed	N=15 Symptomatic SMA type 1 2x SMN2	Therapeutic dose (n=12): 100% event free survival at 2 years post dose	Therapeutic dose: 9 (75%) sits without support for ≥ 30 seconds and 2 (17%) walking independently 2 years post dose
LT-001 Phase 4	Long term follow-up of START	*Ongoing*	N=13 Symptomatic SMA type 1 2x SMN2	Therapeutic dose (n=10): 100% event free survival at mean 5.2 (range 4.7 to 6.1) years of age	Therapeutic dose: No recorded loss of milestones, however 4/10 (40%) patients received nusinersen in study therefore maintenance of efficacy cannot be solely attributed to OA.
STR1VE-EU (CL-302) Phase 3	Single-arm *process B*	*Complete*†	N=33 Symptomatic SMA type 1 2x SMN2	97% event free survival 1 (3%) died at mean 17.1 (range 6.9 to 18.8) months of age	9 (27%) sits without support for ≥30 seconds 1 (3%) walking independently at mean 17.1 (range 6.9 to 18.8) months of age
STR1VE-US (CL-303) Phase 3	Single-arm *process B*	Completed	N=22 Symptomatic SMA type 1 2x SMN2	91% event free survival 1 (5%) died 19 (86%) completed the study at 18 months of age	13 (59%) sits without support for ≥30 seconds 1 (5%) walking independently at 18 months of age
SPR1NT (CL-304) Phase 3	Single-arm *process B*	Ongoing	N=30 Presymptomatic SMA SMN2 x2 n=14; x3 n=15; x4 n=1	2x SMN2: 100% event free survival at median 15.6 (range 8.8 to 18.8) months of age 3x SMN2: 100% event free survival at median 15.2 (range 3.3 to 21.1) months of age	2x SMN2: 11 (79%) sits without support for ≥30 seconds and 4 (29%) walking independently at median 15.6 (range 8.8 to 18.8) months of age 3x SMN2: 6 (40%) walking independently at median 15.2 (range 3.3 to 21.1) months of age
LT-002 Phase 4	Long term follow-up of STR1VE and SPR1NT	*Ongoing*	Pre- and symptomatic SMA 2/3/4x SMN2	-	-

* Two different processes, A and B, have been used to manufacture OA. Process B is claimed to be manufactured with the commercial process.

† STR1VE-EU completed in September 2020, however only interim data (June 2020) were available for this assessment.

‡ Event-free survival defined as time to either death or permanent ventilation. Permanent ventilation is defined as requirement of ≥16-hour respiratory assistance per day continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation in START and as tracheostomy or ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation in other trials.

§ Walking independently is defined as 'takes independent steps' or 'walks independently' in START and as 'the ability to take at least five steps independently displaying coordination and balance' in other trials.

Table 2 Review Group alternative base-case cost-effectiveness results of OA versus nusinersen for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment before 6 months of age.

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
Nusinersen	€2,487,257	€2,262,237	€2,059,909	€2,811,870
Onasemnogene abeparvovec	€3,498,244	€3,204,438	€3,002,671	€4,129,150
Incremental costs	€1,010,987	€942,201	€942,762	€1,317,280
Life years				
Nusinersen	10.29	10.28	7.94	10.28
Onasemnogene abeparvovec	17.16	17.15	12.05	17.15
Incremental life years	6.87	6.87	4.11	6.87
QALYs				
Nusinersen	4.44	4.44	3.15	4.44
Onasemnogene abeparvovec	9.44	9.44	6.31	9.44
Incremental QALYs	5.00	5.00	3.16	5.00
ICER (€/QALY)	€202,001	€188,392	€298,469	€263,389

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 3 Review Group alternative base-case cost-effectiveness results of OA versus BSC for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment before 6 months of age**.**

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
BSC	€3,514,024	€137,976	€134,924	€255,112
Onasemnogene abeparvovec	€131,837	€3,402,982	€3,015,103	€4,404,935
Incremental costs	€3,382,188	€3,265,006	€2,880,179	€4,149,822
Life years				
BSC	2.28	2.28	2.11	2.28
Onasemnogene abeparvovec	19.98	19.95	13.45	19.95
Incremental life years	17.70	17.66	11.33	17.66
QALYs				
BSC	0.21	0.21	0.21	0.21
Onasemnogene abeparvovec	12.02	12.00	7.64	12.00
Incremental QALYs	11.81	11.79	7.43	11.79
ICER (€/QALY)	€286,413	€277,022	€387,717	€352,095

Results versus BSC are presented using unanchored naïve comparison (no MAIC weighting applied to OA).
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 4: Applicant base case cost-effectiveness results of OA versus nusinersen for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment before 6 months of age.

