

# L'amyotrophie spinale : Histoire d'une maladie mortelle et incurable qui, dans 102 heures, va peu à peu disparaître...

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# Conflits d'intérêt

Investigateur coordonnateur des essais

Endear, Cheerich Shine (Biogen)

Sunfish, et Firefish (Roche)

Nathis SMA (Co-financement par Roche)

AVXS 101 (Avaxis)

AVXS 304 (Avaxis)

Registre français des patients traités

Membre du SAB de Biogen et Avaxis et SMA Europe, consultance auprès de Biogen

# Un phénotype très large...

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# Standard de soin !!!

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Wang et al, *J Child Neurology* 2007  
Mercuri et al, *Neuromuscular Disorder* 2018

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- Respiratoire

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# Standard de soin !!!

- Respiratoire
- Orthopédique
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- Nutrition

Wang et al, *J Child Neurology* 2007

Mercuri et al, *Neuromuscular Disorder* 2018

# Standard de soin !!!

- Respiratoire
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- Vaccination

Wang et al, *J Child Neurology* 2007

Mercuri et al, *Neuromuscular Disorder* 2018

# Standard de soin !!!

- Respiratoire
- Orthopédique
- MPR
- Nutrition
- Vaccination
- Santé osseuse....

Wang et al, *J Child Neurology* 2007

Mercuri et al, *Neuromuscular Disorder* 2018













**Avec une amyotrophie spinale, tout est plus lent,  
tout est plus fatigant, tout est plus compliqué...  
Aller à l'université, aller en vacances, trouver et  
garder un emploi, avoir une petite amie...**



**Avec une amyotrophie spinale, tout est plus lent,  
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Aller à l'université, aller en vacances, trouver et  
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**Mais tout  
est  
possible**



**Avec une amyotrophie spinale, tout est plus lent,  
tout est plus fatigant, tout est plus compliqué...  
Aller à l'université, aller en vacances, trouver et  
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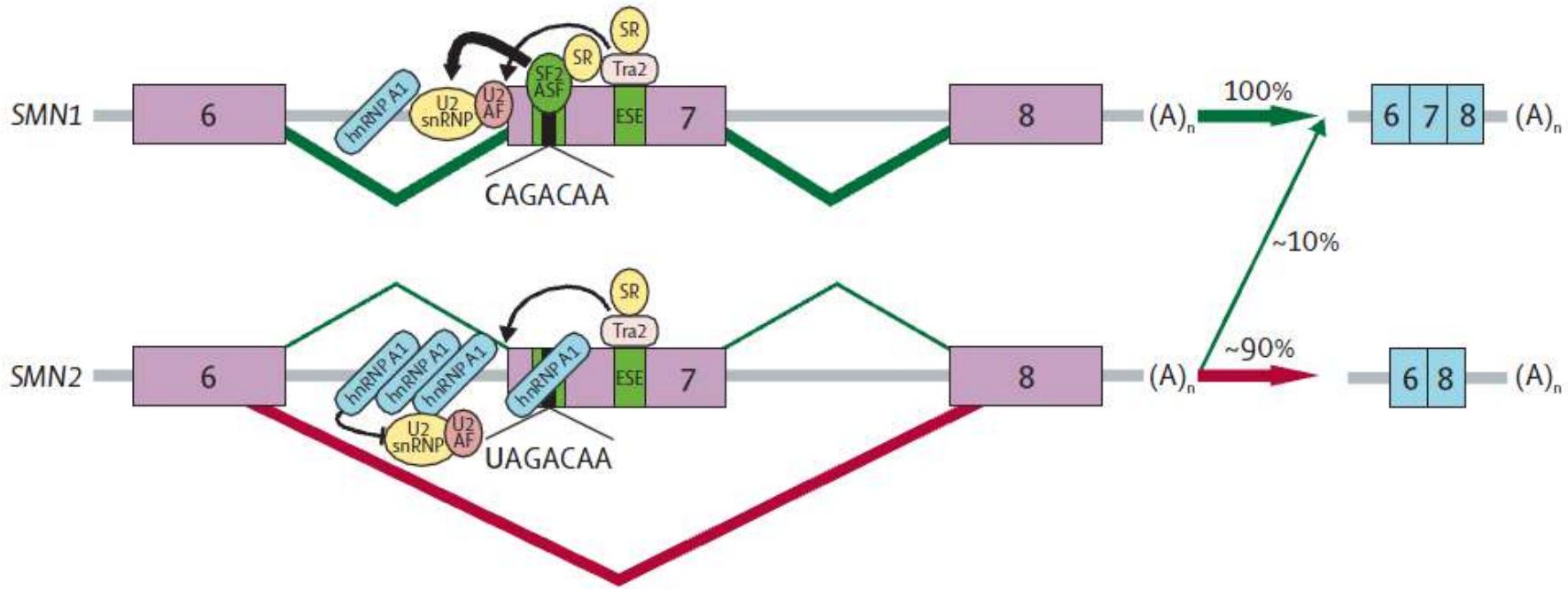


