

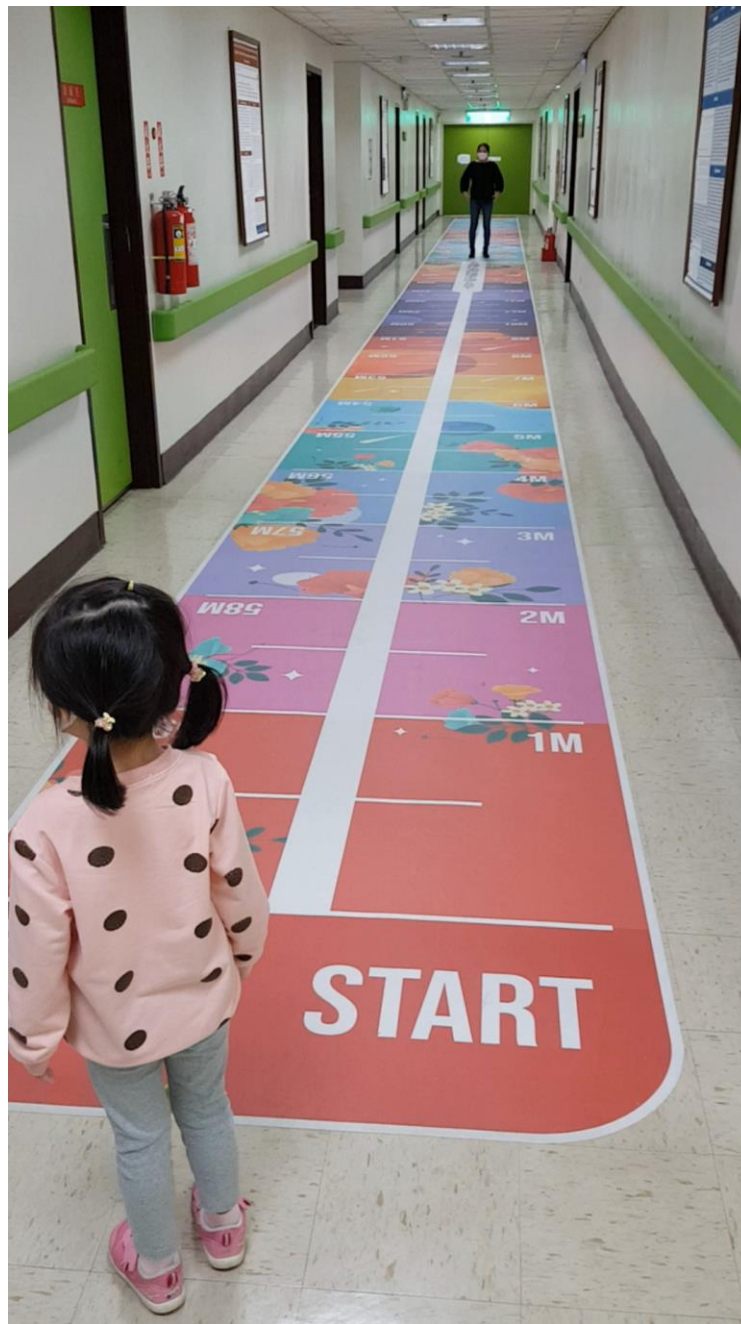
# Zolgensma 基因治療在脊髓 性肌肉萎縮症的治療新角色

台北榮民總醫院 小兒神經科

許庭榕 主任

TingRong Hsu, M.D.,Ph.D.

# 這是什麼疾病？



zolgensma®  
(onasemnogene  
abeparvovec)

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民總醫院

Taipei Veterans General Hospital

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## 首名罕病SMA基因治療健保給付案 首期款項已繳 (圖)



The Central News Agency 中央通訊社

2023年9月14日 週四 下午6:49



衛福部中央健康保險署長石崇良（後中）14日出席台灣生命之窗慈善協會活動，觀看罕病脊髓性肌肉萎縮症（SMA）藥物擴大給付紀錄片首播，他在致詞時表示，全台首劑健保給付的SMA基因治療藥物已使用在患者身上，也已付款，採分期方式，未來盼能幫到更多人。



中央社記者陳婕翎攝 112年9月14日



- SMA disease introduction
- What is gene therapy?
- Role of ZOLGENSMA: one-time only treatment in SMA
- Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis
- Key Takeaways

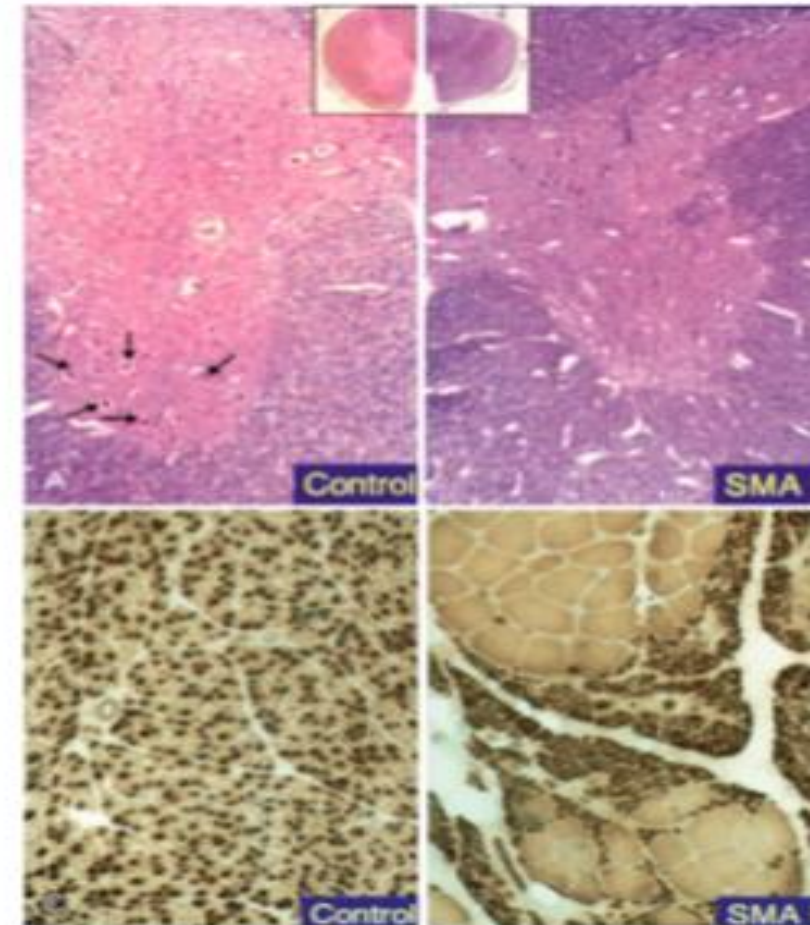
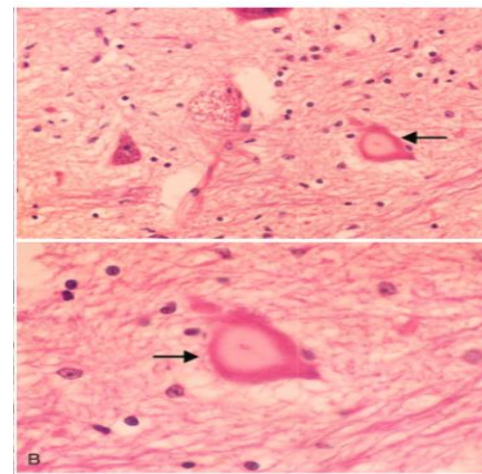
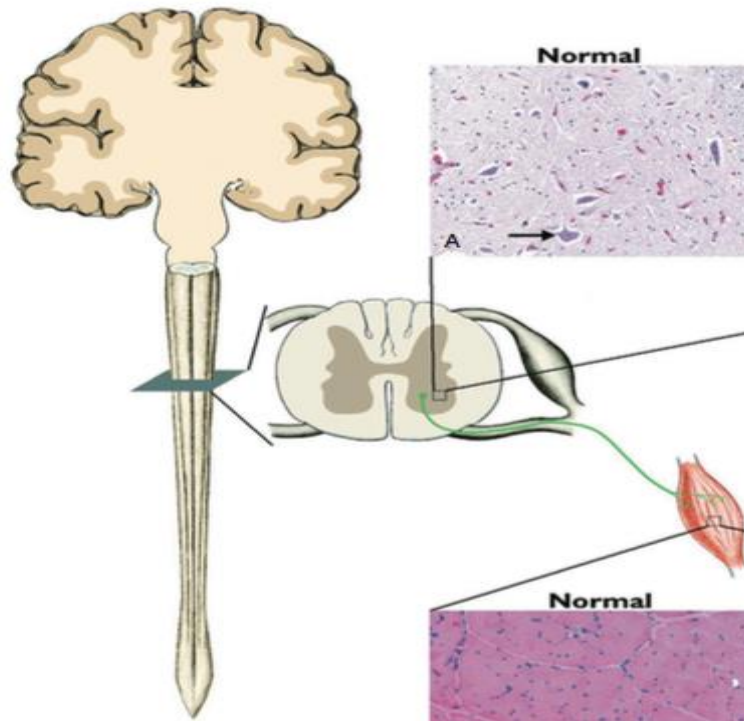


# Spinal Muscular Atrophy (SMA) introduction

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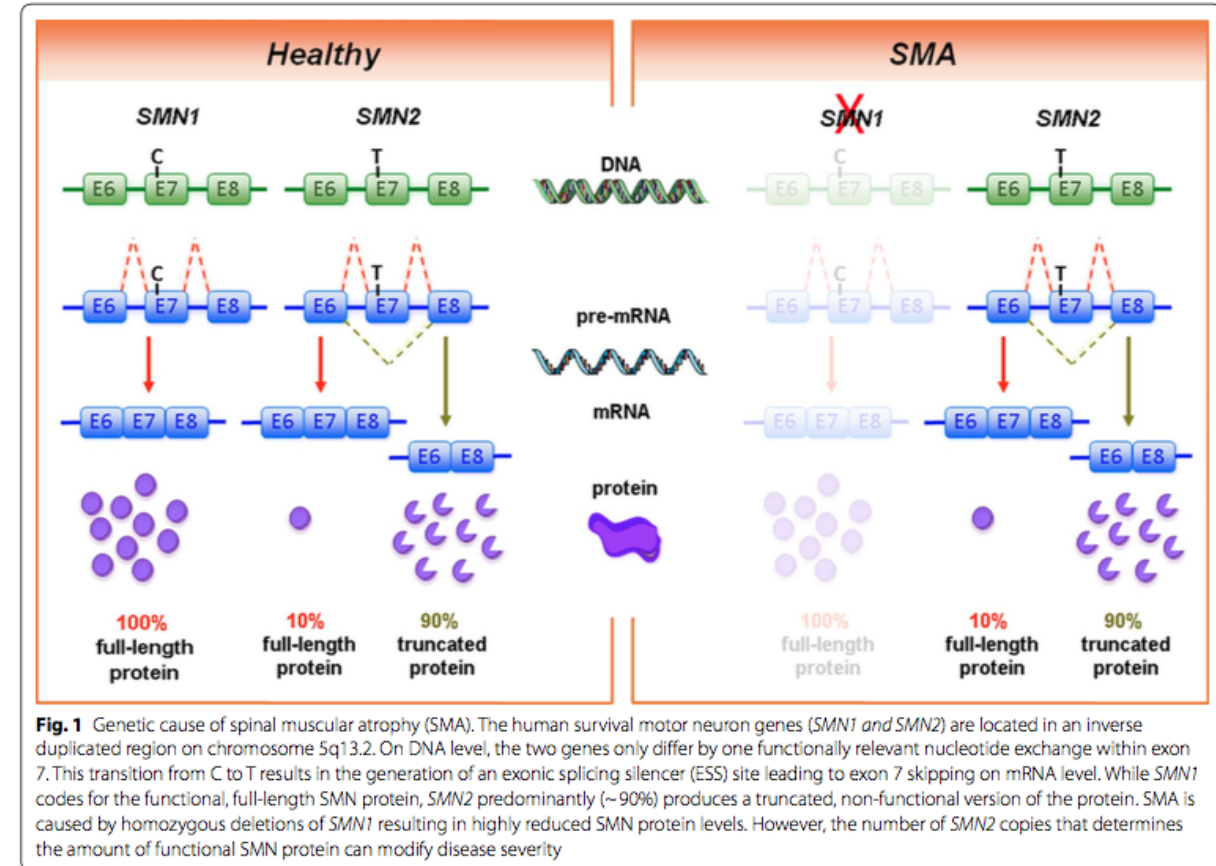
# Spinal muscular atrophy (SMA)

- Rare disease.
  - 1: 10000?
- Progressive muscular weakness
- with the loss of anterior horn cells in the spinal cord
- leading cause of infant mortality



# Genetics

- The SMN1 gene
  - Deletions of : 95~ 98%
  - Small intragenic mutations or gene conversions from *SMN1* to *SMN2*: 2~5%
  - De novo mutations rate: 2%
    - Relatively high--> this region of chromosome 5 is unstable
- The SMN2 gene
  - No copies in 10~15% population
  - Correlation between *SMN2* copies and phenotypes
    - Not all *SMN2* copies of are equal



# SMA is a rare neurodegenerative disorder

## - “Time is motor neurons”

### Pathophysiology

SMA is characterized by the **irreversible loss of motor neurons**, resulting in progressive muscle weakness<sup>1,2</sup>

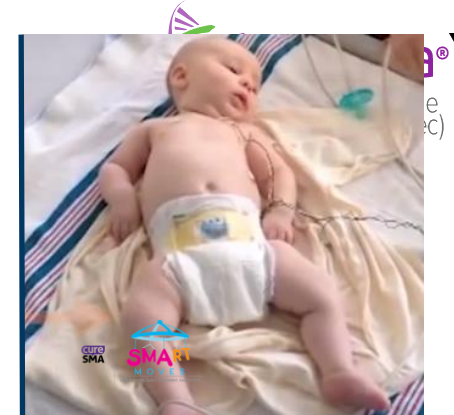
### Epidemiology

The incidence of SMA is approximately **1 in 17,000 live births in Taiwan**<sup>3</sup>

### Phenotypes

Patients with SMA present across a gradient of varying phenotypes, but are classified by “**types**” defined by **age of disease onset** and **maximum motor function achieved**<sup>5,6</sup>

Frog-leg position<sup>7</sup>



Impaired head control<sup>8</sup>



Floppy baby syndrome<sup>9</sup>



SMA, spinal muscular atrophy.

1. Lin CW, et al. *Pediatr Neurol*. 2015;53(4):293-300; 2. Glascock J, et al. *J Neuromuscul Dis*. 2018;5(2):145-158; 3. Weng WC et al. *Genet Med*. 2021 Feb;23(2):415-420. 4. Su YN, et al. *PLoS One*. 2011 Feb 25;6(2):e17067.; 5. MedlinePlus (2020). If a genetic disorder runs in my family, what are the chances that my children will have the condition? Available at: <https://medlineplus.gov/genetics/understanding/inheritance/riskassessment/>. Last accessed: March 2021; 6. Wirth B, et al. *Annu Rev Genomics Hum Genet*. 2020;21:231-261; 7. CureSMA. Available at: <https://www.curesma.org/smartmoves/know-the-warning-signs/>. Last accessed: March 2021; 8. Oskoui M, et al. Spinal muscular atrophy:125 years later and on the verge of a cure. In: Sumner CJ, Paushkin S, Ko CP; Spinal Muscular Atrophy: Disease Mechanisms and Therapy. London: Academic Press. 2017; 1st Edition:3-19; 9. Image from Novartis Gene Therapies. Videos on file (2018).



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# SMA classification

## The classification of SMA is evolving



### HISTORICAL SMA CLASSIFICATION

Was by age of onset and maximal motor milestone achieved<sup>1</sup>



- TYPE 0: Prenatal onset, no motor milestones achieved
- TYPE 1: Onset <6 months of age, unable to sit
- TYPE 2: Onset 6–18 months of age, able to sit
- TYPE 3: Onset in early childhood to early adulthood, able to walk
- TYPE 4: Onset >30 years of age, able to walk

### EVOLVING SMA CLASSIFICATION

focuses on current functional status and therapy response<sup>2–5</sup>



Nonsitters



Sitters



Walkers

Table 88-1 Classification of Clinical Subtypes of Spinal Muscular Atrophy

Clinical Type of Spinal Muscular Atrophy	Age at Onset	Highest Function Achieved	Natural Age of Death
Type I (severe, Werdnig–Hoffman disease)	0–6 months	Never sit	<2 years
Type II (intermediate)	7–18 months	Never stand	>2 years
Type III (mild, Kugelberg–Welander disease)	>18 months	Sit and stand	Adult
Type IV (adult)	Second or third decade	Walk during adulthood	Adult



- Clinical features of SMA Type 1<sup>1-3</sup>
  - Weakness and hypotonia (i.e. floppy baby syndrome)
  - Areflexia
  - Impaired head control
  - Reduced bulbar function including impaired swallowing and feeding
    - Weak cry and cough
  - Tongue fasciculations
  - Paradoxical breathing (“belly breathing”) and bell-shaped chest due to intercostal muscle weakness (sparing the diaphragm)
  - Alert, attentive, preserved eye movements and sensation

**Frog-leg position<sup>5</sup>**



**Impaired head control<sup>\*6</sup>**



**Floppy baby syndrome<sup>7</sup>**



Though infants may appear unaffected at birth, weakness can present within the first few months of life as rapid denervation occurs<sup>3,4</sup>

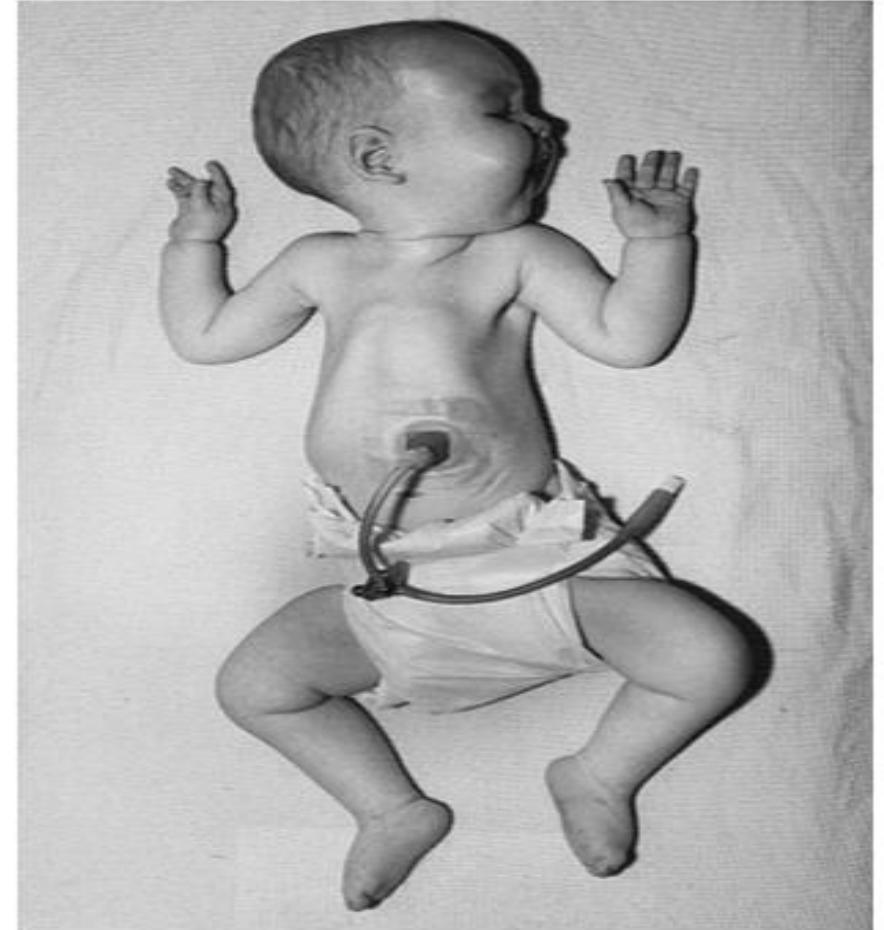
\*Reprinted from Oskoui M, *et al.* Spinal muscular atrophy: 125 years later and on the verge of a cure. In: Sumner CJ, Paushkin S, Ko CP; Spinal Muscular Atrophy: Disease Mechanisms and Therapy. London: Academic Press. 2017; 1st Edition:3-19. SMA, spinal muscular atrophy.

1. Darras BT and Finkel RS. Natural history of spinal muscular atrophy. In: Sumner CJ, Paushkin S, Ko CP; Spinal Muscular Atrophy: Disease Mechanisms and Therapy. London: Academic Press. 2017; 1st Edition:399-421; 2. Kolb SJ, *et al.* *Neurol Clin.* 2015;33(4):831-846; 3. Wang CH, *et al.* *J Child Neurol.* 2007;22(8):1027-1049; 4. Swoboda KJ. *J Clin Invest.* 2014;124(2):487-490; 5. CureSMA. Available at: <https://www.curesma.org/smartmoves/know-the-warning-signs/>. Last accessed: March 2021; 6. Oskoui M, *et al.* Spinal muscular atrophy: 125 years later and on the verge of a cure. In: Sumner CJ, Paushkin S, Ko CP; Spinal Muscular Atrophy: Disease Mechanisms and Therapy. London: Academic Press. 2017; 1st Edition:3-19; 7. Image from Novartis Gene Therapies. Videos on file (2018).



