**Supplementary Table 3.** Illustrative quotationsfrom country appraisal reports of nusinersen and voretigene neparvovec

NUSINERSEN: Other criteria considered in assessment - quotations 1

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| **Country** | **Impact on QoL** | **Innovation** | **Nature of population** |
| **BELGIUM** |  |  |  |
| **BENELUXA** |  |  |  |
| **ENGLAND** | “…SMA has a substantial effect on the quality of life of patients, carers & their families “ | “…an innovative treatment and the first disease-modifying therapy for SMA. However…data presented did not suggest …substantial benefits relating to the innovative nature …that had not been captured in the economic analyses.“ | “…nature of the eligible population\* as part of its decision making and, in particular, the circumstances in which nusinersen could be recommended as a cost-effective treatment” |
| **FRANCE** |  | "Spinraza is the first treatment available for this disease." |  |
| **GERMANY** | “…patient-relevant therapeutic effect, in particular … improvement of the life quality…in the sense of symptomatology and severity considered relevant to patients” |  |  |
| **NETHERLANDS** | "The disease burden of SMA type 1 and type 2 / 3a is determined on the basis of the loss of  quality of life..." |  |  |
| **NORWAY** | "...relatives can have an improved health-related quality of life if the patient is functioning better."  " The model calculates that patients get better quality of life as new motor skills are obtained functions, such as sitting, standing and walking"  "...has received from relatives that some Norwegian patients are dependent on continuous 24 hours assistance..."  "…patients will be able to live longer with a significantly better one quality of life..." |  |  |
| **Country** | **Impact on QoL** | **Innovation** | **Nature of population** |
| **SCOTLAND** | “… has the potential to improve the quality and dignity of life | “Nusinersen can change the prognosis of all types of SMA, and is considered a step-change in the management of the condition."  “Clinical experts advised that Nusinersen represents a major therapeutic advancement in the management of SMA….in infants with type 1 SMA…” |  |
| **SWEDEN** | “…a reasonable relationship between cost and effect should be sought, as measured in improved health and increased quality of life” |  |  |
| **U.S** | "Effective treatment ...may reduce anxiety and stress among caregivers and wider communities"  "patients may be entirely dependent on family members who expend intense emotional and physical effort when constantly caring for a patient." | "Spinraza has a novel mechanism of action and is the first FDA approved treatment that modifies disease progression" |  |

NUSINERSEN: Other criteria considered in assessment - quotations 2

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| **Country** | **Rarity** | **Severity** | **Unmet need** |
| **BELGIUM** |  |  |  |
| **BENELUXA** | " Spinraza is an orphan medicine. A pharmaco-economic analysis is purely optional and was not part of the application file" |  | “At present there is no alternative to symptomatic treatment and the compensation of lost functions.” |
| **ENGLAND** | “Committee acknowledged the difficulty of appraising drugs for very rare conditions”  " The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease. " | " The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease." | “…no disease-modifying therapies for SMA. Current treatments are based on symptom control …to maintain movement and function for as long as possible and to improve quality of life “ |
| **Country** | **Rarity** | **Severity** | **Unmet need** |
| **FRANCE** | "...its rarity with an incidence estimated at 0.26 / 100,000 patients in type I and 1.23 / 100  000 patients in type II..." | "Spinal muscular atrophy 5q is a serious disease, with an impact on the vital prognosis..."  "...the significant severity of ASA, and particularly in types I and II where the vital prognosis is engaged..." | "There is no alternative in the treatment..."  " identified unmet medical need" |
| **GERMANY** | Nusinersen.. "Orphan Drug". … additional medical benefits for orphan drugs are already covered… G-BA determines orphan drugs, which have a turnover of 50 million euros in the last twelve calendar months, the extent of the added benefit…justifying authorization.” |  |  |
| **NETHERLANDS** | "Nusinersen is one of the medicines that have been on the market in recent years come to treat a rare, serious disease (orphan drugs)." | " SMA is a serious, progressive muscle disease" | "At present there is no alternative for SMA other than symptomatic treatment and the compensation of lost functions" |
| **NORWAY** |  | "...considers that SMA is very serious"  " SMA is a serious illness that can lead to premature death and great loss of health-related quality of life" | " There is currently no other disease-modifying treatment for SMA" |
| **SCOTLAND** |  | “devastating, progressive condition characterised by neuromuscular deterioration” | “Clinical experts consulted by SMC considered that there is unmet need for a disease modifying treatment…” |
| **SWEDEN** |  |  | "A higher cost per QALY can usually be accepted when the difficulty is high or if there are few other treatments to choose from.” |
| **U.S** | "Considering that SMA is a rare disease..." | "SMA is a condition of particularly high severity and rapid progression" |  |

