**Supplementary Table 2.** Issues raised across countries for nusinersen and voretigene neparvovec

**NUSINERSEN**

Grey = standard process, White = supplemental process

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **General** | **Description** | **BENELUXAI** | **ENGLAND STA** | **FRANCE** | **NL** | **BELGIUM** | **GERMANY** | **NORWAY** | **SCOTLAND** | **SWEDEN** | **U.S Ultra-RDT** |
| Lack of subgroup data | Only included entire population in the model, not subgroups | X |  | X |  |  |  |  |  |  |  |
| Lack of data on SMA III |  |  | X |  |  |  | X |  | X |  |
| No/limited evidence for SMA 0 /IV |  |  | X |  | X |  |  |  |  | X |
| Lack of data on respiratory deterioration In children with SMA type II or III |  |  |  |  |  |  | X | X |  |  |
| Optimum dose unclear | Dose regimen in trials different from licensed dosing | X | X |  | X | X | X | √ | √ | √ |  |
| Possible bias in results of open label study | Two main trials stopped early, patients enrolled in open label study. Event-free survival data may be confounded by treatment switching | X | X |  |  |  |  | X | X |  |  |
| Baseline characteristic imbalances | Imbalances in baseline characteristics of open label extension study participants (participants came from two different studies) |  | X |  |  |  |  | X |  |  |  |
| Imbalances in baseline characteristics of ENDEAR population – treatment group had much more progressive symptoms than control |  |  |  |  |  |  | √ |  | X | X |
| Uncertainty around eligible population | Difficult to estimate how many patients would be eligible for treatment – may be higher than company estimates |  |  |  |  | X |  | √ |  | X |  |
| Criteria to be classified as a responder unclear (permanent or single response) |  |  |  |  |  | X |  |  |  |  |
| Narrow eligibility criteria |  |  |  |  | X |  |  |  |  | X |
| Uncertainty as to whether drug will be used primarily for pre-symptomatic or other types |  |  |  |  |  |  |  |  |  | X |
| Small sample size | Limited sample size |  |  |  |  |  |  | X |  | X |  |
| Small sample size limits generalizability |  |  |  |  |  |  |  |  |  | X |
| Resource use | Uncertainty around resource use needed for specific patients during administration (e.g. some need anaesthetic, some don’t) |  |  |  |  |  |  | √ |  | X |  |
| Natural history uncertainties | Progression of patients cannot be predicted with certainty - severity and motor performance of different types more on a continuum than distinct groups |  | X |  |  | X |  |  |  |  |  |
| **Clinical uncertainties: clinical effect** | **Description** | **BENELUXAI** | **ENGLAND STA** | **FRANCE** | **NL** | **BELGIUM** | **GERMANY** | **NORWAY** | **SCOTLAND** | **SWEDEN** | **U.S Ultra-RDT** |
| When to stop treatment | Uncertain how long treatment should last or what causes it to be discontinued |  | X | X |  |  |  | X |  | X |  |
| Uncertain what percentage of patients will actually have treatment discontinued after a 14-month evaluation |  |  |  |  | X |  |  |  |  |  |
| Uncertainty about HRQL | Poor QoL documentation for patients over 18, or diagnosed long ago |  |  |  |  |  |  | X |  |  |  |
| Uncertainty how much improvement in HRQL patients will experience in the short tem |  |  |  |  |  |  | X |  | X |  |
| Optimistic QoL measure (higher than in comparable conditions) |  |  |  |  |  |  |  |  | X |  |
| QoL assessment not possible due to low response rates |  |  |  |  |  | X |  |  |  |  |
| No demonstrated impact on QoL |  |  | X |  |  |  |  |  |  |  |
| Size of benefits | Benefits of nusinersen were valued by patients, but size remains unknown | X | X |  |  |  | X | X |  |  |  |
| Treatment may have effect on disease progression in patients >18, but it is unknown how large effect could be |  |  |  |  |  |  | X |  |  |  |
| Uncertainties for various SMA subgroups (due to heterogeneity of disease and morbidity) |  | X |  |  |  | X | X |  | √ |  |
| Small subgroup sizes and imbalance between subgroups |  |  |  |  |  | X | X |  |  | X |
| Uncertain long term effect | Long-term data relies on observational studies | X |  |  |  |  |  | X | X |  |  |
| Uncertainty around long-term benefit and tolerance |  | X | X | X | X | X | X |  | X | X |
| Relationship between improved motor function and survival unclear |  | X |  |  |  |  |  |  |  |  |
| Lack of data on long-term safety (repeated lumbar punctures, risk of thrombocytopenia and renal toxicity) and efficacy |  |  |  |  |  |  |  |  |  | X |
| Effects on survival unclear – there were no deaths during the CHERISH study |  | X |  |  |  |  | X |  |  |  |
| Lack of information about survival in control group |  |  |  |  |  |  |  |  | X |  |
