A Summary:

Nusinersen (also known as SPINRAZA™) treatment for those diagnosed with SMA Type 1

Nusinersen (SPINRAZA™) is the first drug developed specifically to treat 5q SMA.

This leaflet aims to provide a summary for any parents who are considering the possibility of treatment for their child who has SMA Type 1. It's intended to be used in your discussions with your medical team.

The most common form of SMA is known as '5q SMA' due to its genetic cause. 5q SMA includes the different 'Types' or clinical classifications Types 1, 2, 3 and 4. For more information about 5q SMA and its causes, please see:

www.smauk.org.uk/information

For more information about nusinersen and how it works, please see:

www.smauk.org.uk/nusinersen

spinal muscular atrophy uk

Help for today, hope for tomorrow

Includes

What does nusinersen do and how does it work?

SMA affects a set of nerve cells called the lower motor neurons which run from the spinal cord out to our muscles. The lower motor neurons carry messages that make it possible for us to move the muscles that we use to crawl and walk, to move our arms, hands, head, and neck, and to breathe and swallow.

For our lower motor neurons to be healthy, we need to produce an important protein called Survival Motor Neuron (SMN) protein. Most people have two working copies of a gene called *Survival Motor Neuron 1* (*SMN1*)[1], which means they can produce enough SMN protein. People who have 5q SMA have mutations or deletions in both copies of their *SMN1* gene.

Having two faulty *SMN1* genes means that an individual is only able to produce very low amounts of the SMN protein. This causes their lower motor neurons in their spinal cord to deteriorate. Messages from their spinal cord don't efficiently get through to their muscles, making movement difficult. Their muscles waste due to lack of use and this is known as muscular atrophy.

Another gene called *SMN2* produces a small amount of SMN protein. In SMA, *SMN2* partially compensates for the lack of a functional *SMN1* gene. It's sometimes called the 'back-up' gene. People have 0 – 8 copies of the *SMN2* gene. Having more copies of *SMN2* means that more SMN protein can be made, usually resulting in reduced condition severity.

Nusinersen is a highly-specialised medicine that can increase the amount of SMN protein produced by the *SMN2* gene[2].

It's currently not known how much SMN protein is needed by other cells in the body, but experiments with laboratory mice indicate that increasing SMN protein levels in many different cell types has a greater treatment effect than when increased in the motor neurons alone.

In collaboration with researchers, nusinersen was developed by Ionis Pharmaceuticals and Biogen Idec. The clinical trials conducted by Biogen have been with children with SMA Types 1, 2 or 3; there have been no trials in infants with SMA Type 0 or adults with SMA Types 1, 2 or 3 or SMA Type 4.

You can find more information about how nusinersen works, here:

www.smauk.org.uk/more-detail-on-how-nusinersen-works-in-sma

More about how nusinersen is given and why

To have the best chance of working, nusinersen needs to reach the motor neurons within the spinal cord. The spinal cord and brain together make up the **central nervous system** (**CNS**). This is bathed by what is called **cerebrospinal fluid** (**CSF**). The CSF has three main functions: it protects the CNS from trauma; it supplies nutrients to nervous system tissue; it removes waste products caused by cerebral metabolism (all the chemical reactions involved in maintaining the living state of the cells involved in the CNS).

The cerebrospinal fluid is separated from the blood circulating in the rest of the body by the **blood-brain barrier**. This acts as a border protecting the brain from any pathogens (bacteria, viruses or other microorganisms that can cause disease) and toxins (poisons originating from plants or animals) in the blood circulatory system that could cause brain infections. At the same time it allows vital nutrients to reach the brain. The blood-brain barrier also restricts the ability of drugs to pass into the CSF and reach the central nervous system.

If nusinersen is given by an intravenous (IV) injection into the blood stream, it cannot cross the blood-brain barrier to reach the central nervous system. Currently, therefore, the only way nusinersen can reach the spinal cord and motor neurons in the CNS is for doctors to use what's called an intrathecal (IT) injection directly into the cerebrospinal fluid. They do this using a **lumbar puncture procedure**.