“ Gustaw : 4 mois



”

# SMN gene

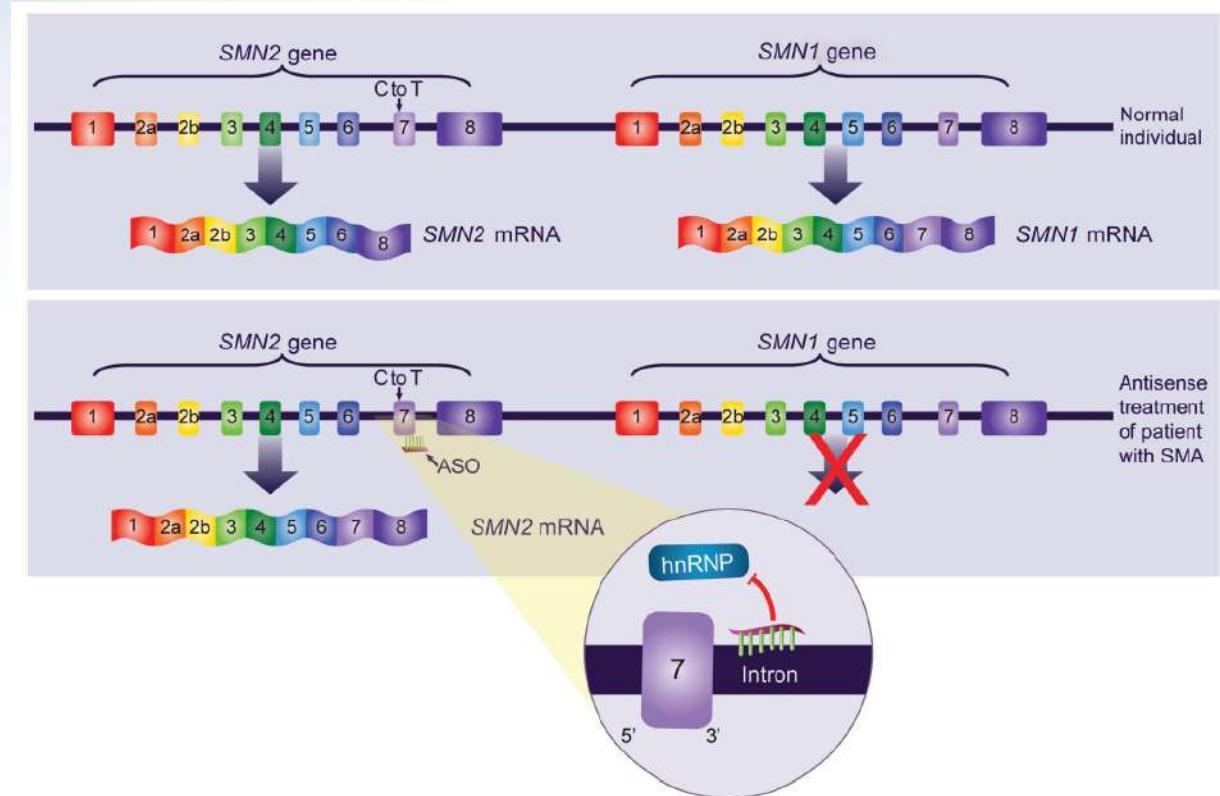


**Figure 3: Pre-mRNA splicing of SMN1 and SMN2**

In SMN1, an exonic splicing enhancer (ESE), which contains the nucleotide cytosine (C) at position six in exon seven (Ex7+6), is recognised by splicing factor 2 or alternative splicing factor (SF2/ASF), which interacts (thick black arrow) with the U2 class of small nuclear ribonuclear protein (U2 snRNP) to remove intron six. Other splicing factors (eg, Tra2) determine splicing through interactions (thin black arrow) with ESE elements found centrally within exon seven. Serine and arginine (SR)-rich proteins might also exert a positive splicing effect. In SMN2, the ribonucleotide uridine (transcribed from thymidine) at Ex7+6 favours exon seven exclusion by binding to heterogeneous nuclear ribonuclear protein (hnRNP) A1, a negative splicing factor. Moreover, SF2/ASF no longer recognises this sequence motif. Binding of hnRNP A1 is also believed to prohibit U2 snRNP binding to the branch point, which results in about 90% of SMN2 final mRNA transcripts with no exon seven. The positive splicing factors downstream (thin black arrow) are functioning and could account for exon seven inclusion in about 10% of SMN2 transcripts.

