



Spinraza

Spinal Muscular Atrophy

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Overview

- Acronyms
- Spinal Muscular Atrophy background and epidemiology
- Spinraza Clinical Evidence
- Review Clinical Policy

Acronyms

- SMA = spinal muscular atrophy
- HINES = Hammersmith Infant Neurological Examination
- HFMSE = Hammersmith Functional Motor Scale Expanded
- WHO = World Health Organization
- CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
- SMN = survival motor neuron

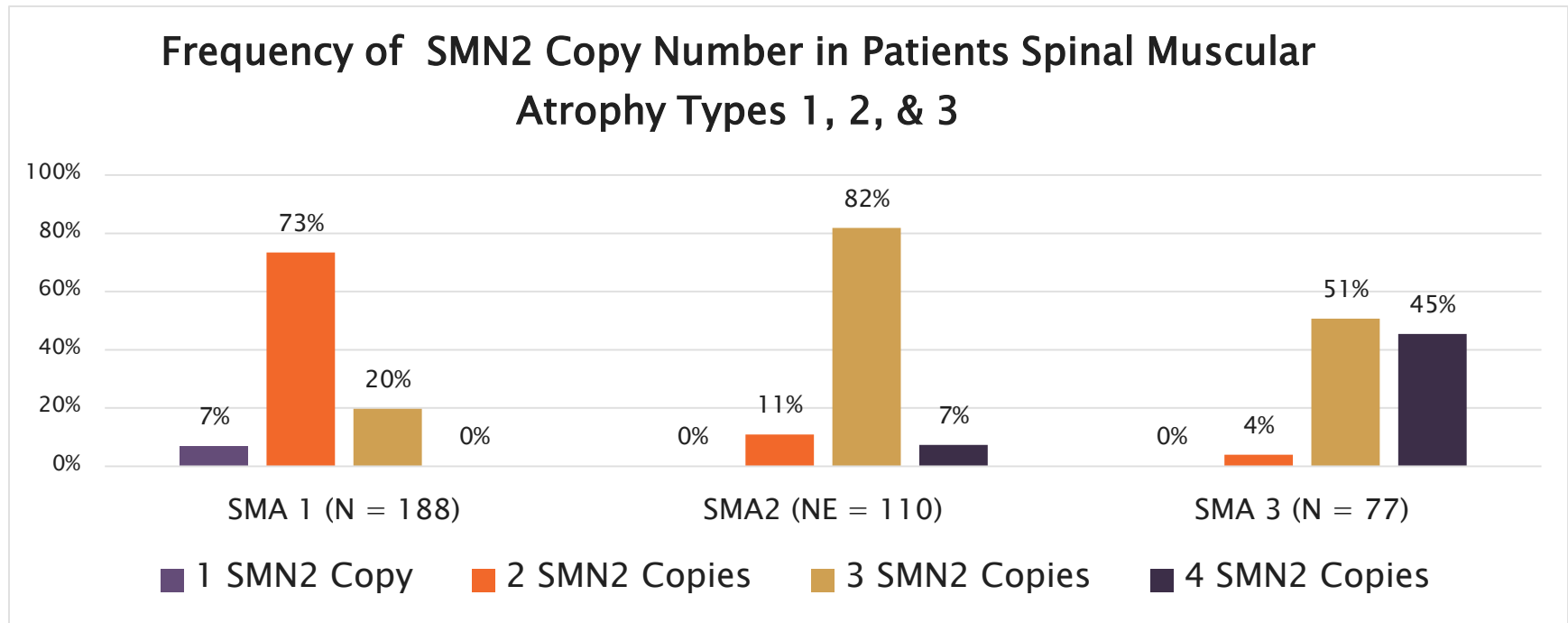
Spinal Muscular Atrophy (SMA)

- SMA is characterized by the degeneration of anterior horn cells that results in muscular atrophy
- 95% of SMA is caused by homozygous deletion or mutation of the 5q13 survival motor neuron (SMN1) gene
 - Incidence 1:11,000 live births
- SMA is the most common genetic cause of childhood mortality

SMA

- In the absence of SMN1 gene, SMN protein production is dependent on the SMN2 gene
- Each patient with SMA has at least one copy of the SMN2 gene
- Presence of SMN2 does not prevent SMA, only 10-25% of SMN2 genes produce full length
- SMN2 has a single translationally silent nucleotide difference that causes exon 7 skipping resulting in SMN protein deficiency
- Severity of disease is correlated to the number of copies of SMN2
- SMA is categorized into several types based on age of onset and severity.