Injections of nusinersen are given as follows:

A series of **loading doses** are administered to get the level of the drug to an effective concentration for the patient – this is the amount of the drug in the CSF. These take place:

- On the first day of treatment, day 0
- Then around day 14, day 28 and day 63

There are then **maintenance doses** every 4 months to maintain the level.

As nusinersen has to be injected into the spinal cord and cannot cross the blood-brain barrier, it may have limited ability to reach cells in other parts of the body.

Lumbar puncture procedure - This is when a needle is inserted through the skin into the space between the vertebrae (backbones) of the lower spine. Doctors may use x-ray or ultrasound to locate the best place for the needle insertion and they will usually use a local anaesthetic such as a 'numbing cream', although occasionally a general anaesthetic may be considered necessary. A small amount of CSF is drawn-off before nusinersen is injected over one to three minutes.

What have the clinical trial results shown for children with SMA Type 1?

Biogen has conducted several trials treating children with SMA Types 1, 2 and 3.

You can read more about how clinical trials work, including the different phases of trials, here: www.smauk.org.uk/clinical-trials

➢ The ENDEAR Trial

Biogen's clinical trial, called ENDEAR[3,4], was with 122 children with SMA Type 1 of whom two-thirds were treated with nusinersen. One third of these received sham treatment – a small needle prick to the skin over the lumbar area of the spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection.

At a pre-specified time point in this study, the interim analysis of results showed a significantly higher number of patients in the nusinersen group had a motor-milestone response compared with patients in the sham group. This resulted in the trial being ended early after 13 months and patients from the sham group being moved on to active treatment. It is important to note that when this trial ended some children had completed the trial and had treatment for all 13 months, others were only part-way through.

The results for all the treated children, no matter how long their treatment had been, were that:

- 51% improved their **developmental motor milestones** as measured on the **HINE scale[5]** for assessing motor function compared with 0% of the placebo group. These were the **additional** skills gained for the treated group:
    - 22% of infants had head control;
    - 10% could roll over;
    - 8% could sit without support;
    - 1% able to stand, compared with 0% of the placebo group.
- 71% of the treated group made a 4-point gain using the **CHOP-INTEND[5]** (a second scale that also measures **motor function**) compared with 3% of the placebo group.
- 61% of the treated group did not require permanent ventilator support and were still alive. Permanent ventilator support is

The aim of treatment is to achieve any of these outcomes, but it's not possible to say with any certainty that treatment will lead to these improvements for any individual child.

defined as more than 16 hours non-invasive ventilation support (NIV such as BiPap) for more than 21 days due to the impact of the condition. It does not include those who have to have NIV due to an ongoing infection. This compared with 32% of the placebo group.

➢ Clinical Trials Overview

In general, evidence suggests that early treatment may be necessary to maximise the benefit of the drug[3]. Clinical experience and understanding of the usual course of SMA without treatment (the natural history) suggests that earlier treatment is more beneficial. This is because nusinersen may preserve the function of neurons and muscles and the earlier the treatment, the more healthy neurons and muscles there are that may be preserved. This, in turn, suggests that treatment in those with less severe symptoms (i.e. those who have more healthy neurons and muscles) may have the greater effect on outcomes[6].

Our website publishes updates regularly. You may want to check to see whether any further studies have been reported since this sheet was updated:
www.smauk.org.uk/key-clinical-trial-results

What are the possible side effects of nusinersen?

Any drug, even ones that are commonly prescribed or sold over the counter, may cause possible side effects. Side effects of medications will have been noted and reported during their clinical trials. They're also picked up through the ongoing systems that are in place to monitor medications and their use in the 'real world'. All possible side effects are always listed in the Patient Information Leaflet or Summary of Product Characteristics that accompany a medication; they are grouped as 'very common' / 'common' / 'uncommon' / 'rare'. Reporting side effects of medications is hugely important in order to protect people and is everyone's responsibility. See:

www.nhs.uk/common-health-questions/medicines/what-are-side-effects/

Your child's medical team will discuss possible side effects with you before you decide whether to go ahead with treatment. If your child starts treatment, they will explain any signs or symptoms you need to look for. They will also monitor other aspects of your child's health and wellbeing, for example they will monitor your child's blood pressure. If you have any questions or concerns, make sure to ask them.

