NICE Evidence Review to consider whether people who have SMA Type 3 who are unable to walk can benefit from nusinersen treatment & therefore should be included in the Managed Access Agreement.

Submission to NICE via Biogen

Evidence submitted with consent:

- Survey conducted in January 2020 asking about 'The Impact of Not Being Eligible for Treatment on Those Who Have SMA Type 3 and Their Families' and follow-up comments October 2020 (**Appendix 1**).

- PROMS follow-up surveys of two children who had lost their walking ability after July 2018, have been receiving treatment but are subject to the stopping criteria of needing to walk 5 steps after a year of treatment (**Appendices 2 & 3**).

- Testimonies from adults in Europe who have SMA Type 3, have lost their ability to walk and have been treated with nusinersen (**Appendix 4**).

- Importance of Treatment Outcomes to those with Type 2 and Type 3 October 2020 survey (**Appendix 5**).

1. The impact of SMA Type 3 and best supportive care

Within this clinical classification of SMA Type 3, the condition impacts as follows:

1.1 Childhood

The symptoms and effects of **SMA Type 3a** usually begin between 18 months and 3 years.

The symptoms and effects of **SMA Type 3b** usually begin after 3 years, but before adulthood.

Each child is affected differently but, in general, children with SMA Type 3 are bright and engaging. However, their SMA causes:

- muscle weakness on both sides of their body
- muscle weakness closest to the centre of their body as these muscles are more severely affected than muscles furthest away
- legs that are weaker than arms

As they get older, their intellectual and sexual development isn't affected, but their SMA usually causes them to have:

- difficulties with standing and walking. This usually happens later for children with SMA Type 3b than for children who develop symptoms at an earlier age.
- difficulties keeping up with daily activities. For example, if they have been able to walk or climb stairs, they may lose this ability. Some children may fall more easily because of their muscle weakness. If they're sitting on the floor, they may need help to get up.
- muscles supporting the spinal column that are weakened. This means that some children develop a sideways curvature of their spine[1] (scoliosis).
- a reduced ability to move due to some joints becoming tight (contractures), restricting their range of movement.
- a tendency to become weaker after infections and at times of major growth, such as puberty.

1.2 Late teens and into adulthood

Many who have been diagnosed at a younger age will have lost their ability to walk during childhood – some very early on, others in their teens. Most will at least use manual wheelchairs during these years due to their muscle weakness and the fatigue this creates. Many will already use powerchairs. Muscle weakness brings with it, loss of independence to fulfil daily personal tasks like washing, dressing and undressing. Though their bladder and bowel control aren't affected, they may need help getting to, and sitting on, the toilet.

Most people who have lost their walking ability due to SMA Type 3 don't have swallowing or breathing difficulties and their life expectancy isn't affected[2]. However, as there is no distinct line between a diagnosis of SMA Type 2 and SMA Type 3, some who have been 'clinically classified' as Type 3 do experience these challenges.

1.3 Outcomes of best supportive care

Our survey respondents describe very clearly what these outcomes are and the progressive nature of the condition:

"Our grandchild is losing upper body strength weekly and her only hope of continuing using her arms to write, draw, cake decorate, hold a drink, feed herself, dress, wash etc.is to have treatment, she is well aware of this." **Grandparent of teenager age 16 – 18 years (T5 in Appendix 1) January 2020**

"*Since the survey in January 2020, I have regressed even further. I now cannot lift my arms at all. My swallow is even weaker; I cannot drink normal water without choking, I have to drink fizzy water if I don't want to swallow it the wrong way. I have lost the ability to lift my legs onto my footplate (even if I try and use my arms to lift my legs I am unable) Chewing is much harder, my jaw burns when I eat and I often have to stop intermittently. I cannot cough at all. All of this and I'm still not eligible*!'" **The same teenager age 16 – 18 years (T5 in Appendix 1) October 2020**

"Since I have been denied access to Spinraza my condition has continued to get worse and is taking away my independence." **Young adult age 19 – 28 years (YA1 in Appendix 1) January 2020**

"As I have progressed my anxiety/panic attacks have become more, in the time since nusinersen has been approved by NICE, I have lost the ability to transfer by myself from my wheelchair/toilet/bed and car! I am fast losing the ability to do any weight bearing at all. This has caused me extreme anxiety; I'm losing any independence that could have been saved." **Adult age 59+ years (A16 in Appendix 1) January 2020**

SMA is a progressive neuromuscular condition. Though improvements in medical care and management as outlined in the International Standards of Care for SMA mean that people with SMA and their families can expect a better quality of life than was possible in the past, best supportive care cannot prevent the progression of this condition.