Clinical phenotype of SMA correlates with the number of copies of the SMN2 gene



Feldkötter M, et al. Am J Hum Genet. 70:358-368, 2002.

SMA 0

- Onset: Prenatal
- Symptoms: areflexia, facial diplegia, atrial septal defects, joint contractures
- Functional Status:
 - severe weakness,
 - hypotonia,
 - decreased fetal movements
- Life Expectancy: Less than 6 months

SMA 1 (Werdnig-Hoffman)

- Onset: < 6 months
- Symptoms:
 - Profound hypotonia
 - poor head control
 - reduced or absent tendon reflexes
 - paradoxical breathing
 - tongue and swallowing weakness
 - Alert, attentive, and bright at time of diagnosis
- Functional Status: Never rolls or sits unassisted
- Life Expectancy: typically < 2 years

SMA 2

- Onset: 7 – 18 months
- Symptoms:
 - Proximal leg weakness more than arms
 - Orthopedic complications of bone and joint development (Progressive scoliosis/Joint contractures)
 - Intercostal muscle weakness
- Functional Status:
 - Able to sit unassisted
 - May stand but never able to walk
 - Cognition is normal
- Life Expectancy: 20 year survival rate 77% - 93%

SMA 3 (Kugelberg-Welander)

- Onset: > 18 months generally before age of 18 years
- Symptoms:
 - Progressive proximal weakness in legs more than arms
 - Little to no respiratory weakness
 - Cognition is not altered.
- Functional Status:
 - Able to sit, stand, & walk independently
 - Typically need a wheelchair when nearing puberty
- Life Expectancy: Adult

SMA 4

- Onset: 20 – 30 years
- Symptoms: Similar to SMA 3
 - Leg weakness
 - Upper limb weakness
- Functional Status: Ambulatory
- Life Expectancy: Normal

Age Appropriate Motor Milestone Development

Motor Milestone	Expected Age of Attainment in Healthy Baby
Full Head Control	5 months
Independent Sitting	7 months
Walking with support (cruising)	11 months
Standing unaided	12 months

Current SMA Treatment

Primarily focused on improving quality of life

- Pulmonary and Respiratory Support
- Digestive health and proper nutrition
- Orthopedic and musculoskeletal complications

Spinraza[®] (Nusinersen)

- Spinraza is the first and only FDA-approved treatment for Spinal Muscular Atrophy (SMA)
- Antisense oligonucleotide that modulates splicing of SMN2 pre-mRNA to promote inclusion of exon 7, that increases the amount of full-length SMN protein

Spinraza – Administration & Cost

- Administered through intrathecal injections
 - Initial Treatment Four loading doses
 - First 3 doses 14 days apart
 - Forth dose 30 days after the third dose
 - Maintenance doses every 4 months thereafter
- The wholesale acquisition cost for the first year of treatment is \$750,000; and \$375,000 in subsequent years

Spinraza - Clinical Evidence

Study CS5 (NURTURE)

- **Type:** Open label, multi-center, multi-national, single arm study to determine efficacy of nusinersen in preventing or delaying death or ventilation in genetically diagnosed infants with pre-symptomatic SMA
- **Regimen:** 12 mg Intrathecal bolus injection on days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778
- **Demographics:**
 - N=17 at time of interim analysis
 - 12/17 had 2 SMN2 gene copies; 5/17 had 3 copies
 - Median age at first dose = 19 days

Study CS5 (NURTURE) - Endpoints

- **Primary Endpoints:**

- Death
- respiratory ventilation (invasive or non-invasive ≥ 6 hours/day or continuously for 7 or more days or tracheostomy)

- **Secondary Endpoints:**

- Clinical manifestation of SMA (ability to crawl, stand, or walk)
- Motor function milestones:
 - HINES, CHOP-Intent, WHO guidelines
- Growth parameters (weight, length, head & chest circumference)

Study CS5 (NURTURE) – Inclusion Criteria

- \leq six weeks old
- Gestational age 37-42 weeks for singleton births; 34-42 weeks for twins
- genetic documentation of 5q SMA homozygous deletion or mutation or compound heterozygous mutation
- Genetic documentation of two or three copies of SMN2
- Ulnar CMAP \geq mV at baseline
- Adequate nutrition and hydration (without gastrostomy)
- Body weight \geq 3rd percentile for age using appropriate country-specific guidelines

Study CS5 (NURTURE) – Exclusion Criteria

- Hypoxemia ($O_2 < 96\%$ awake or asleep without supplemental O_2 or respiratory support)
- Clinical manifestations of SMA at screening or prior to first injection
- Hx of brain or spinal cord disease that would interfere with LP procedure, cerebrospinal fluid circulation, or safety assessments
- Implanted shunt or central nervous system catheter
- Hx of bacterial meningitis or viral encephalitis
- Clinically significant abnormalities in hematology or chemistry
- Tx with other investigational drugs to treat SMA
- Diagnosis of neonatal respiratory distress syndrome requiring surfactant replacement therapy or invasive ventilator support.