Nusinersen's possible side effects were noted and reported in the clinical trials. Both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)[7] found it to have an acceptable safety profile and as such it noted there can still be a number of side effects that should be monitored for. These and the possible frequency ('very common' / 'common' / 'uncommon' / 'rare') are listed in the Patient Information Leaflet or Summary of Product Characteristics that accompany the medication.

➢ Effects on blood clotting

Platelets are important components of the blood that are necessary for clotting of blood. If the platelet level is low, there is a risk of bruising and bleeding or haemorrhage. Nusinersen (and other therapies that work in the same way) can affect the levels of platelets in the blood.

Doctors may check platelet levels before starting nusinersen and then at regular points for as long as treatment continues, though this is currently not required in the UK. If the platelet count is very low (below 50: normal levels are 100 - 150), it may not be safe to go ahead with the administration of nusinersen.

➢ Effect on kidney function

Nusinersen (and other therapies that work in the same way) can affect how well the kidneys work, particularly how effectively the tiny filtering units, called glomeruli, can filter waste products from the blood. Doctors may check kidney function by a blood test and by testing a urine sample before starting nusinersen and then at regular points for as long as treatment continues.

➢ Other possibilities

The following other possibilities were reported during clinical trials, but these may not have been due to the treatment itself; for example, they could have been due to the SMA or an unrelated infection:

- Respiratory symptoms, including breathing difficulties and lung collapse
- Constipation
- Low salt levels

- Skin rash
- High temperature
- Drooling and excess saliva production
- Runny nose

Risk of Hydrocephalus

This is a condition in which fluid builds up in the brain, typically in young children, enlarging the head and sometimes causing brain damage. There can be many different causes.

A small number of cases of hydrocephalus were picked up via the 'reporting side effects' systems in place; most cases developed after 2 to 4 loading doses[8]. This side effect was classified as 'rare' and involved a form of hydrocephalus caused by over or under production of CSF during treatment with nusinersen. From September 2018 healthcare professionals were advised by the UK Medicines and Healthcare products Regulatory Agency (MHRA) to discuss this risk with parents considering the treatment.

What are the possible side effects of the lumbar puncture procedure?

There are a number of side effects that can happen due to the procedure rather than the medication. The most frequent are:

- Local pain / discomfort in the back at the site of the lumbar puncture. This should settle within a few days.
- Headache, sometimes with vomiting. This usually settles within a day or two, but occasionally can continue for a longer period and need hospital treatment

Other much rarer complications include:

- Bleeding – this is unlikely unless there is a problem such as a low platelet count. If a disorder is identified that predisposes to bleeding, advice will be given as to whether it is safe to go ahead.
- More persistent headaches. When these symptoms are more persistent, it may be because there is a continuing small leak of the fluid (CSF) and very rarely this can then need treatment to stop the continuing leakage.

Mostly the procedure is carried out without sedation or general anaesthesia. If either of these are required, though healthy individuals usually cope well, there are additional risks for anyone who has a pre-existing medical condition, such as SMA. For instance, if breathing is already affected by SMA, breathing problems may develop. Individuals can also feel and be sick, feel dizzy or seem agitated when coming around from the anaesthetic or sedation. Monitoring by medical staff before, during and after the procedure helps to minimise these risks.

What are the long-term effects of nusinersen treatment?

As with any new therapy, more is learnt about it the longer it's used. Clinical trials for nusinersen treatment only began in 2011, so there's only experience since this date, meaning that the longer-term outcomes are not yet known. However, Biogen is conducting a further follow-up study called SHINE. This involves patients who previously completed the ENDEAR (Type 1) trial and the CHERISH (Type 2) trial.

Nusinersen has also been given as a treatment in a number of countries to many children with SMA Type 1 via Biogen's Expanded Access Programme since autumn 2016. It's also available in many countries now via their health systems – the ages and Types of SMA covered varies. 'Real world' data can be collected from these.

You can read summaries of published articles that review treatment outcomes that have been seen in these 'real world' studies, here: www.smauk.org.uk/other-published-summaries-of-treatment-outcomes

Is any other care and management needed as well as nusinersen?