2. The impact and outcomes of nusinersen treatment for those who have Type 3 and have lost walking ability

Due to the barriers to access to treatment in the UK for this group, our ability to obtain reports has been very limited. Our evidence of the impact of treatment is as outlined in the Patient Reported Outcomes attached as follows:

Appendix 2. Child A age 6 who lost her walking ability after July 2018 and has had access since August 2019

Appendix 3. Child B age 4.5 years who lost his walking ability after July 2018 and has had access since October 2019

Appendix 4. Adults A, B and C from Serbia; Adult D from Belgium; Adult E from France

These reports highlight the positive impact of nusinersen treatment for all these children and adults who had lost their walking ability. Most importantly, they make it clear what outcomes matter to people, what makes a difference to life, and what outcomes we strongly suggest the evidence review should be considering.

3. Expectations of treatment

In general, both clinical trial and real-world evidence for all current drug development suggests that early treatment may be necessary to maximise the potential benefits. Though we acknowledge this, the importance of stabilisation or even the smallest meaningful benefit for people impacted by a progressive muscle wasting condition cannot be stressed enough. In 2019, **96.7% of 1,327 validated responses to SMA Europe's SMA Community survey** stated they would "*consider it to be progress if there was a drug to stabilise their current clinical state*."

3.1 Expectations are similar to the comparator group classified as Type 2

As part of a wider survey in September – October 2020, people were asked how important improvements in different aspects of their health and daily living would be if these could be affected by a drug treatment. As respondents agreed to the results being published on SMA UK's website they were not contacted again for further consent to share this information.

	SMA Type 3 lost walking ability		**SMA Type 2**	
Ages	**18 – 65+**		**18 - 64**	
	Total 19		**Total 34**	
	Very important			
	%	Nos	%	Nos
Improved motor milestones - e.g. ability to sit, stand, walk	84	16	75	18
Improved breathing ability	53	10	82	28
Improved swallowing / ability to eat	47	9	85	29
Improved ability to communicate	37	7	41	14
Improved stamina and reduced fatigue	79	15	65	22
Improved fine motor skills (e.g. movement of fingers)	74	14	82	28
Increased independence	95	18	74	25
Reduced reliance on caregivers and personal assistants	79	15	71	24

Though clearly not a matched sample, the outcomes that are important to both groups are not dissimilar and their importance is likely to be a reflection of how their SMA is impacting on them at the moment, with the adults with SMA Type 3 who replied to this survey perhaps, on the whole, experiencing a slower disease progression. (**Appendix 5** for the full table)

3.2 Expectation of our survey respondents

"*I am getting weaker and want to have treatment to maintain what strength I have left and for an independent future. And do things myself, rather than asking for help all the time. I want to get stronger so I can use my hands and arms for day to day life activities like brushing my teeth, washing, writing, using cutlery, holding my computer controller*." **Teenager age 13 – 15 years (T1 in Appendix 1) January 2020**

"*It would provide me with strength, independence, stop deterioration and preserve my dignity*." **Teenager age 13 – 15 years (T3 in Appendix 1) January 2020**

"*Any stabilisation of their condition would be a miracle. We are realistic and any sort of stabilisation or slowing of the effects would make such a difference in their lives."* **Aunt of two teenagers ages 13 – 15 years (T2 & T3 in Appendix 1) January 2020**

"I'm not looking for major improvements, just a sense of stability so I can carry out my future how I want to live it. My arms are already getting weaker and weaker and so is my breathing and my swallow. It's said there isn't enough benefit to me having the treatment as I wouldn't regain or maintain the ability to walk. But that's not what's important to me! I just want to be able to not choke on my packet of crisps and to be able to lift my cup of tea to my mouth!!!