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
Nusinersen	€2,470,038	€3,620,011	€3,468,533	€3,932,460
Onasemnogene abeparvovec	€2,420,277	€3,485,570	€3,426,522	€3,799,155
Incremental costs (€)	-€49,761	-€134,441	-€42,011	-€133,304
Life years				
Nusinersen	10.29	10.28	7.94	10.28
Onasemnogene abeparvovec	17.16	17.15	12.05	17.15
Incremental life years	6.87	6.87	4.11	6.87
QALYs				
Nusinersen	4.44	4.44	3.15	4.44
Onasemnogene abeparvovec	9.44	9.44	6.31	9.44
Incremental QALYs	5.00	5.00	3.16	5.00
ICER (€/QALY)	-€9,943	-€26,881	-€13,300	-€26,654
	Negative ICERs indicate that OA is less costly and more effective than nusinersen, providing a saving of between €9,943 and €26,881 across the three countries for every additional QALY of benefit.			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 5: Applicant cost-effectiveness results of OA versus BSC for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment before 6 months of age.

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
BSC	€108,591	€809,053	€833,248	€962,865
Onasemnogene abeparvovec	€2,428,358	€3,461,432	€3,400,218	€3,812,772
Incremental costs	€2,319,767	€2,652,370	€2,566,970	€2,849,907
Life years				
BSC	2.28	2.28	2.11	2.28
Onasemnogene abeparvovec	19.98	19.95	13.45	19.95
Incremental life years	17.70	17.66	11.33	17.66
QALYs				
BSC	0.21	0.21	0.21	0.21
Onasemnogene abeparvovec	12.02	12.00	7.64	12.00
Incremental QALYs	11.81	11.79	7.43	11.79
ICER (€/QALY)	€196,444	€225,038	€345,554	€241,798

Results versus BSC are presented using unanchored naïve comparison (no MAIC weighting applied to OA).
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 6 Number of patients treated with OA as estimated by the Review Group

	Included eligible Population & cost	Year 1	Year 2	Year 3	Year 4	Year 5
Reimbursement claim						
Belgium*	All eligible Incident (up to 3 copies of SMN2) and Prevalent Type 1	12.53	10.65	9.23	-	-
Netherlands	Incident and Prevalent Type 1	15.10	15.21	10.24	11.51	11.65
Ireland	Incident and Prevalent Type 1	3.96	3.92	3.15	3.46	3.43
Licensed indication (additional to above)						
Belgium*	Prevalent Type 2 or 3 with up to 3 copies of SMN2	31.70	31.70	0	-	-
Netherlands	Incident and Prevalent Type 2 or 3 with up to 3 copies of SMN2	50.65	50.68	2.92	2.96	2.99
Ireland	Incident and Prevalent Type 2 or 3 with up to 3 copies of SMN2	21.36	21.35	0.90	0.89	0.88

*Three year budget impact only required for Belgium.

Table 7 Gross and net drug-budget impact of OA for the population included by Applicant in reimbursement claim and the additional impact of including the full population (in brackets)

	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Gross						
Belgium*	€25.8m (€65.4m)	€21.9m (€65.4m)	€19m (€0m)	-	-	€66.8m (€130.7m)
Netherlands	€29.4m (€98.5m)	€29.6m (€98.6m)	€19.9m (€5.7m)	€22.4m (€5.7m)	€22.7m (5.8m)	€123.9m (€214.3m)
Ireland	€9m (€48.8m)	€8.9m (€48.8m)	€7.2m (€2m)	€7.9m (€2m)	€7.8m (€2m)	€40.9m (€103.7m)
Net						
Belgium*	€20.5m (€48.8m)	€15m (€40.5m)	€12.4m (-€9.8m)	-	-	€47.9m (€79.5m)
Netherlands	€22.3m (€73.5m)	€18.9m (€61m)	€11m (-€10.6m)	€12m (-€6.1m)	€10.1m (-€11.3m)	€74.4m (€106.7m)
Ireland	€7m (€37.5m)	€5.98m (€31.9m)	€4.5m (-€5.1m)	€4.7m (-€3m)	€3,99m (-€5.4m)	€26.2m (€55.8m)

Budget impact based on Review Group estimates of the treated population for the reimbursement claim (additional budget impact for total licensed population in brackets).
*Three year budget impact only required for Belgium.