# Mechanism of IONIS drug

Humans have a second copy of the gene (*SMN2*) which is nearly identical to *SMN1* but, due to mis-splicing of its pre-mRNA, results in very low levels of functional SMN protein



MOE-modified nucleotides confer (1) increased affinity to the target mRNA (McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities associated with ASO containing only the phosphorothioate linkages (Henry et al. 2000)

	 AVXS-101	 SPINRAZA® (nusinersen)	 branaplam	 RG7916 	 SMA olesoxime	 CK-2127107
Mechanism	Increases SMN			SMN Independent		
Strategy	SMN Gene Replacement	SMN2 Splicing Modifier			Neuroprotectant	Muscle Activator
Drug Type	Gene Therapy	ASO	Small Molecule			
Delivery Method	IV	Intrathecal	Oral			
Dosing	One Time	4 Loading Doses Then Once Every 4 Months	Once Weekly	Once Daily		Twice Daily
Body Distribution	Systemic	CNS Only	Systemic			
Current Target Population	Type I	Approved All Types	Type I	Type I-III	Type II-III	Type II-IV

	 AVXS-101	 SPINRAZA® (nusinersen)	 branaplam	 RG7916 	 olesoxime	 CK-2127107
Mechanism				Increases SMN		SMN Independent
Strategy	SMN Gene Replacement			SMN2 Splicing Modifier	Neuroprotectant	Muscle Activator
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	 AVXS-101	 SPINRAZA® (nusinersen)	 branaplam	 SMA RG7916	 olesoxime	 CK-2127107
Mechanism				Increases SMN		SMN Independent
Strategy	SMN Gene Replacement			SMN12 Splicing Modifier	Neuroprotectant	Muscle Activator
Drug Type	Gene Therapy	ASO		Small Molecule		
Delivery Method	IV	Intrathecal		Oral		
Dosing	One Time	4 Loading Doses Then Once Every 4 Months	Once Weekly	Once Daily	Twice Daily	
Body Distribution	Systemic	CNS Only		Systemic		
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	 AVXS-101	 SPINRAZA® (nusinersen)	 branaplam	 RG7916	 SMA Foundation	 PTC THERAPEUTICS	 CK-2127107		
Mechanism			Increases SMN		SMN Independent				
Strategy	SMN Gene Replacement	SMN2 Splicing Modifier		Neuroprotectant		Muscle Activator			
Drug Type	Gene Therapy	ASO	Small Molecule						
Delivery Method	IV	Intrathecal	Oral						
Dosing	One Time	4 Loading Doses Then Once Every 4 Months	Once Weekly	Once Daily		Twice Daily			
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Mechanism		Increase SMN			SMN Independent	
Strategy	SMN Gene Replacement		SMN 2 Splicing Modifier		Neuroprotectant	Muscle Activator
Drug Type	Gene Therapy	ASO		Small Molecule		
Delivery Method	IV	Intrathecal		Coral		
Dosing	One Time	4 Loading Doses Then Once Every 4 Months	Once Weekly		Once Daily	Twice Daily
Body Distribution	Systemic	CNS Only		Systemic		
Current Target Population	Type I	Approved All Types	Type I	Type I-III	Type II-III	Type II-IV

# 2 novembre 2017

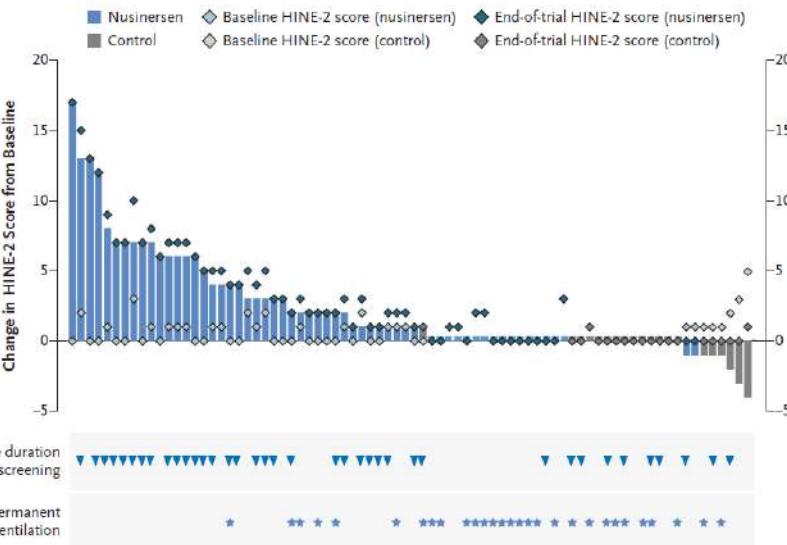
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

## Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group\*

### ABSTRACT



## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

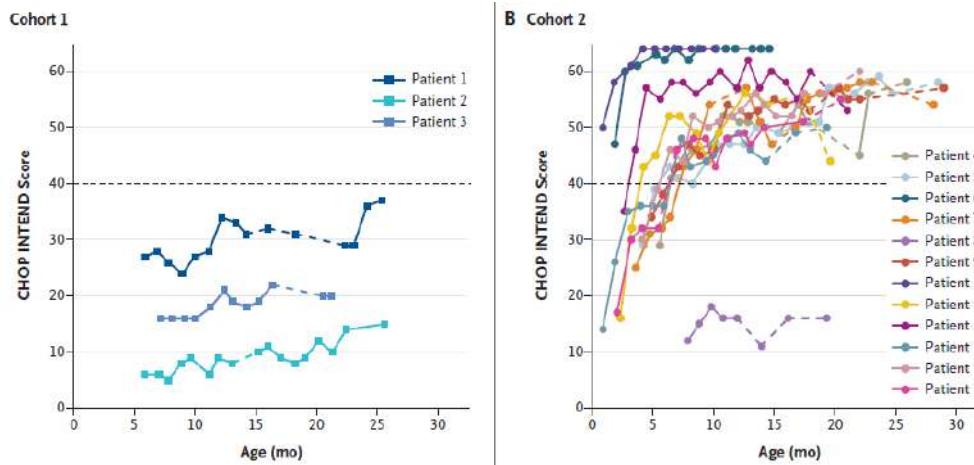