| Life expectancy uncertain, but nusinersen could meet short LE criterion for early onset SMA |  | √ |  |  |  |  |  |  |  |  |
| Long-term effect has not yet been demonstrated | X |  |  | X |  |  | X |  |  |  |
| Long term effect on patients that could walk as a result for nusinersen is based on results from only 1 or 2 patients. | X |  |  |  |  |  | X |  |  |  |
| Possible adverse events not reported | Adverse events from administration not reported (considered outweighed by benefit of treatment) |  |  |  |  |  | X | X | X |  |  |
| Drug administration difficulty | Difficulty with intrathecal administration, especially in arthritis patients |  |  | X |  |  |  |  |  |  |  |
| Value and feasibility patients with scoliosis and previous scoliosis surgery unknown | X |  |  |  |  |  |  |  |  |  |
| **Clinical uncertainties: economic model** | **Description** | **BENELUXAI** | **ENGLAND STA** | **FRANCE** | **NL** | **BELGIUM** | **GERMANY** | **NORWAY** | **SCOTLAND** | **SWEDEN** | **U.S. Ultra-RDT** |
| Uncertain cost | Costs vary depending on approach used | X |  |  | X | X |  | X |  | X |  |
| Uncertainty around ICER | X |  |  | X | X |  |  |  |  |  |
| ICERs higher than conventional levels |  | √ |  | X | X |  | X | √ | √ | X |
| Uncertainty around cost-effectiveness related to lack of robust evidence |  | X |  |  |  |  |  |  |  |  |
| Survival uncertainty | Company's assumption of survival in the comparator arm for SMA I is overestimated |  |  |  |  |  |  |  |  | X |  |
| Overestimation of patients stopping treatment | Assumption is made that a certain percentage of patients will stop treatment (little effect). This is difficult to expect in practice | X |  |  | X | X |  |  | X |  |  |
| Patients with current scoliosis surgery techniques no longer seem to have to stop using nusinersen | X |  |  | X | X |  |  |  |  |  |
| Model did could not accurately reflect company’s stopping rule |  | X |  |  |  |  |  |  |  |  |
| No clear stopping rule |  |  |  |  |  |  |  | X |  |  |
| Transition states | Estimation of patients having achieved high health conditions appears optimistic. | X |  |  |  |  |  | X | X |  |  |
| Plateau state in model: results show large proportion of patients achieve "high health conditions" before plateau takes effect |  |  |  | X |  |  |  |  |  |  |
| High level of uncertainty given the sparsity of existing evidence |  | X |  |  |  |  | X |  |  |  |
| Model assumes patients don’t deteriorate before death |  |  |  |  |  |  | X |  | X |  |
| Quality of life | Quality of life data used in models highly uncertain |  |  |  | X |  |  | X |  |  |  |
| Uncertain utility value | Different mapping methods give different results: QoL uncertain | X |  |  | X | X |  | X |  |  |  |
| Difficult to identify robust utility values in babies/young children, none of the available sources were ideal; utility values highly uncertain |  | X |  |  |  |  | X |  |  |  |
| Difficulty to quantify carer utility |  | X |  |  |  |  | X |  |  |  |
| Mapping method used not validated for population | X | X |  | X | X |  |  |  |  |  |
| Assumption of generalizability | Populations included in children; effects were assumed to be the same in adults | X |  |  |  | X |  | X |  | X |  |
| Best symptomatic care vs. palliative care is not the same in all countries - affects reporting of overall and progression free survival | X |  |  |  | X |  |  |  |  |  |
| External validity not applied to subgroups | X |  |  | X | X |  |  |  |  |  |
| Individual variation is not reflected in the analysis of average patients in the health economic model. |  |  |  |  |  |  | X |  |  |  |
| Lack of long-term data in model | Individual variation in presentation not reflected in model |  |  |  |  |  |  | X |  |  |  |
| Potential overestimation of long-term effectiveness | X |  |  | X | X |  | X | X | X | X |
| Company's base case results are based on assumptions which maintain favorable outcomes for nusinersen |  |  |  |  |  |  |  | X |  |  |
| Assumption about more optimistic disease duration, resulting more favourable ICERs | X |  |  | X | X |  |  | X |  |  |
| Model complexity | Complexity of model prevented thorough understanding of its functioning and added to uncertainty |  | X |  |  |  |  | X |  |  |  |
| Healthcare costs | Health care costs key driver of model, but difficult to estimate; very uncertain |  | X |  |  |  |  |  |  |  |  |
| Uncertainty about resource use when administering nusinersen, as some patients must be anesthetized and others not |  |  |  |  |  |  |  |  | X |  |
| General willingness to accept greater uncertainty | Stated general willingness to accept greater uncertainty, despite the many issues raised |  | √ |  |  |  | √ | √ | √ |  |  |

