A Summary:

Nusinersen (also known as SPINRAZA™) treatment for those diagnosed with SMA Type 2 or 3

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

This leaflet aims to provide a summary for anyone who affected by SMA Type 2 or 3 who's considering the possibility of treatment with nusinersen for their child, or themselves. It's intended to be used in your discussions with your / your child's 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 Types 2 & 3?

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 CHERISH Trial

Biogen's clinical trial, called CHERISH[3] was with children with SMA Type 2 aged 2-12 years. Participants had to be able to sit independently and have no history of the ability to walk independently. They also couldn't take part if they needed help with breathing, had significant curvature of the spine, or were fed via a gastric tube. 126 children were screened and enrolled with the trial; the youngest child was aged 2 years, the oldest child was aged 9 years.

The trial was set up to assess how children treated intrathecally with nusinersen via a lumbar puncture (see section "How is nusinersen given?") on days 1, 29 and 85, and with a maintenance dose on day 274, compared to those having a sham procedure – a small needle prick to the lower back, which was covered to simulate the appearance of a lumbar puncture. Children and families didn't know whether they were receiving the nusinersen or sham treatment (a double-blind study). The assessment of the impact (or outcome) of the treatment was to be primarily measured using a physiotherapy assessment tool called the Hammersmith Functional Motor Scale-Expanded (HFMSE)[4,5].

Multiple imputation is a generally accepted approach to the problem of missing data. It aims to allow for the uncertainty about the missing data by creating several different plausible **imputed** data sets and appropriately combining results obtained from each of them.

Two thirds (84) of the children received nusinersen treatment; 42 received the sham procedure. The first child underwent the first part of the procedure on November 24th 2014, and the last child's last visit was on February 20th 2017.

The study had set a pre-specified time point of 31st August 2016 for an **interim analysis** of the results. This was when all children had been enrolled for at least 6 months and at least 39 children had completed the 15-month assessment.

	Children who had had full 15 months treatment – **observed data**	Children who had had at least 6 months treatment – **multiple imputed data**	**Total**
Nusinersen Treatment	35	49	**84**
Sham Treatment	19	23	**42**
Total	**54**	**72**	**126**

Table 1. Numbers of children taking part in the Interim Analysis

The interim analysis of these children's outcome measures confirmed the positive effect of nusinersen. This led to the trial being ended early, as it was considered unethical to continue to give the sham procedure to a group of children when nusinersen was effective at treating symptoms.

All the children who had not had a 15-month assessment were invited to attend a visit that represented the end of the double-blind study period; by this time, some but not all of these children had completed the 15-months treatment schedule. At this visit, all assessments that had been scheduled for the 15-month assessment were performed. The results of **all** children who accepted this invitation were therefore presented as the **final analysis**.

	Children who had had full 15 months treatment – **observed data**	Children who had had at least 6 months treatment – **multiple imputed data**	**Total**
Nusinersen Treatment	66	18	**84**
Sham Treatment	34	8	**42**
Total	**100**	**26**	**126**

Table 2. Numbers of children taking part in the Final Analysis

The Results

- In the **interim analysis**, the HFMSE score for the nusinersen treated group improved by an average of 4.0 points compared to their original baseline scores, whereas those in the sham group showed an average decrease in their scores by -1.9 points. Therefore, there was an average difference of 5.9 points between the treatment and sham groups, which is a statistically significant result.

- In the **final analysis**, the HFSME score for the nusinersen treated group improved by an average of 3.9 points compared to their original baseline scores, whereas those in the sham group showed an average decrease of -1.0 points. Therefore, there was an average difference of 4.9 points between the treatment and sham groups, which was a statistically significant result. 57% of nusinersen-treated patients showed an improvement of at least 3 points in their HFMSE score from baseline to month 15, compared to 26% in the sham group which was a statistically significant result.

- In the **final analysis**, 20% of children receiving nusinersen treatment achieved at least one new developmental motor milestone compared to 6% in the sham group. Statistically this difference was not found to be significantly higher.