NOVEMBER 2, 2017

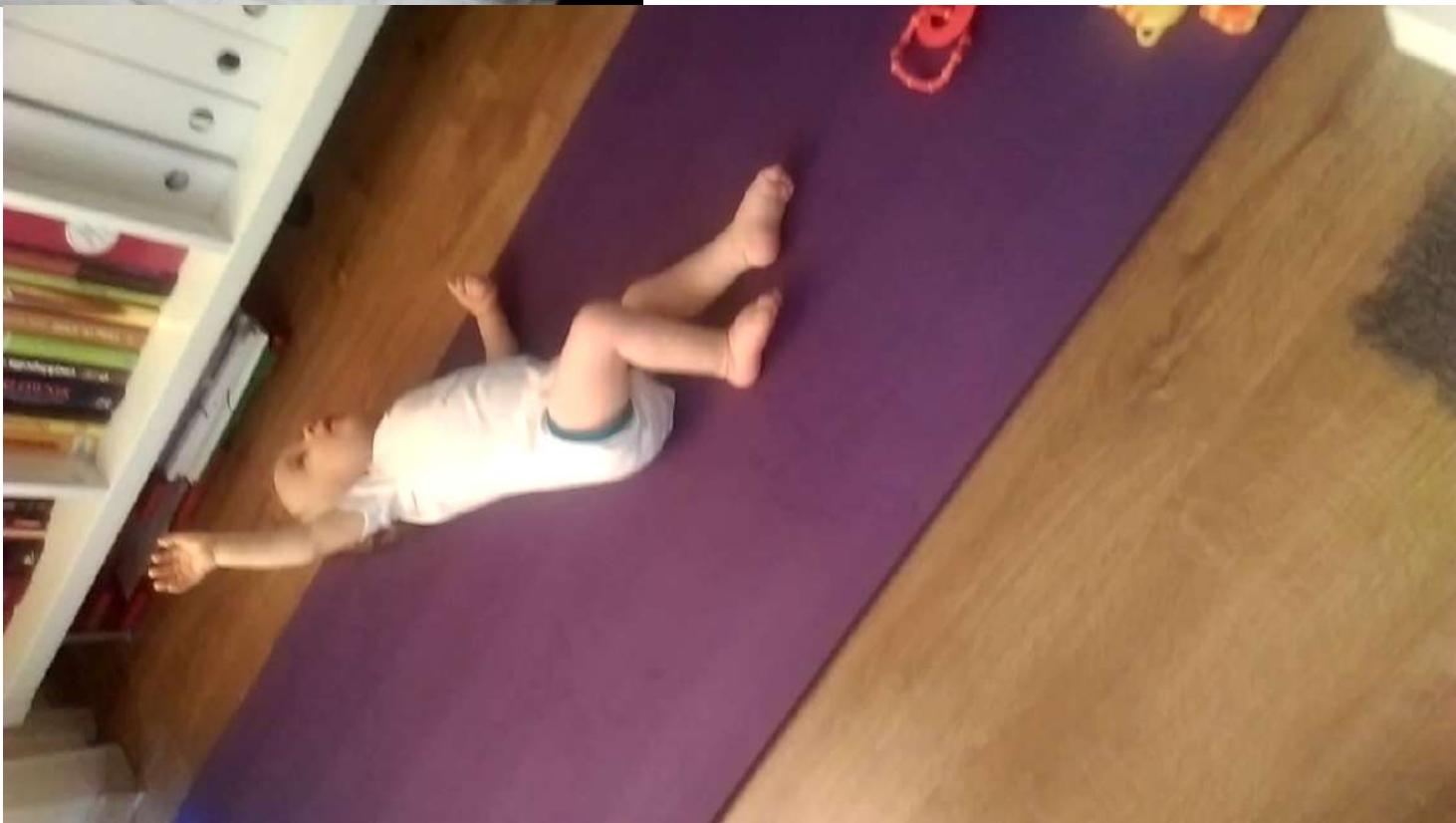
VOL. 377 NO. 18

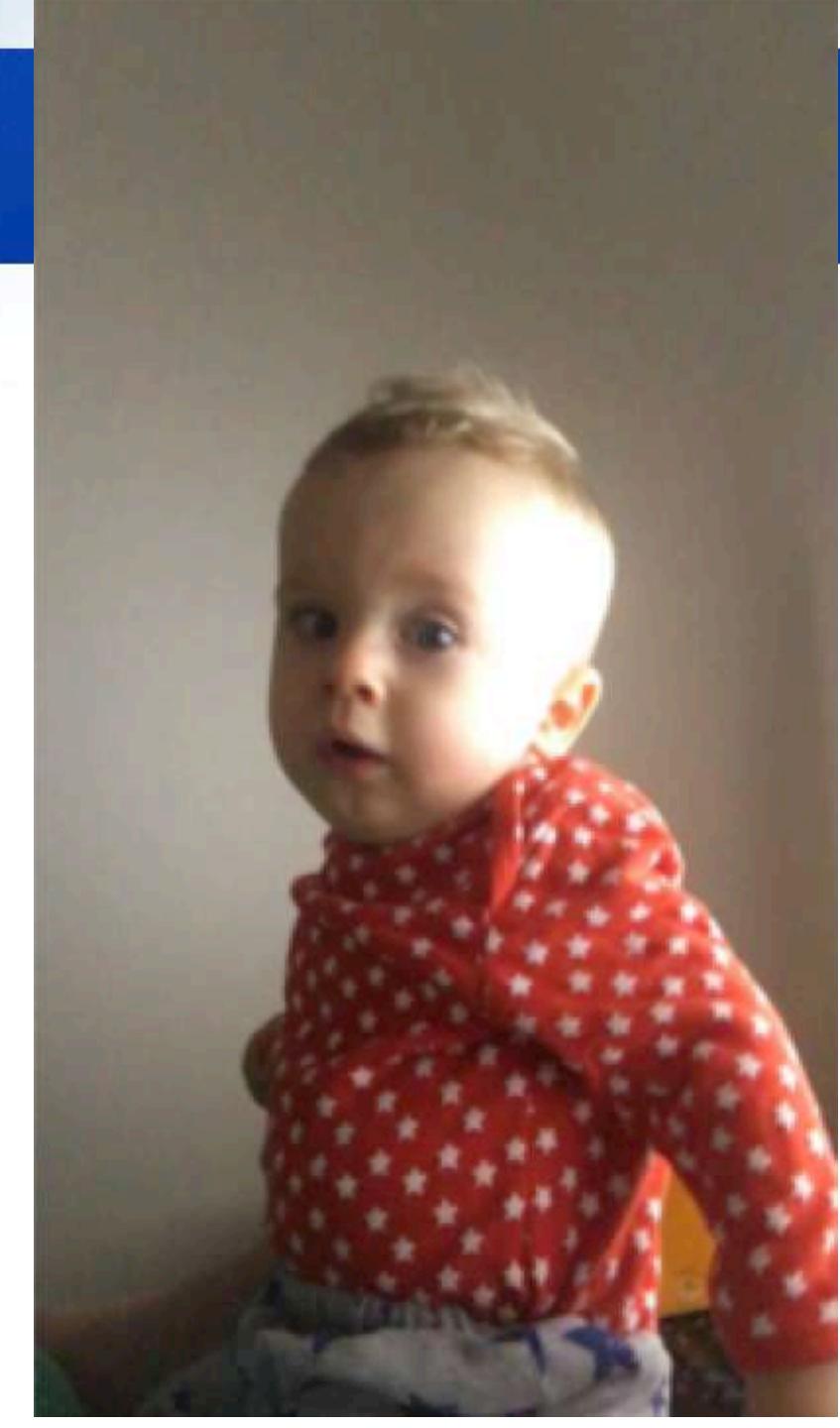
## Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

