**Q and As from Patient groups – submitted 8th March – replies below from Novartis 16th April. No response to date from Scotland - enquiry to Ian Horrocks at Glasgow; SMC couldn't assist**

## Who can access NHS England funded zolgensma treatment?

### 1. Which children are potentially eligible for treatment?

**England:**

**From NHSE advice 16th March 2021**

a) Children with SMA Type 1 up to 6 months of age
b) Children with SMA Type 1 over 6 months of age and below 12 months of age
c) Children with type 1 SMA who are over 12 months old within the scope of the drug's European Medicines Agency (EMA) marketing authorisation
d) Children with type 1 SMA who have been using treatment e.g., with nusinersen (Spinraza) or Risdiplam (Evrysdi) and fall within the scope of the European Medicines Agency marketing authorisation.
e) Any pre-symptomatic SMA infants identified who have up to 3 copies of the SMN2 gene

Children in any of these groups who are having more than 16 hours per day of non-invasive ventilation, or who have a tracheostomy, are not eligible, under draft NICE recommendations. These recommendations could change following NICE consultation.

Children in groups b, c and d will be considered by a national multi-disciplinary team (NMDT) made up of clinical experts from the gene therapy centres and other centres. The NMDT will consider a number of clinical factors in their decision making based on clinical experience in the UK and abroad, data from the trials and the European consensus statement.

Children in groups a and e will be considered for treatment by the gene therapy centre they have been referred to and will only need wider NMDT discussion if their case is complex.

There will be a process for an appeal which can be made by the referring clinician.

Scotland make their own decisions about which children are eligible for treatment and will treat any eligible children in a centre in Scotland. Wales will follow the same position as NHS England and any eligible children will be treated in the English centres. Northern Ireland will fund those children included in the NICE guidance and any eligible children will be treated in Northern Ireland.

### 2. Do children have to live in the UK?

Hospital treatment is free of charge for people who are ordinarily resident in the UK. This does not depend on nationality, payment of UK taxes, National Insurance contributions, being registered with a GP, having an NHS number, or owning property in the UK. The legal duty to assess patients' eligibility for hospital treatment lies with the NHS body providing treatment. Most hospitals have overseas visitors' managers or their equivalents to do this assessment. They make their assessments in line with the charging regulations and based on evidence provided by the patient.

EU residents are able to access treatment in the UK with the explicit agreement of their home country. It is likely that prioritisation will be given in the first instance to treating all eligible UK

patients. There is a mechanism for centres to be reimbursed for treatment for patients coming from the EU

### 3. If my child is eligible for treatment, what tests need to be done to confirm if it's going to be safe for my child?

From Novartis Gene Therapies:

Once your child has had the genetic test confirming they have 5q SMA with a bi-allelic mutation in the SMN1 gene and that they have

- 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.

They will need to be assessed at one of the specialist paediatric neuromuscular centres*. At the centre, your child will be weighed and will need to have a range of blood tests to make sure it is safe for your child is able to have gene therapy. These tests include:

- AAV9 antibody testing
- liver function tests:
- full blood count
- kidney function
- cardiac enzymes

It should be possible to complete these tests and have the results within a few days. Genetic tests can take a few weeks,

A small number of children may have developed AAV9 antibodies before they are tested. Depending on the antibody titre level the presence of these antibodies could mean that it's not possible to administer zolgensma. Recent evidence suggests that only a small number of children may become ineligible for this reason (around 5 in 100 children tested). If AAV9 antibody titres are reported to be above 1:50, your child may be re-tested. AAV9 antibody results are valid for 30 days.

If the results of the other tests (liver function, full blood count, kidney function, cardiac enzymes) are not clear, these may indicate it wouldn't be safe to administer zolgensma. Any such results would be discussed fully with you.