The answer is absolutely, yes. Nusinersen is not a cure for SMA Type 1. While new treatments are important, it's essential to get other more basic care and intervention correct. One of the biggest impacts on individuals with SMA has been with the introduction of the International Standards of Care for SMA (SoC)[9]. These set out recommendations based on the minimal care and support that **anyone with SMA should receive wherever they live and whatever treatment regime they're under**. They include breathing support, nutritional support and advice, physiotherapy, spinal and bone care, and palliative care. It's likely that any new treatment will be more likely to be more effective if all other aspects of medical care are optimised.

Palliative care is an active approach to care, aiming to support the physical, emotional, cultural, spiritual and practical needs of the infant and family from the point of diagnosis onwards. The overall aim is to achieve the best quality of life for any child and their parents and carers.

Are there any other drug treatments or trials for 5q SMA?

Nusinersen is the only treatment currently available through the NHS. There are other treatments potentially on the horizon (see: www.smauk.org.uk/drug-treatments-screening-whats-happening-now). It's important that you get the most up-to-date information from your medical team about what these might be and whether your child may potentially be eligible for any of these or for any current or upcoming clinical trials.

Future clinical trials will have defined entry criteria and whilst some may allow entry for children on nusinersen, others may not. Similarly, any new potential treatment has to go through a standardised appraisal and approval process and, if approved by the NHS, it is possible – even likely – that specific eligibility criteria would be spelt out. Again, whilst some may include children on nusinersen, others may not. If a change from one treatment to another is being considered, criteria may include, for example, a length of time that needs to have elapsed since the last treatment.

All clinical trials are listed on the global website www.clinicaltrials.gov

Each listing includes details such as eligibility criteria, where in the world the trial is taking place and whether the trial is currently recruiting.

I may be interested in nusinersen, what should I do now?

Talk to your child's medical team. If they agree that treatment is safe and potentially beneficial for your child, and your child meets the criteria for eligibility for access as set out by your country's NHS (see: www.smauk.org.uk/uk-access-now), it's still a very personal decision whether to ask to go ahead. Clinical trial results have been published and follow-up data is being collected but, as for any new treatment, uncertainties remain around both the long-term outcomes and the specific outcomes for any individual child.

Your medical team will assess your child and consider the potential risks and benefits of treatment with nusinersen. They will use knowledge from clinical trials and subsequent 'real world' data to help inform you about the possible benefits of treatment for your child. They will also tell you if they think that the risks of treatment outweigh any possible benefits. Make sure that you ask them if you have any questions, for example about: benefits that you might see with your child's motor function; breathing ability; ability to eat and drink; ability to communicate and length of life.

You may also want to ask about the possibility of your child having a long-term disability and the potential impact that this may have

If you do decide to go ahead with treatment, you can change your mind at any time, even after you've signed the form consenting to treatment. If you want to withdraw or stop treatment, discuss this with the doctors; they'll completely respect your wishes and ensure other appropriate care and support is in place.

on your need for specialist equipment, home environment, school and impact on independent living.

If you decide you want to go ahead, doctors will explain again about the treatment and what it involves. They will tell you about what agreement is in place for your part of the UK - how the NHS will fund your child's treatment and for how long (for example in England a 5-year Managed Access Agreement (MAA) started in July 2019). Doctors will assess your child's eligibility in line with the agreement and explain how they will provide treatment. This will include talking with you about what criteria there are for deciding if treatment is working and should continue, or if it should be stopped, so that you're clear about this as well. For example, doctors may want to stop treatment if they don't feel it's in your child's best interests, perhaps because their condition has worsened. If this did happen, they would discuss this fully with you and make sure other appropriate support and care is in place.

Your medical team will then ask you to record that you understand what they've said and give your permission for treatment. They'll talk to you about the plan for when and how this would take place.

Sources of Support

Your medical team are the best people to talk to about the treatment, and about the hospital and community support available to you.

In a more general way, **Spinal Muscular Atrophy UK** provides a Support and Outreach Service for families by email, phone, text and outreach home-visiting. Our team offer personalised support and information and are available to answer questions and talk things through. Though we don't give medical advice, we can discuss with you the support you and your family can access.