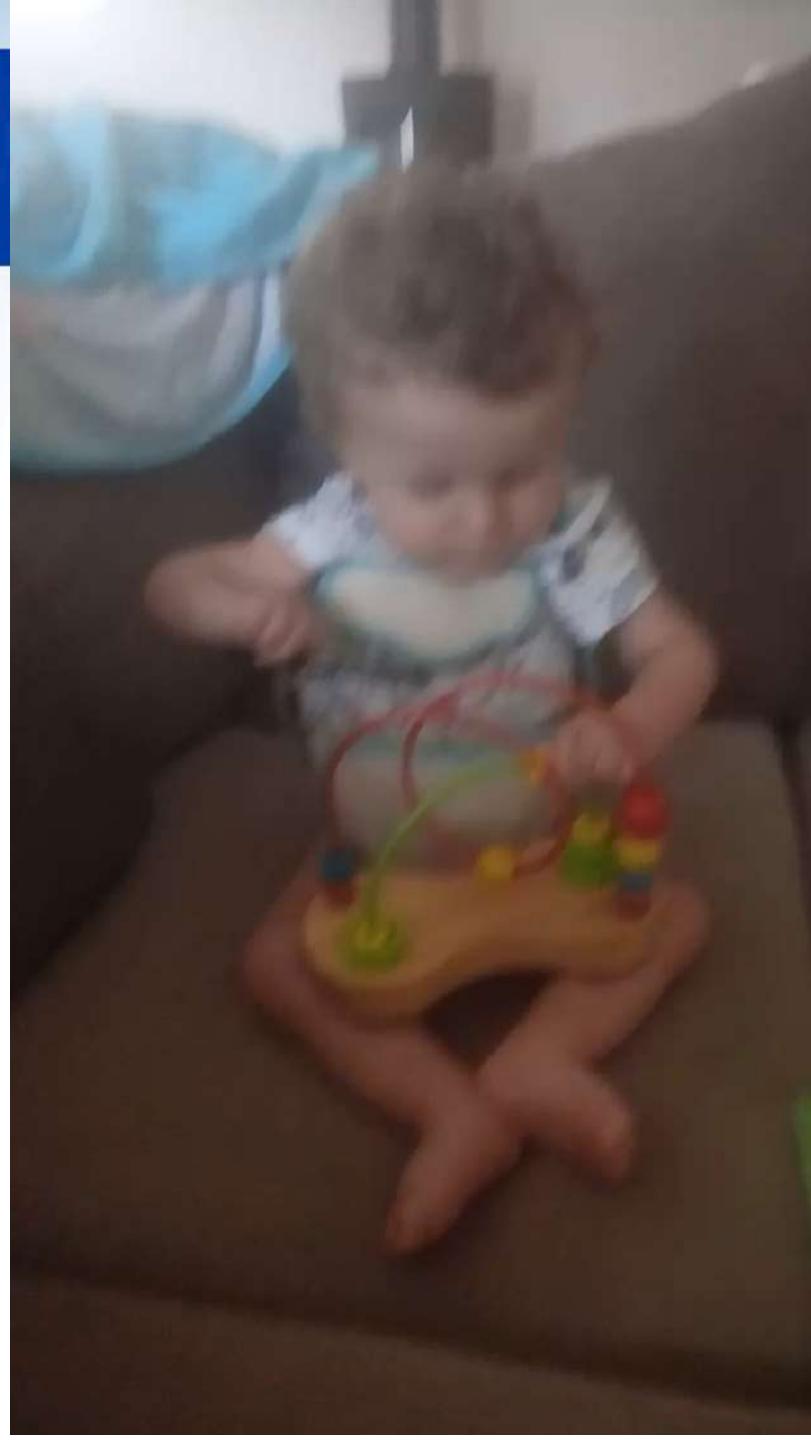
J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

### ABSTRACT









# Et plus tard....



*Cela fait un an et deux mois qu'on n'a pas été hospitalisé pour une infection respiratoire*

*Ca fait deux mois qu'on aspire XX seulement matin et soir, pendant les soins respi "d'hygiène", pour le reste de la journée il n'a pas besoin d'être aspiré*

*XX a commencé à déglutir assez bien, il prend pour le déjeuner et pour le soir jusqu'à 70-100 ml de soupe ou purée (au mieux). Cela fait un mois qu'il mange sans tousser ou faire des fausses routes, même si les quantités qu'il prend sont limitées et fluctuantes. Les choses se sont amélioré très très nettement sur le plan respiratoire, et un peu de progrès soutenu sur le plan de la déglutition également.*

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SMA1

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SMA2

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SMA1

CS3b : 8 patients (3 survivors) +  
1 patient (Shine)