NUSINERSEN: Other criteria considered in assessment - quotations 3

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| **Country/HTA body** | **Financial burden of SMA** | **Impact on specialised services** |
| **BELGIUM** |  |  |
| **BENELUXA** |  |  |
| **ENGLAND** | “.. many compelling examples of the financial burden of living with SMA from the patient experts…“ |  |
| **FRANCE** |  | "...potentially negative impact on the organization of care due to the need regular intrathecal drug administration, which should be done in hospital environment" |
| **GERMANY** |  |  |
| **NETHERLANDS** |  |  |
| **NORWAY** |  |  |
| **SCOTLAND** | "Improvements ...can reduce financial pressures..." | “Impact on patient and/or service delivery since treatment would require admission, allocation of theatre time, and availability of trained specialists to administer the intrathecal dose. Patients with less severe SMA who have stable disease may require more frequent review and attendance for administration of Nusinersen, compared with current arrangements” |
| **SWEDEN** |  | “…there is uncertainty about resource use when administering Spinraza, when some patients have to be anesthetized and others not, according to one of TLV's experts.” |
| **U.S** |  |  |

VORETIGENE NEPARVOVEC: Other criteria considered in assessment - quotations 1

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| **Country/HTA body** | **Impact on QoL** | **Innovation** | **Nature of population** |
| **ENGLAND (NICE)** | "severely affects the quality of life of people with the condition, and their families and carers."  "progressive nature of the vision loss means that patients are under pressure to continually adapt and accept the slow decline in vision while having uncertainty about the future, and that this causes substantial anxiety"  "...also places a significant burden on family members because they have to provide physical and emotional care to patients while experiencing considerable psychosocial consequences of their own"  "acknowledged that even a small improvement in vision would be important for people with the condition" | "...discussed the innovative nature of voretigene neparvovec, noting that it is the first licensed gene therapy for vision loss." | "...noted that the population for which voretigene neparvovec is indicated includes children and young people"  "...recalled that there were considerable uncaptured benefits related to sustaining vision in children, and that these had been considered qualitatively in its decision making" |
| **FRANCE (HAS)** |  | " LUXTURNA is the first gene therapy treatment based on an adeno-associated viral vector having MA in the treatment of patients with visual loss due to hereditary retinal dystrophy associated with bi-allelic mutations of the *RPE65* gene" | "Considering ... its beginning being either early after birth (severe forms evolving rapidly), or later in childhood and adolescence with a slower progression of the disease..." |
| **GERMANY  (G-BA)** |  |  |  |
| **NETHERLANDS** | "The burden of disease cannot be determined properly, but is expected, if the psychological side is taken into account of the disease, probably high."  " The patients' association used the meeting during the meeting  made the possibility of recording, where a patient has explained the impact of this progressive disease, which eventually leads to blindness, has daily life. She also indicated that she and her loved ones live in constant fear and insecurity  about what she can and cannot do tomorrow or next year." |  |  |
| **Country/HTA body** | **Impact on QoL** | **Innovation** | **Nature of population** |
| **NORWAY (NOMA)** |  | " VN is the first gene therapy to treat an inherited retinal disease" |  |
| **SCOTLAND (SMC)** | " Improvement in functional vision could have a significant impact on the quality of lives of patients, family and carers. Patients could be more independent, lead a more normal life and some may be able to return to education or work"  "...leads to lifelong disability that has far-reaching consequences in terms of economic and social burden. People living with the condition have stated that it can affect opportunities in education, the labour market, and in day to day life that others with normal vision take for granted such as; socialising at night or driving...there is a ripple effect across the family, not only due to the direct consequences of supporting a loved one with a disability, but also because of the emotional toll attached to passing on or being at risk from a genetic disorder." | "Voretigene neparvovec is the first medicine to be licensed for the treatment of inherited retinal dystrophy"  "...represents an important innovation that addresses an unmet need and could alleviate the burden of progressive disability" |  |
| **SWEDEN (TLV)** | "Limitations in patients' distress, especially in low-light, representative environments.  centers a very important clinical aspect of the disease and affects the patient's quality of life negatively" |  |  |
| **Country/HTA body** | **Impact on QoL** | **Innovation** | **Nature of population** |
| **U.S (ICER)** | " Impacted individuals and advocacy organizations emphasized the challenges of growing up with low vision for both affected children and their parents/families. Individuals with *RPE65*-mediated retinal disease described the significant time and energy they have had to dedicate towards adapting to constantly deteriorating vision."  "Individuals with low vision often contend with feelings of social isolation"  "Several individuals who received VN appreciated the improvements in self-confidence, mobility, and independence that they felt following treatment. These benefits may not be adequately captured in the QALY."  "Loss of visual function has been shown to diminish the quality of life significantly." | "... first gene therapy entering the market in the US that targets a disease caused by mutations in a specific gene and will offer the first treatment option for individuals with RPE65-mediated retinal disease." |  |