# Type I SMA (Werdnig–Hoffman disease)

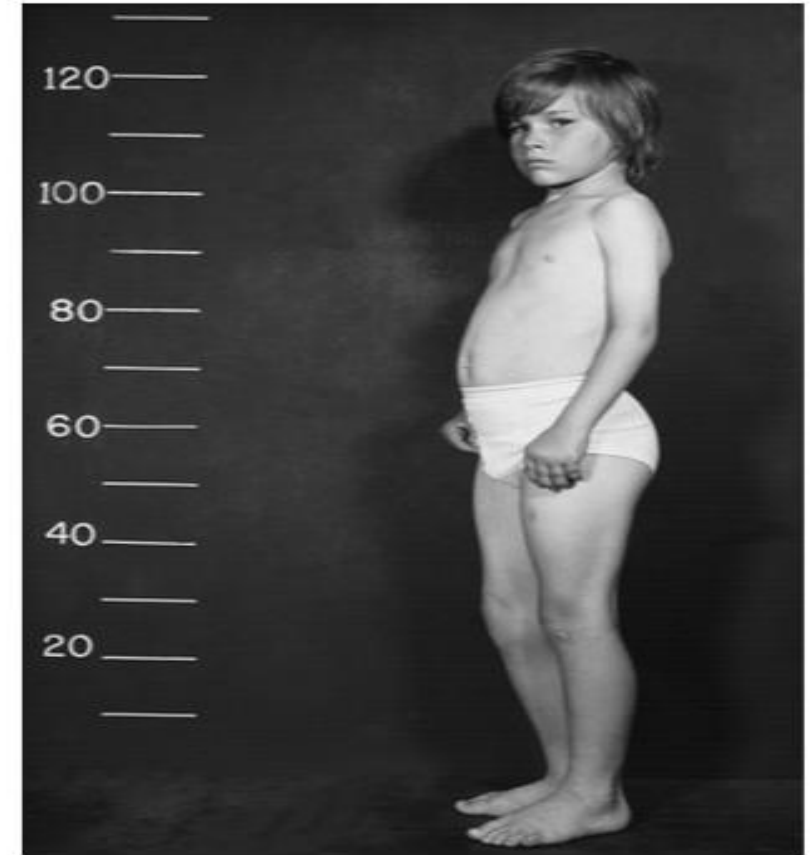
- < 6 months.
- hypotonia
- progressive symmetric and proximal weakness
- Intercostal muscle weakness
- "Bell-shaped" chest
- Paradoxical breathing pattern
- Tongue fasciculation



**Fig. 88-3** This patient with spinal muscular atrophy type I, or Werdnig–Hoffmann disease, is severely affected and required a gastric feeding tube. There is little or no movement of the shoulders, whereas the fingers and toes remain active. The typical posture of flexion of the knees and abduction of the legs at the hips is evident. The weakness of the intercostal muscles, coupled with relatively normal diaphragmatic contractions, results in marked chest deformity.

# Type III SMA (Kugelberg–Welander disease)

- > 18 months
- General weakness:
  - Marked weakness and atrophy of the shoulder girdle, Lumbar lordosis, Abdominal protuberance.
- May ultimately need to use a wheelchair
- Little to no respiratory muscle weakness or severe scoliosis (↑ the risk if loss of ambulation)
- The calves can be prominent and be confused with BMD
- Often ↑CK levels, usually no more than 5-fold, and may lead to an erroneous evaluation for myopathy
- EMG/ NCV is useful to indicate a neurogenic versus myopathic disorder
- Life expectancy: not significantly different with normal population



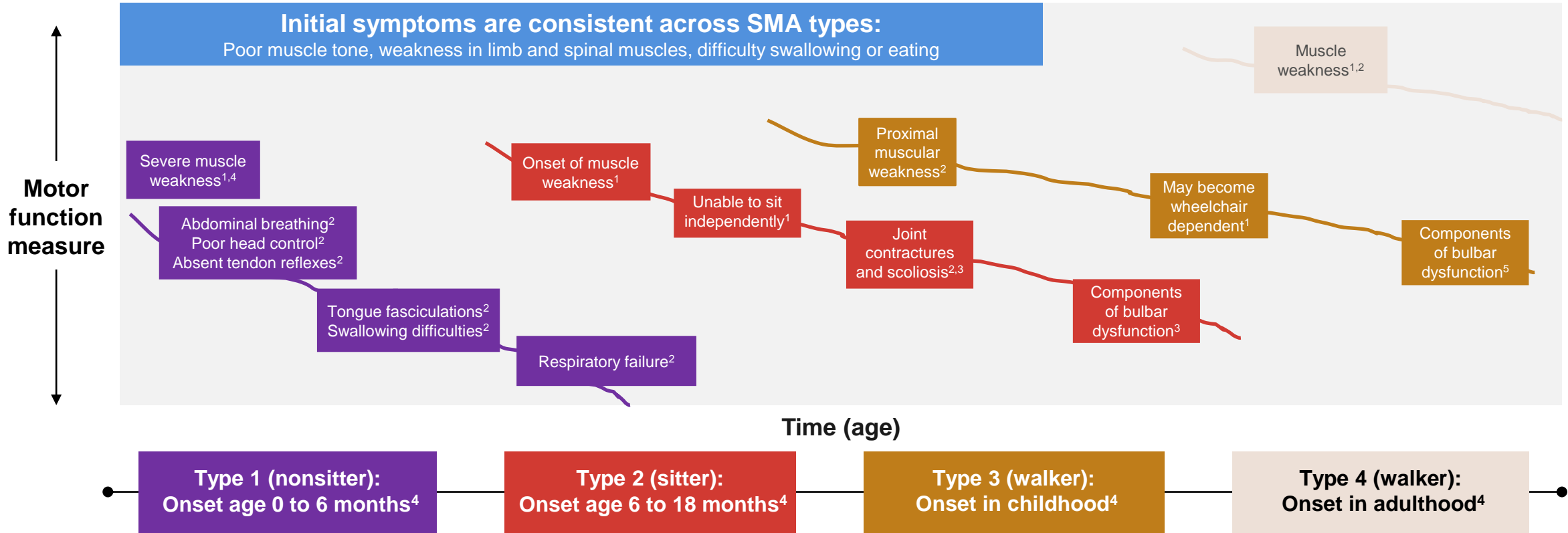
**Fig. 88-4** This patient with juvenile proximal hereditary muscular atrophy (Kugelberg–Welander disease) has generalized weakness. Marked weakness and atrophy of the shoulder girdle are present. Lumbar lordosis, as well as abdominal protuberance related to abnormal weakness, is common.



# 只要沒有治療，全部 SMA 病人都會漸進性退化



## Functional Decline Milestones



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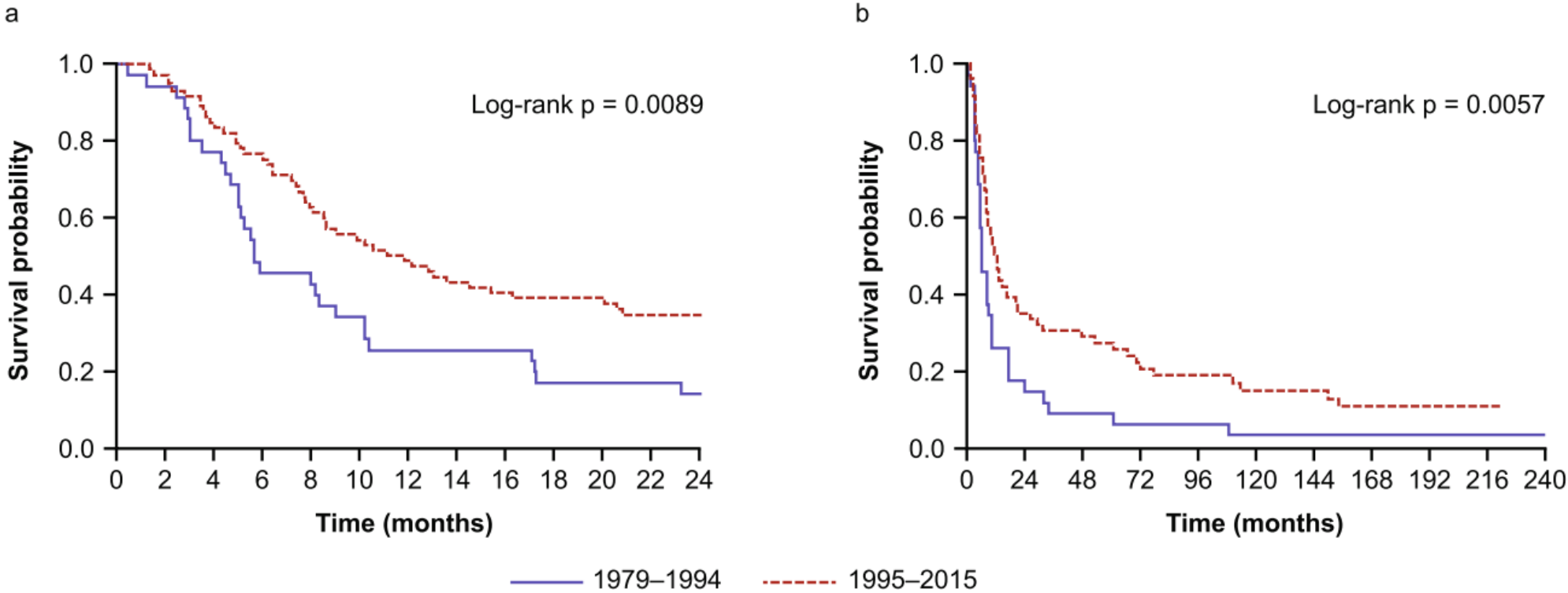


Fig 1. (a) 24-month and (b) 240-month survival probability of Taiwanese patients diagnosed with spinal muscular atrophy Type I during 1979–1994 (n = 35) or 1995–2015 (n = 73).

Ou SF, Ho CS, Lee WT, et al. Natural history in spinal muscular atrophy Type I in Taiwanese population: A longitudinal study. *Brain Dev.* 2021;43(1):127-134.



# Time is Lower Motor Neurons

## SMA 沒有治療都會一直退化，進步程度跟發病時間有關



### Early treatment can result in:

- Rescue of motor neurons<sup>1,2</sup>
- Improved neuromuscular junction function<sup>1,2</sup>
- Prevention of disease progression<sup>1,2</sup>



**SMN protein is a survival motor neuron protein, not a resurrection motor neuron protein<sup>3</sup>**

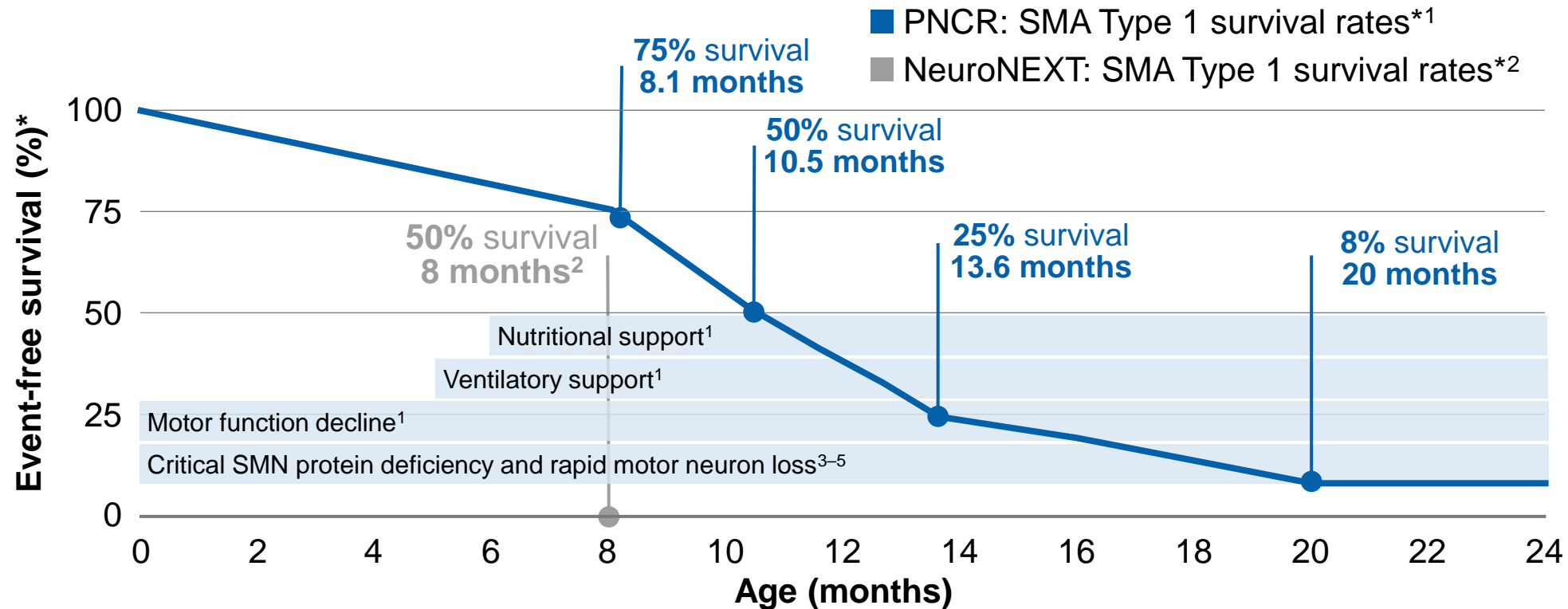


**SMN levels in healthy adults are similar to those in patients with SMA<sup>4</sup>**



# Natural history: The most severe forms of SMA carry a high incidence of mortality if untreated

- “Time is motor neurons”



More than 90% of untreated patients with SMA Type 1 did not survive or needed permanent ventilatory and nutritional support by 2 years of age<sup>5</sup>

\*Event-free survival for PNCR = no death, and no need for ≥16 hours/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n=23 (Type 1 patients with two copies of *SMN2*). Survival for NeuroNEXT = no death, or no tracheostomy; n=20.<sup>1,5</sup>

NeuroNEXT, National Network for Excellence in Neuroscience Clinical Trials; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy; survival motor neuron; *SMN2*, survival motor neuron 2 gene.

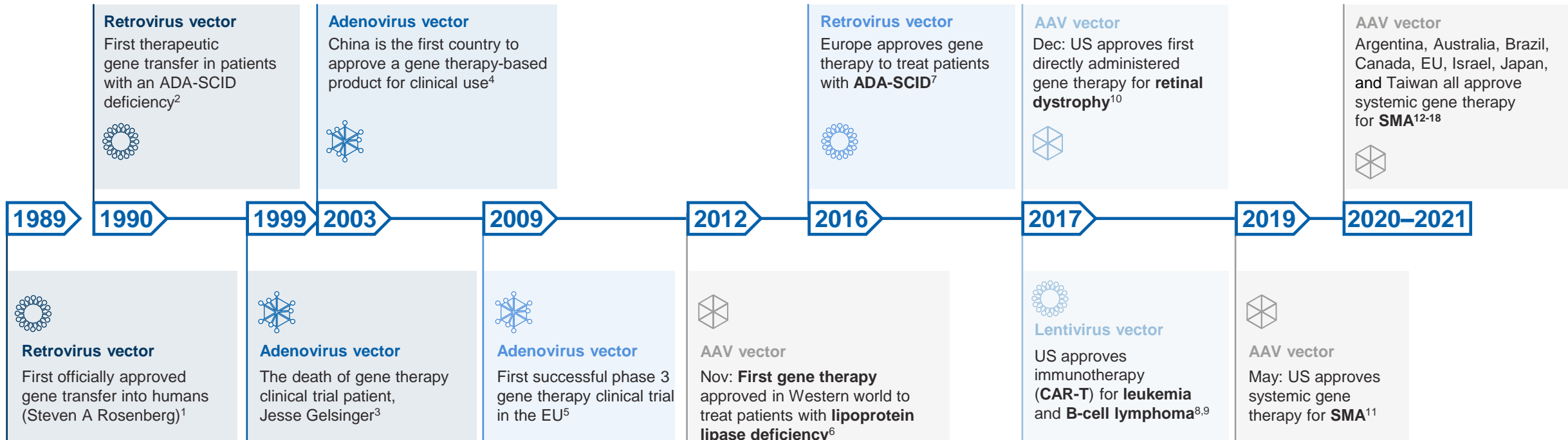
1. Finkel RS, et al. *Neurology*. 2014;83(9):810-817; 2. Kolb SJ, et al. *Ann Neurol*. 2017;82(6):883-891; 3. Finkel RS. *Neuromuscul Disord*. 2013;23(2):112-115; 4. Finkel RS, et al. *Mol Neurobiol*. 2018;55(8):6307-6318; 5. Swoboda KJ, et al. *Ann Neurol*. 2005;57(5):704-712.



# What is gene therapy?

---

# Viral Vectors for Gene Therapy Have Evolved Over the Past 30 Years



	<b>Voretigene neparvovec</b> Leber Congenital Amourosis	<b>Onasemnogene abeparvovec</b> Spinal Muscular Atrophy	<b>Betibeglogene autotemcel</b> <sup>19</sup> beta-thalassemia	<b>Elivaldogene autotemcel</b> <sup>20</sup> cerebral adrenoleukodystrophy	<b>Autologous CD34+</b> Adenosine Deaminase Deficiency	<b>Eladocagene exuparvovec</b> <sup>21</sup> Aromatic L-amino acid decarboxylase (AADC) deficiency
<b>US FDA approved</b>	<b>2017</b>	<b>2019</b>	<b>2022</b>	<b>2022</b>	<b>-</b>	<b>-</b>
<b>EMA authorized</b>	<b>2018</b>	<b>2020</b>	<b>2019</b>	<b>2021</b>	<b>2016</b>	<b>2022</b>

18

[illegible]

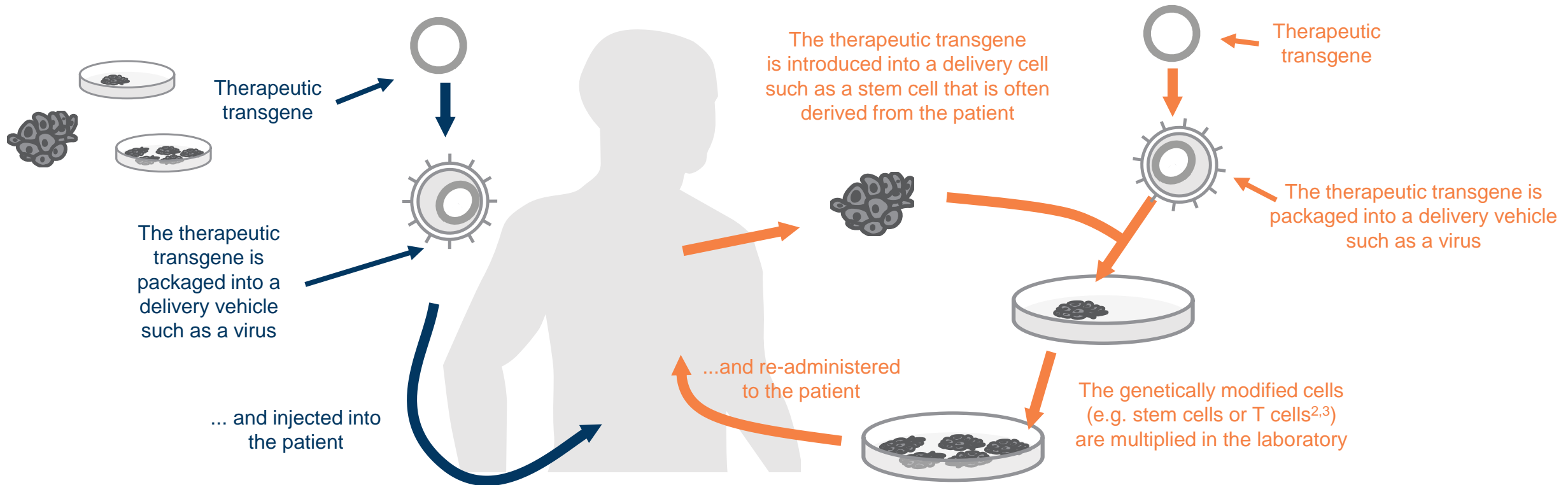
# Gene therapy delivery

## Direct delivery

Direct gene delivery via injection in vivo to target tissues

## Cell-based delivery

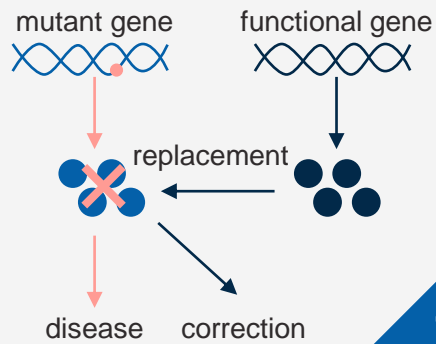
Modification of cells in culture (ex vivo), followed by cell expansion and injection



# Approaches to gene therapy

## Gene replacement

### Gene replacement

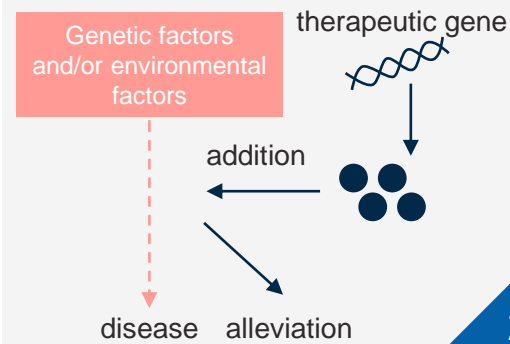


For **monogenic diseases**;  
involves replacing a  
mutated gene that causes  
disease with a healthy gene

1

## Gene addition

### Gene addition

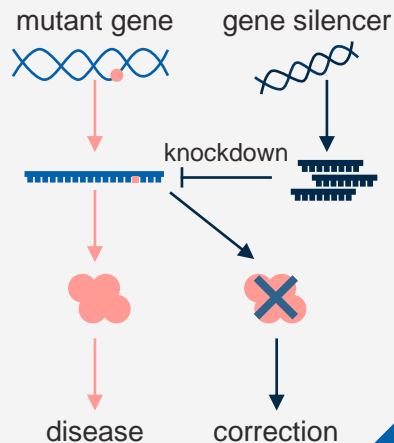


For complex and infectious  
diseases; introduces a new  
gene into the body to help  
fight a disease, often to  
supplement a targeted  
therapeutic agent