EAP 76 patients

SMA2

”

“

SMA1

CS3b : 8 patients (3 survivors) +  
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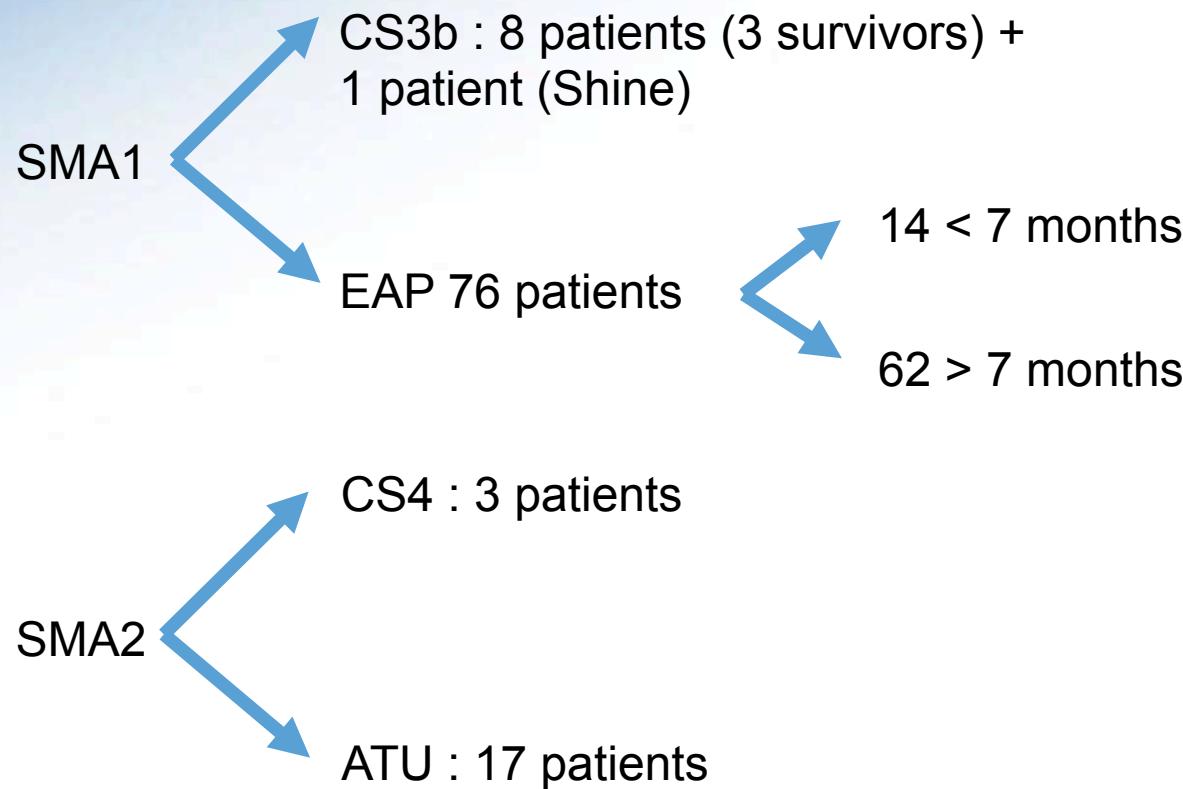
14 < 7 months