### 4. Where are the Centre(s) that will offer the treatment?

The following sites have been identified as treatment centres:

- Evelina London Children's Hospital (part of Guy's & St Thomas' NHS Foundation Trust) and with agreement to develop a sub hub at Great Ormond Street Hospital for Children NHS Foundation Trust
- Manchester University NHS Foundation Trust
- Sheffield Children's NHS Foundation Trust
- University Hospitals Bristol and Weston NHS Foundation Trust

- **Which one would my child go to?**
- **How would my child get referred?**
- **When will it actually start happening?**

- **Would my child get treated straight away or might they have to wait? If so, how will children be prioritised?**

There is a good geographical spread of centres and each gene therapy centre will receive referrals from specific paediatric neuromuscular centres in their region. At the point of referral families will be asked if they would be willing to travel to another gene therapy centre if required. Referrals will be made through a bespoke electronic referral form and must come from one of the paediatric neuromuscular centres.

The local gene therapy centre will discuss all eligible cases that are referred to them with the NMDT not just those patients within their caseload.

The NMDT will decide which children are eligible for treatment and also how urgent it is that they should be treated. Children who are under six months old and who are either newly diagnosed and symptomatic or pre-symptomatic will be prioritised for treatment.

**5. Do we need to isolate for my child to have zolgensma therapy?**

From Novartis Gene Therapies:

It's not necessary to isolate to receive gene therapy or because of treatment with gene therapy:

- AAV9 antibody results are valid for 30 days.
- The AAV9 vector is not able to replicate so there are no risks to other people.

Isolation would only be necessary due, for example, to Covid 19 and Government guidance that affects you due to your personal circumstances

NHSE confirm Agree

**6. If my child is on another treatment at the moment and eligible to move to zolgensma, what do I need to know?**

From Novartis Gene Therapies:

There are no clinical trials that have looked at treatment outcomes when zolgensma has been given after other active treatment therapies. There is a growing body of real-world evidence where it has been used; treatment has been successful, and children have continued to attain milestones.

Similarly, there are cases where children have been treated with zolgensma and then used another active treatment. Given that zolgensma is designed to address the genetic root cause of SMA, it is not anticipated there should be a need to receive other currently available active drug treatments.

Any supportive treatment that your child may be receiving to help control their SMA symptoms is likely to continue. If your child is currently receiving another active drug treatment for SMA, they will need to come off this to allow them to have zolgensma.

The National Multi-Disciplinary Team will advise on how long the period should be between an eligible patient having treatment with nusinersen or risdiplam and having treatment with Zolgensma. In clinical trials of Zolgensma, a period of 120 days was left between treatments, but this was to ensure that the outcomes of Zolgensma treatment could be wholly attributed

to Zolgensma and not to any other treatment. The 120 days will not be applied in standard clinical practice but the time period between treatments may vary between children based on individual circumstances.

### 7. Can my child resume the treatment they have stopped after they have had zolgensma?

From Novartis Gene Therapies:

Given that zolgensma is designed to address the genetic root cause of SMA, it is not anticipated there should be a need to receive other currently available active drug treatments. Clinicians will need to discuss any exceptional cases with NHS England or equivalent organisations in Scotland, Wales and Northern Ireland.

### 8. Can my child have a further treatment later on – after having had zolgensma?

From Novartis Gene Therapies:

Zolgensma is designed to address the genetic root cause of SMA and continue working into the long-term following a single dose. An immune response to the adeno-associated viral vector that delivers the therapeutic gene will occur after infusion of onasemnogene abeparvovec. Repeat zolgensma therapy would provoke an immune response and therefore a repeat round of therapy cannot be given.

As zolgensma is designed to address the genetic root cause of SMA, it's not anticipated there should be a need to receive other currently available drug treatments after gene therapy. Clinicians will need to discuss any exceptional cases with NHS England or equivalent organisations in Scotland, Wales and Northern Ireland.

### 9. How is the actual treatment delivered? How long does it take?

From Novartis Gene Therapies:

Zolgensma is administered in a specialist hospital as a one-time intravenous (IV) infusion. It takes over 60 minutes to deliver the treatment.

### 10. Does it hurt?

From Novartis Gene Therapies:

Apart from the need to set up a drip (intravenous cannulation) for your child – which usually goes into the arm. This does involve the sensation of a sharp scratch, the infusion itself should not cause any pain.

### 11. What if my child is too unwell for treatment on the day, or there is a problem with staffing or treatment delivery at the Centre?

