6th edition

REPORT

Strengthened knowledge of SMA

LIS-N & LER-N

Educational meeting in SMA

7th of December, 2022

Biogen

Biogen - 212931 - Juni - 2023

Introduction

The 2022 edition of the annual Lis-n & Ler-n gathering for Nordic HCPs with a professional interest in spinal muscular atrophy (SMA) took place as a digital event on 7 December 2022. The title of this year's meeting was Strengthened knowledge of SMA and the keynote presentations addressed themes relating to long-term outcomes of medical treatment of SMA and the impact on the disease course. The overall objective of the Lis-n & Ler-n meeting is to continue to provide a platform for discussing and sharing experiences with evolving SMA care and a changing treatment landscape, to build resilience and help both patients, care givers and HCPs prepare for the future.

About SMA and nusinersen

SMA is a rare neuromuscular disease caused by a mutation in the survival motor neuron 1 gene (SMN1)[1]. The lack of functional SMN protein causes degeneration and loss of motor neurons in the brain and spinal cord, leading to progressive muscle weakness and atrophy[2]. SMA is categorised as type 0–IV according to age of onset and severity. Although some teenagers and adults with later onset of symptoms can maintain near normal motor function for periods of time, the disease inevitably has a progressive course in all patient groups if left untreated[3–5].

Spinraza® (nusinersen) is the first medical treatment to be approved for the treatment of SMA. Nusinersen is an antisense oligonucleotide (ASO) that acts by modifying pre-mRNA splicing of *SMN2* to produce functional, full-length SMN protein[6]. Nusinersen is administered by intrathecal injection with the aid of lumbar puncture; the recommended dose is 12mg irrespective of the weight and age of the patient, given initially as four loading doses on Days 0, 14, 28 and 63, and then as maintenance therapy every four months[6]. Data from the nusinersen clinical development programme[7–10], as well as experience from clinical practice[11], have documented stabilisation or improvement in functional levels with treatment across different age groups and types of SMA.

Since its launch in 2017[12], nusinersen has fundamentally transformed the treatment landscape for patients with SMA. The introduction of alternative treatment options in recent years has been positive for this patient group and contributed to further development of the field[13,14]. Prior to nusinersen, the life expectancy for children with the most severe forms of SMA was no more than two years[15]. The experience with nusinersen shows that these patients can achieve almost normal growth and motor development, provided that treatment is initiated before the onset of symptoms[7].

Real-world evidence supporting nusinersen in adult patients with SMA

The Summary of Product Characteristics (SmPC) for Spinraza® was recently updated to reflect real-world findings that treatment with nusinersen can stabilise or improve motor function in adult patients with SMA types II and III, and that adult safety data are consistent with the safety profile of nusinersen in children.[6] Spinraza® is the only treatment option for SMA that includes real-world evidence (RWE) in adult patients in its product label. The SmPC update also included the removal of the black warning triangle, which means that Spinraza® is no longer subject to subject to additional monitoring by regulatory authorities.

A recent critical review and meta-analysis evaluated the effectiveness of nusinersen in children and adults with SMA included in 30 RWE studies involving more than 2,600 patients, and found that treatment with nusinersen either improved or stabilised motor function in SMA patients in all age groups.[11] Patients on treatment with Spinraza were compared with patients who did not revieve any treatment. Patients who were not treated with nusinersen experienced worsening of the disease with reduced function.[11] Biogen was not involved in this systematic review.

References:
1. Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. Proceedings of the National Academy of Sciences [Internet]. 1999 May 25;96(11):6307–11. Available from: https://doi.org/10.1073/pnas.96.11.6307. **2.** Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: Diagnosis and management in a new therapeutic era. Muscle Nerve [Internet]. 2015 Feb 1;51(2):157–67. Available from: https://doi.org/10.1002/mus.24497. **3.** Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology [Internet]. 2012;79(18):1889–97. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23077013. **4.** Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. Neuromuscular Disorders [Internet]. 2016 Feb 1;26(2):126–31. Available from: https://doi.org/10.1016/j.nmd.2015.10.006. **5.** Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c–4. Eur J Neurol [Internet]. 2018 Mar 1;25(3):512–8. Available from: https://doi.org/10.1111/ene.13534. **6.** Spinraza Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/spinraza-epar-product-information_en.pdf. **7.** De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscular Disorders [Internet]. 2019 Nov;29(11):842–56. Available from: https://doi.org/10.1016/j.nmd.2019.09.007. **8.** Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med [Internet]. 2018;378(7):625–35. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29443664. **9.** Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med [Internet]. 2017;377(18):1723–32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29091570. **10.** Darras BT, Chiriboga CA, Iannaccone ST, Swoboda KJ, Montes J, Mignon L, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. Neurology. 2019 May 21;92(21):e2492–506. **11.** Coratti G, Cutrona C, Pera MC, Bovis F, Ponzano M, Chieppa F, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis [Internet]. 2021;16(1):430. Available from: https://doi.org/10.1186/s13023-021-02065-z. **12.** BiogenLinc. Spinraza. https://biogenlinc.com/products/sma/spinraza/. **13.** Zolgensma Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf. **14.** Evrysdi Summary of Product Characteristics . https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf. **15.** Markowitz JA, Singh P, Darras BT. Spinal muscular atrophy: a clinical and research update. Pediatr Neurol. 2011/12/27. 2012;46(1):1–12.

Biogen - 212931 - Juni - 2023

SIMON TOFTGAARD JESPERSEN

Muskelsvindfonden, Denmark

Born in 1989 with SMA type 2, Simon Toftgaard Jespersen has been chairman of the Danish patient support organisation Muskelsvindfonden (Muscular Dystrophy Foundation) since 2019. In addition to his administrative duties as chairman, Simon also acts as master of ceremonies at Muskelsvindfonden's annual Grøn Koncert (Green Concert) music festival events. Simon lives in Århus on the east coast of Jutland together with his partner and daughter.

LLUÍS PUJADAS

Medical Affairs, Biogen Europe

Dr Lluís Pujadas is a Global Senior Medical Manager within the neuromuscular disease team at Biogen Europe. Dr Lluís Pujadas holds a PhD in Medicine from the University of Barcelona.

SEAN WALLACE

Oslo University Hospital, Norway

Dr Sean Wallace is a senior consultant at the Department of Paediatric Neurology at Oslo University Hospital, and head of the Norwegian Society for Child Neurology. Dr Wallace obtained his medical degree from the University of Liverpool in 2001 and completed his PhD at Oslo University Hospital in 2016.