VORETIGENE NEPARVOVEC: Other criteria considered in assessment - quotations 2

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| **Country/HTA body** | **Rarity** | **Severity** | **Unmet need** |
| **ENGLAND (NICE)** | "RPE65-mediated inherited retinal dystrophies are rare and serious" | "...committee acknowledged that RPE65-mediated IRD is a rare, serious and debilitating condition that severely affects the lives of patients, families and carers." | "There are no licensed treatments currently available in the UK for RPE65-mediated IRD."  "...concluded that there was a high unmet need in people with RPE65-mediated IRD, and that voretigene neparvovec is a step change in the treatment of this condition" |
| **Country/HTA body** | **Rarity** | **Severity** | **Unmet need** |
| **FRANCE (HAS)** | "Hereditary retinal dystrophies resulting from biallelic mutations of the RPE65 gene are rare, highly disabling diseases, beginning early in children or young adults  and which lead to legal blindness" | "Considering ...the severity of the pathology progressing systematically towards blindness..." | " To date, there is no treatment to prevent or restore functional vision in patients with inherited retinal dystrophy due to a biallelic mutation in the RPE65 gene.... Therefore, the medical need is not covered in the care of patients with hereditary retinal dystrophy resulting from confirmed biallelic gene mutations RPE65"  " There is no therapeutic alternative"  " LUXTURNA therefore responds to the identified medical need." |
| **GERMANY (G-BA)** | "....approved as a medicine to treat a rare condition... According to § 35a paragraph 1 sentence 11 1st half. SGB ​​V, the additional medical benefit from the approval is deemed to be proven"  " Based on the legal requirement in § 35a paragraph 1 sentence 11 1st half. SGB ​​V that the added benefit of an orphan drug is considered to be proven by the approval" |  |  |
| **NETHERLANDS** | "...considers the rarity of the disorder to be designated in one center" |  | " There is no effectively proven treatment available for retinitis pigmentosa, LCA and SECORD" |
| **NORWAY (NOMA)** |  | "Hereditary retinal dystrophy caused by mutations in the *RPE65* gene is severe"  " ...it can be difficult to carry out a traditional, randomized controlled trial of efficacy. Therefore, a lower requirement for documentation can be accepted. " | "There is no treatment that can curb vision loss in hereditary retinal dystrophy today"  " Biallelic *RPE65* mutations cause progressive vision loss and ultimately total blindness, and it is a great need for effective treatment" |
| **Country/HTA body** | **Rarity** | **Severity** | **Unmet need** |
| **SCOTLAND (SMC)** | "...is a rare genetic condition and requires highly specialised management " | "... is chronic and severely disabling due to loss of vision" | "There are no other medicines licensed for this condition ...There is therefore a high unmet need in these patients. Clinical experts...considered that voretigene neparvovec fills an unmet need in this therapeutic area because there are no other treatments available."  "There is currently no treatment available that can impact on either the progression or outcome of the condition" |
| **SWEDEN (TLV)** | " The rarity of the condition in combination with the treatment class is new contributes to, and can to some extent explain, several uncertainties associated with this evaluation." | "TLV considers that the severity of the disease is high based on significant functional loss" | " The need of effective treatments is considered to be large"  " There are currently no treatments with proven efficacy to slow down  progression or reset the vision function of the current patient group." |
| **U.S (ICER)** | "...for ultra-rare diseases such as this, decision-makers in the US and in international settings often give special weighting to other benefits and contextual considerations... lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than may be applied…." | "Individuals may become severely visually impaired during childhood, adolescence, or early adulthood; however, nearly all become fully blind in adulthood" |  |

VORETIGENE NEPARVOVEC: Other criteria considered in assessment - quotations 3

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| --- | --- | --- |
| **Country/HTA body** | **Financial burden of condition** | **Impact on specialised services** |
| **ENGLAND (NICE)** | "Adult carers experience stress from managing the financial effects of having to reduce paid work to care for children, and to pay for adaptive aids and travel to specialist appointments."  "noted that there is a substantial financial impact on families..." |  |
| **FRANCE (HAS)** |  | "...likely to have an impact on the organization of care due to hospital administration in the operating room under controlled aseptic conditions, the limited number of centers authorized to perform subretinal injection limited ... the need to carry out a genetic diagnostic test... However, this impact should be very low in view of the rarity of the disease" |
| **GERMANY (G-BA)** |  |  |
| **NETHERLANDS** |  |  |
| **NORWAY (NOMA)** |  |  |
| **SCOTLAND (SMC)** |  | "...may be implications for the service in determining patient eligibility for treatment..." |
| **SWEDEN (TLV)** |  | "...expertise, ie the clinical centers, and the specialist the medical staff, who participated in the clinical program...cannot be extrapolated to Swedish clinics ...which can affect the incidence of complications as well as the result of administration" |
| **U.S (ICER)** |  |  |