Improved lower body strength wouldn't affect my life half as much as upper body strength improvements. My arm strength is the thing that affects me every minute of the day - I'm already in a wheelchair so it doesn't make much difference if Spinraza helps me stand up for a few seconds, I still couldn't go to the toilet independently. The creative activities that I'm most passionate about require arm strength, not leg strength (such as painting, drawing, cake decorating etc.) I can't imagine not being able to do these things anymore and yet soon I won't have to imagine it because it will be real. Spinraza's benefits have been measured through tests of leg strength which just isn't what is important in daily practical life. I would still use a wheelchair even if I could walk a few paces." **Teenager age 13 – 15 years (T5 in Appendix 1) January 2020**

"*Been struggling a lot more in recent years with upper body strength and would really like to improve this or at least maintain it*.' **Teenager age 13 – 15 years (T4 in appendix 1) January 2020**
With the improved strength of my body I would hope to gain the ability to stand and possibly walk a few steps unaided which would allow me to gain more independence." **Young Adult age 19 – 28 years (YA4 in Appendix 1) January 2020**

"*If a treatment is available to help me stay at or improve my ability slightly then it is worth it, my condition is only going to get worse so surely trying to stop it, delay it or improve it by any means is better than nothing, I would rather stay the way I am now being able to do some things for myself rather than not be able to do anything at all which is the way it will end up going."* **Adult age 29 – 38 years (A1 in Appendix 1) January 2020**

"*To stabilise his condition would be marvellous but to improve it would be more than I could ever wish for."* **Mother of adult age 49 – 58 years (A14 in Appendix 1) January 2020**

"*To stop progression would be a miracle! Any other improvements would be very gratefully received!*" **Adult age 59+ years (A16 in Appendix 1) January 2020**

4. Issues with the use of the clinical classification of Type as a criterion for access to treatment

4.1 'Typing' wasn't introduced as a way to decide who should access treatment

"*The clinical classifications and 'Typing' of SMA was introduced in 1990 by a committee of clinicians and geneticists to promote collaborative studies between different centres and to identify the genes of SMA. Their classification was based primarily on the age of onset and the age of death, with the ability to sit unaided and stand and walk unaided added on*."[3]

The classifications were never meant as a way to make decisions about who should / should not have access to treatment.

4.2 There are significant overlaps between 'Type 2' and 'Type 3'

The International Standards of Care for SMA[4,5,6] make two very clear statements that call into question why those who have a clinical classification of Type 3 and have lost the ability to walk have been treated differently from those with a clinical classification of Type 2:

'Considering that type 3 patients who lost ambulation share many aspects with type 2 patients, the two groups are collectively indicated as "sitters", while the type 3 patients who are still ambulant are indicated as "walkers". Type 1 patients are indicated as non-sitters.'[4]

We also note the overlap in *SMN2* copy numbers between the two groups:

SMA Type	Usual age of symptoms	*SMN2* copies	
		'usual number'[1]	'range'[10]
Type 1	Younger than 6 months	2	1-3
Type 2	6-18 months	3	2-4
Type 3a	Under 3 years	3	3-5
Type 3b	Over 3 years	4	
Type 4	Over 18 years	4-6	

Table adapted from Tillmann et al. 2018[7]

As stated in the articles that inform the International Standards of Care for SMA: *'Although there is a strong correlation between* SMN2 *copies and severity of the disease, there are exceptions and in individual cases the number of* SMN2 *copies may not predict the severity of the phenotype.'*

These comments from our respondents reinforce the point:

"*I am so close to being able to be eligible as I needed aids all my life to help me walk and now more like a type 2 rather than type 3, I can't walk since 8 years*." **Teenager age 13 – 15 years (T1 in Appendix 1) January 2020**

"*The diagnosis needs to be as dynamic as the condition…The etymology of the disease dictates that wherever people start on the continuum of SMA they are on an ever-decreasing scale. As such if you start as a type 3 or type 2 eventually those people have the same end point*." **Child A's parents October 2020 (Appendix 2)**

Perhaps the most telling and pertinent example of this overlap and reality of what it is to be a Type 2 or 3 'sitter' is in the following from France:

"*At the start of 2018, the French government planned to reimburse Spinraza only for type 2 adults and not type 3.*

"The AFM Patient Group therefore made an appointment with the chief of staff of the Minister of Health to plead the cause of types 3.

"At this meeting, the Director and the President of the AFM were accompanied by Adult F age 31 years who has SMA Type 3 and is non-ambulant, and Adult G age 25 years who has SMA Type 2.

"The physical impact of their SMA is quite comparable, though Adult G is perhaps slightly more mobile than Adult F.

"At the meeting, they simply informed Chief of Staff that if he maintained his decision, one of the two could have access to the treatment but not the other because one was type 2 and the other type 3 - and that if he or one of the doctors could explain what differentiated an adult type 2 from a non-ambulant type 3 and therefore determine which of the two would actually have access to the treatment, the AFM Patient Group agreed they would not raise any difficulties; but that on the other hand, if they were unable to determine who was type 2 and who was type 3, they believed that both should have access to treatment given their state of health.