- The incidence of adverse events and serious adverse events were similar between the nusinersen and control groups[3] (see section "What are the possible side effects?").

In their article summarising the results, Mercuri et al[3] say:

"This trial had some limitations. For example, the strict eligibility criteria (i.e., no severe contractures or scoliosis, outlying HFMSE scores, respiratory insufficiency, or reliance on a gastric tube) meant that the enrolled population was more homogeneous and younger than the population that is encountered in the clinical-practice setting. In the trial, 16% of the enrolled children were 6 years of age or older. The results we report here are consistent with the results of previous open-label studies that enrolled children up to 15 years of age. ***The studies showed that nusinersen had positive effects in populations of children with SMA type 2 or 3 that were broader and more heterogeneous than the population enrolled in this trial.****"*

➢ Longer-term Results from the Phase 1 and 2 Studies for Later-Onset SMA

The results of a follow-up study of the longer-term effects of nusinersen treatment for patients with later-onset SMA were published in 2019[6]. This was of children age 2 – 15 years who had initially received nusinersen as part of the first, early phase 1 and 2 studies into nusinersen. Though none of these children were included in the CHERISH (Type 2) phase 3 trial (results above) and ENDEAR (Type 1) trial that resulted in nusinersen being approved for SMA, these phase 1 and 2 studies were vital to the development of these two trials.

The trial and follow-up study were conducted to assess how the motor function of patients treated with nusinersen changed over time compared to measures from a different study that followed up untreated children with SMA (natural history study). Motor function was assessed using the Hammersmith Functional Motor Scale expanded (HFMSE), the 6-minute walk test (how far you can walk in six minutes on the flat), and the Upper Limb Module (which assesses only the function of the arms).

The World Health Organisation (WHO) definition of walking unaided is that the person can take at least five steps independently in the upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

In the **Phase 1** study, which started in October 2012, there were 28 children: 11 with SMA Type 2; 17 with SMA Type 3. Of the children with SMA Type 3: 4 could no longer walk unaided and 13 were still able to walk unaided. All participants received three nusinersen injections into the spine (intrathecal) - at days 1, 29 and 85. As safety was the primary concern in this early testing of nusinersen, the medication was given in different dosages to ensure it was safe, before all participants in Phase 2 were given the highest dose (12mg) for each injection.

Of these original 28 children, 24 went on to have all doses in **Phase 2**, the longer follow-up part of the study, where participants received treatment after 1 year (from the beginning of the trial), then at six monthly intervals – 4 doses in total on days 1, 169, 351 and 533. The date of the last child's last treatment was January 24th 2017, and participants were followed up after this.

The main findings from the follow-up study were:

HFSME Results

- 9 out of 11 children with SMA Type 2 showed a clinically significant improvement as they had an increase of 3 or more points from their initial assessment in the HFMSE. Overall, the average improvement for these children was 10.8 points which is clinically significant
- 4 out of the 11 children with Type 3 showed a clinically significant improvement as they had an increase of 3 or more points from their initial assessment in the HFMSE. This included one child who was non ambulant. Overall, the average improvement for these children was 1.8 points which is not regarded as clinically significant.

An increase of 3 points or more from the time of an initial assessment in the HFSME is considered clinically significant for Type 2 and Type 3, no matter what the timeframe is for this increase.

Six-minute walk test (6MWT) Results

- Infants with SMA Type 2 are not expected to walk. One infant with SMA Type 2 age 2.1 years at first dose, gained the ability to walk. They first completed the 6MWT at the day 650 visit (total distance walked 25.5 metres) and demonstrated continuous improvements over time; by day 1,150 visit, their 6MWT was 180 metres.
- Children with SMA Type 3 showed clinically meaningful progressive improvements from their baseline in the 6MWT with an average improvement in walking distance of 92 metres by day 1,150.
- 2 of the 4 children who were previously able to walk but had lost that ability before the baseline assessment regained the ability to walk independently during the course of the studies. In addition, 6 of the 12 children (50%) assessed at the day 253 visit demonstrated clinically meaningful improvements in 6MWT distance (previously defined as ≥ (greater or equal to) 30-metre increase from their baseline) and 8 of 8 (100%) demonstrated clinically meaningful improvements by day 1,050.