GIORGIA CORATTI

Catholic University of the Sacred Heart, Rome, Italy

Dr Giorgia Coratti is a paediatric physiotherapist specialising in neuropsychomotor development and rehabilitation at the Catholic University of the Sacred Heart in Rome, where she holds a PhD in Neuroscience. Dr Coratti's responsibilities include clinical neuropsychomotor assessment of children with neuropsychiatric disorders, as well as acting as research therapist in phase 1–3 and observational clinical trials.

Acknowledgements

Chair
Sean Wallace, Oslo University Hospital, Norway

Sponsor
Biogen Norway

Abbreviations

6MWT	6-Minute Walk Test
AAV	adeno-associated virus
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	confidence interval
CNS	central nervous system
CPAP	continuous positive airway pressure
EAP	expanded access programme
EMA	European Medicines Agency
FDA	(United States) Food and Drug Administration
HFMSE	Hammersmith Functional Motor Scale-Expanded
HINE	Hammersmith Infant Neuromuscular Examination
IT	intrathecal
IV	intravenous
NBS	new-born screening
NIV	non-invasive ventilation
NMD	neuromuscular disorders
RCT	randomised controlled trial
RNA	ribonucleic acid
RULM	Revised Upper Limb Module
SMA	spinal muscular atrophy
SMN	survival motor neuron
SmPC	Summary of Product Characteristics
WHO	World Health Organization

Biogen - 212931 - Juni - 2023

SIMON TOFTGAARD JESPERSEN

Muskelsvindfonden, Denmark

Life on wheels – an SMA patient perspective on life and treatment

With medical treatment now the established standard of care for children with newly diagnosed SMA, the SMA patient community is increasingly being split into those who can and those who cannot access treatment – especially in countries with very strict access criteria, such as Denmark. In the opening keynote presentation at Lis-n & Ler-n 2022, Simon Toftgaard Jespersen, chairman of Danish patient support organisation Muskelsvindfonden (Muscular Dystrophy Foundation) stated that although he was fortunate to have grown up in a supportive family who helped him make the best of the situation and live as normal a life as possible, the advent of treatments for SMA has made him re-evaluate some aspects of his life as an untreated SMA patient, in a way that has at times threatened to disrupt his equanimity and focus on the good things in life.

Simon Toftgaard Jespersen is 33 years old and lives in Århus on the east coast of Jutland together with his partner and 10-month-old daughter. He has a master's degree in Media Science, but admits that the job as chairman of Muskelsvindfonden takes up most of his time. "Most of my life is devoted to embracing diversity and supporting projects to help disabled people and promote our agenda," he says. In addition to the administrative work as chairman, Simon also acts as master of ceremonies at Muskelsvindfonden's annual Grøn Koncert (Green Concert) music festival events. But whenever Simon introduces himself to a new audience, there is one thing that often gets left out: "A lot of the time I don't mention I have SMA type 2," he says. "I don't leave it out intentionally – I simply forget!"

> *"A lot of the time I don't mention I have SMA type 2. I don't leave it out intentionally – I simply forget!"*

When Simon was born in 1989, as the first of three children, he was a perfectly normal and healthy baby at first. When at the age of two he

Biogen - 212931 - Juni - 2023

was diagnosed with SMA, his parents were told he would probably not survive another year. After the initial sense of shock and profound loneliness as parents of a child with a rare, deadly disease, his parents joined Muskelsvindfonden, which became an important source of support. Simon describes how his parents decided not to allow SMA to stand in their way of having a happy and functioning family. Thanks to their determination, Simon was able to grow up and enjoy a comparatively normal childhood in his hometown. His parents made a concerted effort to raise Simon normally and rejected the suggestion by the local council that he should go to a special school for disabled children. Instead, they insisted that he should attend the local school, where he was the only one in a wheelchair out of a total of 800 students. "That was probably the best investment they could have made in my life! I had to do what all the other children did – no allowances were made because of my disability," says Simon.

Back in the early 1990s when Simon was first diagnosed with SMA, and all through his school years, there was no prospect of a treatment for SMA – instead, Simon and his family were encouraged to make the best of the situation and

> *"From an early age, I chose not to focus on my disability – my disability is not who I am and it doesn't define me."*

focus on the things that Simon could do, rather than his limitations. Simon is grateful to his parents for choosing the path of the "good life" for him. "From an early age, I chose not to focus on my disability," he says. "Even though I am usually the odd one out in company, and I am constantly having to adapt and make compromises, my disability is not who I am, and it doesn't define me." Thanks to his parents' efforts, Simon feels he has been able to shape his life in a way that is not too different from most able-bodied people, despite starting out in life with a death sentence hanging over his head. As Simon puts it: "I may have been diagnosed with SMA type 2, but I don't feel sick!"

However, that does not mean the realities of the diagnosis and disease do not affect his life. Despite feeling well, Simon has had to spend his adult life juggling the SMA accoutrements of physiotherapy sessions and regular medical check-ups, orthoses and corsets, operations, mobility aids, breathing machines, and the extensive need for assistance on a daily basis. "It is not always easy," he says. "I am constantly dependent on other people, and as I grow older, I can feel myself decline, becoming less able to do things on my own and more dependent

> *"The best way I can describe my experience of living with SMA type 2 is that I am feeling strong, but at the same time I am feeling weak."*

on people and equipment." Simon says that having a family of his own has made him realise that his limitations and physical decline is not just affecting him but also his family. "The best way I can describe my experience of living with SMA type 2 is that I am feeling strong, but at the same time I am feeling weak." For Simon, a key element in making the best of life with SMA has been to focus on what is important in life. "For a time I believed that the way to a good life for me was becoming the best version of myself, by doing a lot of exercise and physiotherapy every day and sticking to a healthy lifestyle," he says. "During the first year of the corona pandemic I lost 15 kg – but then I realised this wasn't actually making me feel any better!" Instead, Simon decided that although he would like to feel stronger, the most important this in his life is how he feels, and how his family is doing.

When the first treatment for SMA became available, it came as a surprise to Simon, having been told all through his childhood that there would never be a treatment. "When the treatment became available, it made me re-evaluate the way I had been focusing on other things in my life," he said. "I started asking myself questions around how long I might be able to live, and whether I will ever be able to improve." Simon admits that for him it was something of a shock and a disruption to his life. While he wholeheartedly embraces treatment as a blessing for patients with SMA and sees it as the future of SMA, he also fears that for some, it may be a curse.