X Issue considered but not addressed √ Issue considered and addressed

**Additional information:**Addressed = it was discussed but further explained/countered/considered acceptable anyway  
Not addressed = it was just raised  
Lack of long-term data to be supported by the longer term SHINE study

**VORETIGENE NEPARVOVEC**

Grey = standard process, White = supplemental process

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Other considerations** | **Description** | **FRANCE** | **NL** | **U.S** | **ENGLAND HST** | **GERMANY** | **NORWAY** | **SCOTLAND** | **SWEDEN** |
| **General** | **Description** |  | | | | | | | |
| Uncertainty about eligible population | 'Sufficient viable retinal cells' not fully defined in MA, so need to consider how the decision for treatment eligibility would be made |  |  |  | √ | X |  |  |  |
| Characteristic differences | Small differences in baseline characteristics in study 301/302 |  |  |  | √ | X |  |  |  |
| Differences in study performance between centers |  |  |  |  | X |  |  |  |
| Age of study participants different than country population |  | X |  |  |  |  |  |  |
| Ceiling effect could be observed because of the already high baseline values in the mobility score |  |  |  |  | X |  |  |  |
| Possible influence of the natural development of children and adolescents on the performance of the tests remains unclear |  |  |  |  | X |  |  |  |
| No safety/efficacy data available for patients <4 years |  |  |  |  | X |  |  |  |
| Generaliseability issues | Clinical studies only recruited patients with one particular IRD diagnosis |  |  |  | √ |  |  |  |  |
| Unclear why some patients experience improvement and others do not |  | X |  |  |  |  |  |  |
| Data based on small number of heterogeneous patients - treatment benefit may not be generaliseable |  | X |  |  |  |  | X |  |
| Study eligibility | In study 101/102, eligibility criteria did not require sufficient viable retina cells in line with MA |  |  |  | X |  |  |  |  |
| Dosage | In study 101/102, most patients had much smaller doses than licensed dose |  |  |  | X |  |  |  |  |
| QoL | No direct measure of HRQoL used in the clinical trials - lack of patient-reported outcomes was a key limitation |  |  | X | X |  |  |  |  |
| Company-created questionnaire not validated |  |  | X |  | X | X |  |  |
| No suitable QoL data |  |  |  |  | X |  |  |  |
| The impact on quality of life is not demonstrated to date | X |  | X |  |  |  |  |  |
| Absence of (robust) QoL data | X |  |  |  |  | X |  |  |
| Improvements in daily living but unclear how it relates to QoL |  |  |  |  |  |  | X |  |
| Information about quality of life not properly collected |  | X |  |  |  |  |  |  |
| Discount rate | Uncertainty of lower discount rate could be applied for a treatment restoring people to full/near full health - uncertainty around whether patients will reach this health status with treatment |  |  |  | X |  |  |  |  |
| Uncertainty around measures used | MLMT measure may result in ceiling effect and underestimate treatment effect |  | X |  |  | X |  | X |  |
| Company developed MLMT - uncertainty around what represents a clinically relevant improvement |  | √ | X |  |  |  | X |  |
| MLMT was considered acceptable instrument of short term efficacy, but all measures were needed for decision making about clinical effectiveness |  |  |  | X |  |  |  |  |
| Visual function questionnaire indicated improvements in daily living - unclear how this relates to QoL |  |  |  |  |  |  | X |  |
| Novel outcome measure (MLMT), has not been correlated with real world outcomes |  |  | X |  |  |  |  |  |
| Participants were not blinded |  | X |  |  |  |  |  |  |
| Potential bias | High potential bias due to open study design, lack of blinding |  |  |  |  | X | X |  |  |
| Population | Very small number of individuals have received the treatment |  |  | X |  |  | √ |  | √ |
| Procedure | There were procedural deviations in test procedure of the intervention group |  |  |  |  | X |  |  |  |
| **Clinical uncertainties: clinical effect** | **Description** | **FRANCE** | **NL** | **U.S** | **ENGLAND HST** | **GERMANY** | **NORWAY** | **SCOTLAND** | **SWEDEN** |
| Lack of long-term evidence | No long-term clinical evidence, but biologically possible that treatment effect likely continues |  |  |  | X |  | X | X | X |
| Duration of treatment effect unclear | X | X | X |  | X | X | X | X |
| No information on whether patients who may lose treatment effect would benefit from re-treatment |  | X |  |  |  |  | X |  |