Study CS5 (NURTURE)

Results of Interim Analysis

- Interim analysis when 17 of 25 patients enrolled and 13 patients had reached day 64
- Gender: 67% males; 33% female
- Mean baseline CHOP-Intend 48.9 and 53.5 with 2 or 3 SMN2 copies respectively
- Mean baseline HINES 2.3 and 4.8 with 2 or 3 SMN2 copies respectively

Study CS5 (NURTURE) Results of Interim Analysis

- **Primary Endpoints**
 - No deaths
 - No invasive respiratory intervention or tracheostomy
 - No infants require non-invasive ventilation for ≥ 6 hours/day continuously for 7 or more days

Study CS5 (NURTURE) Results of Interim Analysis

- Secondary Endpoints
 - Majority of infants gained weight over time, consistent with normal development
 - 4 of 10 infants met criteria for growth failure at day 183
 - 3 of 4 continued to gain weight over time, 1 required percutaneous gastric tube
 - Motor function improvement
 - 12 of 13 patients had improvement in the HINE motor milestones at day 64 (9 had 2 SMN2 copies)
 - 10 of 10 patients at day 183 (7 with 2 SMN2 copies)
 - 5 of 5 patients with 2 SMN2 copies at day 302

HINE Motor Milestone Achievements

Milestone	Total no. of infants achieving milestone (n=13)	2 copies of SMN2 (n=9)	3 copies of SMN2 (n=4)
Full Head Control	9	5	4
Sitting independently	5	4	1
Standing (with support or unaided)	3	2	1
Walking (with or without support)	1	1	--

Study CS5 (NURTURE) Results of Interim Analysis

- Safety
 - 5 (29%) experienced a severe adverse event, none related to the study drug.
 - 3 (18%) AE considered related to the study drug
 - Muscular weakness and weight bearing difficulty (n=1)
 - Hyperreflexia and tachycardia (n=1)
 - Increased AST/ALT and pyrexia (n=1)

Study CS3B (ENDEAR)

- **Type:** Randomized, double-blind, sham procedure-controlled study to determine clinical safety and efficacy of nusinersen in infantile onset SMA.
- **Regimen:** 12 mg Intrathecal bolus injection on days 1, 15, 29, 64, 183, 302, 421, 540, 659, 778
- **Demographics:**
 - N=17 at time of interim analysis
 - 12/17 had 2 SMN2 gene copies; 5/17 had 3 copies
 - Median age at first dose = 19 days

Study CS3B (ENDEAR) - Endpoints

- **Primary Endpoints:**

- Motor function milestones HINE Section 2
 - ≥ 2 point increase in ability to kick; or
 - ≥ 1 point increase in head control, rolling, sitting, crawling, standing, or walking; and
 - Improvement in more categories of motor milestones than worsening.
- Event-free survival
 - Time to death
 - Permanent ventilation: tracheostomy or ≥ 16 hours ventilator support per day for > 21 days

Study CS3B (ENDEAR) - Endpoints

- Secondary Endpoints:
 - Proportion of patients with increase from baseline in CHOP-INTEND motor function scale of ≥ 4 points based on assessment at the later of the day 183, 302, or 394 study visits
 - Survival rate
 - % patients not requiring permanent ventilation
 - Time to death or permanent ventilation in subgroups of patients above and below study median disease duration
 - % patients with peroneal CMAP amplitude increasing to or maintained at 1 mV compared to baseline at the later of day 183, 302, or 394 study visits

Study CS3B (ENDEAR) – Inclusion Criteria

- Genetic documentation of 5q SMA homozygous deletion, homozygous mutation or compound heterozygous mutation
- At least two copies of SMN2
- Onset of clinical signs and symptoms consistent with SMA at ≤ 6 months
- ≤ 7 months of age at screening
- At study entry adequate nutrition and hydration (without gastrostomy)
- Body weight $\geq 3^{\text{rd}}$ percentile for age using appropriate country-specific guidelines
- Receiving medical care consistent with guidelines set out by the Consensus Statement for Standard of Care in SMA
- Gestational age 37 to 42 weeks₀