2

## Gene inhibition “knockdown”

### Gene inhibition

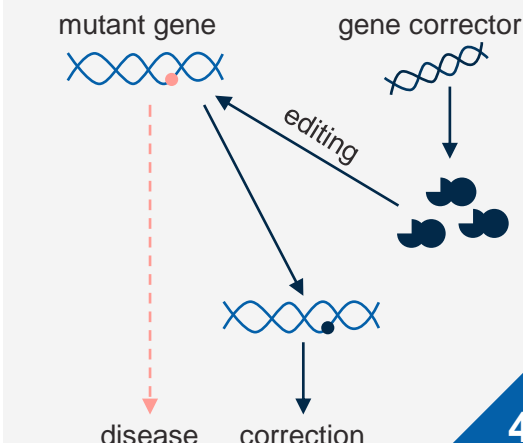


Inactivating a mutated gene  
that is over producing its  
product by targeting RNA

3

## Gene editing

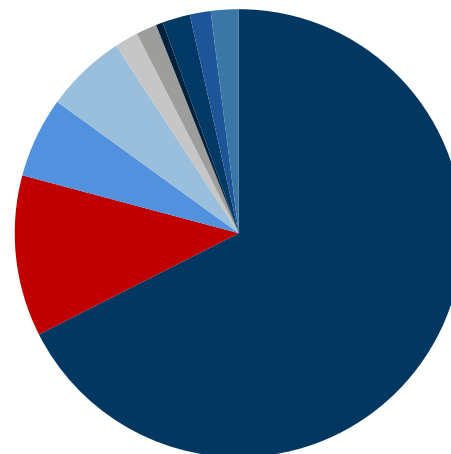
### Gene editing



Making a targeted change to  
the gene sequence

4

## Diseases studied in gene therapy studies<sup>1</sup>



- **CANCER** 67.4% (n=2144)
- **MONOGENIC DISEASES** 11.6% (n=370)
- INFECTIOUS DISEASES 5.8% (n=186)
- CARDIOVASCULAR DISEASES 5.8% (n=186)
- NEUROLOGICAL DISEASES 1.7% (n=55)
- OCULAR DISEASES 1.5% (n=47)
- INFLAMMATORY DISEASES 0.5% (n=15)
- OTHER DISEASES 2.0% (n=65)
- GENE MARKING 1.5% (n=49)
- HEALTHY VOLUNTEERS 2.0% (n=63)






Disease	Disease Pathogenesis	Viral Vector Platforms	Primary Target	Transgene Persistence
<b>Hemophilia B</b>	Monogenic	AAV5* or AAV-SPARK100*	<u>Liver</u> <ul style="list-style-type: none"> <li>Non-dividing</li> <li>Regenerative</li> </ul>	Non-human primates: 5.5 y <sup>a,b,3</sup> Dogs: 4.5 y <sup>a,2</sup> ; 8 y <sup>b,4</sup> Humans: 4 <sup>a,4</sup> ; 15 y <sup>b,6</sup>
<b>RPE65-related Retinal Disease</b>	Monogenic	AAV2	<u>Retinal Pigment Epithelial Cells</u> <ul style="list-style-type: none"> <li>Non-dividing</li> <li>Long-lived</li> </ul>	Dogs: 10 y <sup>a,7</sup> Humans: 7.5 y <sup>a,8</sup>
<b>Spinal Muscular Atrophy</b>	Monogenic	AAV9	<u>Motor Neurons</u> <ul style="list-style-type: none"> <li>Non-dividing</li> <li>Long-lived</li> </ul>	Humans: 6 y <sup>a,9</sup>

1. The Journal of Gene Medicine. Indications Addressed by Gene Therapy Clinical Trials website. Available at: <https://a873679.fmphost.com/fmi/webd/GTCT>. Accessed April, 2022 2. Nathwani AC, et al. Mol Ther. 2011;19(6):979-995. 3. Callan MB, et al. PLoS One. 2016 Mar 24;11(3):e0151800. 4. Nathwani AC, et al. N Engl J Med. 2014;371(21):1994-2004. 5. Cideciyan AV, et al. Proc Natl Acad Sci USA. 2018;110(6):E517-E525. 6. Buchlis G, et al. Blood. 2012; 119(13):3038-3041. 7. Cideciyan AV. Documenta Ophthalmologica. 2014;129(1 Suppl 1):13-14. 8. Leroy PB, et al. Ophthalmic Research 2022 9. Mendell JR, et al. Neurology. 2021; 93(7):832-841; Suppl 1. 10. Persistence of treatment effect. <sup>b</sup> Transgene persistence determined by presence in tissues. \*Mult- serotypes in AAV : Etranacogene dezaparvovec(AAV5), Fidanacogene elaparvovec(AAV9), Zilucarsgene elaparvovec(AAV2).



# Different classes of viral vectors for gene therapy

Most of the original viral genes have been replaced with a desired transgene<sup>1–4</sup>

	Vector		Major Advantage	Limitation
<b>Integrating</b> <i>Transgene integrates with host genome</i>	Retrovirus		Persistent gene transfer in <b>dividing cells</b>	Only transduces dividing cells; integration might induce oncogenesis in some applications
	Lentivirus*		Persistent gene transfer in most tissues	Integration might induce oncogenesis in some applications
<b>Non-integrating</b> <i>Transgene does not integrate with host genome</i>	HSV-1		Large packaging capacity; strong tropism for <b>neurons</b>	Inflammatory; transient transgene expression in cells other than neurons. Potentially immunogenic
	Adenovirus		Extremely efficient transduction of most tissues	Capsid mediates a potent inflammatory response. Highly immunogenic
	Adeno-associated virus (AAV)		Low or non-inflammatory; non-pathogenic, <b>tropism for neurons</b>	<b>Small packaging capacity</b> limits the range of therapeutic genes that can be used in this system

\*Lentiviral vectors are derived from the retroviral class of viruses<sup>5</sup>.

1. Nayak S, Herzog RW. *Gene Ther* 2010;17(3):295–304; 2. Nayerossadat N, et al. *Adv Biomed Res* 2012;1:27; 3. Bouard D, et al. *Br J Pharmacol* 2009;157(2):153–165; 4. Vannucci L, et al. *New Microbiol* 2013;36(1):1–22; 5. Chira S, et al. *Oncotarget* 2015;6(31):30675–30703; 6. Lukashev AN, Zamyatnin AA Jr. *Biochemistry (Mosc)* 2016;81(7):700–708; 7. Thomas CE, et al. *Nat Rev Genet* 2003;4(5):346–358.

# AAV vectors are versatile gene therapy vehicles<sup>1-4</sup>

## Infection (Transduction)

- AAVs can be engineered for selective cell targeting and optimized transduction.<sup>1,2</sup>
- rAAVs are protein-based nanoparticles that cross the cell membrane and deliver genetic cargo to the nucleus.<sup>1</sup>



## Tropism

- AAVs target numerous cell/tissue types; ≥12 distinct serotypes display varying efficiencies in different cell types.<sup>3,4</sup>
- A few naturally occurring serotypes (eg, AAV9) efficiently cross the blood–brain barrier.<sup>5</sup>

## Safety

- Without the original viral genome, AAVs are nonpathogenic<sup>2</sup> and unable to replicate like the wild-type virus.<sup>6</sup>
- AAVs are generally nonintegrating and less immunogenic than other viruses.<sup>1,2</sup>

## Versatility

- AAV vectors are very stable; they are able to withstand wide temperature and pH changes with little to no loss in activity.<sup>1</sup>
- This robust stability allows for different administration routes and specialized delivery strategies.<sup>1</sup>

**AAVs are fully engineered (non-enveloped and lacking viral DNA) and can be customized for specific functionality depending on the affected gene and target tissue<sup>1,2</sup>**

AAV, adeno-associated virus

1. Naso MF, et al. *BioDrugs*. 2017;31(4):317–334. 2. Thomas CE, et al. *Nat Rev Genet*. 2003;4(5):346–358. 3. Ai J, et al. *Sci Rep*. 2017;7:40336. 4. Vance MA, et al. *AAV Biology, Infectivity and Therapeutic Use from Bench to Clinic*. Available at: <https://www.intechopen.com/books/gene-therapy-principles-and-challenges/aav-biology-infectivity-and-therapeutic-use-from-bench-to-clinic>.

23 Last accessed: July 2020. 5. Foust KD, et al. *Nat Biotechnol*. 2009;27(1):59–65. 6. Hollinger K, Chamberlain JS. *Curr Opin Neurol*. 2015;28(5):522–527.



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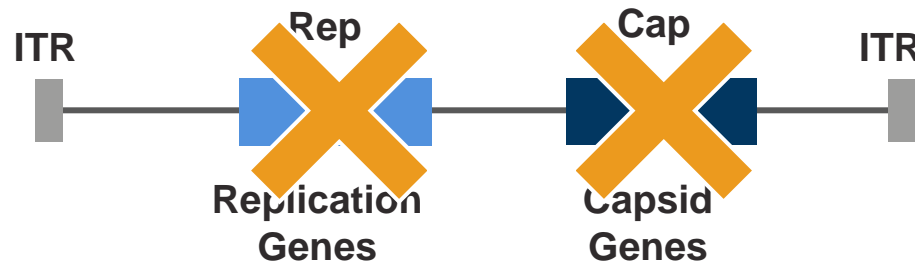
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# Constructing an AAV Vector<sup>1,2</sup>

## Representative AAV virus

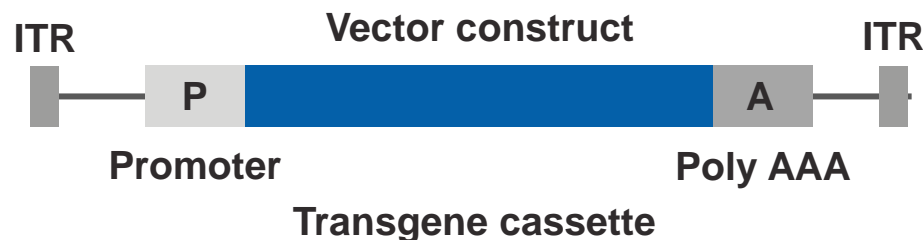
### Structure of wild-type virus genome



AAV viral vectors are made by:

- **Deleting the natural viral genes to make the virus replication incompetent and replacing with a “transgene cassette”**
- Sequences placed between the inverted terminal repeats (ITRs) include a promoter, the gene of interest, and a Poly AAA signal
  - Mutated ITRs give the transgene polyadenylation ability to form self-complementary molecule

## Representative AAV vector



AAV, adeno-associated virus; ITR, inverted terminal repeat; Poly, polyadenylation.

Diagram adapted with permission from Wang D, Gao G.<sup>2</sup>



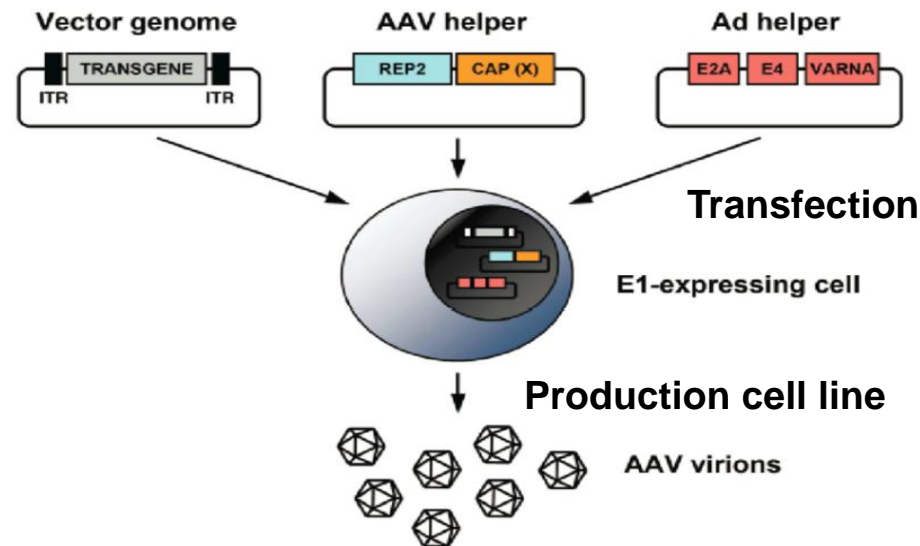
# AAV production overview: Development and production

The AAV production process is complex and sophisticated

## 1. Transgene development<sup>1</sup>

cDNA is reverse transcribed from human mRNA (no introns)<sup>1,2</sup>

## 2. AAV GT production<sup>3</sup>



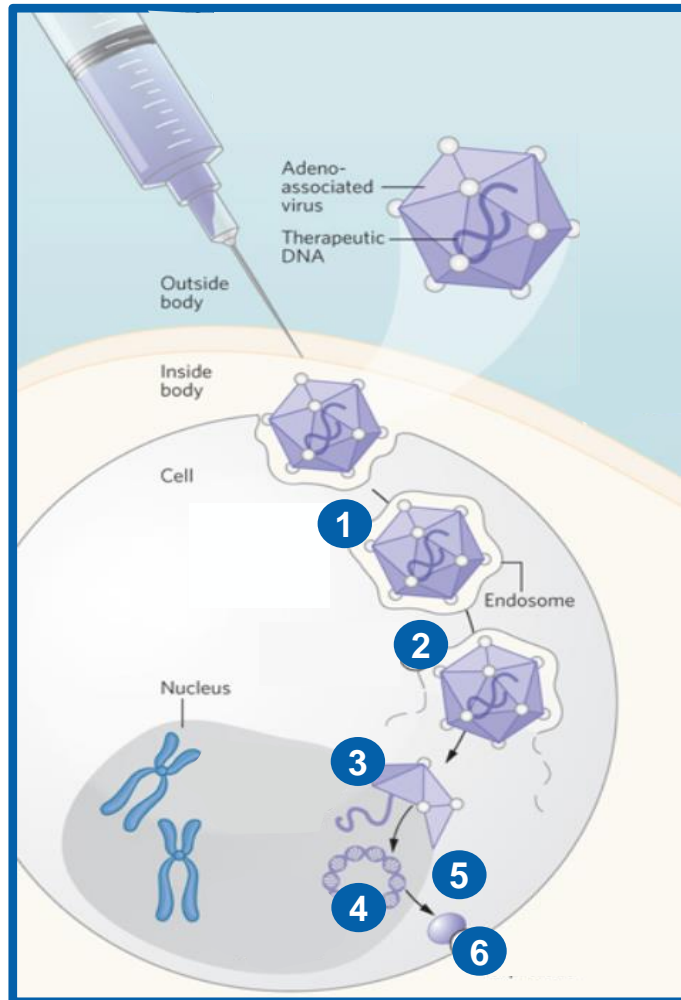
## 3. Concentration and purification / quality assurance<sup>3</sup>

Figure reproduced from Ayuso E, et al. 2010<sup>2</sup>.

AAV, adeno-associated virus; Ad, adenovirus; cDNA, complementary DNA; GT, gene therapy; ITR, inverted terminal repeat.

1. Liu C. *Methods Mol Biol* 2013;1027:183–201; 2. McCarty DM, et al. *Gene Ther* 2001;8:1248–1254; 3. Ayuso E, et al. *Curr Gene Ther* 2010;10:423–436

# How AAV gene therapy works



- 1 Virus taken into the cell via endosome
- 2 Endosome breaks down
- 3 Virus binds to cell nucleus and release contents
- 4 DNA forms circular episome
- 5 Start transcription and translation
- 6 Targeted protein expressed

# Role of ZOLGENSMA: one-time only treatment in SMA patients

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# SMA 健保給付條件(112/6/1)

## 1.6.4.Nusinersen(如 Spinraza)、risdiplam ( 如Evrysdi ) :

1.限用經標準檢測方法 MLPA(Multiplex Ligation Dependent Probe Amplification) 或 NGS 檢測 SMN1 基因變異之個案，並具以下(1)、(2)、(3)、(4)、(5)、(6)任何一個條件：

- (1)具3 個 ( 含 ) 以下 SMN2 基因拷貝數，經新生兒篩檢即將發病之個案，限使用 nusinersen。
- (2)Nusinersen限使用於3 歲內發病確診，且開始治療年齡未滿 7 歲者。
- (3)Risdiplam限使用於治療年齡兩個月以上，3歲內發病確診，且開始治療年齡未滿 7歲者。
- (4)Nusinersen限使用3 歲內發病確診且開始治療年齡滿7歲者，且臨床評估運動功能指標RULM $\geq$ 15之SMA個案。
- (5)Risdiplam限使用 3歲內發病確診且開始治療年齡滿 7歲至未滿 18歲，且臨床評估運動功能指標 RULM $\geq$ 15。
- (6)Risdiplam限使用於 3歲內發病確診，且開始治療年齡滿 18歲以上，且臨床評估運動功能指標 RULM $\geq$ 15，並經小兒神經專科、神經科醫師判定下列任一情形，致無法使用nusinersen藥品：

I .施行過脊椎融合術

II.脊椎側彎嚴重(Cobb Angle $\geq$ 50度)

III.對於施行麻醉有困難



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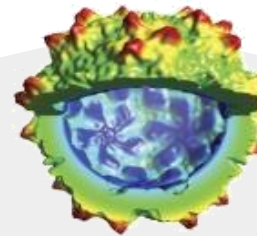
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修訂後給付規定		修訂後給付規定	修訂後給付規定	修訂後給付規定	修訂後給付規定	修訂後給付規定
<p><u>1. 6. 7. Onasemnogene abeparvovec (如 Zolgensma suspension for Intravenous Infusion): (112/8/1)</u></p> <p><u>1. 限用於治療年齡 6 個月以下，經標準檢測方法 MLPA(Multiplex Ligation-Dependent Probe Amplification)或 NGS(Next Generation Sequencing)檢測基因確診，及 SMN2 基因檢驗報告，且經衛生福利部國民健康署認定之脊髓性肌肉萎縮症(Spinal muscular atrophy, SMA)病人，但不適用於已使用呼吸器每天 12 小時以上，且連續 30 天以上者。</u></p> <p><u>2. 需檢附下列資料，經 2 位以上專家之專家小組特殊專案審查核准後使用：</u></p> <p><u>(1)經衛生福利部國民健康署認定 SMA 罕見疾病個案之臨床症狀影片：</u></p>	無	<p><u>I. 經新生兒篩檢(含產前診斷)，SMN2 基因拷貝數<math>\leq 2</math>，內容需至少出現 1 項肌肉相關異常：</u></p> <p><u>i. 新生兒姿態異常。</u></p> <p><u>ii. 新生兒哭聲弱。</u></p> <p><u>iii. 新生兒肌張力低下。</u></p> <p><u>II. 非經新生兒篩檢(含產前診斷)，SMN2 基因拷貝數<math>\leq 3</math>，內容需包含下列各項：</u></p> <p><u>i. 全身性低張力及對稱性近側端為主的肌無力。</u></p> <p><u>ii. 深部肌腱反射減低或消失，如：膝反射、踝反射、二頭肌反射。</u></p> <p><u>(2)病歷摘要。</u></p> <p><u>(3)標準運動功能評估(CHOP INTEND、HINE Section 2、WHO motor milestones)之影片，倘上述評估項目任一項已達滿分，應繼續評估下列任一項目</u></p> <p><u>I. BAYLEY-III(gross motor skills)。</u></p> <p><u>II. 若以 HFMSE 評估須滿兩歲。</u></p> <p><u>III. 若以 RULM 評估須滿兩歲六個月。</u></p>	<p><u>3. 排除條件：</u></p> <p><u>(1)需使用侵入性呼吸器或血氧飽和度<math>&lt;95\%</math>。</u></p> <p><u>(2)經酵素免疫分析法檢測，血液中 Anti-AAV9 抗體效價<math>&gt;1:50</math>。</u></p> <p><u>(3)已使用過 Nusinersen 或 Risdiplam。</u></p> <p><u>4. 療效評估時機、判定及執行者：</u></p> <p><u>(1)標準運動功能評估時機：</u></p> <p><u>I. Onasemnogene abeparvovec 治療前。</u></p> <p><u>II. Onasemnogene abeparvovec 治療後，每 4 個月評估 1 次，倘 CHOP INTEND 或 HINE Section 2 或 WHO motor milestones 任一項評估已達滿分，應繼續評估下列任一項目：</u></p> <p><u>i. BAYLEY-III(gross motor skills)。</u></p> <p><u>ii. 若以 HFMSE 評估須滿兩歲。</u></p> <p><u>iii. 若以 RULM 評估須滿兩歲六個月。</u></p> <p><u>(2)標準運動功能評估判定者：</u></p>	<p><u>I. 需由提供 Onasemnogene abeparvovec 治療之兒科專科醫師選擇下列各項適合療效評估工具，並判定評估結果：</u></p> <p><u>i. CHOP INTEND。</u></p> <p><u>ii. HINE Section 2。</u></p> <p><u>iii. WHO motor milestones。</u></p> <p><u>II. 倘上述任一項目評估已達滿分，則以下列任一項目繼續評估：</u></p> <p><u>i. BAYLEY-III(gross motor skills)。</u></p> <p><u>ii. 若以 HFMSE 評估須滿兩歲。</u></p> <p><u>iii. 若以 RULM 評估須滿兩歲六個月。</u></p> <p><u>(3)標準運動功能評估執行者：</u></p> <p><u>需由受過訓練之兒科專科醫師或物理治療師執行。</u></p> <p><u>5. 使用本類藥品治療每年應檢附年度追蹤報告書，包括每 4 個月評估 1 次之標準運動功能、發展里程碑之錄影影片，並評估追蹤療效(下列評估需在 SMA 病人非急性住院期間執行，且病人需遵從標準支持治療)，且每年均需符</u></p>	<p><u>合下列各條件：</u></p> <p><u>(1)存活。</u></p> <p><u>(2)在非急性住院期間，不得使用呼吸器每天 12 小時以上，且連續 30 天以上。醫師須提交第 1、5、10、30 天之錄影影片。</u></p> <p><u>(3)用藥後追蹤 CHOP INTEND、HINE Section 2、WHO motor milestones 評估分數至少有一次不低於起始治療前該項標準運動功能第 1 次評估分數。如上述評估項目之評估分數每次均低</u></p> <p><u>前該項標準運動：次評估分數，則效。</u></p> <p><u>(4)倘 CHOP INTEND Section 或 WHO motor milestones 任一項目，且評</u></p> <p><u>有一次不低於開</u></p> <p><u>運動功能第 1 次</u></p> <p><u>若評估項目之評</u></p> <p><u>均低於開始該項</u></p> <p><u>能之第 1 次評估</u></p> <p><u>示未達療效。</u></p>	<p><u>修訂後給付規定</u></p> <p><u>i. BAYLEY-III(gross motor skills)。</u></p> <p><u>ii. 若以 HFMSE 評估須滿兩歲。</u></p> <p><u>iii. 若以 RULM 評估須滿兩歲六個月。</u></p> <p><u>(5)用藥後追蹤發展里程碑(獨自坐立<math>\geq 30</math> 秒或獨自站立<math>\geq 10</math> 秒或獨自行走<math>\geq 5</math> 步)，不得有退化。</u></p> <p><u>6. 使用本藥品需完成個案系統登錄，亦需登錄每次評估療效或停止評估後，於此系統登錄結果。</u></p> <p><u>7. Onasemnogene abeparvovec 或 nusinersen 或 risdiplam 限擇一使用，且不得互換。</u></p>