Upper Limb Module Results

- The children with SMA Type 2 were seen to progressively improve in their upper limb scores; all those with SMA Type 3 achieving the maximum score by the end of the study.

The findings of this study suggest that in treatment of SMA Types 2 and 3 with nusinersen, there may be long-term (2-3 years) positive effects on muscle function.

➢ Clinical Trials Overview

In general, evidence suggests that early treatment may be necessary to maximise the benefit of the drug[7,8]. 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[9].

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 / your child's medical team will discuss possible side effects with you before you decide whether to go ahead with treatment. If you or your child start treatment, they will explain any signs or symptoms you need to look for. They will also monitor other aspects of your / your child's health and wellbeing, for example they will monitor 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)[10] 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 which 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.

➢ Effects 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[11]. 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 adults and 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 is 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 an 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 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 CHERISH (Type 2) trial and the ENDEAR (Type 1) trial.

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

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 is 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.

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

The answer is absolutely, yes. Nusinersen is not a cure for 5q SMA. 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)[12]. 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 are under**. They **may include** breathing support, nutritional support and advice, physiotherapy, spinal care and bone care, and palliative care. It's likely that any new treatment will 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 patient and family from the point of diagnosis onwards. The overall aim is to achieve the best quality of life for all.

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 you /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 those 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 those 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 / your child's medical team. If they agree that treatment is safe and potentially beneficial, and you / 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.

Your medical team will assess you / 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 you /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 / your child's mobility and breathing. Discuss what outcomes matter to you in terms of how you / your child manage(s) day-to-day life.

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.

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 / 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 / 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 / your child's best interests, perhaps because the 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:

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. and Melki, J. (1995) 'Identification and characterization of a spinal muscular atrophy-determining gene', *Cell*, 80(1), pp. 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 (last accessed 13th September 2019)

3. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. New England Journal of Medicine. 2018;378(7):625-35.

4. O'Hagen JM, Glanzman AM, McDermott MP, Ryan PA, Flickinger J, Quigley J, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscular Disorders. 2007;17(9):693-7.

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 (last accessed 13th September 2019)

6. Darras BT, Chiriboga CA, Iannaccone ST, Swoboda KJ, Montes J, Mignon L, Xia S, Bennett CF, Bishop KM, Shefner JM, Green AM, Sun P, Bhan I, Gheuens S, Schneider E, Farwell W, De Vivo DC; ISIS-396443-CS2/ISIS-396443-CS12 Study Groups (2019) Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. Neurology 92: e2492-e2506.

7. Servais L, Farra M, Finkel R S, Kirschner J, Muntoni F, Sun P, Gheuens S, Schneider E, Farwell W. 'Nusinersen demonstrates greater efficacy with shorter disease duration: final results from the ENDEAR study in infants with Spinal Muscular Atrophy' www.smauk.org.uk/files/files/Research/Poster%203.pdf (last accessed 13th September 2019)

8. De Vivo et al. (2019) Nusinersen in Infants Who Initiate Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Efficacy and Safety Results From the Phase 2 NURTURE Study (S25.001). Neurology 92 (15 Supplement). SEE CONCLUSION - https://n.neurology.org/content/92/15_Supplement/S25.001 (last accessed 13th September 2019)

9. Sumner C.J., Crawford T.O. 'Two breakthrough gene-targeted treatments for spinal muscular atrophy: challenges remain' J Clin Invest. 2018: 128(8): 3219-3227

10. European Medicines Agency (2017) 'Committee for Medicinal Products for Human Use Assessment Report Spinraza' (EMA/289068/2017). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_- (last accessed 13th September 2019)

11. 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 (last accessed 13th September 2019)

12. A Guide to the 2017 International Standards of Care for SMA www.smauk.org.uk/international-standards-of-care-for-sma (last 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