Nusinersen for treating spinal muscular atrophy [ID1069]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 05/09/18 **email:** TACommE@nice.org.uk /NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**TreatSMA**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose
Name of commentator person completing form:	Kacper Rucinski Dr Gennadiy Ilyashenko

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The first serious concern with the draft recommendation is that it seems to restrict itself to the RCT data while ignoring the available real-world evidence (RWE) generated in post-MA clinical use of the drug. In case of clinical research in phenotypically varied ultra-rare disorders like SMA, where RCT data cannot reasonably cover all the disease manifestations, it crucial that all available evidence is considered whilst appraising the intervention authorised in treatment of the entire spectrum of the disorder, consistently with the drug's label. RWE evidence on nusinersen effects across the SMA spectrum, which is increasingly being published in academic journals, is largely supportive of the RCT results, even as it additionally covers other populations. TreatSMA has made it available to the Committee at the consultation stage. In particular, the committee had received studies on long-term effect of nusinersen treatment in patients classified as SMA type 1 older than 6 months. The Committee was also briefed about the real-life benefits of nusinersen treatment in presymptomatic and early symptomatic patients. Furthermore, the clinical experts have highlighted to the Committee during the initial appraisal meeting that their observations indeed correlate to evidence reported by caregivers. For instance, since the 2017 start of the nusinersen expanded access programme at the Great Ormond Street Hospital in children with the most severe form of SMA, not a single child has passed away, for the first time in the hospital's history. We need to note that a recent class-IV evidence by Aragon-Gawinska *et al*, who analysed nusinersen efficacy in post-MA setting in a sample of 33 SMA type 1 patients aged 8 to 113 months, concludes that the functional improvement due to treatment was unrelated to their age at start of treatment or the number of *SMN2* copies (doi: 10.1212/WNL.0000000000006281). We at TreatSMA have anecdotal evidence of similar nusinersen efficacy in 6 adult patients with symptoms consistent with borderline SMA type 1 and 2 phenotype, with an increase of several HINE points ([redacted]) over 6 months of nusinersen treatment. We find this apparent disregard to RWE puzzling, especially considering the rarity of the disorder and the challenges related to generating data across the entire phenotypic spectrum of this monogenic disease. Increasingly, HTA agencies worldwide attach significant weight to RWE, considering it a better predictor of the treatment's effects in clinical practice. In many cases, high-quality RWE is regarded on a par with RCT evidence (several meta-analyses of HTA practice in various countries are available in academic journals). Thus, we suggest that the Committee reviews the draft ACD in consideration of all the available evidence, including in particular published and unpublished data from global clinical practice.
2	We are concerned that the negative recommendation seems to rely predominantly on the uncertainty of long-term effects of treatment, in an apparent disregard for the pathological mechanism of spinal muscular atrophy and the molecular mechanism of action of nusinersen intervention. The drug, as evidenced in clinical studies, increases the amount of cell-available SMN protein through modifying the splicing of the SMN2 gene, thus addressing the root cause of SMA pathology (i.e., the deficiency of the SMN protein in motor neuron cells).

	There is no plausible, scientific reason to speculate that the SMN2-targeting action of this antisense oligonucleotide could stop at one point. Contrary: long-term observations confirm that nearly all patients in whom the drug has been effective continue improving over years, albeit, naturally, in a variable degree. The short span of the observations in the two phase-III clinical trials did not always show major milestone achievement over the trial duration, however long-term data, including self-reported data, offer no doubt that improvement continues. While long-term data is yet to be generated, as is the case with every new drug, we stress that in view of the drug's mechanism there is no sane reason to doubt that treatment will offer increasing benefits to patients over time.
3	We are concerned that the model inadequately estimates the disease burden for UK patients and their carers, which in turn likely translates into incorrect estimation of disease state disutilities. The patient and carer health state estimation appears to have been based exclusively on a single study with data collected predominantly in Spain (Bastida et al), a country with an entirely different social care system and significantly lower associated costs; data from other countries than Spain in that study is of low quality and should be avoided in pharmacoeconomic analyses. Rough calculations carried out by TreatSMA and based on data sourced from the UK families suggest that an average disease-related financial burden ranges from around £80,000 a year in SMA type 2-3 to more than £200,000 a year in severe patients (usually classified as SMA type 1 or weak type 2). As an example, a standard basic NHS care package for SMA type 1 that consists of a provision of a single night carer for 10 hour daily carries an associated cost to NHS of £109,500 (3,650 hours contracted at £30/h). Further disease-related costs for the taxpayer include, among others: planned hospital visits, unplanned hospitalisations (including at PICU/ICU – several times a year in SMA type 1), equipment (orthoses, ventilator, cough assist, specialised wheelchair, bed, standing frame, etc., all of which have to be regularly replaced as the child grows), house adaptations (LA packages of up to £50,000), school adaptations, additional school staff member (TA) or, sometimes, specialised schooling, physiotherapy, OT, cost of mobility / car adaptations, and finally, significant loss of earnings for the family (and the cost of associated disability/housing benefits and tax credits that usually have to be provided instead). While not all of the cost would disappear with treatment right away, based on RWE the majority of treated patients are expected to significantly improve functionally over time, with improvements expected to continue for the lifetime of the patient (due to the drug's mechanism of action). Furthermore, early initiation of treatment would in all likelihood prevent functional decline and, consequently, significantly reduce the need for highly specialised care packages. For instance, thanks to preventing respiratory deterioration – which nusinersen has been proven to do in the vast majority of treated patients – the treatment will make the £109,500 night care package unnecessary. Consequently, it is entirely plausible that in some subgroups of patients, the savings brought about by early pharmacological intervention may approach the drug procurement costs even at its list price. It is worth pointing out that a HTA in even a relatively poor eastern European country Poland has assumed the annual medical and loss-of-productivity costs (excluding schooling, mobility and adaptations) in case of a SMA 1 type patient at approx. £95,000 (PLN 460,018). Summing up, TreatSMA is of the view that the disease burden has been severely underestimated in the company's economic model, whilst the Committee's expressed view that it has been overestimated is entirely unfounded.

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4	While we understand and share the global outrage at the list price of nusinersen, we need to stress that any pharmacoeconomic analyses that result in allowing or disallowing access to the only effective treatment should be based on the actual purchase price and the effective budget impact. We are aware that the manufacturer has offered substantial discounts and risk-sharing arrangements in other countries. We request that the nusinersen appraisal is reviewed in full accordance with the drug's label based on the manufacturer's full commercial offer.
5	NICE's continuous reliance on QALY analysis in determining the value of an intervention has been a subject of sustained criticism in academic circles, especially when it relates to interventions in orphan diseases. Currently, out of all EU countries, only UK and Poland use QALY as the principal determinant in reimbursement decisions, with Poland planning to move away from it at least in orphan diseases from 2019. All the other European countries use a QALY value as one of secondary parameters in HTA. Most recently, Scotland has established a separate appraisal pathway for orphan drugs in which the QALY analysis plays a supportive role. This is justified based on a distinct character of the majority of orphan conditions (80% of which are of genetic origin) as well as on different economic considerations related to the development of orphan drugs. We understand that it is not easy to change an established practice, but we, the SMA families, do not want to be hostages of a methodology that has long been discredited and replaced everywhere else with methodologies better suited to appraising orphan drugs. We need to underline that in all other European country, results of technology appraisal of nusinersen in SMA have been positive, which puts an even bigger question mark over the approach used by NICE to the detriment of thousands of those who suffer from SMA.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your

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