Study CS3B (ENDEAR) – Exclusion Criteria

- Hypoxemia ($O_2 < 96\%$ awake or asleep without supplemental O_2 or respiratory support)
- Clinical signs and symptoms consistent at birth or within 1 week of birth
- Active infection requiring systemic antivirals or antibiotics
- Hx of brain or spinal cord disease would interfere with LP injection
- Presence of shunt or CNS catheter
- Clinically significant abnormalities in hematology or chemistry lab
- Treatment with other investigational drug for SMA
- Care giver not compliant with treatment guideline
- Other condition that would interfere with the conduct and assessment of the study

Study CS3B (ENDEAR) – Results

- 78 patients reached the 6 month evaluation
 - 51 nusinersen arm and 27 sham procedure
 - 1 patient in each study group withdrew
 - 21.6% (11/51) patients in nusinersen group died compared to 37% (10/27) patients in the sham-control group
- 55 patients were included in the motor milestone evaluation
 - 39 in nusinersen group and 16 in sham-control
- Study was suspended prior to the planned end of the study due to positive interim analysis

Study CS3B (ENDEAR) – Results

- Demographics – sham-control group was sicker at baseline
 - Median age of onset 6.5 weeks for nusinersen patients compare to 8 weeks for sham-control
 - 26% (21) of nusinersen patients required respiratory support at baseline compared to 15% (6) in the sham-control
 - Total motor milestone score at baseline was 1.41 (sd 1.15) for the nusinersen group vs 1.52 (sd 1.42) in the sham-control

Study CS3B (ENDEAR) – Results

- 41% of nusinersen patients achieved a motor milestone response compared to 0% in the sham-control ($P < 0.0001$)
- Motor Milestones Achieved
 - 9 patients (18%) achieved full head control
 - 5 patients (10%) achieved independent sitting
 - 1 patient (2%) achieved standing

Study CS3B (ENDEAR) – Results

- 63% of nusinersen patients achieved ≥ 4 point increase from baseline on the CHOP-INTEND compared to 3% of sham-control
- Sham-control had an average 7-10 point decline between 6 and 12 months whereas nusinersen had a 9-10 point increase over a similar period
- Overall 29% reduction in the risk of death or permanent ventilation (Hazard Ratio = 0.71)
- 79% reduction in risk of death

Study CS3B (ENDEAR) – Results

	Nusinersen (n = 39)	Sham-control (n = 16)
Alive and did not require permanent ventilation, %	66	51
Alive, %	85	58
Not requiring permanent ventilation, %	81	78
Median time on ventilator support, % (range)	27.1 (0–95.2)	43 (0 – 91.5)

Study CS3B (ENDEAR) – Serious Adverse Events

	Nusinersen (n = 80), %	Sham-control (n = 41), %
Respiratory distress	24	24
Respiratory failure	21	34
Pneumonia	18	10
Acute respiratory failure	14	17
Atelectasis	14	5
Aspiration pneumonia	8	10
Cardiorespiratory arrest	6	7
Pneumonia viral	6	2
Rhinovirus infection	8%	5%

Study CS3B (ENDEAR) – Adverse Events

	Nusersen (n = 80), %	Sham-control (n = 41), %
Lower respiratory infection	43	29
Upper respiratory infection	39	34
Constipation	30	22
Teething	14	7
Upper respiratory tract congestion	6	2
Aspiration	5	2
Ear infection	5	2
Scoliosis	5	2

Study CS2 and CS12: SMA type II or III Patients

- **Type:**
- CS2 was a phase I/2a, open label, multicenter, multiple dose-escalation study
- CS12 was a phase 1 open label, multicenter, multiple extension to CS2 or CS10 conducted in patients with later onset SMA

Study CS2 and CS12 – Inclusion Criteria

- CS2
 - Genetic documentation of 5q SMA homozygous deletion, homozygous mutation or compound heterozygous mutation
 - Clinical signs attributable to SMA
 - Males and females 2 to 15 years
 - Estimated life expectancy > 2 years from screening
- CS12
 - Satisfactory completion of dosing and all study visits in CS2 or CS10
 - Estimated life expectancy > 2 years from screening

Study CS2 and CS12 – Exclusion Criteria

- Respiratory insufficiency defined by necessity for invasive or non-invasive ventilation during a 24-hour period
- Medical necessity for GI tube, where most feeds are given via tube
- Previous scoliosis surgery that would interfere with LP injection
- Hx of brain or spinal cord disease including tumors, or abnormalities by MRI/CT that would interfere with LP injection
- Presence of shunt or CNS catheter
- Hx bacterial meningitis
- New condition or worsening of existing condition
- Dosing in CS2 or CS10 within 180 days of screening, or longer ago than 396 days from screening
- Treatment with other investigational SMA drug
- Clinically significant lab abnormalities
- Active infection requiring systemic antivirals or antibiotics