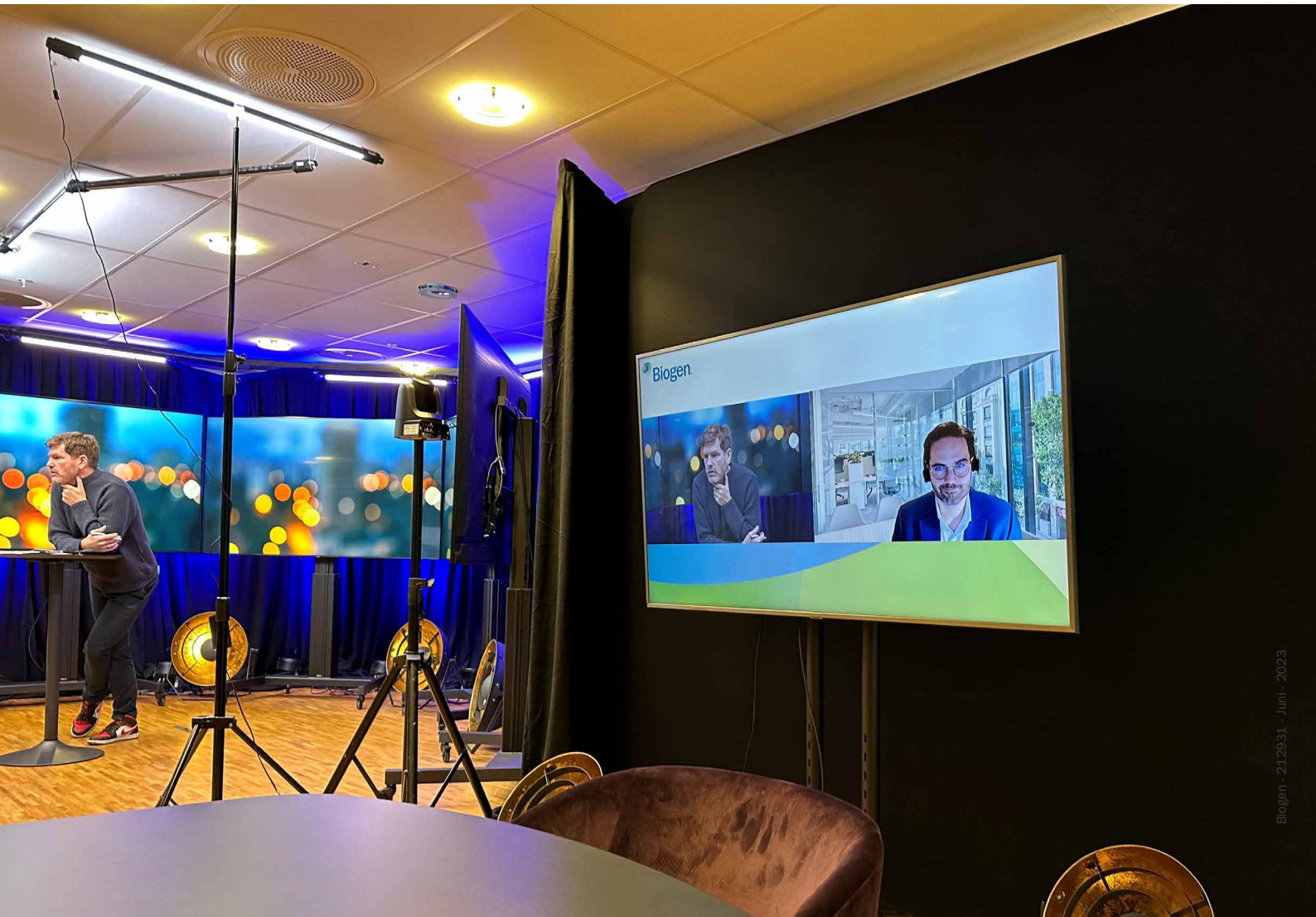
Biogen - 212931 - Juni - 2023

"The fact that there is now treatment available may undermine the identity as someone living with SMA for some patients, make them doubt themselves and whether they are good enough as they are."

"The fact that there is now treatment available may undermine the identity as someone living with SMA for some patients, make them doubt themselves and whether they are good enough as they are."

In Denmark, where the criteria for SMA treatment are stricter than almost anywhere else in Europe, the accessibility issue is threatening to tear the SMA community apart. "As chairman of Muskelsvindfonden, I have witnessed more parents crying with frustration over not being able to access treatment, than over the SMA diagnosis itself," Simon says. "The difficulty in accessing treatment is creating an A team and a B team, and families who are unable to get treatment are left feeling disappointed and abandoned." Simon is resigned to the thought that he is part of the last generation living with SMA type 2 in Denmark – an "SMA dinosaur," as he describes himself. But he is concerned that the debate around access to treatment for SMA patients in Denmark continues to be dominated by the high cost of treatment rather than the benefits to patients, and that the current polarised debating climate may become the new normal.

Biogen - 212931 - Juni - 2023



LLUÍS PUJADAS

Medical Affairs, Biogen Europe

Nusinersen – five years after launch

When nusinersen was first launched in 2017, it was the first treatment to be approved for SMA and thus represented the dawn of a new era in the care and management of SMA. Since then, more than 13,000 SMA patients in 66 countries around the world have been treated with nusinersen[1], and Biogen is continuing to invest in the nusinersen life cycle to address unmet medical needs in SMA. In the second keynote presentation at Lis-n & Ler-n 2022, Dr Lluís Pujadas, who is senior medical manager within the NMD team at Biogen Europe, outlined how nusinersen is fundamentally changing the disease course of presymptomatic and symptomatic SMA by continuing to deliver meaningful improvements in infants, children and adults with SMA[2,3].

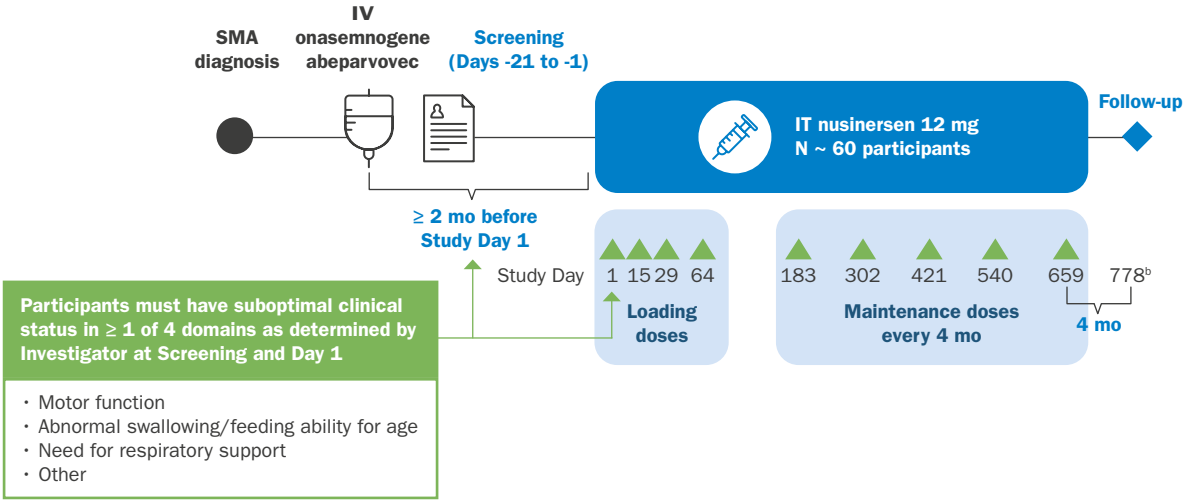
> *"Nusinersen is fundamentally changing the disease course of presymptomatic and symptomatic SMA by continuing to deliver meaningful improvements in infants, children and adults with SMA."*