| Lack of evidence around long-term risk | X | X | X |  |  | X |  |  |
| Unclear whether further deterioration will be prevented |  | X |  |  |  | X |  |  |
| Results of clinical trials uncertain | Small sample size |  |  |  | X |  | X |  | √ |
| Limited follow-up |  |  |  | X |  | X |  |  |
| Efficacy not demonstrated in all patients. Only determining factor was presence of sufficient viable retinal cells |  |  | X |  |  |  | X |  |
| Risks and complications | Treatment well tolerated but there are risks/complications associated with intraocular surgery required for sub-retinal injection that could have long-term consequences |  |  |  |  |  |  | X |  |
| Repetition of treatment | Uncertainty as to whether treatment would be repeated. No data available |  | X |  |  |  |  |  |  |
| **Clinical uncertainties: economic model** | **Description** | **FRANCE** | **NL** | **U.S** | **ENGLAND HST** | **GERMANY** | **NORWAY** | **SCOTLAND** | **SWEDEN** |
| Uncertain assumptions in economic model | Uncertain assumptions around how long treatment effect lasts |  |  |  | X |  |  |  |  |
| 10 year treatment waning period |  |  |  | X |  |  |  |  |
| Hazard rations highly uncertain |  |  |  | X |  |  |  |  |
| Hard to validate whether company method of modeling disease course over time provides reasonable distribution of patients in various health states over time |  |  |  |  |  | X |  | X |
| Treatment effect may be underestimated |  |  |  |  |  |  |  |  |
| Development in the comparator arm is based on historical control and extrapolation of data after the first year. |  |  |  |  |  | X |  |  |
| Long-term effect as key driver of economic model | Method of modeling long-term data introduced uncertainty |  | X |  | X |  |  |  |  |
| Effects expected to last for decades, but results limited to 3-4 years of follow-up (7.5 in study 101/102) |  |  |  | √ |  |  | X |  |
| Shorter durations of treatment effect results in substantial increases in the ICER |  |  |  |  |  |  | X |  |
| Not possible to know how long treatment will down vision loss |  |  |  |  |  | X |  |  |
| Uncertainty if model fully captured outcomes of importance for patients | Primary outcome (MLMT) not included in model |  | X | X | √ |  |  | X |  |
| Small sample size | Small sample size and data was not pooled |  |  |  | √ |  |  |  |  |
| Transition probabilities derived from small patient numbers |  | X |  |  |  |  | X |  |
| Model used | Parametric multistate model considered overly complex |  |  |  | √ |  |  |  |  |
| Cost effectiveness model is of insufficient quality and creates uncertainty |  | X |  |  |  | √ |  |  |
| Uncertain if model correctly reflects patients' disease pictures |  |  |  |  |  |  |  | √ |
| Limited data due to lack of disease natural history knowledge |  |  | X |  |  |  |  |  |
| Uncertainties in utility measures | Uncertain assumptions around utility values |  |  |  | X |  |  | X |  |
| Only small number of clinicians took part |  |  |  | X |  |  | X | X |
| QoL may have been underestimated |  | X |  | X |  | X |  |  |
| HUI3 values lacked faced validity |  |  |  | X |  |  | X |  |
| Disutilities of AEs were likely to overestimate effect in a population with significant visual impairment |  |  |  | √ |  |  |  |  |
| Might not fully reflect target population |  |  | X |  |  |  | X |  |
| Indirectly obtained utility values |  | X |  |  |  |  |  | X |
| Lack of QoL data |  |  |  |  |  | X |  | X |
| QoL results cannot be taken into account since the assessment was a secondary judgment criterion not integrated into the hierarchical test analysis procedure | X |  |  |  |  |  |  |  |
| High cost | Treatment cost in relation to health benefits is high |  |  | √ |  |  |  | X |  |
| Extremely high upfront cost for single dose treatment - likely to have significant service implications and associated with financial risk to service of predicted long-term benefits don't materialise |  |  |  |  |  |  | X |  |
| Less health gain in later years; cost effectiveness for population may be less favorable than modeled |  | X |  |  |  |  |  |  |
| Distribution of high one-time cost uncertain (e.g. over three years as with other medications) |  | X |  |  |  |  |  |  |
| General willingness to accept greater uncertainty | Stated general willingness to accept greater uncertainty, despite the many issues raised |  |  |  | √ | √ | √ | √ | √ |

X Issue considered but not addressed √ Issue considered and addressed

**Additional information:**Addressed = it was discussed but further explained/countered/considered acceptable anyway  
Not addressed = it was just raised