Drug Treatments for Infants with SMA Type 1

People with SMA do not have enough of a protein called 'survival motor neuron' (SMN) protein. This protein is essential for the nerve cells, known as motor neurons, that help control muscles. Motor neurons are found in the brain and spinal cord and they make contact with muscles.

The SMN protein is made in our cells from two genes, *SMN1* and *SMN2*. People who have SMA lack the *SMN1* gene but have the *SMN2* gene, which mostly produces a short SMN protein that does not work as well as a full-length protein.

The treatments below work by increasing the levels of full-length SMN protein in the body. They do so by using two different mechanisms.

Nusinersen **Also known as and referred to in this table as Spinraza™**	**Onasemnogene abeparvovec** **Also known as and referred to in this table as Zolgensma™**
How it works (The Technology) Spinraza ™ is a synthetic antisense oligonucleotide (a small piece of genetic material) that targets the *SMN2* gene and enables it to produce more functional, full-length SMN protein.	**How it works (The Technology)** Zolgensma™ is a gene therapy that delivers a healthy copy of the *SMN1* gene to motor neurons. So that the gene can reach the cells, it is packaged within a harmless virus – an adeno-associated virus subtype known as AAV9. These viruses are non-infectious, will not create more copies of themselves, and are unlikely to affect the DNA of treated patients. AAV9 is found in the natural environment, so some people, including some infants with SMA, may have natural immunity to the virus. This means that they would be ineligible to receive the treatment for safety reasons. Therefore, infants with SMA Type 1 would need a blood test to see if they have immunity before they could be considered for treatment.
How is it delivered? Spinraza™ is delivered directly into the cerebrospinal fluid (CSF). Doctors access the CSF using a lumbar puncture - a needle is inserted through the skin into the space between the vertebrae (back bones) of the spine. Doctors may use ultrasound or another imaging method to locate the best place for the insertion and they usually use a local anaesthetic such as 'numbing cream', although occasionally a general anaesthetic may be considered necessary. (con…)	**How is it delivered?** Zolgensma™ is a single, one-time treatment, which is injected into the bloodstream (intravenously). On the day of receiving Zolgensma™, doctors place a cannula (small flexible tube) into a vein in the arm or leg using a needle. The needle is then removed leaving the cannula in place. Zolgensma™ is given through the cannula over 60 minutes. Once the treatment has been delivered, the site is 'flushed' with saline solution. (con…)

How is it delivered? (continued) A small amount of CSF is drawn off and then Spinraza ™ is injected over one to three minutes. Injections are given as follows: On the first day of treatment, day 0; then day 14; day 28; day 63 Then once every 4 months Treatment continues for as long as the treating clinician and person/family agree the outcomes are beneficial.	**How is it delivered? (continued)** All patients are treated with corticosteroids before and after the treatment, in order to prevent side effects. Corticosteroids are given for at least three months, usually by mouth. After that period of time, the treating doctor assesses when and how corticosteroids can be stopped.
Which infants with SMA Type 1 would be able to have treatment? An infant has to be 'well enough' in the opinion of the doctors who are treating the patient.	**Which infants with SMA Type 1 would be able to have treatment?** An infant has to be 'well enough' in the opinion of the doctors who are treating the patient. The infant also have to have passed the screening test for immunity to AAV9.
Which cells and tissues in the body does it reach? Our nervous system is protected by a border called the 'blood-brain barrier'. Spinraza™ cannot cross this border, so it has to be delivered directly into the CSF. Upon injection, Spinraza™ reaches the motor neurons and other cell types in the spinal cord. It may have limited ability to reach other parts of the body. We currently do not know how much SMN protein may be needed in other parts of the body.	**Which cells and tissues in the body does it reach?** Upon injection into the bloodstream, the virus (AAV9) is able to cross the 'blood-brain barrier' and deliver the gene to motor neurons. It is understood that Zolgensma™ reaches cells throughout the body (brain, heart, liver, skeletal muscle and other tissues).
What is the long-term effect on the patient's genetic make-up? Spinraza™ treatment is **not** classified as a gene therapy (see section above: **How it works – The Technology**). It does not remain in the body long-term, which is why doses have to be repeated regularly.	**What is the long-term effect on the patient's genetic make-up?** Zolgensma™ is classified as a gene therapy (see section above: **How it works – The Technology**). At present, researchers believe that it is unlikely that there will be any long-term effects on the patient's genetic make-up, or that these changes will be passed on to their offspring. However, gene therapy is a relatively new technology and long-term data is not available yet to be able to confirm its long-term safety.