The clinical development programme for nusinersen has provided comprehensive and robust data on the efficacy and safety of nusinersen across a wide patient population. In the ENDEAR study, treatment with nusinersen resulted in significant and clinically meaningful improvements in motor function and event-free and overall survival among infants diagnosed with SMA before the age of six months, compared with sham control[4]. Likewise, the CHERISH study confirmed significant and clinically meaningful improvements in motor function among children with later-onset SMA[5]. Both pivotal studies were terminated early, having demonstrated the treatment benefit of nusinersen in pre-specified interim analyses sufficiently convincingly that continued sham control treatment was deemed unethical[4,5]. In the pre-symptomatic setting, the ongoing NURTURE study has shown that early proactive treatment with nusinersen in infants with

Biogen - 212931 - Juni - 2023

RESPOND: Study Design

Phase 4, open-label, multicenter, single-arm study of nusinersen in children who previously received IV onasemnogene abeparvovec (NCT04488133; study ongoing)a



IT = intrathecal; IV = intravenous; SMA = spinal muscular atrophy
[a]The study design reflects a protocol amendment (PV2.0 15July2022).
[b]Or 4 months from last dose.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04488133

a genetic diagnosis of SMA prior to the onset of symptoms is associated with substantial clinical benefit and a favourable benefit-risk profile[2]. In a pre-specified interim analysis, all infants in the study were alive and none required permanent ventilation, and further achieved motor development milestones inconsistent with the natural history of SMA type 1 and 2[2]. Patients who completed the nusinersen treatment studies were eligible for inclusion in the open-label SHINE extension study, which has since confirmed the long-term safety and efficacy of nusinersen for up to five years[6].

Life cycle activities – the RESPOND study

The phase 4 development programme for nusinersen will include studies documenting the efficacy and safety of higher doses in treatment-naïve patients or patients previously treated with the approved dose of nusinersen (DEVOTE; NCT04089566) and in SMA patients previously treated with risdiplam (ASCEND; NCT05067790). In addition, enrolment has begun in the RESPOND study (NCT04488133) which will evaluate the efficacy and safety of nusinersen in patients with a suboptimal clinical response to AAV vector-based gene therapy onasemnogene abeparvovec. The background for the RESPOND study is that although the overall treatment goal in SMA is to address the SMN deficiency and preserve motor neurons[7,8], different therapies may affect target cell types differently and yield different amounts of functional SMN protein. Findings from preclinical animal models and limited human post-mortem studies that AAV9-mediated gene therapy may transduce only a subpopulation of motor neurons[9–11] provide a scientific rationale for investigating whether nusinersen can potentially increase SMN protein production in untransduced motor neurons and thereby bring additional clinical benefit in the treatment of SMA. The RESPOND study will enrol SMA patients with one or more *SMN2* copies, who are younger than 36 months and have received onasemnogene abeparvovec at least two months prior to receiving their first nusineren dose in RESPOND, and are deemed by the investigator to have had a suboptimal clinical response to onasemnogene abeparvovec with respect to motor function and/or nutritional or respiratory status. The primary endpoint in RESPOND is the total HINE Section 2 motor milestone score, and key secondary endpoints include safety and change in CHOP INTEND, HFMSE and RULM scores.

Biogen - 212931 - Juni - 2023

Nusinersen SmPC update 2022

In his presentation at Lis-n & Ler-n 2022, Lluís Pujadas also highlighted some important updates to the nusinersen SmPC, which was updated in February 2022. The updated version of the SmPC incorporates real-world evidence that demonstrate that adult SMA patients may benefit from significant and cumulative improvements in motor function when treated with nusinersen[3,12,13], stating that "real-world clinical findings support the effectiveness of nusinersen to stabilise or improve motor function in some SMA adult Type II and III patients[6]." In addition, the 'black triangle' label has been removed from the nusinersen SmPC, indicating that nusinersen has been shown to have a favourable safety profile that remains consistent in the long term[6]. Guidance is also provided in the updated SmPC on how to proceed in case a dose of nusinersen is delayed or missed, to allow patients to stay on track with their treatment[6]. Lluís Pujadas emphasised that nusinersen is as yet the only SMA treatment to have demonstrated this level of real-life clinical benefit and safety in all ages and SMA types, with dosing flexibility to help patients and their families fit the treatment around their lives.

> *"The updated version of the SmPC incorporates real-world evidence that demonstrate that adult SMA patients benefit from significant and cumulative improvements in motor function when treated with nusinersen."*

References:

1. BiogenLinc. Spinraza. https://biogenlinc.com/products/sma/spinraza/. **2.** De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscular Disorders [Internet]. 2019 Nov;29(11):842–56. Available from: https://doi.org/10.1016/j.nmd.2019.09.007. **3.** Coratti G, Cutrona C, Pera MC, Bovis F, Ponzano M, Chieppa F, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis [Internet]. 2021;16(1):430. Available from: https://doi.org/10.1186/s13023-021-02065-z. **4.** Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med [Internet]. 2017;377(18):1723–32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29091570 **5.** Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med [Internet]. 2018;378(7):625–35. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29443664. **6.** Spinraza Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/spinraza-epar-product-information_en.pdf. **7.** Kariyawasam D, Carey KA, Jones KJ, Farrar MA. New and developing therapies in spinal muscular atrophy. Paediatr Respir Rev [Internet]. 2018;28:3–10. Available from: https://www.sciencedirect.com/science/article/pii/S1526054218300484 **8.** Talbot K, Tizzano EF. The clinical landscape for SMA in a new therapeutic era. Gene Ther [Internet]. 2017;24(9):529–33. Available from: https://doi.org/10.1038/gt.2017.52. **9.** Meyer K, Ferraiuolo L, Schmelzer L, Braun L, McGovern V, Likhite S, et al. Improving Single Injection CSF Delivery of AAV9-mediated Gene Therapy for SMA: A Dose–response Study in Mice and Nonhuman Primates. Molecular Therapy [Internet]. 2015 Mar 1;23(3):477–87. Available from: https://doi.org/10.1038/mt.2014.210. **10.** Foust KD, Nurre E, Montgomery CL, Hernandez A, Chan CM, Kaspar BK. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. Nat Biotechnol [Internet]. 2009;27(1):59–65. Available from: https://doi.org/10.1038/nbt.1515. **11.** Thomsen G, Burghes AHM, Hsieh C, Do J, Chu BTT, Perry S, et al. Biodistribution of onasemnogene abeparvovec DNA, mRNA and SMN protein in human tissue. Nat Med [Internet]. 2021;27(10):1701–11. Available from: https://doi.org/10.1038/s41591-021-01483-7. **12.** Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A, Petri S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol [Internet]. 2020 Apr 1;19(4):317–25. Available from: https://doi.org/10.1016/S1474-4422(20)30037-5. **13.** Maggi L, Bello L, Bonanno S, Govoni A, Caponnetto C, Passamano L, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. Journal of Neurology, Neurosurgery & Psychiatry [Internet]. 2020 Nov 1;91(11):1166. Available from: http://jnnp.bmj.com/content/91/11/1166.abstract