## ZOLGENSMA (Onasemnogene abeparvovec) delivers a fully functional copy of human *SMN* to treat the genetic root cause of SMA<sup>1,2</sup>



### Recombinant AAV9 capsid shell



Able to deliver across the blood–brain barrier and into the spinal cord<sup>1</sup>

Designed not to integrate into genome of the patient<sup>1</sup>



#### Continuous promoter

A CB promoter allows for high and sustained expression of the delivered *SMN* gene<sup>1</sup>

#### Human *SMN* gene

Designed to deliver a fully functional copy of the human *SMN* gene<sup>2</sup>

#### Self-complementary AAV inverted terminal repeats (scAAV ITR)

The scAAV ITR allows for rapid protein expression from double-stranded DNA after human *SMN* gene delivery<sup>1</sup>

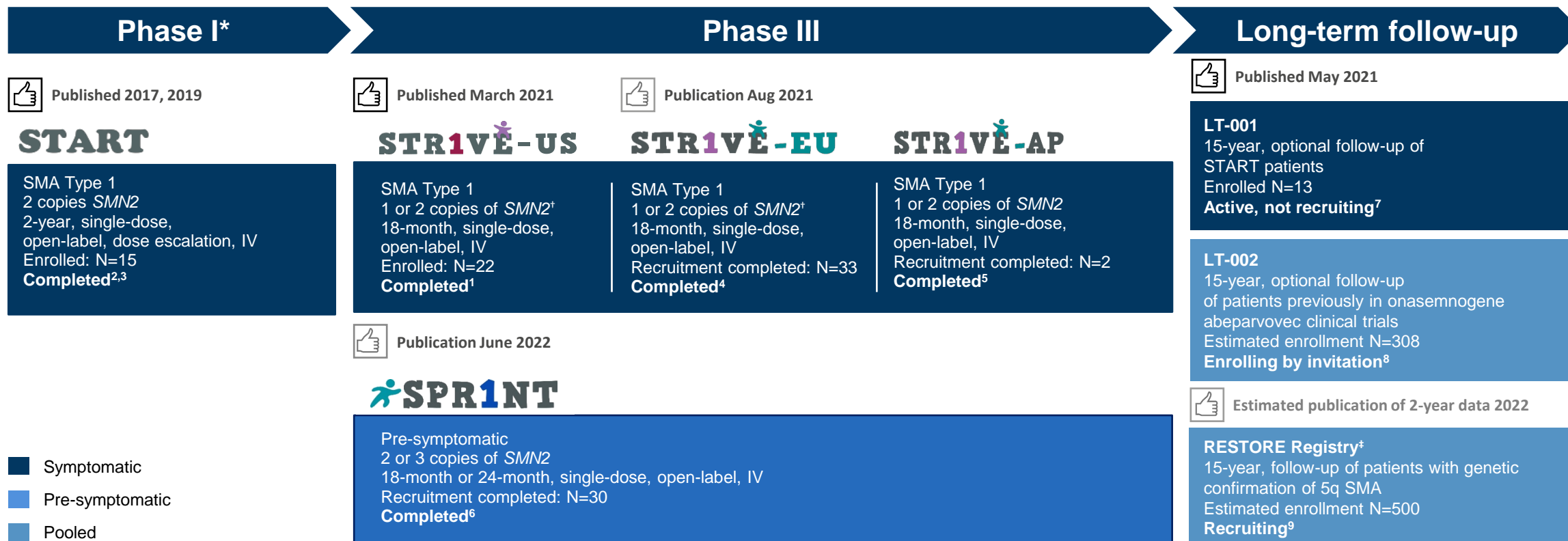
AAV2, adeno-associated virus serotype 2; AAV9, adeno-associated virus serotype 9; BGH poly A, bovine growth hormone polyadenylation; CB, chicken  $\beta$ -actin; CMV, cytomegalovirus; ITR, inverted terminal repeat; SMA, spinal muscular atrophy; SMN, survival motor neuron; SV, simian virus.

1. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Neuroscience and Nervous System Disorders. Chapter 2: Exploring the current landscape of nervous system gene-targeted therapies. In: Stroud C, Bain L; Advancing gene-targeted therapies for central nervous system disorders: Proceedings of a workshop. Washington (DC): National Academies Press; 2019.

2. FDA (2019). (onasemnogene abeparvovec) PI. Available at: <https://www.fda.gov/media/126109/download>. Last accessed: February 2021.



# Clinical trial programs ZOLGENSMA—clinical trial program



\*STRONG is a Phase I trial of intrathecal onasemnogene abeparvovec on clinical hold pending further discussions regarding pre-clinical findings;<sup>10</sup> <sup>†</sup>All enrolled patients had 2 copies of *SMN2*; <sup>‡</sup>Observational real-world evidence registry; <sup>§</sup>Patients with *SMN1* point mutations or the *SMN2* gene modifier mutation (c.859G>C) may enroll but will not be included in the efficacy analysis sets.

IV, intravenous; SMA, spinal muscular atrophy; LTFU, long-term follow-up; RWE, real-world evidence; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene; Q4, fourth quarter of calendar year.

1. Day JW, et al. *Lancet Neurol.* 2021; 20(4):284–293; 2. Mendell JR, et al. *New Engl J Med.* 2017;377(18):1713–22; 3. Al Zaidy S, et al. *Pediatr Pulmonol.* 2019; 54(2):179–185; 4. ClinicalTrials.gov Identifier: NCT03461289; 5. ClinicalTrials.gov Identifier: NCT03837184; 61.

Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. *Nat Med* (2022); Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of *SMN2* at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med* (2022)

.7. Mendell JR, et al. *JAMA Neurol.* 2021; 78(7):834–841. 8. ClinicalTrials.gov Identifier: NCT04042025; 9. ClinicalTrials.gov Identifier: NCT04174157; 10. ClinicalTrials.gov Identifier: NCT03388581



# ZOLGENSMA was efficacious and well-tolerated in SMA patients



## Access Snapshot for ZOLGENSMA® (onasemnogene abeparvovec-xioi) suspension, for intravenous infusion



\*Insurance approval rate based on data from 24May2019-31Oct2020, all patients <2years of age for whom a payer decision was known

\*\*As of June 2022, including clinical trials, commercially, and through the managed access programs

\*insurance approval rate based on data from 24 May 2019 to 31 Oct 2020. all patients <2 years of age for whom a payer decision was unknown.

\*\*As of June 2022. including clinical trials, commercially and through the managed access programs.

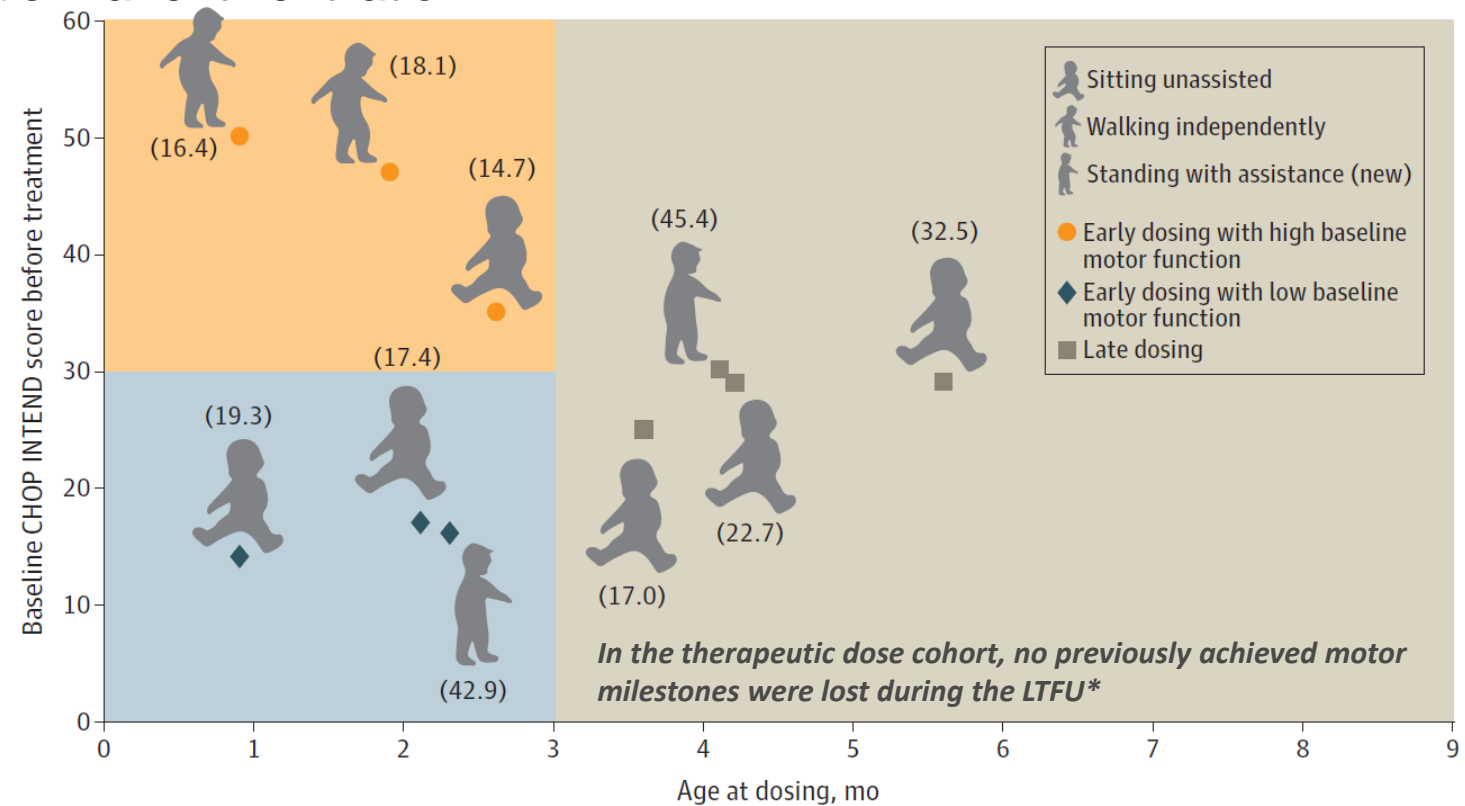
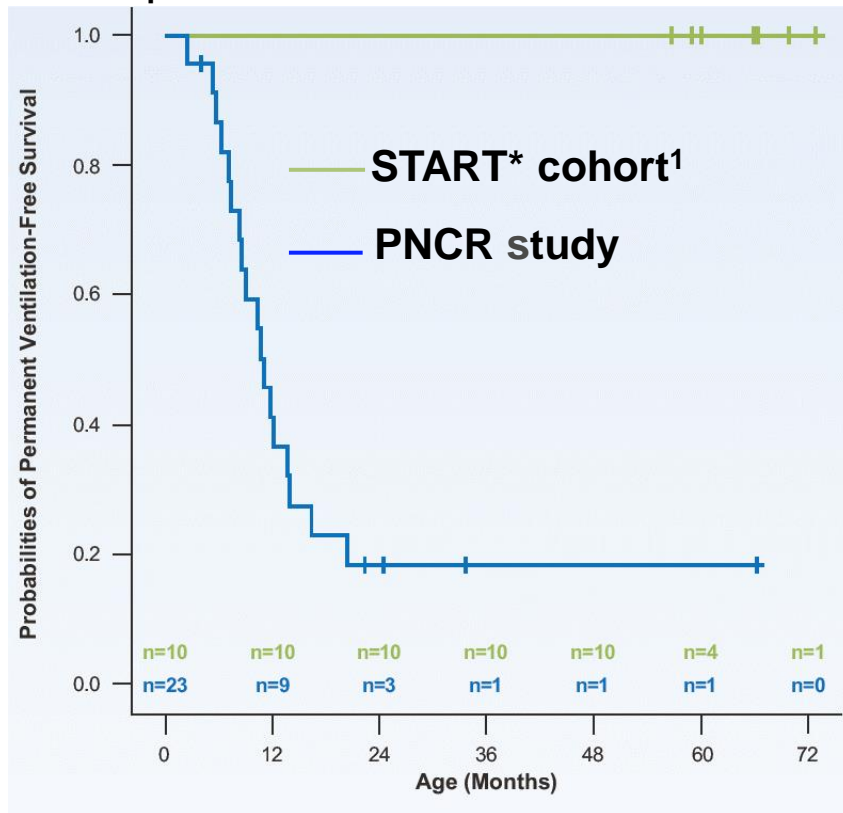


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As of December 19, 2019 (no visits in 2020),  
10/10 patients remained alive and free of permanent ventilation<sup>1</sup>



Mean (range) age in years: 5.2 (4.7-6.1)

Mean (range) time in years since treatment: 5.0 (4.6-5.6)

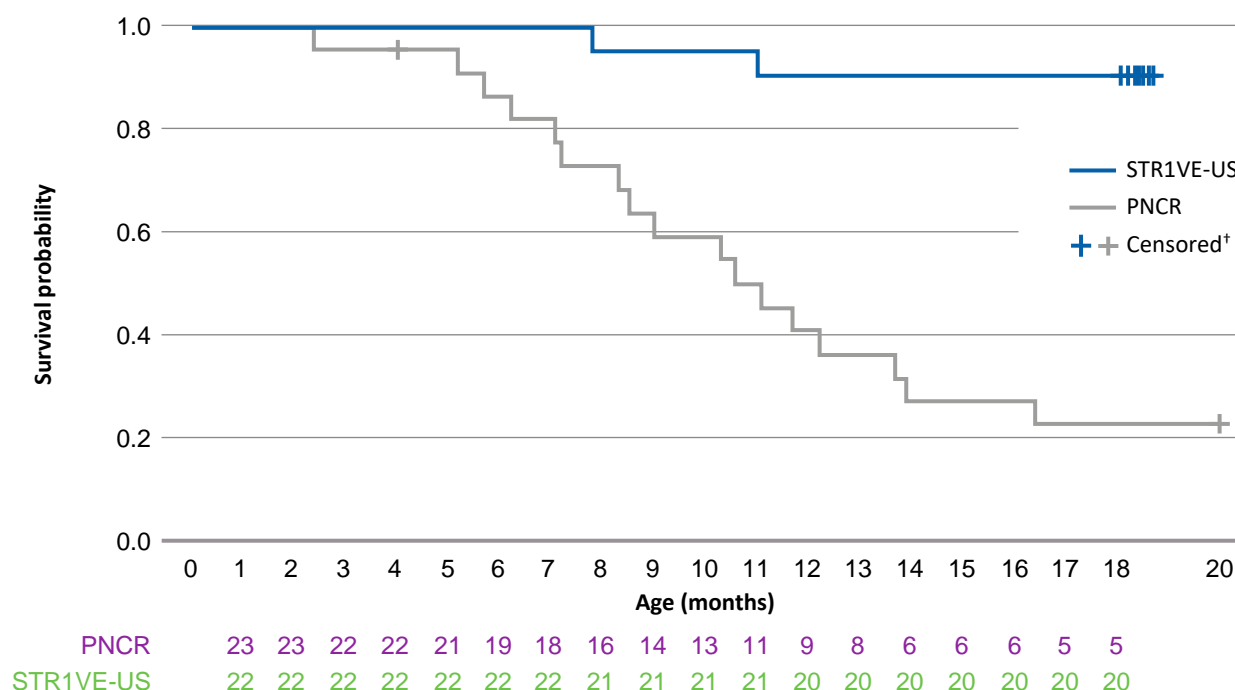
\*Study number: NCT02122952. The START study also included a low-dose cohort, which is not presented here<sup>3</sup>.

LTFU, long-term follow-up; PNCR, Pediatric Neuromuscular Research Network. 1. Mendell JR, et al. MDA 2021 poster;

Figure: Mendell JR, et al. JAMA Neurol. 2021; 78(7):834-841

# STR1VE-US: Unprecedented survival free of death or permanent ventilation compared to natural history for patients with SMA Type 1<sup>1</sup>

**20/22 (91%) patients survived\* without requirement of permanent ventilation at 14 months of age<sup>1</sup>**



This compares with 6/23 (26%) untreated patients in the PNCr cohort ( $p < 0.0001$ )<sup>1</sup>

## START

In START, all 12 patients<sup>‡</sup> were alive after 24 months of follow-up<sup>2</sup>

\*Tracheostomy or  $\geq 16$  hours daily non-invasive ventilation support for  $\geq 14$  days in the absence of an acute reversible illness or perioperative ventilation;

<sup>†</sup>One patient was censored prior to 18 months of age (at ~4 months).

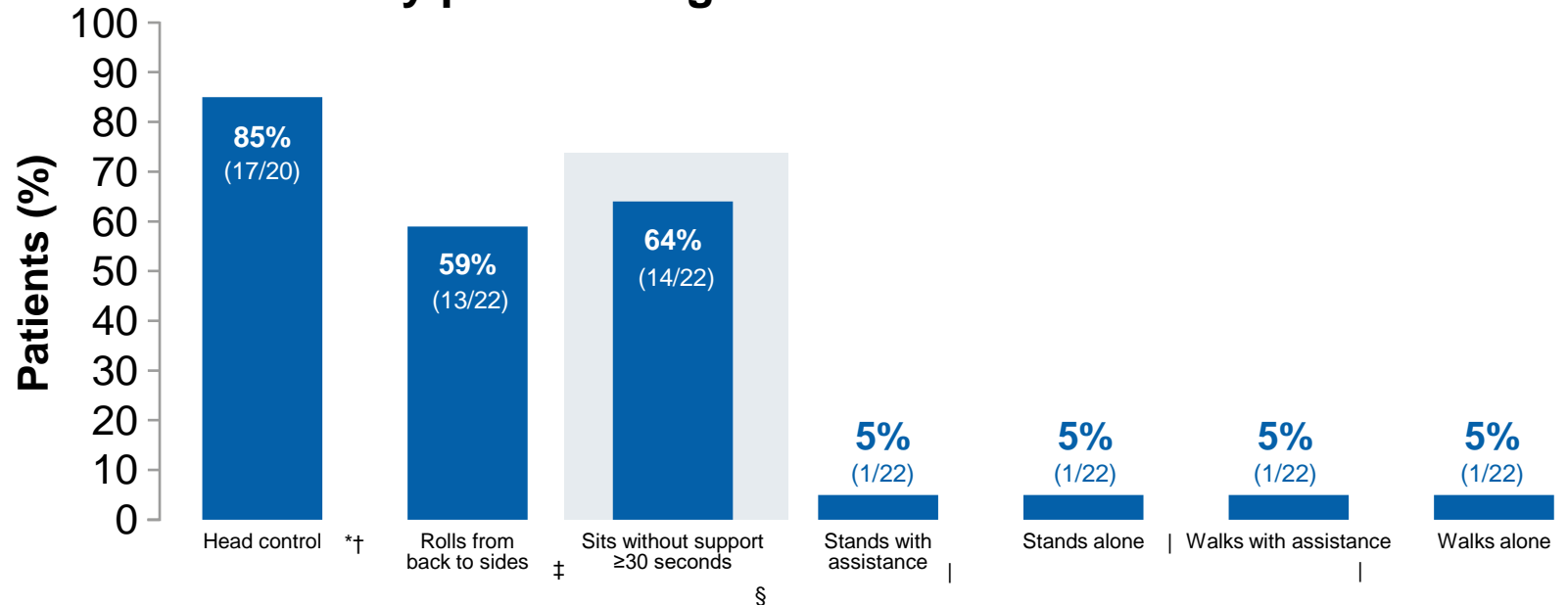
This patient was in the PNCr cohort. In the STR1VE-US cohort, all patients were censored at the end of the study; <sup>‡</sup>Patients received the therapeutic dose.

PNCr, Pediatric Neuromuscular Clinical Research Network.

1. Day JW, et al. *Lancet Neurol.* 2021; 20(4):284–293 (Suppl); 2. Al Zaidy S, et al. *Pediatr Pulmonol.* 2019; 54(2):179–185.



