NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15)

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of onasemnogene abeparvovec within its marketing authorisation for treating pre-symptomatic spinal muscular atrophy.

Background

Spinal muscular atrophy, or SMA, is a rare genetic disorder that causes muscle weakness and progressive loss of movement. It is most commonly caused by defects in the gene SMN1, which leads to degeneration of motor neurones in the spinal cord (this is termed '5q SMA'). The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing. SMA causes substantial disability and may lead to increased mortality and reduced life expectancy. The most severe types of SMA typically cause death before age 2 years, although people with later-onset types of SMA usually live into adolescence or adulthood. The SMN2 gene also encodes the SMN protein and can partially compensate for the loss of the SMN1 gene. However, most SMN protein produced by this gene is not functional. An individual with SMA who has more copies of the SMN2 gene will produce more functional SMN protein and may be better able to compensate for the loss of the SMN1 gene, potentially leading to less severe disease[1]. SMA has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts.

SMA is a heterogeneous condition, which is often grouped into 5 main types, based on the age of onset of symptoms and how much motor function the person has. The types of SMA decrease in severity from type 0, in which symptoms arise before birth and babies survive for only a few weeks, to type 4 (adult-onset) which is associated with mild motor impairment and a normal life span. Types 0 and 4 are rarely diagnosed. In SMA type 1, symptoms arise before age 6 months and babies are unable to sit independently; babies with SMA have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In type 2 SMA, the onset of symptoms is between age 7 and 18 months, and people with this condition are often severely disabled and unable to walk unaided. Type 3 SMA is a heterogeneous condition, with a varying degree of muscle weakness appearing between age 18 months and 18 years; most people with type 3 SMA can walk or sit unaided at some point, but many lose mobility over time. The number of SMN2 gene copies can differ by SMA type[2].

Currently in England, only a small number of children are diagnosed with SMA before symptoms appear (known as pre-symptomatic SMA) if a sibling has been diagnosed with SMA. Pre-symptomatic diagnosis is done through genetic testing. Pre-

symptomatic SMA later develops into other SMA types 0 to 4, depending on when symptoms occur.

It is estimated that approximately 1 in 10,000 people are born with SMA[1], suggesting that about 65 people are born with SMA per year in England. Approximately 60% of all new diagnoses of SMA are SMA type 1[3].

No active treatments are currently routinely available for pre-symptomatic SMA. NICE highly specialised technology guidance 15 recommends onasemnogene abeparvovec as part of a managed access agreement for treating babies with 5q pre-symptomatic SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2. NICE technology appraisal 755 recommends risdiplam for babies with pre-symptomatic SMA with 1 to 4 SMN2 copies and NICE technology appraisal 588 recommends nusinersen for treating pre-symptomatic SMA, both as part of managed access agreements. The use of risdiplam or nusinersen is not considered to be embedded in NHS clinical practice because the availability of these treatments is contingent on further evidence generation and re-appraisal by NICE. Additionally, the significant uncertainties identified prevented NICE's committee from making a positive recommendation during these appraisals, so these treatments are not considered to be routinely commissioned. Therefore, for the purposes of this review, risdiplam and nusinersen will not be considered as comparators.

In the absence of active treatment, the condition is managed through multidisciplinary supportive care. Treatment usually follows guidelines from the International Conference on the Standard of Care for Spinal Muscular Atrophy [4,5]. Supportive care strategies do not affect disease progression but aim to minimise the impact of disability, address complications and improve quality of life. These may involve respiratory, gastroenterology, and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care.

This evaluation will consider onasemnogene abeparvovec use in people with pre-symptomatic SMA. The evaluation will use data collected in the managed access agreement established through NICE's highly specialised technology guidance 15 and in a recent clinical trial.

The technology

Onasemnogene abeparvovec (Zolgensma, Novartis Gene Therapies) is a single-use gene replacement therapy made of a viral vector that has been modified to contain the primary gene for the human survival motor neuron (SMN) protein, which is lacking or mutated in people with SMA. When injected, the vector is expected to carry the gene into the nerve cells, enabling production of sufficient amounts of SMN. It is administered intravenously. Treatment with onasemnogene abeparvovec is expected to be used exclusively in the context of a highly specialised service.

Onasemnogene abeparvovec has a marketing authorisation in the UK and is indicated for the treatment of people with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Intervention(s)	Onasemnogene abeparvovec
Population(s)	People with pre-symptomatic 5q spinal muscular atrophy and up to 3 copies of the SMN2 gene
Subgroups	None
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, age appropriate motor milestones such as sitting, standing, walking) • bulbar function (including, for example, swallowing and ability to communicate) • frequency and duration of hospitalisation • speech and communication • respiratory function • complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • stamina and fatigue • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence

	that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related Technology Appraisals:** Onasemnogene abeparvovec for treating spinal muscular atrophy (2021). NICE highly specialised technology guidance 15. Risdiplam for treating spinal muscular atrophy (2021). NICE technology appraisal 755. Nusinersen for treating spinal muscular atrophy (2019). NICE technology appraisal 588.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) chapters 48,119 and 134 Department of Health and Social Care (2018) The UK Strategy for Rare Diseases. Second Progress Report from the UK Rare Diseases Policy Board NHS England (2019) The NHS long term plan Department of Health & Social Care (2021) The UK Rare Diseases Framework Department of Health & Social Care (2019) The UK strategy for rare diseases: 2019 update to the Implementation Plan for England Department of Health and Social Care (2018) Rare Diseases Glossary. Glossary of commonly used terms and rare diseases initiatives Department of Health and Social Care (2018) The UK Strategy for Rare Diseases. Rare Diseases implementation plan for England UK Rare Disease Forum (2016) Delivering for patients with rare diseases: Implementing a strategy A report from the UK Rare Disease Forum Department of Health and Social Care (2022) NHS outcomes framework March 2022

Questions for consultation

Where do you consider onasemnogene abeparvovec will fit into the existing care pathway for pre-symptomatic SMA?

Would any additional tests be required in clinical practice with the use of onasemnogene aberparvovec in this population?

Do you consider onasemnogene abeparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?

Are their any subgroups which should be considered separately? For example, should subgroups by SMN2 gene copy number be considered?

Do you consider that the use of onasemnogene abeparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which onasemnogene abeparvovec is be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

References

1. NORD “Spinal Muscular Atrophy” (2022) https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/#subdivisions (assessed April 2022)
2. Calucho M, et al. An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018 Mar;28(3):208-215.
3. Spinal Muscular Atrophy UK (2018) https://smauk.org.uk/what-isspinal-muscular-atrophy Accessed April 2022.
4. Mercuri E et al. (2018) Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders, 28(2): 103– 115.
5. Finkel RS et al. (2018) Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders, 28(3): 197–207.