Biogen - 212931 - Juni - 2023

SEAN WALLACE

Oslo University Hospital, Norway

SMA in the Nordics

From a healthcare point of view, the Nordic countries of Norway, Denmark and Sweden have much in common – they are all relatively low-population countries, with universally accessible high-quality, tax-funded public healthcare systems, and with a strong equity and equality ethos in their healthcare service provision. In his keynote presentation at Lis-n & Ler-n 2022, Sean Wallace summarised the current use of disease-modifying treatments for SMA in each of the three countries.

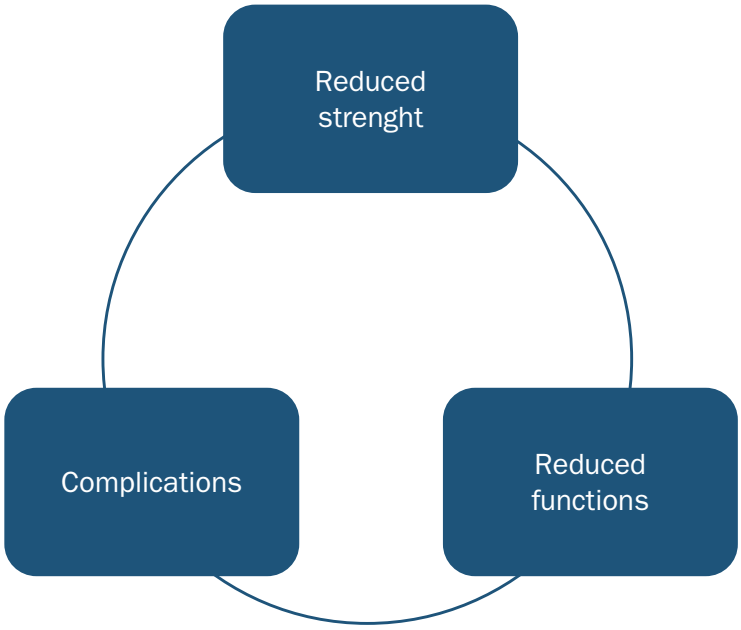
Nusinersen was first introduced in the Nordic region under the auspices of an EAP which commenced in 2017. Since then, a further two disease-modifying agents have become available for the treatment of SMA in Nordic centres: onasemnogene abeparvovec (Zolgensma® , Novartis), an AAV vector-based gene therapy that delivers an *SMN1* transgene into target motor neuron cells in a single IV administration[1]; and risdiplam (Evrysdi® , Roche), an orally administered, small molecule that modifies *SMN2* pre-messenger RNA splicing and increases levels of functional SMN protein[2]. For Sean Wallace, consultant in paediatric neurology at Oslo University Hospital in Norway, and his colleagues, the advent of disease-modifying treatments has allowed a shift in focus in the care of SMA patients, from trying to manage the vicious circle where dwindling muscle strength leads to impaired function and complications, to having an impact on the underlying cause of the disease. “With these treatments, we are able to directly influence muscle strength for the first time,” Sean Wallace told the audience in his presentation. “With that comes the hope of reversing disease progression.”

> *“With these treatments, we are able to directly influence muscle strength for the first time – with that comes the hope of reversing disease progression.”*

Norway

In Norway, the majority of SMA patients are treated with nusinersen, which has been licensed for use in Norway since February 2018 and represents the lion share of the Norwegian experience with

Biogen - 212931 - Juni - 2023



disease-modifying treatment of SMA. All patients initiate treatment at Oslo University Hospital and undergo annual treatment reviews. Patients are eligible for receiving nusinersen if they are under 18 years and have SMA type 1 or 2 with at least two copies of *SMN2*, an oxygen saturation level of at least 95%, and no need for continuous NIV, or SMA type 3a. Criteria for stopping nusinersen include declining motor skills and/or respiratory function, or nutritional status for patients with SMA type 1, but Sean Wallace stressed that other factors are taken into consideration before stopping treatment. "Patients who fulfil any of the stop criteria have to be discussed in the national interest group for SMA and assessed in the context of other care and quality aspects," he said. "As long as the patient can maintain function, the treatment is considered as having an effect."

> ***"As long as the patient can maintain function, the treatment is considered as having an effect."***

SMA was recently included in the Norwegian NBS programme, which is carried out centrally at Oslo University Hospital and covers a total of 26 hereditary diseases. Patients diagnosed with SMA on NBS are eligible for treatment with nusinersen, or onasemnogene abeparvovec up until the age of six months. For older infants, and for patients for whom IT treatment is not feasible, oral treatment with risdiplam is also an option. Treatment switching between nusinersen and risdiplam is permitted, whereas treatment with onasemnogene abeparvovec precludes other treatments. A national SMA registry has been established to allow follow-up of all SMA patients in Norway and ensure that the national treatment guidelines are adhered to.

Denmark

In Denmark there are currently a total of 170 patients with SMA, 50 of whom are under the age of 18. All children with SMA under the age of 10 years are receiving treatment at either of the two national treatment centres in Copenhagen and Aarhus. As in Norway, nusinersen is the most widely used treatment. Patients with SMA type 1 who are not on permanent ventilatory support are eligible for treatment with either of the three approved disease-

modifying agents; presymptomatic treatment is possible for patients with at least two copies of *SMN2*, although use of onasemnogene abeparvovec is limited to patients with no more than three copies of *SMN2*, and risdiplam is limited to patients older than two months. For patients diagnosed with SMA type 2 or 3, treatment with risdiplam is available up to the age of six years; patients with SMA Type 2 can also receive nusinersen until the age of six. Similar to Norway, treatment switching between risdiplam and nusinersen is permitted whereas onasemnogene abeparvovec precludes other treatments. SMA is included in the Danish national NBS, and a national SMA registry has been established for patient-follow-up.