What are the potential risks and how are these managed?	What are the potential risks and how are these managed?
The most common side effects reported in clinical trials (seen in more than ten percent of patients) are back pain, headache and vomiting. Additionally, the following side effects are possible, but the frequency at which they occur is not known: • Serious infection related to lumbar puncture (e.g. meningitis) • Hydrocephalus (build-up of too much fluid around the brain) • Meningitis not caused by an infection. Other products that are in the same medicine group as Spinraza™ have been shown to affect the kidneys and the cells in the blood that help clotting. The treating doctor may run tests to check that these systems are working normally. Management of possible side effects and potential risks of treatment would be discussed with the treating consultant. After the decision has been made to prescribe a patient Spinraza™, patients would also receive a patient information booklet with things to know and understand about Spinraza™ including possible side effects. All side effects should be reported, and patients are encouraged to discuss any side effects with their treating consultant.	The most common side effects reported in clinical trials (seen in more than five percent of patients) are abnormal blood test results ('elevated liver enzymes') and vomiting. There is a risk of serious liver injury with Zolgensma™. To prevent and manage this, patients receive corticosteroids before and after treatment. Prior to receiving Zolgensma™ and at least three months after treatment, patients undergo regular blood tests. The purpose of these tests is to monitor liver and heart function and the amount of platelets (the cells in the blood that help clotting). Management of possible side effects and potential risks of treatment would be discussed with the treating consultant. After the decision has been made to prescribe a patient Zolgensma™, patients would also receive a patient brochure with things to know and understand about Zolgensma™ including possible side effects. All side effects should be reported, and patients are encouraged to discuss any side effects with their treating consultant.

Clinical Trial results	Clinical Trial results
It is important to note that the results from Spinraza ™ and Zolgensma ™ clinical trials are not directly comparable due to different study lengths and methods used to measure efficacy.	
Spinraza™ has been tested in clinical trials since 2011.	Zolgensma™ has been tested in clinical trials since 2014
The pharmaceutical company who developed the treatment (Biogen) conducted a clinical trial, called ENDEAR, with 121 children with SMA Type 1. In the trial, two-thirds of the patients **(80 children)** were treated with Spinraza™.	The pharmaceutical company who developed the treatment (AveXis) conducted a clinical trial, called START, with 15 children with SMA Type 1 under two years of age. In the trial, three patients received a minimally effective dose of Zolgensma ™ and **12 children** received the recommended dose.
One-third (41 children) were sham treated. Sham treated children did not receive Nusinersen Spinraza™, but they experienced the same procedures as the children who *were* treated with it. This means that the people running the clinical trial could more easily analyse the effect of the treatment.	The trial was conducted without a sham arm and all the patients knew they were receiving the treatment.
The trial lasted 13 months and was stopped early as the positive results from the treatment group meant that it was no longer ethical to have children receiving the sham.	The trial lasted 24 months.
Of the 80 children who had received at least one dose of nusinersen before the trial ended **61% were alive** and did not require a ventilator, compared to 32% not receiving treatment.	At 24 months, of the 12 children who received the recommended dose, **100% were alive.**
Motor milestones achieved: Of the 73 patients who received nusinersen for at least six months 51% improved their motor milestones (i.e. the proportion achieving a pre-defined motor-milestone responder criteria) 22% of infants had head control, 10% could roll over, 8% could sit without support, 1% were able to stand. None of the sham-treated children had an improvement.	**Motor milestones achieved:** Amongst the children treated with the recommended dose: 92% achieved head control, 75% could roll over, 92% could sit unassisted.
Breathing Outcomes	**Breathing Outcomes**
Of the 80 children who had received at least one dose of nusinersen before the trial ended **61%**	None of the children needed to use permanent assisted ventilation.

were alive and did not require a ventilator, compared to 32% not receiving treatment.	
Current global availability for infants newly diagnosed with SMA Type 1 Spinraza™ has been available globally since Autumn 2016, initially via Biogen's Expanded Access Programme (EAP) and subsequently, as of May 2019, has been agreed for funding by 27 European countries including England and Wales, Northern Ireland and Scotland.	**Current global availability for infants newly diagnosed with SMA Type 1** Zolgensma™ has only been available via clinical trials. These are now closed to any new infants. On 24th May 2019, Zolgensma™ was licensed for provision in the USA. According to the FDA (US regulator) prescribing information, it is for the treatment of children less than two years of age with SMA, who have mutations in both copies of the *SMN1* gene. This includes children who have not yet experienced symptoms. An application has been made to EMA (the European regulator) for a licence in Europe. It is not yet known what the age restriction will be. NICE's review as to whether to recommend the treatment for provision by NHS England will depend on this licence and what application has been made to NICE by Avexis

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