From Novartis Gene Therapies:

If your child is unwell or there are other issues at the centre it may be necessary to temporarily delay treatment of your child. Your treating physician will make that decision.

## 12. Immediately after treatment what happens? How long do we need to stay at the Centre? When can we go home?

From Novartis Gene Therapies:

Your child will normally need to be admitted at the infusion centre the day before the infusion to allow sufficient time for pre-infusion tests and to start oral prednisolone (a common steroid treatment) to reduce liver side effects. After receiving the infusion, your child will need to stay in hospital for monitoring. Depending on blood test results and as long as there are no complications, children may be able to go home within a few days but with supervision from the infusion centre. In some cases, children and families may need to stay in accommodation close to the infusion centre. The oral steroids will continue for at least two months.

confirm with NHSE Ok – will need further confirmation from the gene therapy centres as there may be slight differences

## 13. What side effects or complications could there be that need to be watched for?

From Novartis Gene Therapies:

Zolgensma has a manageable safety profile when initiated and administered in clinical centres and supervised by a physician experienced in the management of children with SMA.

The most common side effects (which may affect more than 1 in 10 people) are raised liver enzymes and vomiting.

Information for parents/carers is available in the Child Information Leaflet at Zolgensma, INN-Zolgensma(medicines.org.uk) https://www.medicines.org.uk/emc/files/pil.11572.pdf

*Novartis Gene Therapies provided the following info from this leaflet – Is this too much information for this information sheet? – should this info sheet just provide the link? or have them all in the order as below?* NGT comment *'Your choice, we wanted to be comprehensive. A link' NHSE your thoughts?*

You would need to talk to your child's doctor or nurse if your child developed any side effects. These can include:

**Very common (may affect more than 1 in 10 people)**

- increases in liver enzymes (transaminases) seen in blood tests Possible signs you need to look out for after your child is given this medicine include vomiting, jaundice (yellowing of the skin or of the whites of the eyes), or reduced alertness,

**Common (may affect up to 1 in 10 people):**

- increases in liver enzymes (~~aspartate aminotransferase, alanine aminotransferase~~) seen in blood tests Possible signs you need to look out for after your child is given this medicine include vomiting, jaundice (yellowing of the skin or of the whites of the eyes), or reduced alertness.
- 
- vomiting

- fever.

You would need to seek urgent medical attention if your child developed any of the following serious side effects after gene therapy for SMA:

**Common (may affect up to 1 in 10 people)**

- bruising or bleeding for longer than usual if your child has been hurt - these may be signs of a low blood-platelet count.
- pale grey or blue skin colour, difficulty in breathing (e.g., rapid breathing, shortness of breath), swelling of the limbs or abdomen - these may be signs of possible problems with the heart.

**Not known (frequency cannot be estimated from the available data)**

- vomiting, jaundice (yellowing of the skin or of the whites of the eyes) or reduced alertness - these may be signs of injury to the liver.
- bruising easily, seizures (fits), decrease in urine output – ~~these may be signs of thrombotic microangiopathy.~~

Zolgensma is subject to additional monitoring. Side effects should be reported to your child's doctor or nurse.

## 14. What care do we need to put in place when we get home?

From Novartis Gene Therapies:

The active substance in zolgensma may temporarily be excreted through your child's bodily waste. Careful hand hygiene and care with the disposal of any nappies for at least one month after infusion is recommended in the Package Information Leaflet at Zolgensma, Zolgensma (medicines.org.uk) https://www.medicines.org.uk/emc/files/pil.11572.pdf

The International Standards of Care for SMA are the guidelines for care for all children with SMA – whatever drug treatment they are receiving. A copy of the family friendly guide can be found here (https://treat-nmd.org/wp-content/uploads/2019/06/uncategorized-A-Guide-to-the-2017-International-Standards-of-Care-for-SMA_UKEnglish_Digital-v2L.pdf) Your child may need any usual supportive care advised by their clinical team to continue when they go home. They will also need to attend for regular periodic blood test results and follow up clinic appointments for some time following their infusion. These may be able to be carried out locally to your home. Your clinical team will advise you on this. How long this will need to carry on for will depend on your individual child's needs and should be discussed with your treating clinician.