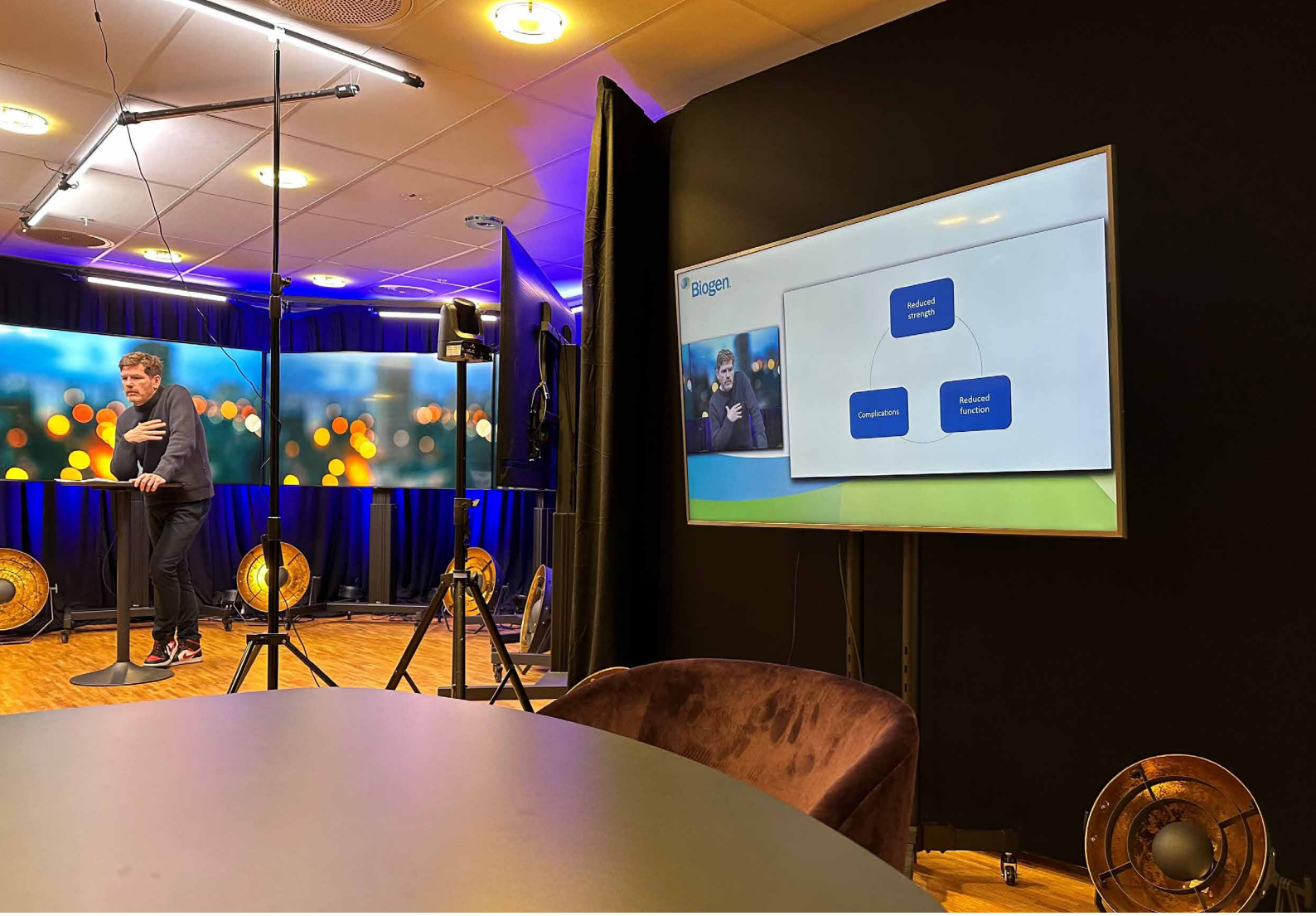
Sweden

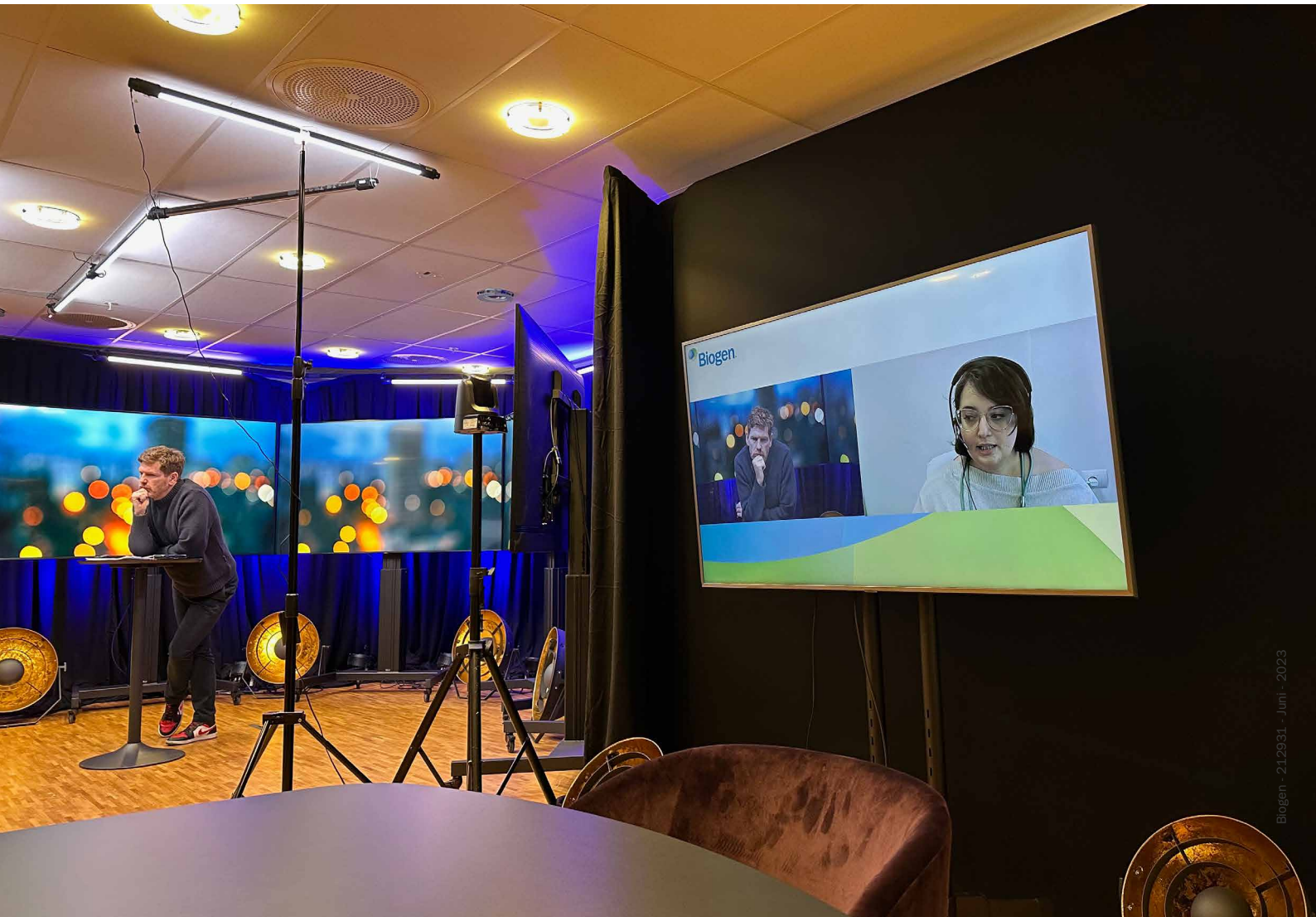
With twice as many SMA patients as Norway, Sweden has the largest SMA patient cohort in the Nordic region, and the longest experience with disease-modifying treatments since the start of the nusinersen EAP in 2017. Under the national Swedish treatment recommendations for SMA, patients weighing less than 13.5kg with genetically confirmed SMA with up to three copies of *SMN2* should be offered treatment with onasemnogene abeparvovec. Patients up to the age of 18 who do not fulfil these criteria should be offered risdiplam as the first choice, or nusinersen. All patients are monitored through the national quality register for SMA. Treatment switching between risdiplam and nusinersen is permitted, and unlike in Norway and Denmark, patients initiated on either risdiplam or nusinersen may also switch to onasemnogene abeparvovec. SMA is not yet covered in the NBS programme, but an application is currently under review and a decision is expected in early 2023.