## Video-confirmed milestones achieved at any point during the STR1VE-US trial



**59% of patients (n=13/22)** achieved sitting independently for ≥30 seconds at the 18 months of age study visit, a primary endpoint<sup>¶</sup>

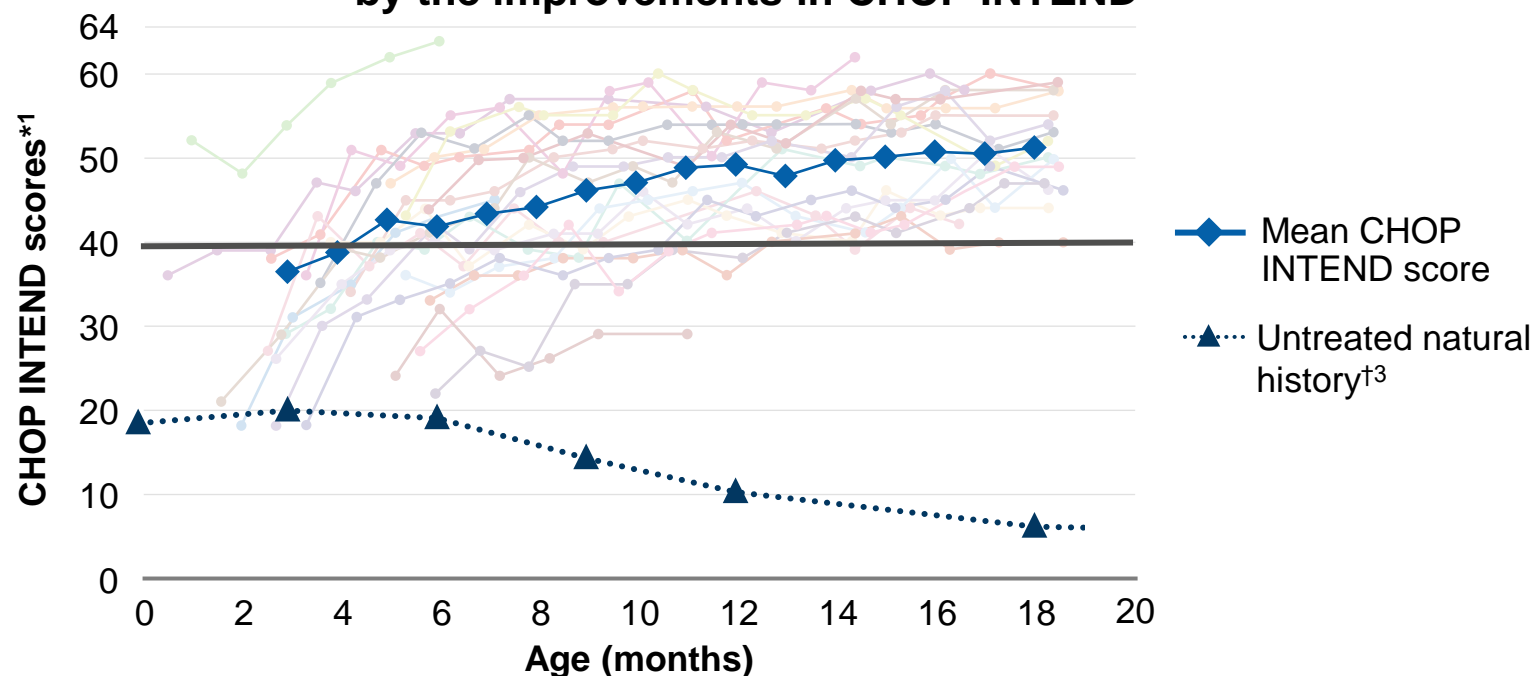
**86% (19/22) of symptomatic patients with SMA Type 1 in STR1VE-US achieved one or more motor milestones. In natural history studies, patients with SMA Type 1 were not able to sit independently**

\*Bayley-III, Gross Motor Subtest, Item #4 (holds head erect ≥3 seconds without support); <sup>†</sup>Two patients demonstrated the milestone of head control at the first screening visit (prior to ZOLGENSMA dosing); therefore n=20 was used for this calculation; <sup>‡</sup>Bayley-III, Gross Motor Subtest, Item #20 (rolls from back to both right and left sides); <sup>§</sup>Bayley-III, Gross Motor Subtest, Item #26 (sits without support ≥30 seconds); <sup>¶</sup>The milestones of stands with assistance, stands alone, walks with assistance, walks alone were all achieved by the same patient; <sup>¶¶</sup>One patient achieved the milestone of sitting independently for ≥30 seconds at 16 months of age but this milestone was not reconfirmed at the Month 18 visit. Bayley-III, Bayley Scale of Infant and Toddler Development – Third Edition; SMA, spinal muscular atrophy.  
1. Day JW, et al. Lancet Neurol. 2021; 20(4):284–293



# Rapid improvement and maintenance of motor function compared to natural history

## Improvements in motor function as demonstrated by the improvements in CHOP INTEND<sup>1,2</sup>



At **1-month post-dose**, mean CHOP INTEND increased by **6.9** (N=22) points from baseline<sup>1</sup>

These values showed further improvement at **14 months post-dose** with a mean increase of **23.5** (n=11) points from baseline<sup>2</sup>

**95% (21/22) of patients have achieved or maintained a clinically meaningful CHOP INTEND score of  $\geq 40$ ; whereas patients with SMA Type 1 in historical controls did not typically achieve and maintain CHOP INTEND scores  $\geq 40$ <sup>†</sup>**

\*Scores on the CHOP INTEND scale of motor function range from 0 to 64, with higher scores indicating better function. The gray dotted line represents the highest CHOP INTEND score that children with the most severe form of SMA would achieve or maintain, according to natural history.<sup>3</sup>

<sup>†</sup>Natural history data from NeuroNEXT prospective natural history study in SMA infants with 2 copies of SMN2.<sup>2</sup>

<sup>‡</sup>Patients who achieve three consecutive CHOP INTEND scores  $\geq 58$  will not continue CHOP INTEND assessments.<sup>1</sup>

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NeuroNEXT, National Network for Excellence in Neuroscience Clinical Trials; SMA, spinal muscular atrophy.

1. Day JW, et al. Lancet Neurol. 2021; 20(4):284–293; 2. Novartis Gene Therapies. Data on file (2019); 3. Kolb SJ, et al. Ann Neurol. 2017;82(6):883-891.



# Maintain nutritional and respiratory status compared to natural history

## Nutritional support

STR1VE-US<sup>1</sup>

**68% (15/22) of patients**  
remained free of non-oral feeding support  
at any time during the study\*

3/22 patients required ongoing nutritional support  
at 18 months of age or discontinuation

## Respiratory support



**68% (15/22) of patients**  
did not require non-invasive ventilatory support at any  
point during the study<sup>†</sup>

4/22 patients required ventilatory support as assessed by  
Trilogy BiPAP data alone at 18 months of age,  
a secondary endpoint

Untreated natural  
history<sup>2</sup>

Most patients with SMA Type 1 **required nutritional  
support** by 12 months of age



Most patients with SMA Type 1 **required respiratory  
support** by 12 months of age

**Most patients maintained independence from nutritional  
and respiratory support compared to natural history<sup>1,2</sup>**

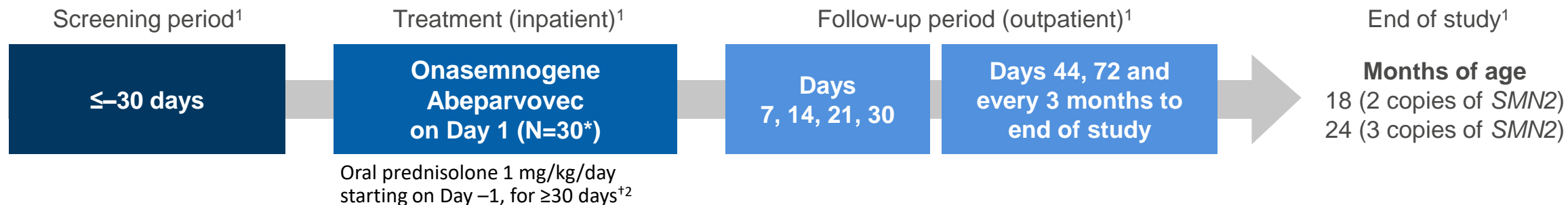
\*Seven patients received some feeding support, four were temporary lasting 6–91 days occurring once per patient. Three were ongoing at the end of study or withdrawal;<sup>1</sup> †Five patients had documented BiPAP use, and two patients had other non-invasive ventilatory support.<sup>1</sup>  
BiPAP, bilevel positive airway pressure; SMA, spinal muscular atrophy.

37 1. Day JW, et al. Lancet Neurol. 2021; 20(4):284–293; 2. Finkel RS, et al. Neurology. 2014;83(9):810-817.



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# SPR1NT: An open-label, single-dose, multicenter clinical trial in pre-symptomatic patients with SMA



## Key inclusion criteria<sup>1</sup>

- Patients aged **≤6 weeks** at dosing
- Bi-allelic *SMN1* mutations, 2 or 3 copies of *SMN2*
- Ability to tolerate thin liquids
- CMAP ≥2 mV at baseline

## Primary efficacy endpoints<sup>1</sup>

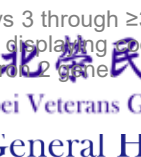
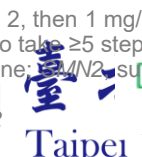
- Functional independent sitting for ≥30 seconds (Bayley) at any visit up to 18 months of age (2 copies of *SMN2*)
- Ability to stand without support for ≥3 seconds (Bayley) at any visit up to 24 months of age (3 copies of *SMN2*)

## Secondary efficacy endpoints<sup>1</sup>

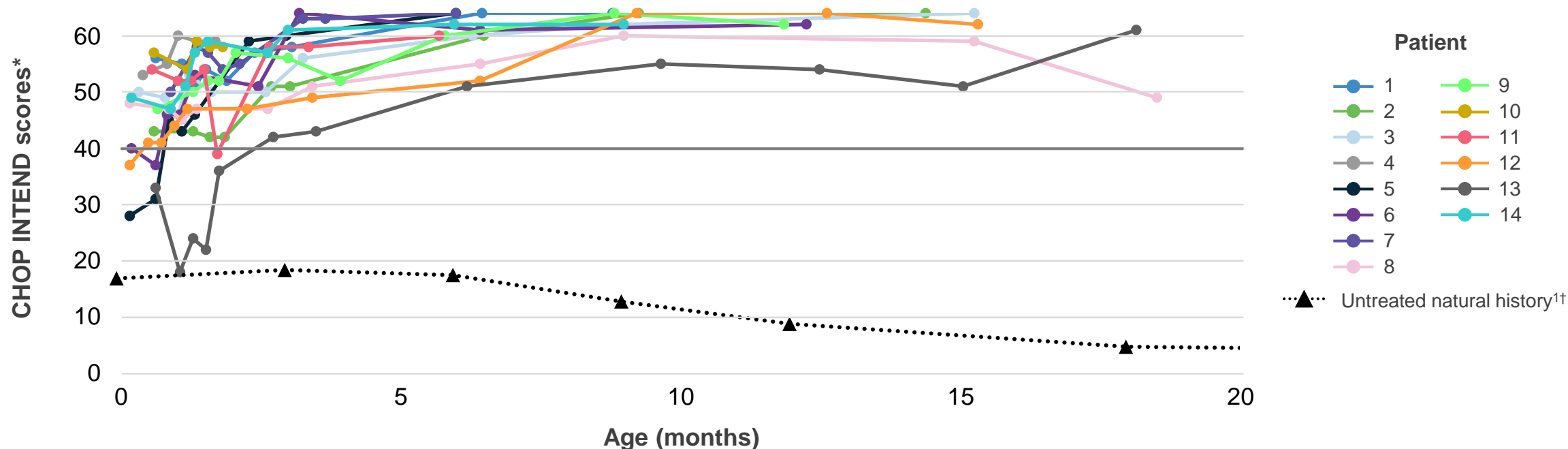
- Survival<sup>‡</sup> at age 14 months and ability to maintain weight<sup>§</sup> without feeding support at any visit up to 18 months of age (2 copies of *SMN2*)
- Ability to walk alone<sup>||</sup> (Bayley) up to 24 months of age (3 copies of *SMN2*)

**SPR1NT is evaluating pre-symptomatic patients ≤6 weeks of age at dosing.**  
**Reported efficacy data reflect June 2020 data cut, n=29\*2**

\*All enrolled patient cohort includes patients with 2 (n=14), 3 (n=15) and 4 (n=1) copies of *SMN2*; <sup>†</sup>Some patients received oral prednisolone 2 mg/kg/day on Days -1 through 2, then 1 mg/kg/day from Days 3 through ≥30; <sup>‡</sup>Survival defined as death or the need for permanent ventilation; <sup>§</sup>Ability to maintain weight at or above 3rd percentile without non-oral /mechanical feeding support at any visit; <sup>||</sup>Ability to take ≥5 steps independently displaying coordination and balance at any visit within the time frame of 24 months (Bayley). CMAP, compound muscle action potential; SMA, spinal muscular atrophy; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene.  
 1. Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med* (2022).; Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of *SMN2* at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med* (2022); 2. Novartis Gene Therapies. Data on file (2020).



## ZOLGENSMA treatment in SMA patients with two copies of *SMN2* demonstrated increases in CHOP INTEND score from baseline\*



**100% of patients (14/14) achieved a CHOP INTEND score of ≥58 points by the end of the study.;**  
**whereas patients with SMA Type 1 in historical controls did not typically achieve and maintain CHOP INTEND scores ≥40<sup>‡</sup>**

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NeuroNEXT, National Network for Excellence in Neuroscience Clinical Trials; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2 gene.

\*Solid gray line denotes CHOP INTEND score of 40. According to natural history, children with the most severe form of SMA do not achieve/maintain CHOP INTEND scores >40 points. †Natural history data from NeuroNEXT prospective natural history study in SMA infants with two copies of *SMN2*.

39 1. Kolb SJ, et al. Ann Neurol. 2017;82:883–891. 2. Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. Nat Med (2022).



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# Motor milestones reached by pre-symptomatic patients with 2 copies of *SMN2*

## Primary endpoint

## Exploratory endpoints<sup>†</sup>

**Sitting without support for ≥30 seconds (Bayley)\***



**100%**  
(14/14)

**achieved this milestone**

**11 of the 14 patients**  
achieved this milestone  
**within the normal range** of 3.8–9.2 months<sup>1</sup>

**Standing alone for ≥3 seconds (Bayley)<sup>†</sup>**



**79%**  
(11/14)

**achieved this milestone**

**7 of the 11 patients**  
achieved this milestone  
**within the normal range** of 6.9–16.9 months<sup>1</sup>

**Walking alone (WHO)<sup>‡</sup>**



**64%**  
(9/14)

**achieved this milestone**

**5 of the 9 patients**  
achieved this milestone  
**within the normal range** of 8.2–17.6 months<sup>1</sup>

Age-appropriate time periods were defined according to the WHO Multicentre Growth Reference Study (MGRS) established windows of achievement for the development of motor milestones.

\*The age range at confirmation was 5.7–11.8 months for patients who achieved sitting without support for ≥30 seconds up to 18 months of age<sup>†</sup>

†The age range at confirmation was 10.9–18.8 months for patients who achieved independent standing alone ≥10 seconds assessed by Bayley-III, gross motor subtest item 40<sup>1</sup>

‡The age range at confirmation was 12.2–18.8 months for patients who achieved independent walking assessed by WHO MGRS.<sup>1</sup>

MGRS, Multicentre Growth Reference Study; *SMN2*, survival motor neuron 2 gene; WHO, World Health Organization.

1. Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy.

40 the Phase III SPR1NT trial. Nat Med (2022).



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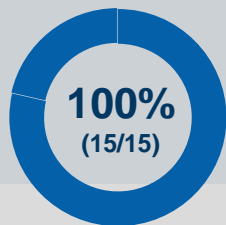
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# Motor Milestones Reached by Pre-symptomatic Patients With 3 Copies of *SMN2*

## Primary endpoint

Standing alone for  
≥3 seconds (Bayley)<sup>†</sup>

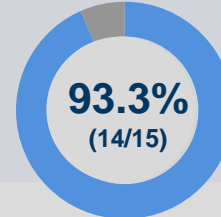


achieved this milestone

14 of the 15 patients  
achieved this milestone  
within the normal range of 6.9–16.9 months<sup>1</sup>

## Secondary endpoints<sup>‡</sup>

Walking alone  
(WHO)<sup>‡</sup>

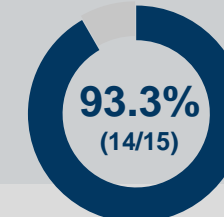


achieved this milestone

11 of the 14 patients  
achieved this milestone  
within the normal range of 8.2–17.6 months<sup>1</sup>

## Exploratory endpoints<sup>‡</sup>

Sitting without support  
for ≥30 seconds (Bayley)<sup>\*</sup>



achieved this milestone

11 of the 14 patients  
achieved this milestone  
within the normal range of 3.8–9.2 months<sup>1</sup>

**Most patients with 3 copies of *SMN2* achieved age-appropriate motor milestones<sup>1</sup>**

Age-appropriate time periods were defined according to the WHO Multicentre Growth Reference Study (MGRS) established windows of achievement for the development of motor milestones. Bayley Scales gross motor subtest item #43: child walks alone. Child takes at least five steps independently, displaying coordination and balance

<sup>\*</sup>The age range at confirmation was 5.7–11.8 months for patients who achieved sitting without support for ≥30 seconds up to 18 months of age<sup>‡</sup>

<sup>‡</sup>The age range at confirmation was 10.9–18.8 months for patients who achieved independent standing alone ≥10 seconds assessed by Bayley-III, gross motor subtest item 401

<sup>‡</sup>The age range at confirmation was 12.2–18.8 months for patients who achieved independent walking assessed by WHO MGRS.1

MGRS, Multicentre Growth Reference Study; *SMN2*, survival motor neuron 2 gene; WHO, World Health Organization.

1. Strauss, K.A., Farrar, M.A., Muntori, F. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of *SMN2* at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med* (2022).



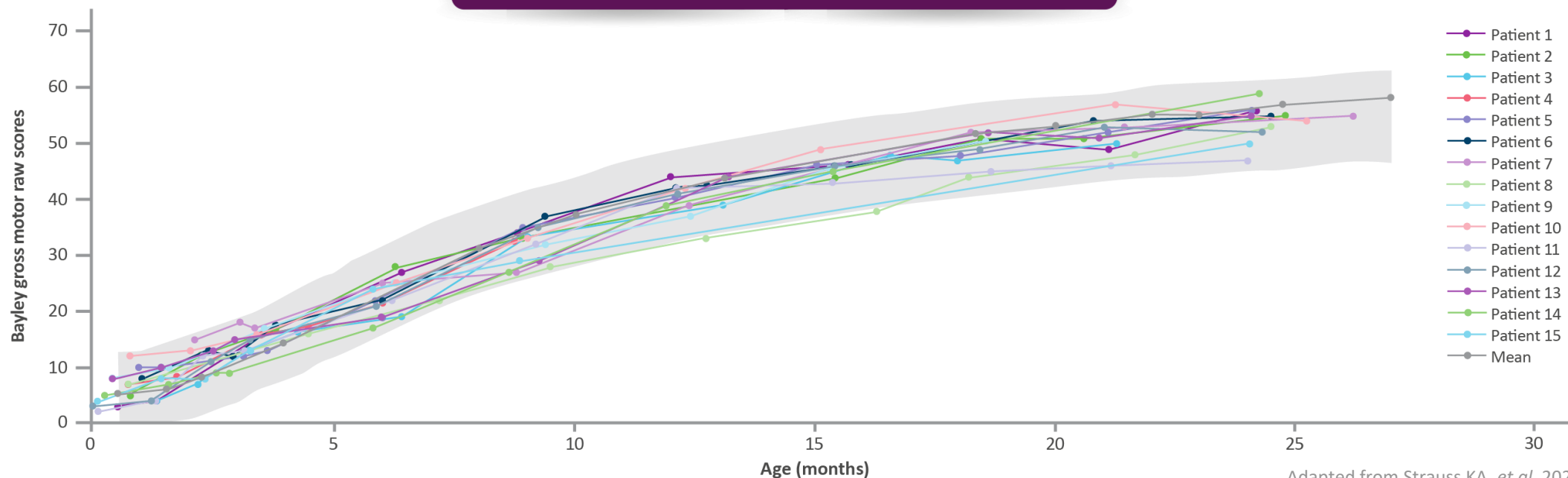
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# Patients had raw Bayley-III gross motor scores within the normal range of non-affected peers<sup>1</sup>

Bayley-III Scales gross motor subtest raw score:<sup>\*</sup>1



Adapted from Strauss KA, et al. 2022.

**All study participants demonstrated steady gains on Bayley-III gross motor scales<sup>1</sup>**

<sup>\*</sup>Bayley-III fine and gross motor normal range [ $\pm 2$  SD] is shown in grey highlight.

SD, standard deviation.