## 15. What help will we be given to get to the treatment Centre and with accommodation and food during all these stages?

**Include in the answer: the rest of my family – who will take care of them? Time off work / for a partner to do all care? Who will arrange all this?**

In England, the four centres have confirmed what arrangements they will put in place for parents/carers to stay close to their child.

Travel costs will be met in line with standard NHS Healthcare Travel Costs Scheme.

http://www.nhs.uk/NHSEngland/Healthcosts/Pages/Travelcosts.aspx

You will be responsible for arranging any time off work or childcare arrangements for other children. The cost of food will not usually be reimbursed.

**Scotland, Wales, Northern Ireland?? Perhaps add link to Scottish Muscle Network here?**

**Response from Novartis Gene Therapies:**

Zolgensma is expected to be made available in a small number of highly-specialised infusion centres in the UK and this may mean that travel away from home is required to receive gene therapy. However, gene therapy is a one-time treatment and so the impact on families will be limited. We expect that ongoing monitoring and clinic visits should be able to be done more locally to the family home.

**16. What support is provided throughout and following treatment, including emotional and psychological?**

All the gene therapy centres have facilities in place to support families holistically throughout the treatment period.

**Scotland, Wales, Northern Ireland??**

**17. What information will be collected?**

- What data will be collected and how?
- Where will all this information be kept?
- Who will see the information?
- What will be done with it?

Clinical Data Collection? Child Reported Outcome Measures (PROMs)?

**Scotland, Wales, Northern Ireland??**

**NHSE**

**Response from Novartis Gene Therapies:**

Any requirements for the collection of child information will be described in the NICE Final Guidance and will be developed in conjunction with the gene therapy centres, SMA REACH and the wider expert clinical community. Novartis Gene Therapies would hope that the clinical data of children treated with zolgensma will be entered into the national SMA registry (SMA Reach) so that doctors can gain the best understanding of how the therapy is being used and how children are benefitting.

Data on your child's developmental milestones, any need for support with feeding and breathing, quality of life measures and need for additional treatments will be part of the data collection. This data will be collected as part of the routine follow up of your child and will link into existing data collection processes with SMA REACH. The gene therapy centres will also use this data for audit and monitoring purposes.

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**18. Does the UK offer private access now?**

- To people living in the UK who don't want to wait and have the money
- To people from outside the UK
- If yes to any of the above groups, what are the eligibility criteria?

**NHSE**

**Scotland, Wales, Northern Ireland??**

**Response from Novartis:**

Novartis Gene Therapies is not aware of any treatment with zolgensma that has taken place privately in England. It would be for the individual infusion centres to decide whether or not to offer private treatment and to decide on the eligibility criteria for these patients. The price charged for private patients or any other patient not eligible for treatment under the NHS is not subject to the agreement in place between Novartis and NHS England and would be subject to a separate commercial pricing agreement.

Zolgensma should be initiated and administered in clinical centres and supervised by a physician experienced in the management of children with SMA.

**Novartis information:**

**MED-UK-ZOL-21-00001**

**Date of preparation: 16th April 2021**

***Specialist paediatric Centres – need to add ones for devolved countries**

- Alder Hey Children's NHS Foundation Trust
- Cambridge University Hospitals NHS Foundation Trust
- Great Ormond Street Hospital for Children NHS Foundation Trust
- Guy's & St Thomas' NHS Foundation Trust
- Leeds Teaching Hospitals NHS Trust
- Manchester University NHS Foundation Trust
- Nottingham University Hospitals NHS Trust
- Oxford University Hospitals NHS Foundation Trust
- Sheffield Children's NHS Foundation Trust
- The Newcastle upon Tyne Hospitals NHS Foundation Trust
- The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- University Hospitals Birmingham NHS Foundation Trust
- University Hospitals Bristol NHS Foundation Trust
- University Hospitals of Leicester NHS Trust
- University Hospitals of North Midlands NHS Trust

Royal Hospital for Children, NHS Greater Glasgow and Clyde