Sean Wallace concluded his presentation at Lis-n & Ler-n 2022 by speculating about the future of SMA treatment in the Nordic countries. One aspect that he anticipates may come up for discussion is the re-classification of SMA diagnosed on NBS as either pre-symptomatic, prodromal or symptomatic, as proposed by Finkel and Benatar[3]. Another, more controversial aspect for discussion is that a sizeable proportion of SMA patients with two *SMN2* copies fail to achieve the desired outcomes of treatment despite being treated promptly after NBS[4], prompting the question of whether in future all patients will be treated in the same way as currently.

References:
1. Zolgensma Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf. **2.** Evrysdi Summary of Product Characteristics . https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf. **3.** Finkel RS, Benatar M. Pre-symptomatic spinal muscular atrophy: a proposed nosology. Brain [Internet]. 2022 Jul 1;145(7):2247–9. Available from: https://doi.org/10.1093/brain/awac125. **4.** Schwartz O, Kölbel H, Blaschek A, Gläser D, Burggraf S, Röschinger W, et al. Spinal Muscular Atrophy – Is Newborn Screening Too Late for Children with Two *SMN2* Copies? J Neuromuscul Dis. 2022;9:389–96.

Biogen - 212931 - Juni - 2023





GIORGIA CORATTI

Catholic University of the Sacred Heart, Rome, Italy

Meta-analysis of nusinersen-treated SMA patients

The clinical efficacy and safety of nusinersen in SMA has been demonstrated in a comprehensive clinical development programme. In 2016, nusinersen became the first medical therapy to be approved by the FDA and EMA for the treatment of SMA based on pivotal RCTs demonstrating significant clinical benefits on disease progression and motor function in early- and later-onset SMA[1–3]. However, as new treatments for SMA are becoming available and the treated patient cohort grows, capturing the real-life experience with nusinersen will be increasingly important to ensure that patients and families gain maximum treatment benefit. A critical review and meta-analysis in patients with SMA Type 2 and 3 found that nusinersen was associated with improved motor function in all observed cohorts, whereas untreated patients invariable became worse[4]. The details of this meta-analyses were presented at Lis-n & Ler-n 2022 by the first author of the publication, Dr Giorgia Coratti, who is a paediatric physiotherapist specialising in neuropsychomotor development and rehabilitation at the Catholic University of the Sacred Heart in Rome.

The meta-analysis conducted by Giorgia Coratti and her team involved a rigorous literature search which identified approximately 400 papers on the efficacy of nusinersen, out of a total of more than 14,000 papers on SMA. Out of these, 19 papers met the strict inclusion criteria, and a further 11 papers reporting outcomes in untreated patients were included to allow natural history comparison. The statistical analysis of the data comprised a descriptive model to help clinicians understand the magnitude of the treatment effect, and a statistical model to evaluate the treatment efficacy within and between predetermined subgroups. In addition to treatment status, the analyses were also stratified according to the age (adult or paediatric) and SMA type (type 2, type 3, or both) of the patient population. The main outcome measure considered in the meta-analysis was motor function as assessed by HFMSE, RULM or 6MWT, respectively[4].

Biogen - 212931 - Juni - 2023

Motor function outcomes

HFMSE was included as an outcome measure in 13 of the studies on nusinersen and five of the natural history studies. Overall, the nusinersen studies showed an improvement in HFMSE score (Figure). The statistical analysis showed an overall pooled mean increase in the HFMSE score of 2.27 points (95% CI 1.41, 3.13) among patients treated with nusinersen, versus a pooled mean reduction of 1.00 point (95% CI 1.33, 0.67) in natural history studies ($p<0.0001$). Given the high level of heterogeneity among the included patient populations and study designs, multivariate meta-regression analysis was performed which confirmed the result when adjusted for age, SMA type, and ambulatory status, as well as over up to 24 months of follow-up.

The analysis of RULM scores showed that while the pooled mean change across treated and untreated patients did not reach statistical significance on its own, adjusting for age and SMA type revealed significantly higher RULM scores in treated patients compared with natural history studies (coefficient [SE]: 1.0 [0.45], $p=0.025$). RULM score improvements were significantly greater among paediatric patients, patients with SMA Type 2, and ambulatory patients, compared with adults, patients with SMA Type 3, and non-walkers, respectively.

Results from 6MWT was included in eight nusinersen studies and five natural history studies. All studies reported significant improvements with nusinersen treatment irrespective of age group, with a pooled mean improvement of 19.80 metres (95% CI 6.70, 32.89) in the nusinersen studies compared with a pooled mean decrease of 8.29 metres (95% CI 19.10, 2.52) in the natural history studies.