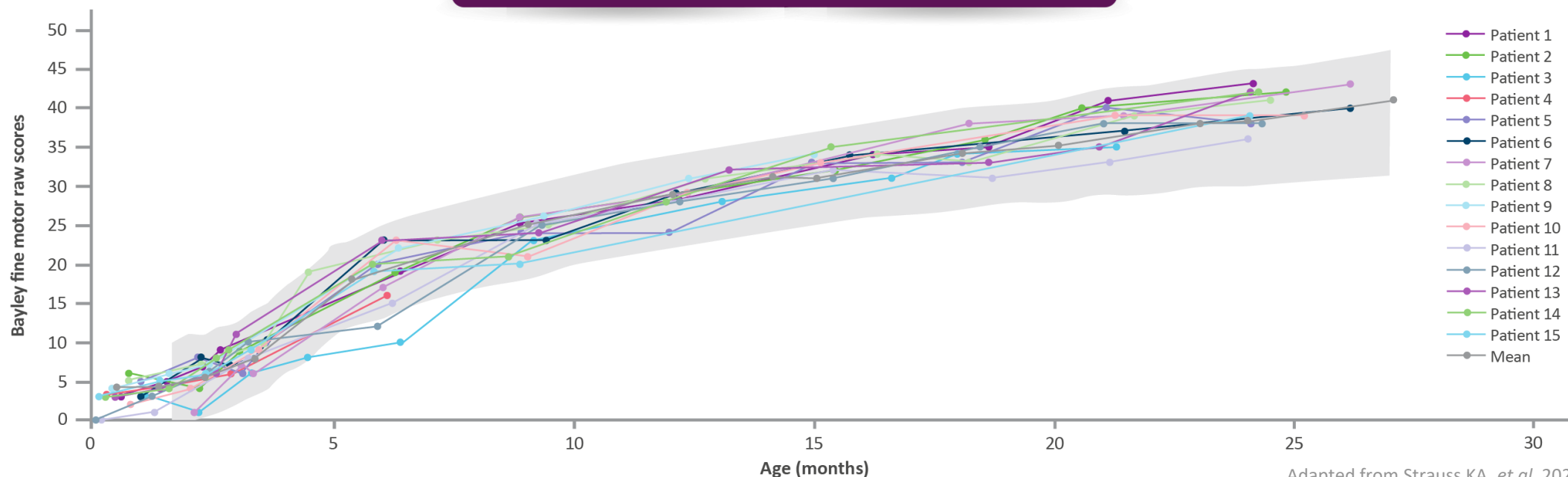
<sup>1</sup> Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy. *Nat Med* (2022).



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# Patients had raw Bayley-III fine motor scores within the normal range of non-affected peers<sup>1</sup>

Bayley-III Scales fine motor subtest raw score:<sup>\*</sup>1



Adapted from Strauss KA, et al. 2022.

**All study participants demonstrated steady gains on Bayley-III fine motor scales<sup>1</sup>**

<sup>\*</sup>Bayley-III fine and gross motor normal range [±2 SD] is shown in grey highlight.  
SD, standard deviation.

1. Strauss, K.A., Farrar, M.A., Muntoni, F. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med (2022)



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# Summary of safety findings from the IV clinical trial program<sup>1</sup>



102 patients received ZOLGENSMA in the IV clinical trial program.

System organ class preferred term	START All (N=15) n (%)	STR1VE- EU <sup>a</sup> N=33 n (%)	STR1VE-US <sup>a</sup> N=22 n (%)	SPR1NT <sup>a</sup> N=30 n (%)	STR1VE-AP <sup>a</sup> N=2 n (%)	Therapeutic IV dose <sup>b</sup> N=99 n (%)
<b>Patient with at least one related serious TEAE</b>	<b>2 (13.3)</b>	<b>6 (18.2)</b>	<b>3 (13.6)</b>	<b>0</b>	<b>0</b>	<b>10 (10.1)</b>
Alanine aminotransferase increased	0	1 (3.0)	1 (4.5)	0	0	2 (2.0)
Aspartate aminotransferase increased	0	1 (3.0)	1 (4.5)	0	0	2 (2.0)
Transaminases increased	2 (13.3)	0	1 (4.5)	0	0	2 (2.0)
Coagulation test abnormal	0	1 (3.0)	0	0	0	1 (1.0)
Pyrexia	0	2 (6.1)	0	0	0	2 (2.0)
Infections and infestations <sup>c</sup>	0	2 (6.1)	0	0	0	2 (2.0)
Metabolism and nutrition disorders <sup>d</sup>	0	2 (6.1)	0	0	0	2 (2.0)
Thrombocytopenia	0	1 (3.0)	0	0	0	1 (1.0)
Hypertransaminasaemia	0	1 (3.0)	0	0	0	1 (1.0)
Hydrocephalus	0	0	1 (4.5)	0	0	1 (1.0)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

<sup>a</sup>Administered dose =  $1.1 \times 10^{14}$  vg/kg; <sup>b</sup>The Therapeutic IV Dose column includes patients who received the therapeutic dose in START and the  $1.1 \times 10^{14}$  vg/kg dose in STR1VE-EU, STR1VE-US, SPR1NT, and STR1VE-AP; <sup>c</sup>Term includes gastroenteritis, rhinovirus infection, and viral infection; <sup>d</sup>Term includes feeding disorder and hypernatremia.

\*One patient died during the screening period and did not receive ZOLGENSMA.

101 of 102 patients (99%)  
experienced at least one TEAE

58 patients (56.9%)  
experienced TEAEs  
considered related to  
treatment by the Investigator

50 patients (49%) experienced  
a SAE, of which 11 (10.8%)  
were considered related to  
treatment

The most frequently reported  
treatment-related SAEs were  
increased liver function test  
(LFTs) findings and pyrexia  
(two of 99 for each; 2.0%)

As of Nov. 12, 2020, 3 deaths  
were reported; this includes  
2 patients in STR1VE-US\*  
and 1 patient in STR1VE-EU



# Summary of AESIs: Hepatotoxicity<sup>1</sup>

LFT elevations initially observed at approximately Day 7 in the IV clinical development program, nearly resolved at approximately Day 14, with another transient increase at Month 1, which returned near baseline concentrations by Month 2

Table 4 Hepatotoxicity adverse events and laboratory findings

Hepatotoxicity	START (N = 15)	STRIVE-EU (N = 33)	STRIVE-US (N = 22)	SPRINT (N = 30)	STRIVE-AP (N = 2)	Total (N = 102)
Reported AEs	4 (26.7%)	18 (54.5)	7 (31.8)	8 (26.7) <sup>a</sup>	0	37 (36.3)
Elevations in LFT results (not reported as AEs)	10 (66.7)	12 (36.4)	13 (59.1)	19 (63.3)	1	54 (52.9)
Postdosing elevations in LFT results	15 (100)	29 (87.9)	20 (90.9)	26 (86.7)	0	90 (90.0)
Elevations in LFT results at baseline (prior to dosing) <sup>b</sup>	9 (60.0)	22 (66.7)	5 (22.7)	20 (66.7)	0	56 (54.9)

AEs adverse events, LFTs liver function tests, ULN upper limit of normal

<sup>a</sup>One of these events did not have laboratory abnormalities that were reported

<sup>b</sup>LFTs included analysis of aspartate aminotransferase, alanine aminotransferase, and bilirubin; all were  $< 2 \times$  ULN

Postmarketing data yielded 375 cases (695 hepatic events) in the following categories:

1. Isolated LFT elevations (337 cases, 591 events)
2. Clinical signs and symptoms (jaundice and ascites) and events of abnormal laboratory tests indicating coagulopathy, hypoalbuminemia, and increased ammonia (14 cases, 42 events)
3. Event terms under the hepatobiliary disorders system organ class (20 cases, 46 events)
4. Reported diagnosis of acute liver failure (four cases, 16 events)

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# Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis

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# 全球多個國家都進行早期 SMA 基因篩檢 (台灣領先世界！)

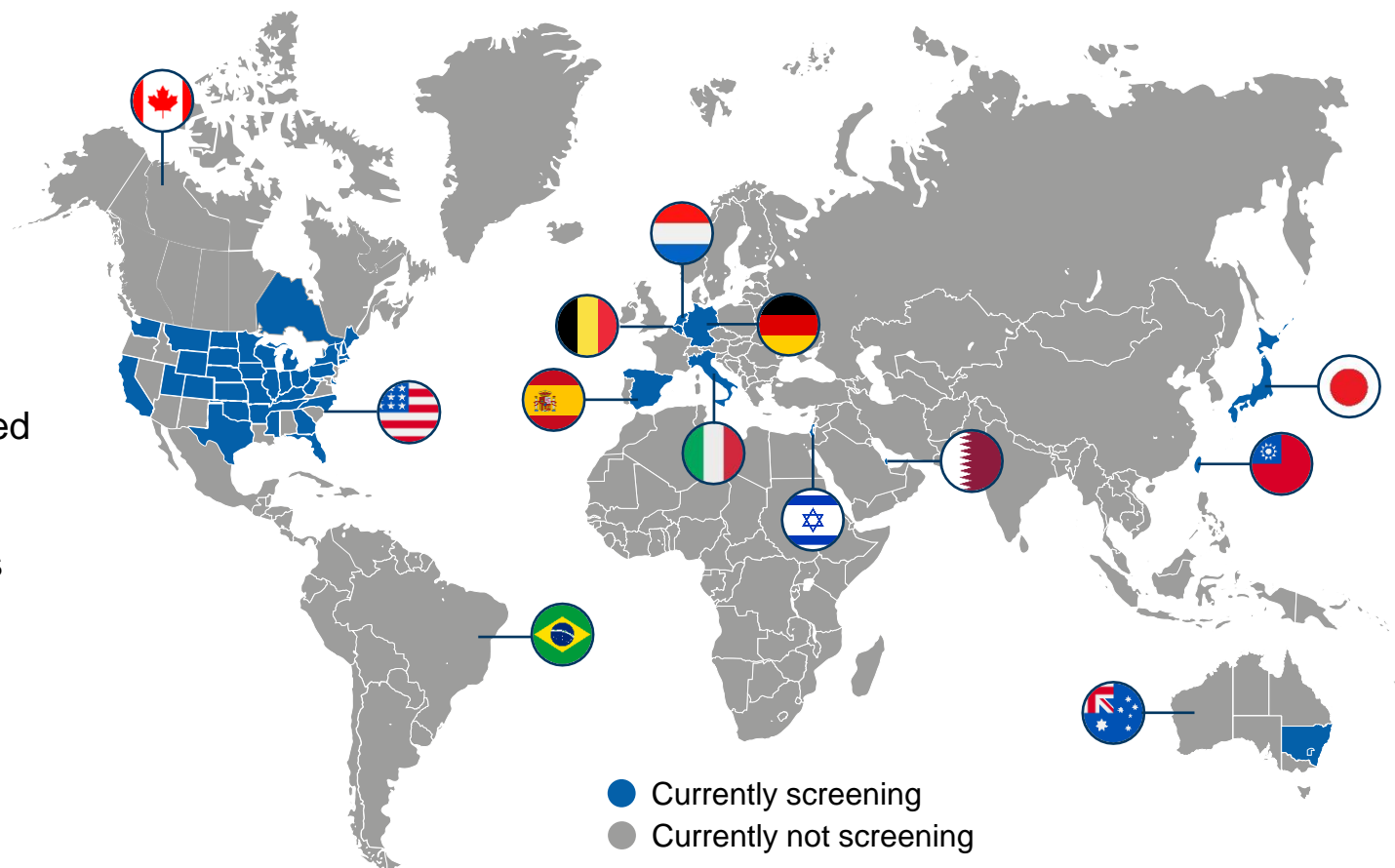


At least 13 countries are starting to implement SMA carrier or NBS worldwide<sup>1-3</sup>

A survey of experts from 152 countries identified nine SMA NBS programs<sup>2</sup>

- To date, these have detected 288 newborns with SMA out of 3,674,277 newborns screened<sup>2</sup>

The annual proportion of newborns to be screened in the coming years is expected to increase steadily<sup>2</sup>



● Currently screening  
● Currently not screening

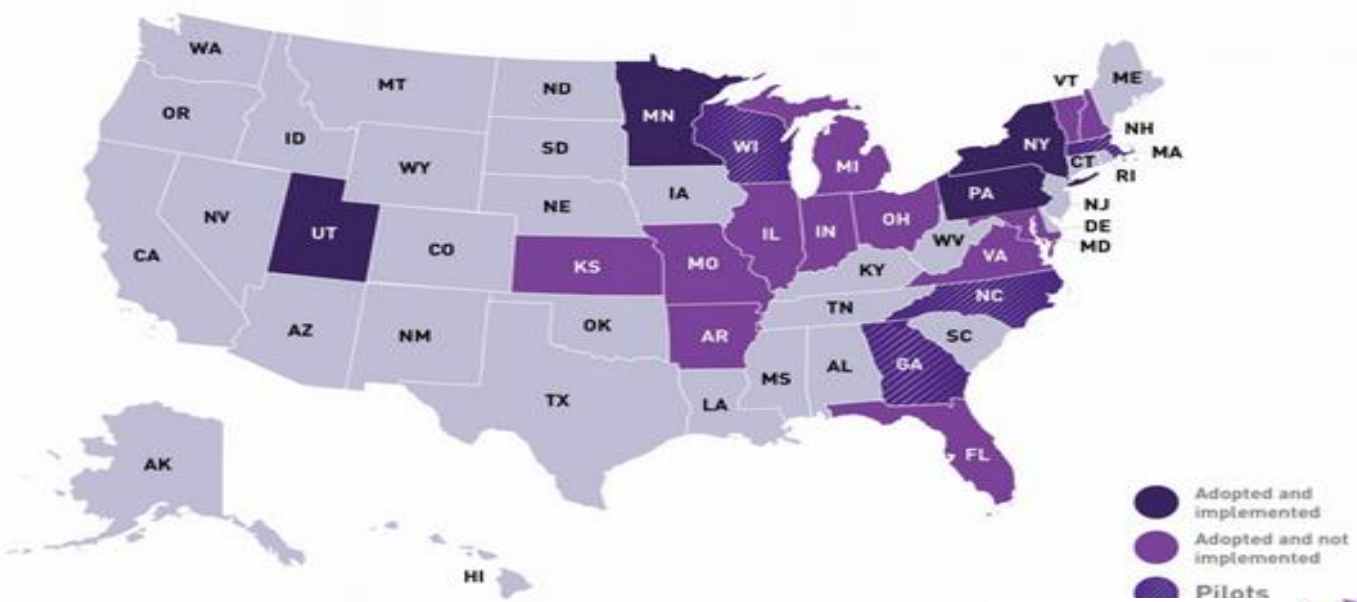
NBS, newborn screening; SMA, spinal muscular atrophy.

1. Kariyawasam DST et al. *EClinicalMedicine*. 2021;33:100742. 2. Dangouloff T et al. *Neuromuscul Disord* 2021;31(6):574-582. 3. CureSMA. Newborn screening map. Accessed September 9, 2021.

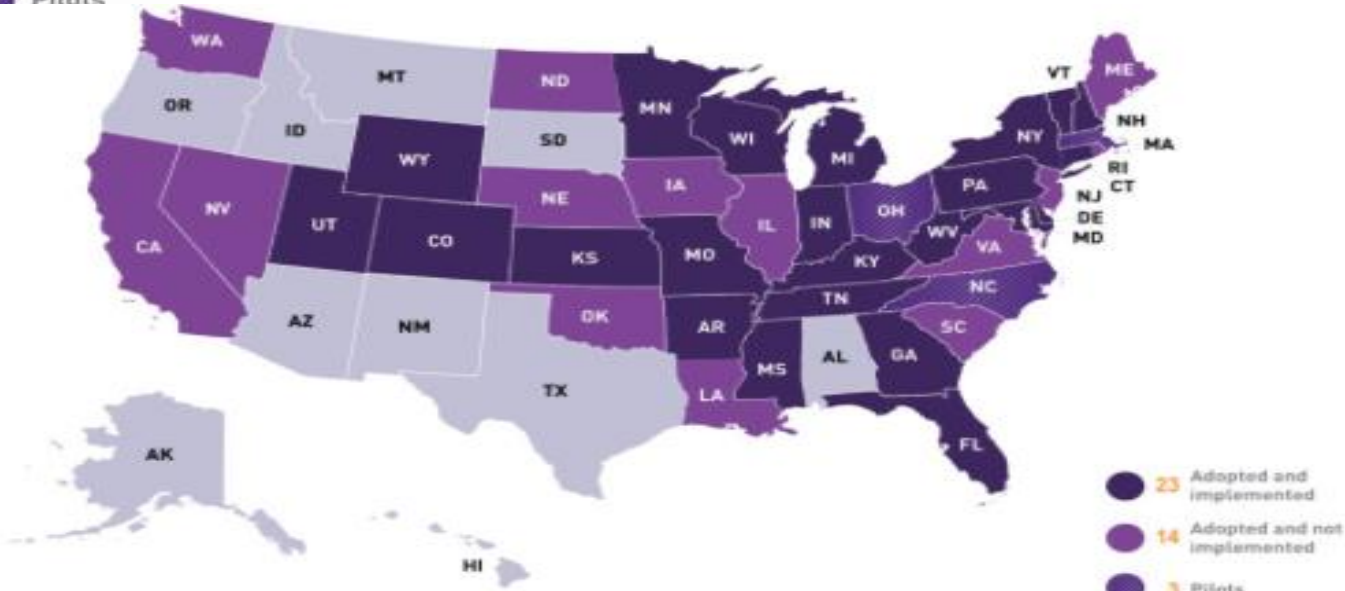
[https://www.curesma.org/wp-content/uploads/2021/06/NBS\\_Maps\\_Screening-and-Non-Screening\\_States\\_CKD\\_v6-28-2021.pdf](https://www.curesma.org/wp-content/uploads/2021/06/NBS_Maps_Screening-and-Non-Screening_States_CKD_v6-28-2021.pdf)



# Newborn screening in US

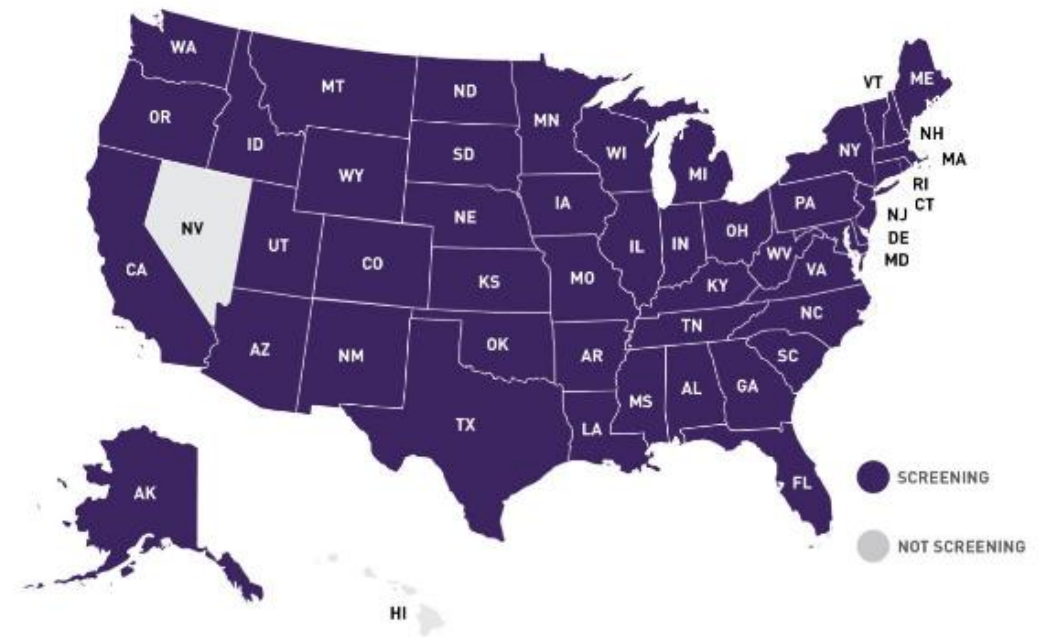


Cure SMA. 2019 advocacy 101.

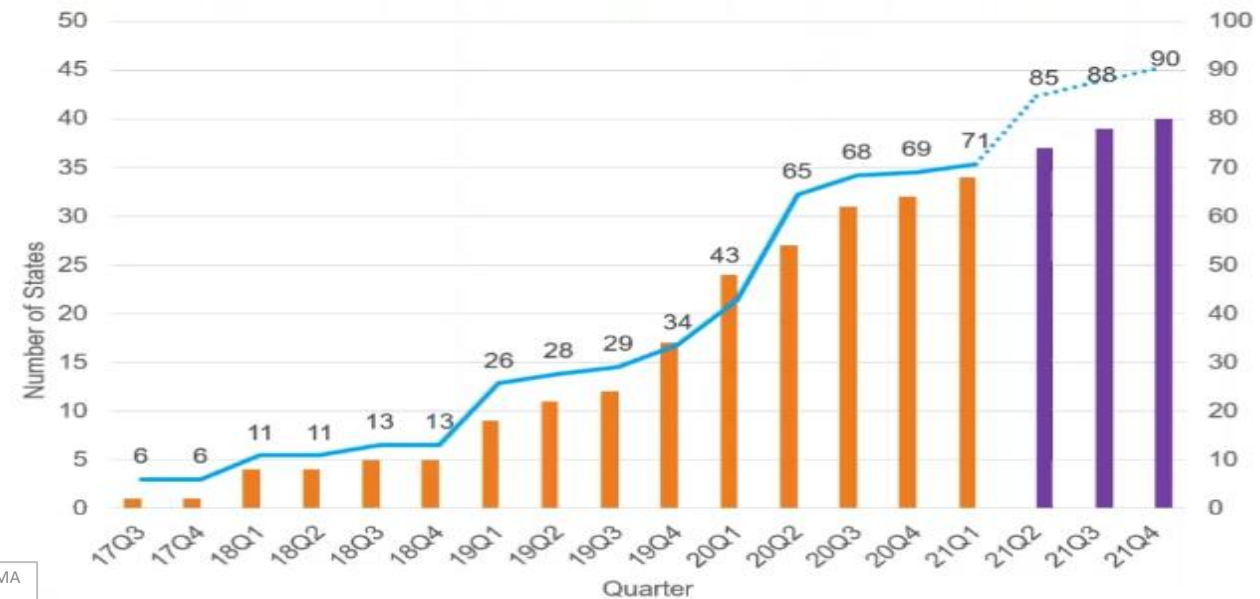


# Big changes in SMA

- Big changes
  - Untreatable  
(以前是不能治療的)
  - Delayed diagnosis  
(以前常常是延誤診斷的)
- Now since 2017
  - 3 medication approved by FDA
  - >50% received treatment
  - >80% screened/ diagnosed at birth.