"Conclusion: access was opened to types 2 and 3 without age restriction." **Mother of adult age 25 years and member of AFM Patient Groups Board**

4.3 A significant number of those classified as Type 3 would not have met the initial WHO criteria for having been able to walk unaided prior to symptom onset

The other issue for a number of people is that to be clinically classified as Type 3, a person must have initially achieved the WHO definition of walking ability:

'*Child takes at least five steps independently in 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.*'[8]

The following passage from the WHO Multicentre Growth Reference Study adds to this by further clarifying what is and isn't considered to be the ability to walk alone:

'*The child shows the capacity to balance the body and to control his or her forward stepping movements. There is no need for assistance, because both the postural adjustment and the stepping movements are engaged in independent walking. An important indicator of this phase of erect locomotion is that movement of the entire body does not accompany the child's stepping movements. This phase does not refer to the child's first independent steps when the child is able to take three or four uncertain steps toward the adult's outstretched hands*.'[8]

As two of our respondents state:

*"We want to again point out that we are perplexed at the way NICE has selected to use a definition of walking ability - taking 5 steps unaided - as an outcome our daughter has to achieve to continue treatment **yet she was never able to attain this at any stage of her life**. As an infant, our daughter swung her body around and wobbled, she could not manage steps on anything except perfectly pan flat ground and could not lift her foot enough to tackle a rug, let alone any form of step. She constantly fell and mainly held on to a grown-up's hands for support. Hence, her GP referral and subsequent investigations into her hips. After a referral to hospital, she was assessed as "walking outside the normal range", this led to a paediatrician's referral, then diagnosis*." **Parent of Child A age 6 years (Appendix 2)**

"*He may have stepped more than 5 steps but never alone or unaided. He may have walked a few minutes back when he was diagnosed unaided not never with a straight back or one foot in front of the other! His back swayed and walked side to side steps*." **Parent of teenager age 13 – 15 years (T1 in Appendix 1)**

There is a strong likelihood that this developmental history would be similar for others who may not be aware of these definitions and who were clinically classified at a time when there was no possibility of treatment and certainly no inkling that such a classification would create a barrier to access.

The result of the devastating impact of creating these artificial barriers is stated very clearly here:

"*Meeting other families has always been important to us and there's a core group of five of us who've got to know each other really well, both us parents and our children. Two of the children have Type 2 and are weaker than our son and two have Type 3 and are stronger than him. All four have now started Spinraza and it doesn't make sense that because he's in the middle he's the only one who can't have treatment. Of course, we're really glad for them, but it makes it even harder for us."* **Parents of Child 1 age 7 – 9 years (C1 in Appendix 1)**

We suggest that using what is clearly a flawed classification system is an unacceptable basis for judging clinical effectiveness of and preventing access to treatment.

5. The impact of not being eligible for treatment

The people who have responded to our surveys have clearly highlighted the impact of NICE and NHS England's decision to restrict access to this treatment. They have not only experienced further physical deterioration due to increasing muscle weakness, but also significant emotional and psychological distress.

In response to the question, '*What impact has not being eligible for nusinersen treatment had on the person who has SMA?*', the following percentages of the 29 respondents strongly agreed / agreed that it had: made them stressed (72%); affected them emotionally (79%); made them anxious (59%); made them angry (79%); affected their day-to-day well-being (62%).

"*Not being eligible for treatment has had a severe impact on my mental health, I have been suffering from anxiety and panic attacks (something I've never experienced before) had trouble sleeping and have lost a considerable amount of weight*." **Adult age 39 – 48 years (A5 in Appendix 1)**

Similarly, of the 18 relatives, the following percentages reported they strongly agreed / agreed that the decision had made them stressed (83%), affected them emotionally (89%), made them angry (89%); affected their day-to-day well-being (61%).

"It has been a devastating blow to us as parents, the whole family feel for him and us all. Watching your child deteriorate over time is heart-breaking and we feel so desperately helpless. Knowing now the treatment is available makes me feel ill and desperately depressed." **Parent of teenager age 13 – 15 years (T1 in Appendix 1)**

Added to this are the adults who have SMA Type 3, were able to walk and would have been eligible for treatment as of 24th July 2019. Now, due to the slow roll out of the MAA to adults and the relentless progressive nature of the condition, a number have lost their ability to walk and find that they too have no access to this treatment.