Further Resources

➢ Biogen's information about Spinraza™

This can be found here: www.medicines.org.uk/emc/product/2715

Open the tab **'Patient Leaflet'** for information about the product including any possible side effects. If you open the tab **SmPC** (Summary of Product Characteristics) you can read their summary of clinical trial results in section 5.1

➢ SMA UK research-related information:

This website section tells you about other research developments: www.smauk.org.uk/drug-treatments-screening-whats-happening-now You may also find our information sheet 'How clinical trials work' useful: www.smauk.org.uk/clinical-trials

You can keep up-to-date by signing up for SMA UK's **monthly E-news**: www.smauk.org.uk/sign-up-for-mailings

➢ SMA UK condition-related information

You'll find a wide range of other leaflets and resources in this section of the website: www.smauk.org.uk/information

If your child has been recently diagnosed, you may find one of these guides helpful: www.smauk.org.uk/recently-diagnosed-with-sma

➢ Standards of Care for Spinal Muscular Atrophy (2017)

You can read or download **A Guide to the 2017 International Standards of Care for SMA** here: www.smauk.org.uk/international-standards-of-care-for-sma

Health & care information you can trust
The Information Standard Certified Member

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References

1. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, Benichou B, Cruaud C, Millasseau P, Zeviani M, Le Paslier D, Frézal J, Cohen D, Weissenbach J, Munnich A, Melki J (1995) Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*, 80: 155-165.

2. Spinal Muscular Atrophy UK (2017) 'More detail on how nusinersen works in SMA.' www.smauk.org.uk/more-detail-on-how-nusinersen-works-in-sma (Accessed 13th September 2019)

3. Servais L, Farra M, Finkel R S, Kirschner J, Muntoni F, Sun P, Gheuens S, Schneider E, Farwell W (2017) Nusinersen demonstrates greater efficacy with shorter disease duration: final results from the ENDEAR study in infants with Spinal Muscular Atrophy. Poster presented at the 22nd International Annual Congress of the World Muscle Society, Saint-Malo, France.

4. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, Chiriboga CA, Saito K, Servais L, Tizzano E, Topaloglu H, Tulinius M, Montes J, Glanzman AM, Bishop K, Zhong ZJ, Gheuens S, Bennett CF, Schneider E, Farwell W, De Vivo DC; ENDEAR Study Group (2017) Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med* 377: 1723-1732.

5. Murphy A, Mayhew A (2019) Physiotherapy-based measures (HINE, CHOP INTEND, HMFSE) for people with SMA and how they are used to monitor treatment outcomes https://smauk.org.uk/physiotherapy-based-measures-hine-chop-intend-hmfse-for-people-with-sma-and-how-they-are-used-to-monitor-treatment-outcomes (Accessed 13th September 2019)

6. Sumner CJ, Crawford TO (2018) Two breakthrough gene-targeted treatments for spinal muscular atrophy: challenges remain. *J Clin Invest* 128: 3219-3227.

7. European Medicines Agency (2017) 'Committee for Medicinal Products for Human Use Assessment Report Spinraza' (EMA/289068/2017). Available at: https://www.ema.europa.eu/en/documents/assessment-report/spinraza-epar-public-assessment-report_en-0.pdf (Accessed 13th September 2019)

8. Medicines and Healthcare products Regulatory Agency (2018) 'Nusinersen (SpinrazaTM): reports of communicating hydrocephalus; discuss symptoms with patients and carers and investigate urgently'. Available at: https://www.gov.uk/drug-safety-update/nusinersen-spinraza-reports-of-communicating-hydrocephalus-discuss-symptoms-with-patients-and-carers-and-investigate-urgently (Accessed 13th September 2019)

9. A Guide to the 2017 International Standards of Care for SMA www.smauk.org.uk/international-standards-of-care-for-sma (Accessed 13th September 2019)

We are grateful to the writers and reviewers who assist us in our information production. A list of who this includes may be viewed here: www.smauk.org.uk/our-writers-and-reviewers-panel

If you have any feedback about this information, please do let us know at: supportservices@smauk.org.uk