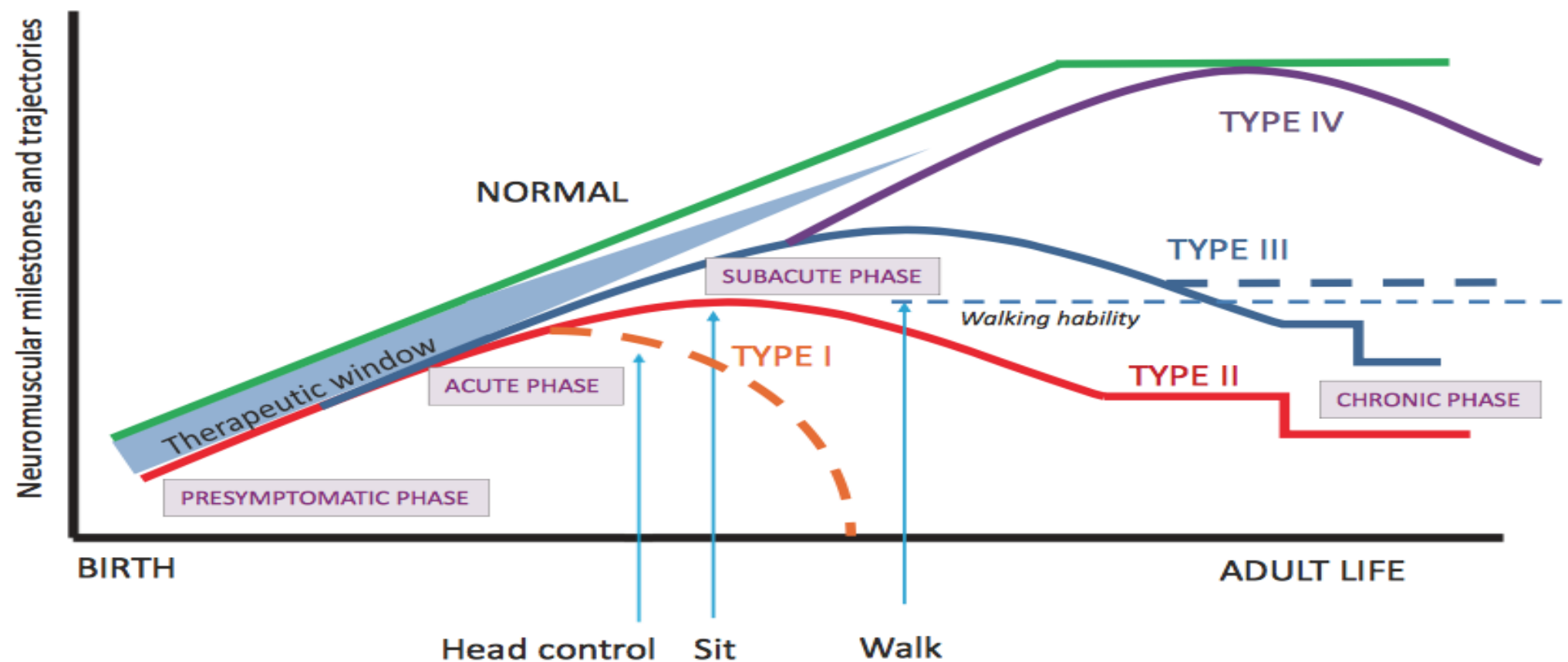


## NBS for SMA – Time to Treat



In Taiwan, nusinersen is approved for the patients who are diagnosed with genetic confirmation as SMA and have 2 or 3 copies of SMN 2 gene, or type I, II, III of SMA patients with symptom onset. Not indicated for permanent ventilated patients. Onasemnogene abeparvovec-xioi is approved for the patients who are diagnosed with genetic confirmation as SMA less than 6 months of age and have 2 or 3 copies of SMN 2 gene, or type I patients with symptom onset. Not indicated for permanent ventilated patients. Risdiplam is not approved in Taiwan.

- When is the best timing for treatment ???



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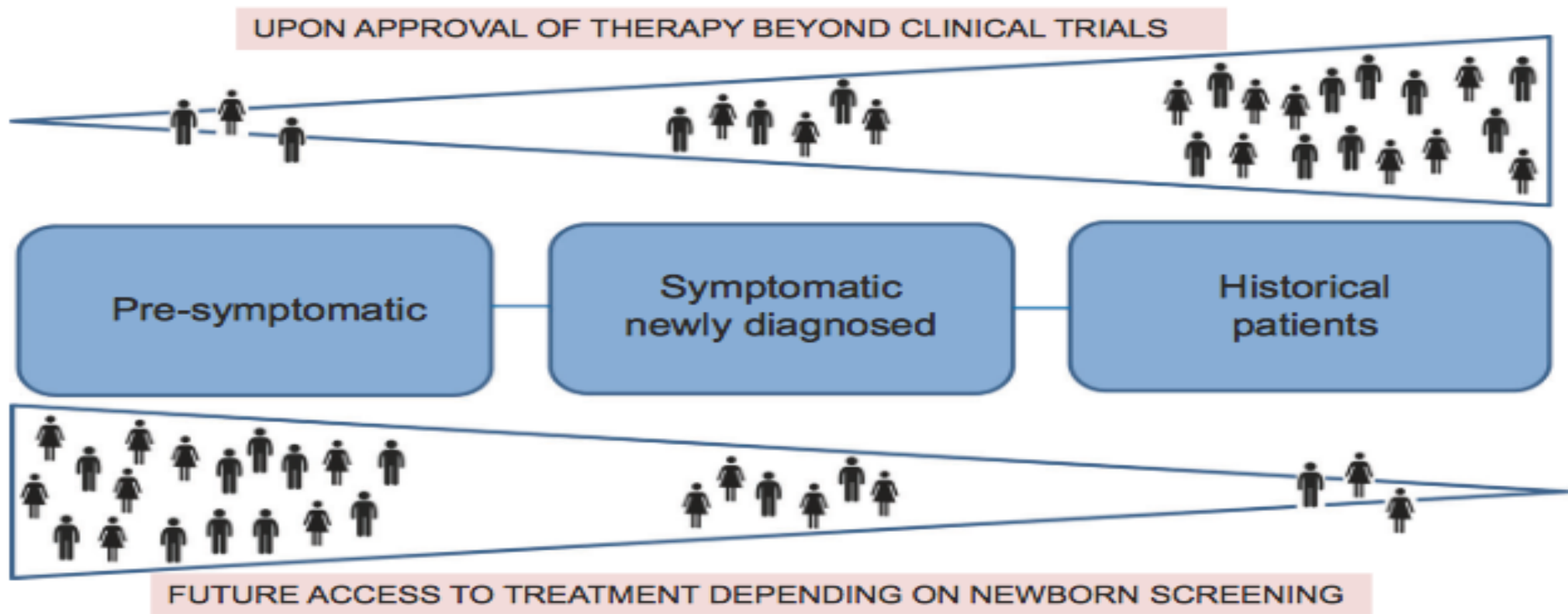
- Clara Serra-Juhe, Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors; *Eur. J. Hum. Genet.* 2019. 27:1774–1782



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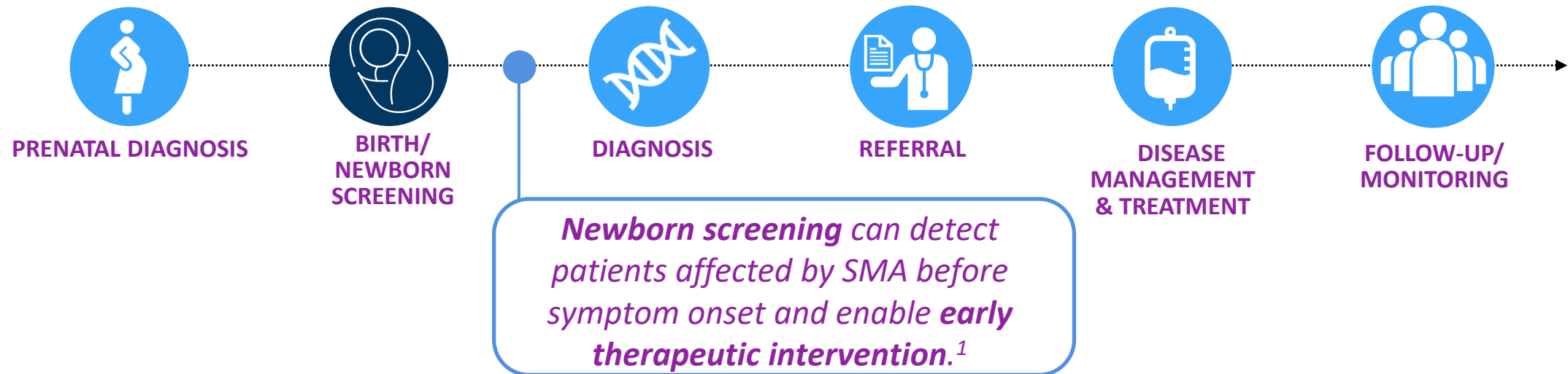
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■ When is the best timing for treatment ???



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Newborn screening identifies at-risk infants who can potentially be spared the consequences of severe, debilitating weakness.



Spinal muscular atrophy is a neurological emergency.<sup>2</sup>

NBS, newborn screening; SMA, spinal muscular atrophy.

1. Chien YH, et al. *J Pediatr.* 2017;190:124–129.e1;
2. Strauss KA, Farrar MA, Muntoni F, et al. *Nat Med.* 2022;1-8.



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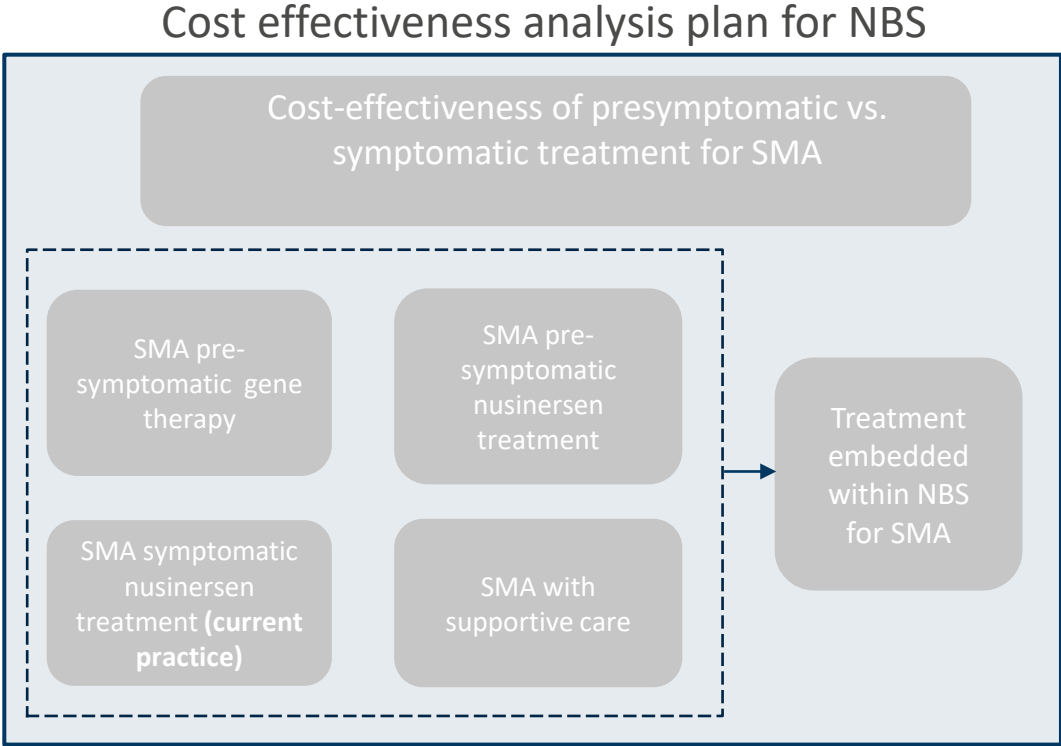
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# Cost Effectiveness Analysis



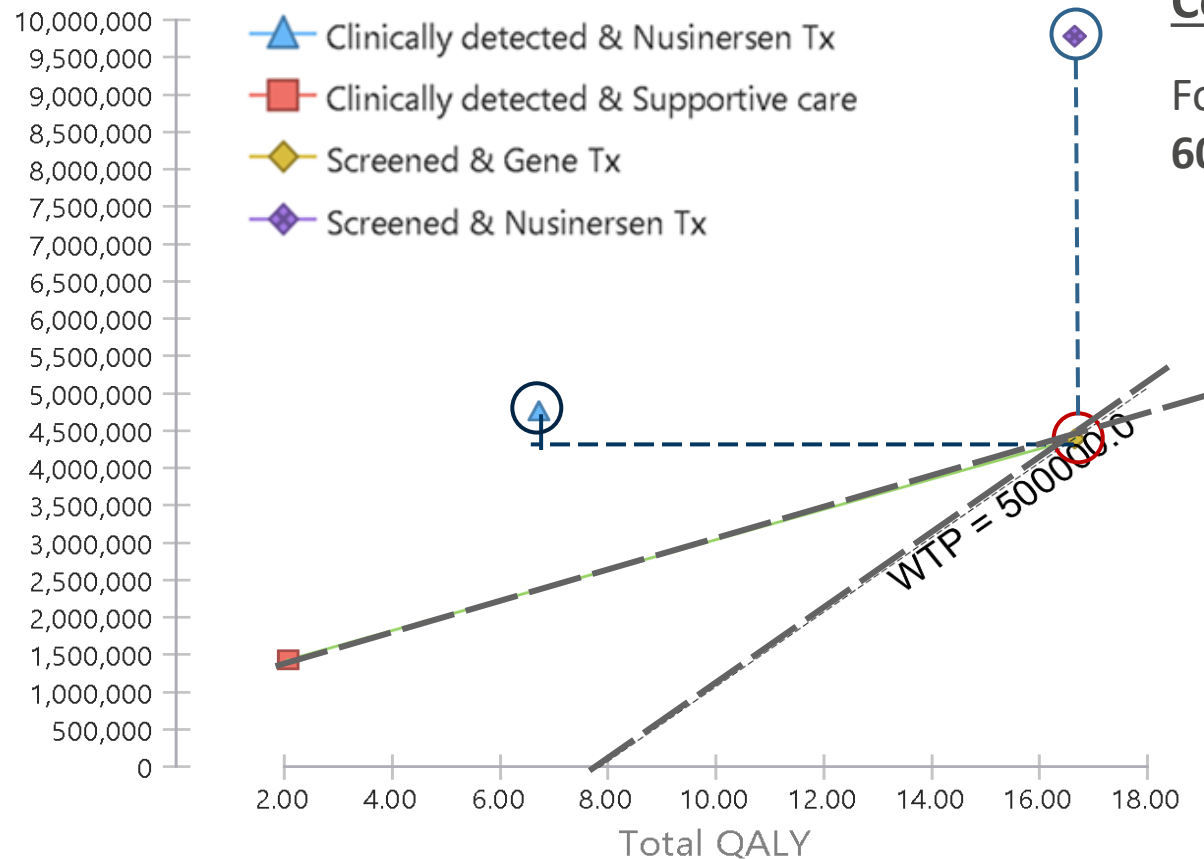
	<b>Perspective</b>	Societal
	<b>Time horizon</b>	5 & 60 years
	<b>Analytical approach</b>	Decision analysis with Markov simulation
	<b>Modelling assumption</b>	Treatment effect sustained over 60 years
	<b>\$ Tx Cost (2018 value)</b>	Nusinersen USD \$75,810 / dose Gene Therapy USD \$1.54 million / dose
	<b>Outcome measure</b>	Quality-adjusted life years (QALYs): - Per infant diagnosed with the condition - Per newborn screened in the population



Shih STF, et al. J Neurol Neurosurg Psychiatry 2021;92:1296–1304.



# Early identification of SMA through **NBS** and treatment with **gene therapy** is cost-effective compared to current practice in Australia.



## Cost-effectiveness plane for four spinal muscular atrophy

Four treatment strategies by Markov cohort simulation over **60 years** from the societal perspective, discounted 3% per annum.

1. **NBS with gene Tx** is **less costly but more effective** than clinically detected with nusinersen Tx
2. **NBS with gene Tx** is **equally effective but significantly less costly** than NBS with nusinersen
3. Changing from clinically detected with supportive care to **NBS with gene Tx** is **cost effective** than the willingness-to-pay

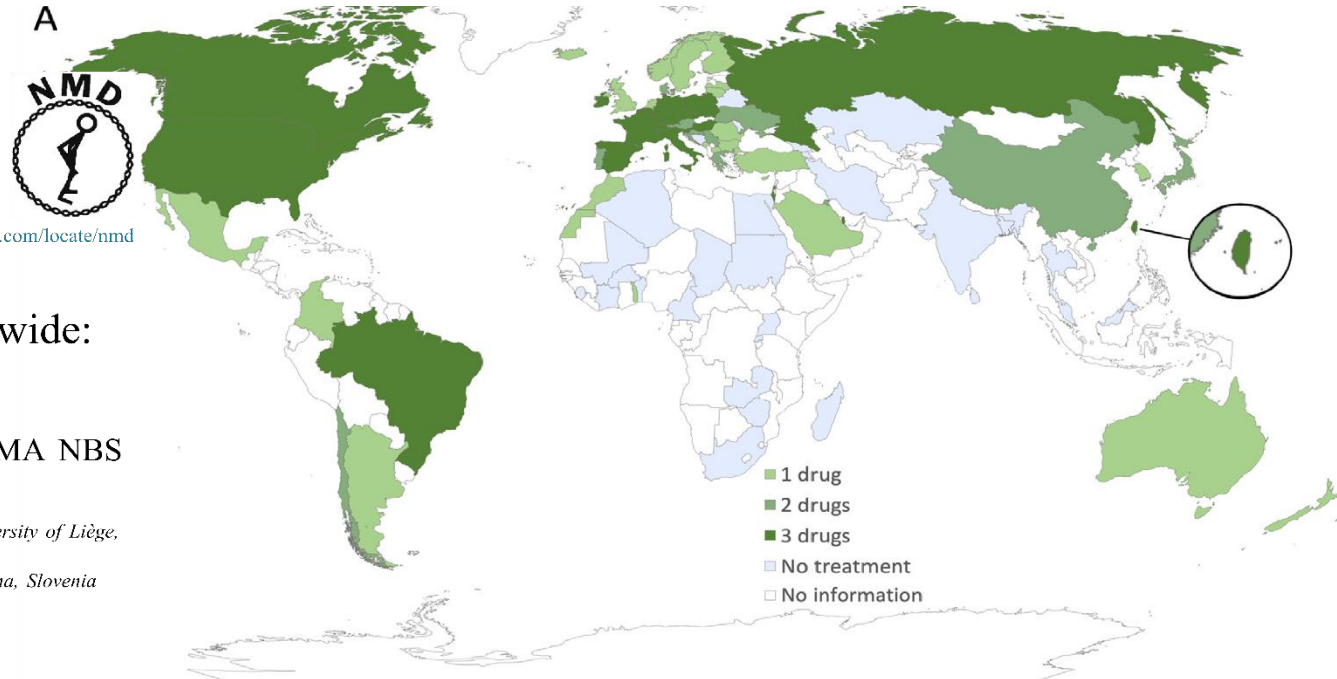
QALY, quality-adjusted; life-year; WTP, willingness to pay: \*The Institute for Clinical and Economic Review adapts a modified approach for 'potential major advance for a serious ultra-rare condition' and recommends a broader willingness-to-pay thresholds from \$50 000 to \$500 000 per QALY  
Shih STF, et al. J Neurol Neurosurg Psychiatry 2021;92:1296–1304.