In January 2020 - when he was eligible and should have been able to start nusinersen treatment, this young adult in his early twenties wrote:

'In September 2019 I completed a Masters Degree and moved back home to be with my parents. In January 2020, I started a new position on a graduate scheme based in my home town. As could be anticipated given my condition, my mobility was constantly deteriorating and the rate of deterioration seemed to be increasing. By way of illustration, when I started my undergraduate degree in 2015, I didn't use a wheelchair at all and could live independently. By the time I finished my Masters in September 2019 I was heavily reliant on a wheelchair and am now sourcing an electric wheelchair to use in conjunction with a wheelchair accessible vehicle as, whilst I can still walk several steps unaided, I am unable to go out without assistance to get me to and from the wheelchair to my current car. My dad currently has to take me to and from work each day.'

Now in October 2020, the distress caused to him and his family by the inability of his neuromuscular centre to start the treatment cannot be overstated. This young man now slips into this ineligible category where suddenly and bewilderingly, just because he has now lost his walking ability the treatment is no longer deemed to be of any use, when it is so clear how important the possibility of at the very least stabilising his condition will be for his future.

6. In conclusion

We hope the reviewers will take the time to read all the comments from the people affected by this decision as they describe very clearly the impact of this condition and quality of life outcomes that are vital evidence of 'clinical' gains. We finish with two that have been sent to us this week – two people who did not respond to the original survey:

"At age 21, (2019) I lost the ability to walk completely, had I had access to Spinraza, I very much doubt I would have lost that ability & would have been able to maintain some strength in my legs to be able to transfer independently. I now, at the age of 22, have to rely on a carer (my mum) to hoist me to & from, my bed, wheelchair & commode (I can no longer use the toilet independently). Why am I, like other type 3 non ambulant people, being left to become as weak, if not weaker, than those who are in receipt of treatment. It is devastating to me & my family. There is a hospital providing Spinraza 5 miles away from me but because I can no longer take 5 steps, I am denied treatment & being left to face an uncertain life, in which I will continue to deteriorate & become weaker."
Young adult age 19 – 28 years (YA7 in Appendix 1)

"I am a woman in my late 40's with type 3 SMA. I do not fit the current criteria for Spinraza, as I cannot walk five steps independently. I stopped walking approximately ten years ago, which was understandably a difficult and emotional change in my life. Despite now needing to use an electric wheelchair, I have continued to live independently and work professionally through this time. In the last five years, my ability to use both my arms against gravity has decreased to the point that I am

now only able to lift my right arm from the elbow. My Consultant has informed me that inevitably I will lose the ability to lift this arm, like I did, the left. The changes of strength in my arms, has significantly affected my independence in multiple ways and has affected my quality of life much more, than when I stopped walking. I now need assistance with all forms of personal care, I cannot transfer from my wheelchair, open doors, lift items, such as a cup of drink and a knife and fork. Home and social life and my career are all now becoming affected. I am losing my independence. Costs for personal assistance have multiplied massively. I have been informed by neurology physiotherapists that there is no programme of exercise that will sustain the strength in my arms. The only thing that seems to help upper mobility and also can improve strength in this area, is drug therapy. I am not embarrassed to say that I am terrified each day by the thought of losing all arm strength and ability. My life will change completely and the constant stress of waiting for this moment to happen is difficult to bear, when you know that there are drugs now available that could potentially help me. I can accept that I will probably not be able to walk again....I can live with that, but please recognise the huge importance of upper mobility and how devastating it can be to lose ability in this area. Spinraza could help massively in enabling people with SMA type 3 to sustain upper strength and therefore some independence within their lives." ***Adult age 49 – 58 years (A15 in Appendix 1)***

Appendices

Appendix 1. The impact of not being eligible to access nusinersen treatment on those who have SMA Type 3 and their families. Patient Groups' survey managed by SMA UK January 2020 and follow up comment October 2020.
Appendix 2. Child A age 6 who lost her walking ability after July 2018 and has had access since August 2019
Appendix 3. Child B age 4.5 years who lost his walking ability after July 2018 and has had access since October 2019
Appendix 4. Adults A, B and C from Serbia; Adult D from Belgium; Adult E from France
Appendix 5. Importance of Treatment Outcomes to those with Type 2 and Type 3 October 2020 survey
Appendix 6. Consent evidence – Jan 2020 surveys and follow up comments
Appendix 7. Consent evidence – Child A and B receiving treatment
Appendix 8. Consent evidence – Adults from Belgium and France
Appendix 9. Consent evidence – Other UK adults
Appendix 10. Consent evidence – Adults from France
Appendix 11. Consent evidence – Adult lost walking ability since July 2019

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