CS2/CS12 - Endpoints

- Motor function milestones HFMSE ≥ 3 points
- Upper Limb Module ≥ 2 points
- 6 minute walk test ≥ 30 meters

CS2 Baseline demographics

Characteristic	SMA II (n=11)	SMA III (n=17)	Total (n=28)
Mean (sd) age years	4.4 (4)	8.9 (4.4)	7.1 (4.7)
Males, n (%)	8 (73)	7 (41)	15 (54)
Mean (sd) age of symptom onset, months	11 (3.4)	22 (13.5)	17.7 (11.9)
Mean (sd) age at SMA dx, mo	15.4 (6.3)	43.6 (32.4)	32.5 (28.9)
SMN2 Copy Number, n (%)			
2	0	1 (8)	1 (4)
3	11 (100)	10 (59)	21 (75)
4	0	6 (35)	6 (21)
% non- ambulatory	11 (100)	4 (24)	15 (54)
Baseline Motor Function, n (%)			
Sitting without support	11 (100)	17 (100)	28 (100)
Standing without support	0	12 (71)	12 (43)
Walking with support	2 (18)	15 (88)	16 (61)
Walking independently	0	13 (76)	12 (46)

CS2/CS12 - Results

Efficacy Measure	Day 253	Day 1,050
HFMSE \geq 3 points SMA2, n/N (%) SMA3, n/N (%)	9/11 (82) 3/16 (19)	6/6 (100) 2/7 (29%)
Upper Limb Module \geq 2 points, SMA2, n/N (%)	5/11 (45)	4/6 (67)
6-minute walk test, \geq 30 meters, SMA3, n/N (%)	6/12 (50)	6/6 (100)

Discussion

- Spinraza (nusinersen) is effective in treating symptomatic SMA infants with 2 SMN2 gene copies and pre-symptomatic SMA infants with 2 or 3 SMN2 gene copies.
- Spinraza is effective in treating patients with later onset SMA2 and SMA3

Clinical Policy – Initial Treatment

Spinraza (nusinersen) is considered proven and medically necessary for treatment of spinal muscular atrophy in patients who meet all of the following criteria:

- Diagnosis of SMA as defined as:
 - homozygous SMN1 gene deletion or mutation; or
 - compound heterozygous mutation (e.g. homozygous deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2]; and
- Presymptomatic infants with only ≤ 3 copies of the SMN2 gene; or
- ≥ 2 copies of the SMN2 gene in symptomatic patients;
- Prescribed by a provider with expertise in treating SMA
- Will be administered intrathecally by or under supervision of a provider with experience in performing LP procedures

Clinical Policy - Initial Treatment

- The following documentation at baseline has been submitted
 - Hammersmith Infant Neurological Exam (HINE) - infant to early childhood
 - Hammersmith Functional Motor Scale Expanded (HFMSE)
 - Upper Limb Module (UML) – non-ambulatory patients
 - Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
 - 6 minute walk test – ambulatory patients
 - Pulmonary status – requirements for invasive or non-invasive ventilation
 - Complete blood count, cystatin-C, coagulation status, urine protein, serum electrolytes including bicarbonate, liver and renal function tests

Continuation of Treatment

- Meets initial approval criteria; and
- Documentation has been submitted demonstrating improvement or maintenance of previous functional status, or patient has achieved and maintained new motor milestones from pretreatment baseline, or disease progression is slower than what would otherwise be unexpected in this population using the following tools:

HINE:

- At least 2 points (or maximal score) in ability to kick; or
- At least 1 point in any other HINE milestone (e.g. head control, rolling, sitting, crawling, etc.); and
- Patient showed improvement in more categories than decline; or

HFMSE: At least 3 points increase in score from pretreatment baseline; or

6MWT: increase of 30 meters if ambulatory; OR

ULM: At least a 2 point increase in score from the pretreatment baseline

CHOP-INTEND: at least a 4 point increase in score from the pretreatment baseline

Duration of Approval

- Initial Approval for 6 months or 5 doses
 - 3 doses 14 days apart
 - 4th dose 30 days after third dose
 - 5th dose four months after the 4th dose
- Continued approval required every 6 months for doses to be administered every 4 months.
- NOTE: Spinraza is not proven or medically necessary for treatment of spinal muscular atrophy without chromosome 5q mutations or deletions, or in pre-symptomatic patients with > 3 copies of the SMN2 gene.

References

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Questions?

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