Implications for SMA care

Putting the results of the meta-analysis into context, Giorgia Coratti stressed that while nusinersen appears to have an adequate effect irrespective of age, SMA type or ambulatory status – as an example, Giorgia Coratti highlighted that an improvement of two points in the HFMSE score may translate into being able to walk up a staircase using alternating steps, or walk down the stairs without using the banister – it is important to counsel patients and families that the outcomes of nusinersen treatment

> *"It is important to counsel patients and families that the outcomes of nusinersen treatment are highly individual."*

are highly individual. All patients will not achieve the same level of improvement, and all patients will not change their disease phenotype. HCPs need to communicate the evidence clearly when assisting patients' and families in making treatment decisions and setting expectations. There remains, in Giorgia Coratti's view, a considerable unmet need for comprehensive care that focuses on delivering meaningful health outcomes and quality of life in SMA, together with integrated care pathways and resilient social and financial systems for supporting patients and families living with SMA.

References:
1. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med [Internet]. 2017;377(18):1723–32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29091570. **2.** Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med [Internet]. 2018;378(7):625–35. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29443664. **3.** de Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscular Disorders [Internet]. 2019 Nov;29(11):842–56. Available from: https://doi.org/10.1016/j.nmd.2019.09.007. **4.** Coratti G, Cutrona C, Pera MC, Bovis F, Ponzano M, Chieppa F, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis [Internet]. 2021;16(1):430. Available from: https://doi.org/10.1186/s13023-021-02065-z

Biogen - 212931 - Juni - 2023

Take-home summaries

Life on wheels – an SMA patient perspective on life and treatment
Simon Toftgaard Jespersen, Muskelsvindfonden, Denmark

"From an early age, I chose not to focus on my disability," says Simon. "My disability is not who I am, and it doesn't define me." Despite starting out in life with an SMA type 2 diagnosis, Simon feels he has been able to shape his life in a way that is not too different from that of most able-bodied people. As chairman of Muskelsvindfonden in Denmark, he strives to be a role model and help patients and families come to terms with the diagnosis and navigate the new treatment landscape for SMA.

Nusinersen – five years after launch
Lluís Pujadas, Medical Affairs, Biogen Europe

Since its launch in 2017, nusinersen has fundamentally changed the clinical management of pre-symptomatic and symptomatic SMA by delivering meaningful improvements in infants, children and adults with SMA. The continued development programme for nusinersen will address unmet medical needs in SMA, including documenting higher doses of nusinersen in treatment-naïve and treatment-experienced patients, as well as nusinersen treatment in SMA patients previously treated with risdiplam or onasemnogene abeparvovec. In addition, real-world evidence supports that nusinersen can stabilise or improve motor function in some SMA adult Type II and III patients.

SMA in the Nordics
Sean Wallace, Oslo University Hospital, Norway

The introduction of nusinersen as the first medical treatment for SMA in 2017, and the subsequent launch of onasemnogene abeparvovec and risdiplam, have allowed clinicians caring for SMA patients to shift their focus from managing the vicious circle of dwindling muscle strength and progressive functional impairment, to stopping the underlying cause of the disease in its tracks. In each of the Nordic countries, treatment recommendations and eligibility criteria are being reviewed continually to ensure that SMA patients who may benefit can access disease-modifying treatments.

Meta-analysis of nusinersen-treated SMA patients
Giorgia Coratti, Catholic University of the Sacred Heart, Rome, Italy

Nusinersen became the first medical treatment to be licensed for SMA by the FDA and EMA, based on pivotal clinical trials demonstrating significant clinical benefits on disease progression and motor function in early- and later-onset SMA. As new treatments for SMA emerge and the treated patient cohort grows, capturing the real-life experience with nusinersen will be increasingly important to ensure that patients and families gain maximum treatment benefit. A critical review and meta-analysis has shown that nusinersen treatment is capable of improving motor function in patients with SMA Type 2 and 3, while untreated patients become progressively worse.

SPINRAZA (nusinersen) - Viktig informasjon

Indikasjon: Behandling av 5q spinal muskelatrofi (SMA).

Dosering: Skal kun startes av lege med erfaring i behandling av SMA, basert på ekspertvurdering av nytte/risiko. Anbefalt dose: 12 mg (5 ml) pr. administrering. Behandling bør starte tidligst mulig etter diagnostisering, med 4 ladningsdoser. 1 dose gis på dag 0, 14, 28 og 63. Deretter bør en vedlikeholdsdose gis 1 gang hver 4. måned. Gis intratekalt ved spinalpunksjon.

Utvalgt sikkerhetsinformasjon:
Pasienter med uttalt hypotoni og respirasjonssvikt ved fødsel vil ikke nødvendigvis ha nytte av behandlingen pga. alvorlig mangel på SMN-protein. Spinalpunksjonsprosedyren kan gi bivirkninger som f.eks. hodepine, ryggsmerter og oppkast. Mulige problemer kan ses hos svært unge pasienter og ved skoliose. Mulig risiko for nyretoksisitet. Måling av proteiner i urin anbefales hvis klinisk indisert, og ytterligere utredning bør vurderes ved vedvarende forhøyede verdier. Mulig risiko for koagulasjonsforstyrrelser og trombocytopeni, inkl. akutt alvorlig trombocytopeni. Laboratorietesting av blodplater og koagulasjon anbefales før behandling hvis klinisk indisert. Kommuniserende hydrocephalus som ikke er relatert til meningitt eller blødning er sett og skal vurderes som mulig årsak ved nedsatt bevissthet. Meningitt, aseptisk meningitt og overfølsomhet er rapportert. Bruk under graviditet bør unngås. Amming skal opphøre eller behandling avsluttes/avstås fra.

Pakninger og priser: Hetteglass injeksjonsvæske, oppløsning 12 mg (5 ml) kr. 973 786,30.

Refusjon: Besluttet innført av Beslutningsforum 12.02.2018 til behandling av barn (0 til fylte 18 år) med SMA under forutsetninger som er angitt på https://nyemetoder.no/metoder/nusinersen-spinraza. Besluttet innført av Beslutningsforum 11.04.2023 til behandling av voksne under forutsetninger som angitt på https://nyemetoder.no/nyheter/beslutningsforum-11-april-spinraza-til-voksne-med-sma-innfores

Reseptgruppe: C

For utfyllende informasjon, se Spinraza SPC godkjent 01/2022 eller FK-tekst på www.felleskatalogen.no

Biogen Norway AS • Vitaminveien 1A, 0485 Oslo • Postboks 4305 Nydalen, 0402 Oslo Tlf.: +47 23 40 01 00 • biogen.no • www.tysabri.no

Biogen - 212931 - Juni - 2023

Vitaminveien 1A | 0485 Oslo, Norway | Tlf: +47 23 40 01 00 | www.biogen.no

Biogen

Biogen - 212931 - Juni - 2023