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## Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go

Tamara Dangouloff<sup>a,1</sup>, Eva Vrščaj<sup>b,1</sup>, Laurent Servais<sup>a,c,\*</sup>, Damjan Osredkar<sup>b,d,\*</sup>, the SMA NBS  
World Study Group<sup>#</sup>

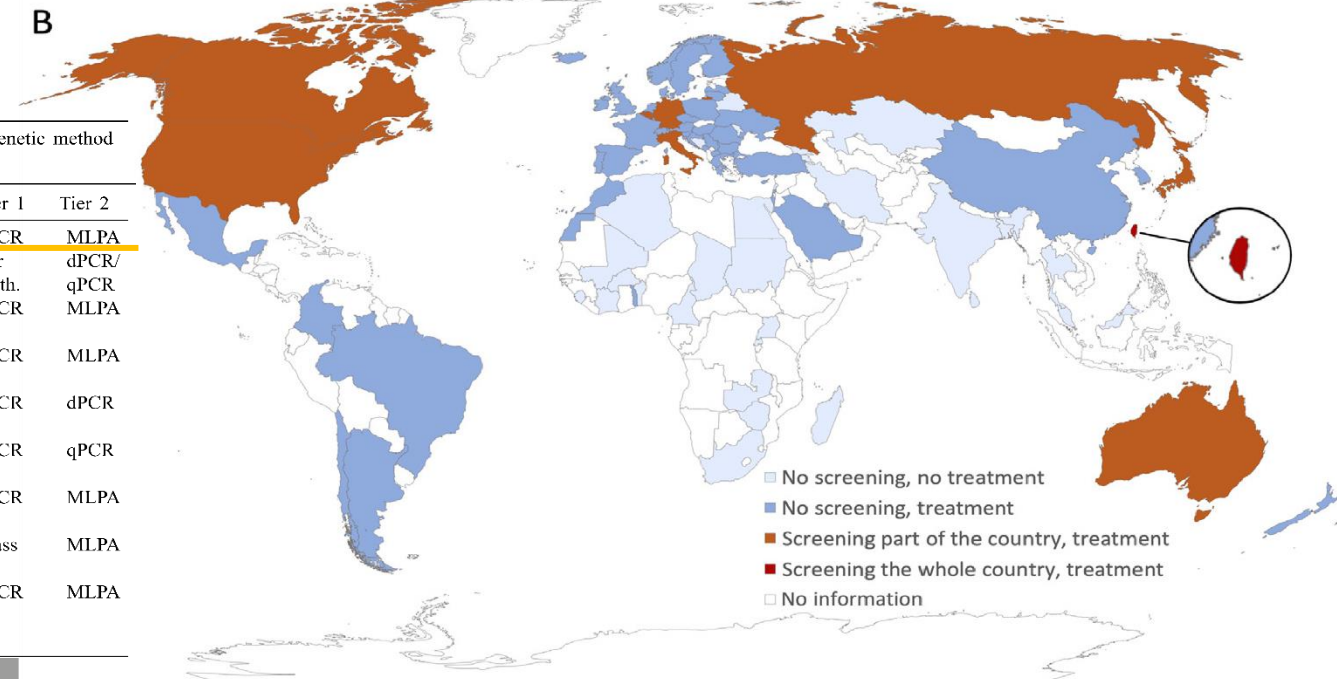
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<sup>b</sup>Department of Pediatric Neurology, University Children's Hospital, University Medical Centre Ljubljana, Bohoričeva 20, 1525 Ljubljana, Slovenia

<sup>c</sup>MDUK Neuromuscular Centre, Department of Paediatrics, University of Oxford, United Kingdom

<sup>d</sup>Medical Faculty, University of Ljubljana, Slovenia

Received 14 February 2021; received in revised form 10 March 2021; accepted 16 March 2021

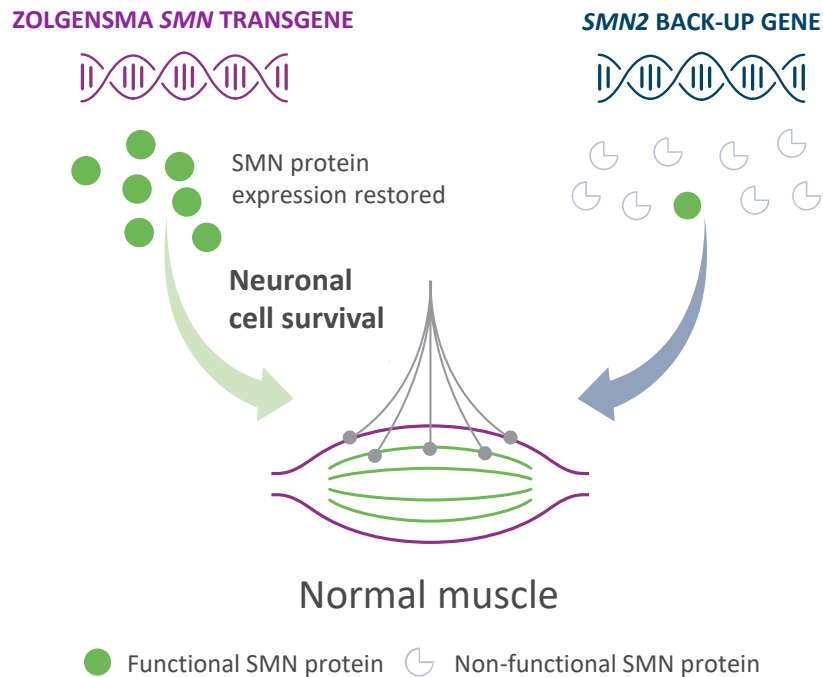


Country (W/P)	NB/y	% NB Screened	Year NBS SMA implemented		Cases	NB screened	False Pos	False neg	Cons Proc	Fund	Site test	Genetic method	
			Pilot	Official								Tier 1	Tier 2
Taiwan (W)	170,000	81–90%	11/14	01/18	20	419,102	8	1	Opt-in	H/P	Us NBS	qPCR	MLPA
USA (P)	3,745,540	61–70%	01/16	07/18	180	2,395,718	10	0	Opt-out	G	Us NBS	Var meth. qPCR	dPCR/MLPA
Germany (P)	780,000 (305,000)	11–20% (87%)	01/18	<1y	43	297,163	0	0	Opt-in	HI	Us NBS	qPCR	MLPA
Belgium (P)	120,000 (55,000)	45% (99%)	03/18	03/21	9	127,329	0	0	Opt-out	Ph/G/Gr	1 Us NBS	qPCR	MLPA
Australia (P)	300,000 (100,000)	21–40% (99%)	08/18	>2y	19	202,388	1	0	Opt-out	Gr/G	1 Us NBS	qPCR	dPCR
Italy (P)	435,000 (68,000)	11–20% (86%)	09/19	NA	12	58,558	0	0	Opt-in	Ph	1 gen lab	qPCR	qPCR
Russia (P)	1,373,550 (15,000)	< 10% (80%)	08/19	3y	0	12,000	0	0	Opt-in	Ph	1 gen lab	qPCR	MLPA
Canada (P)	377,000 (140,000)	31–40% (99%)	01/20	06/20	5	139,810	0	0	Opt-out	G/Ph	1 Us NBS	Mass	MLPA
Japan (P)	864,000 (1 district)	< 10%	05/20	3 y	0	22,209	0	0	Opt-in	Ph/P	1 gen lab	qPCR	MLPA
<b>All</b>	<b>8,100,090</b>	<b>3,081,839</b>			<b>288</b>	<b>3,674,277</b>	<b>19</b>	<b>0</b>					



# ZOLGENSMA is a single-dose IV gene therapy designed to address the genetic root cause of SMA<sup>1,2</sup>

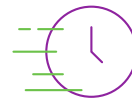
## ZOLGENSMA mode of action<sup>1,2</sup>



## ZOLGENSMA is designed:



To address the genetic root cause of SMA by replacing the deleted or mutated gene with a fully functional copy of the human *SMN1* gene<sup>1</sup>



With self-complementary DNA and a continuous promoter, to rapidly and continuously deliver functional SMN protein required to prevent neuronal cell death<sup>2</sup>

ZOLGENSMA is a gene therapy that delivers a copy of the human *SMN1* gene via AAV9 in a single IV dose<sup>1,2</sup>

# ZOLGENSMA is a one-time-only dose<sup>1</sup>



## How ZOLGENSMA is supplied<sup>1</sup>

ZOLGENSMA is a suspension for IV infusion

ZOLGENSMA is provided as a kit, customized to meet dosing requirements for patients weighing 2.6 kg to 21.0 kg\*

Each kit contains:

- Two to nine vials of ZOLGENSMA
- One alcohol wipe per vial

## Handling ZOLGENSMA<sup>1</sup>

- Must be used within 14 days of receipt.  
Upon receipt, thaw in the refrigerator for approximately 12 hours or at room temperature for approximately 4 hours
- ZOLGENSMA should not be refrozen after thawing
- Once dose is drawn into the syringe, use within 8 hours. Discard if not infused within 8 hours

## Dosing and infusing<sup>1</sup>

- Using a programmable syringe pump, administer ZOLGENSMA as a slow infusion over 60 minutes

\*Number of vials per kit and required number of kits is weight-dependent.

IV, intravenous.

1. EMA (2020). ZOLGENSMA (onasemnogene abeparvovec) SmPC. Available at: [https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf). Last accessed: March 2021..



# ZOLGENSMA: Dosing



Patient Weight Range (kg)	Dose Volume* (mL)
2.6–3.0	16.5
3.1–3.5	19.3
3.6–4.0	22.0
4.1–4.5	24.8
4.6–5.0	27.5
5.1–5.5	30.3
5.6–6.0	33.0
6.1–6.5	35.8
6.6–7.0	38.5
7.1–7.5	41.3
7.6–8.0	44.0

Patient Weight Range (kg)	Dose Volume* (mL)
8.1–8.5	46.8
8.6–9.0	49.5
9.1–9.5	52.3
9.6–10.0	55.0
10.1–10.5	57.8
10.6–11.0	60.5
11.1–11.5	63.3
11.6–12.0	66.0
12.1–12.5	68.8
12.6–13.0	71.5
13.1–13.5†	74.3

Patient Weight Range (kg)‡	Dose Volume* (mL)
13.6–14.0	77.0
14.1–14.5	79.8
14.6–15.0	82.5
15.1–15.5	85.3
15.6–16.0	88.0
16.1–16.5	90.8
16.6–17.0	93.5
17.1–17.5	96.3
17.6–18.0	99.0

\*Dose volume is calculated using the upper limit of the patient weight range for pediatric patients <2 years of age between 2.6 kg and 18.0 kg;<sup>1</sup> The GMAP treatment plan permits dosing for patients up to 18 kg;<sup>1</sup> †Dose volume for pediatric patients <2 years of age weighing ≥13.6 kg will require a combination of onasemnogene abeparvovec kits.<sup>1</sup> ‡Dose volume for patients ≥13.6 kg applies only to the EU label and to EAR, which follows the EU label.<sup>2</sup>

1. Novartis Gene Therapies, Data on file. Treatment Plan for MAP for AVXS-101-MAP-002 (v.5.0). July 6, 2020; 2. Zolgensma (onasemnogene abeparvovec) Summary of Product Characteristics. Available at: [https://www.ema.europa.eu/documents/product-information/zolgensma-epar-product-information\\_en.pdf](https://www.ema.europa.eu/documents/product-information/zolgensma-epar-product-information_en.pdf). Accessed on June 4, 2021.



# Anti-AAV9 antibody titers should be measured prior to treatment



## Test for anti-AAV9 antibodies prior to treatment with ZOLGENSMA

- Perform baseline testing for the presence of anti-AAV9 antibodies prior to ZOLGENSMA infusion
- In the clinical studies, confirmation of anti-AAV9 antibody titers  $\leq 1:50$  was required prior to infusion
- The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated
- Retesting may be performed if anti-AAV9 antibody titers are reported as positive or elevated

**Novartis Gene Therapies is offering the Novartis Gene Therapies Laboratory Testing Program to facilitate efficient anti-AAV9 antibody testing and reimbursement**

AAV9, adeno-associated virus serotype 9.  
FDA (2019). ZOLGENSMA (onasemnogene abeparvovec) PI. Available at:  
<https://www.fda.gov/media/126109/download>. Last accessed: March 2021.



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# Post-treatment management and follow-up<sup>1</sup>

**Treat with systemic corticosteroids (equivalent to 1 mg/kg/day oral prednisolone) before and after infusion<sup>1</sup>**

<b>Corticosteroid dose day:<sup>1</sup></b>	Day 1	Day 2	Day 30 and beyond
<b>Action:<sup>1</sup></b>	24 hours prior to ZOLGENSMA infusion, initiate 30-day corticosteroid regimen equivalent to prednisolone at 1 mg/kg/day	Infuse ZOLGENSMA  Continue the corticosteroid regimen	After 30 days, if AST and ALT are <2x the ULN, and liver function appears normal, taper the corticosteroid dose over 28 days*
			If AST and ALT are >2x the ULN, and liver abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2x the ULN and all other assessments return to normal range, and then taper the corticosteroid dose over the next 28 days*
			Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone*

**Assess patient liver function, platelet count and troponin-I at baseline and for at least 3 months following infusion. Continue monitoring until results are unremarkable**

\*Check liver status clinically and by assessing ALT, AST, total bilirubin and prothrombin time.

ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

1. FDA (2019). ZOLGENSMA (onasemnogene abeparvovec) PI. Available at:

<https://www.fda.gov/media/126109/download>. Last accessed: March 2021.



Assess liver function,\* platelet count and troponin-I at baseline and for at least 3 months following ZOLGENSMA infusion

Test	Baseline	Time from infusion											
		Month 1				Month 2				Month 3			
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Liver function	X	X	X	X	X		X		X		X		X
Platelet count	X	X	X	X	X		X		X		X		X
Troponin-I	X	X	X	X	X				X				X

Continue monitoring until liver function results are unremarkable<sup>†</sup> and platelet counts and troponin-I results return to baseline

\*Liver function to be assessed by clinical exam, AST, ALT, total bilirubin and prothrombin time; <sup>†</sup>Unremarkable liver function results include normal clinical exam, total bilirubin and prothrombin results, and ALT and AST are below 2x ULN. ULN, upper limit of normal; W, week.  
FDA (2019). ZOLGENSMA (onasemnogene abeparvovec) PI. Available at: <https://www.fda.gov/media/126109/download>. Last accessed: March 2021.

[Insert PI and box warning]



**Assess liver function,\* platelet count and troponin-I at baseline and for at least 3 months following infusion**

**Time from infusion**

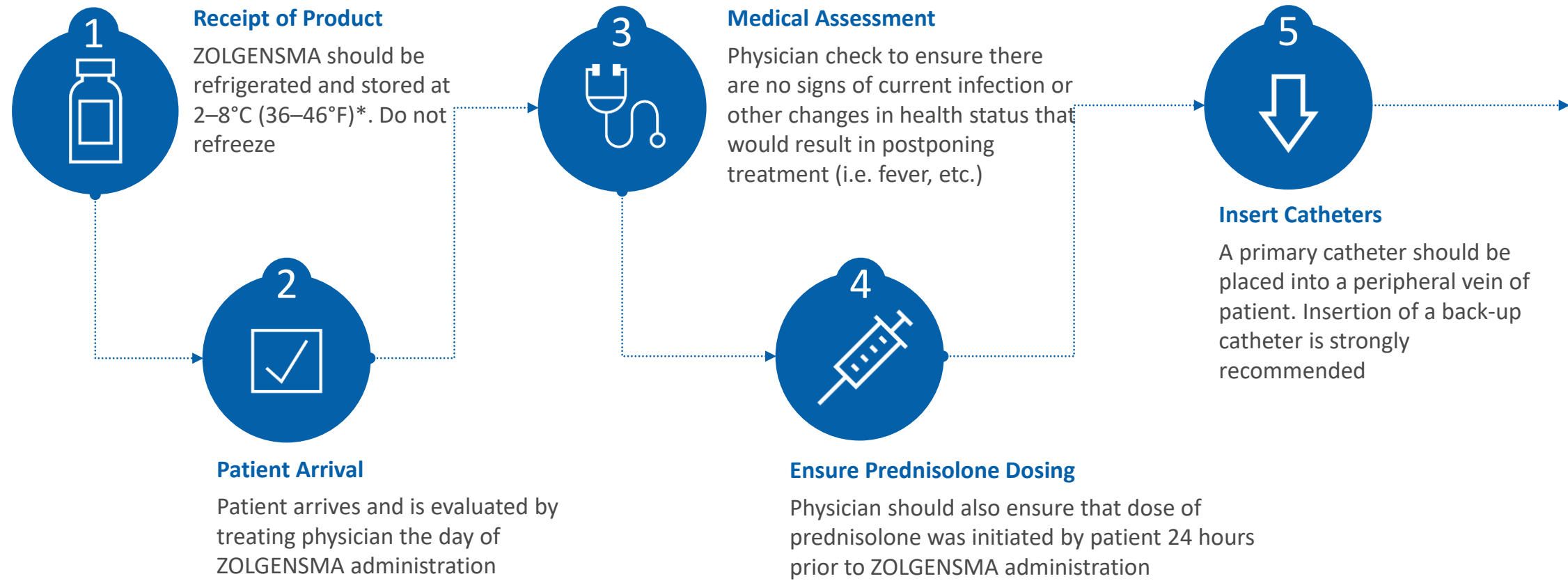
Test	Baseline	Month 1					Month 2				Month 3		
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Liver function	X	X	X	X	X		X		X		X		X
Platelet count	X	X	X	X	X		X		X		X		X
Troponin-I	X	X	X	X	X				X				X

**Continue monitoring until liver function results are unremarkable<sup>†</sup>  
and platelet counts and troponin-I results return to baseline**

\*Liver function to be assessed by clinical exam, AST, ALT, total bilirubin and prothrombin time; <sup>†</sup>Unremarkable liver function results include normal clinical exam, total bilirubin and prothrombin results, and ALT and AST are below 2x ULN. ULN, upper limit of normal; W, week.  
63 FDA (2019). [www.fda.gov/media/126109/download](https://www.fda.gov/media/126109/download) MA (onasemnogene abeparvovec) PI. Available at: <https://>. Last accessed: March 2021.



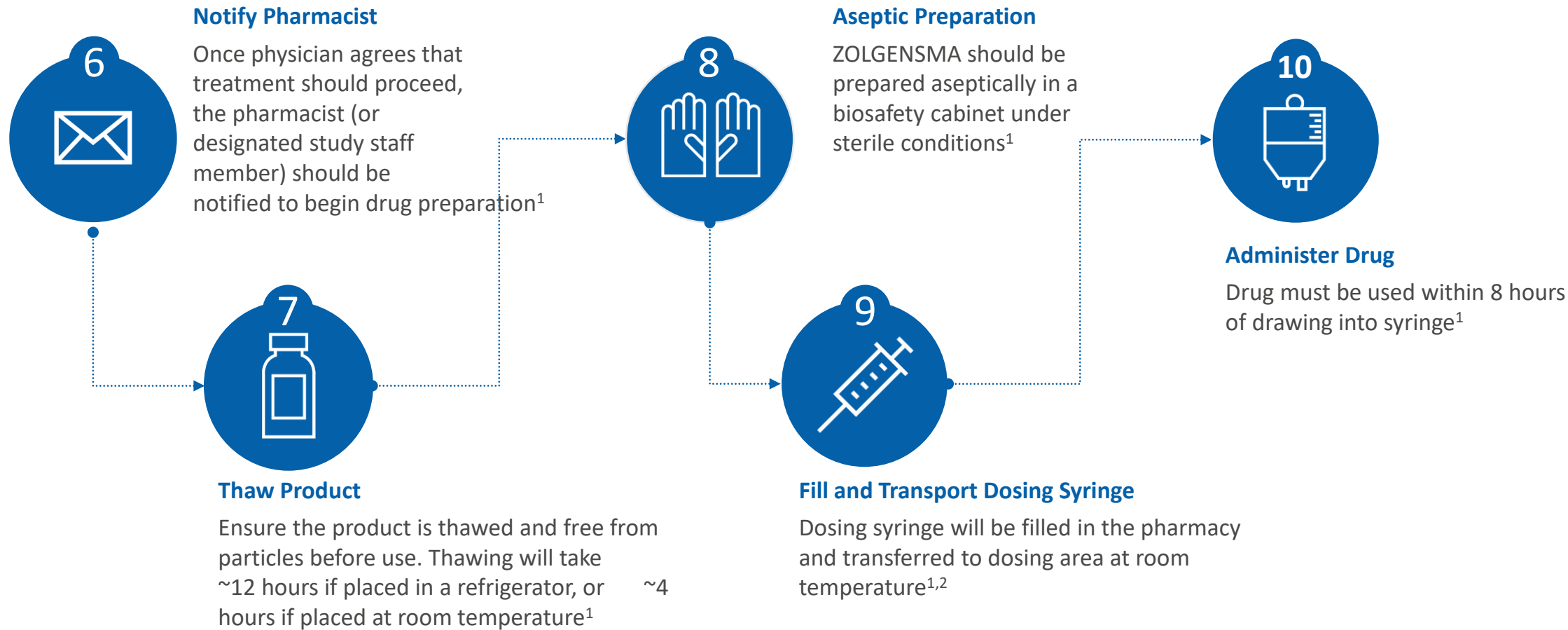
# Infusion day: Key steps (1/2)



\*Or at room temperature if used within 4 hours.  
Novartis Gene Therapies, Data on file. Treatment Plan for MAP for AVXS-101-MAP-002 (v.5.0). July 6, 2020.



# Infusion day: Key steps (1/2)



1. Novartis Gene Therapies, Data on file. Treatment Plan for MAP for AVXS-101-MAP-002 (v.5.0). July 6, 2020; 2. Pharmacy Manual AVXS-101-MAP-002 (v.1.0). January 29, 2020.



# ZOLGENSMA dosing and administration: Summary



- ZOLGENSMA has a nominal concentration of  $2.0 \times 10^{13}$  vg/mL
- ZOLGENSMA is packaged as a sterile suspension and contains no preservative
- Upon receipt at the pharmacy, ZOLGENSMA should **be refrigerated at 2–8°C (36–46°F). Do not refreeze.** ZOLGENSMA must be **used within 14 days of placement in refrigerated 2–8°C (36–46°F) storage**
- Use ZOLGENSMA **within 8 hours of drawing into syringe**

vg, vector genomes.

Novartis Gene Therapies, Data on file. Treatment Plan for MAP for AVXS-101-MAP-002 (v.5.0). July 6, 2020.



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## Key Takeaways:

# Gene therapy can correct the underlying genetic defect One-time-only ZOLGENSMA halts the progression of SMA



Designed for continuous and sustained SMN protein expression<sup>1,2</sup>



Addresses the genetic root cause of SMA by delivering a fully functional copy of the *SMN* gene<sup>3</sup>



One-time-only IV infusion that is administered over 60 minutes<sup>3</sup>



ZOLGENSMA was efficacious and well-tolerated in pre-symptomatic SMA patients with 2 or 3 copies of SMN2<sup>5</sup>



Resulted in achievement of motor milestones and rapid and sustained motor function improvements from baseline<sup>2,4</sup>



Established safety profile demonstrated in three open-label clinical trials and one observational long-term follow-up study<sup>3</sup>

IV, intravenous; SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. Mendell JR, et al. *N Engl J Med*. 2017;377(18):1713-1722; 2. Novartis Gene Therapies. Data on file (2020); 3. FDA (2019). ZOLGENSMA (onasemnogene abeparvovec) PI. Available at: <https://www.fda.gov/media/126109/download>. Last accessed: March 2021; 4. Day JW, et al. *Lancet Neurol*. 2021;In press. 5. Strauss KA, et al. Abstract presented at: MDA Clinical and Scientific Congress. March 13–16, 2022



# Thank you for your attention.

## Acknowledge

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關於中心

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