62 > 7 months

SMA2

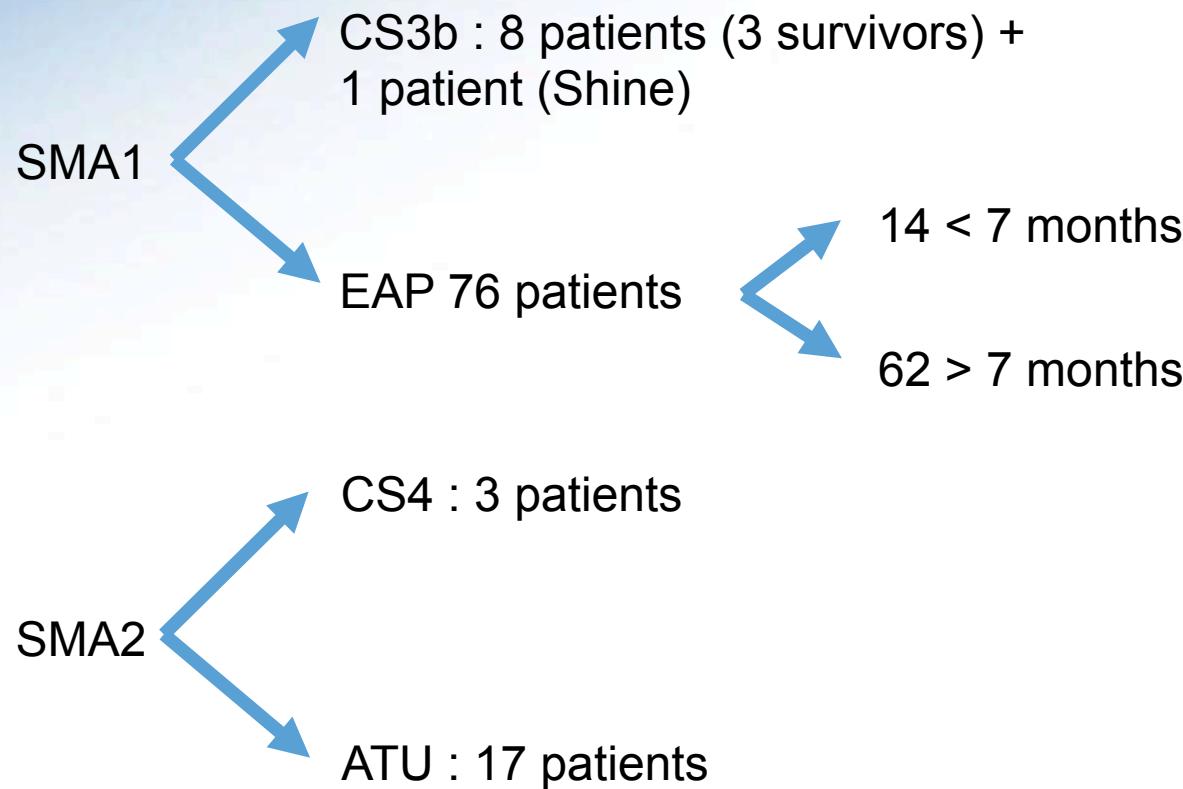
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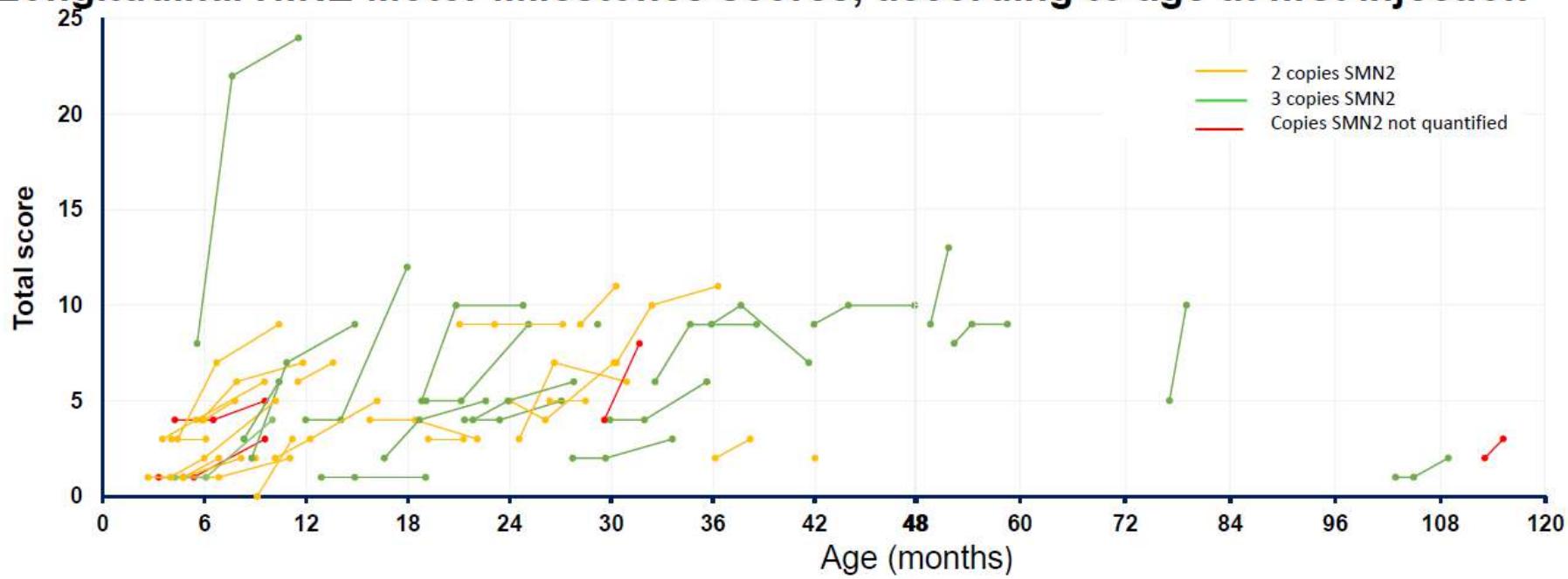


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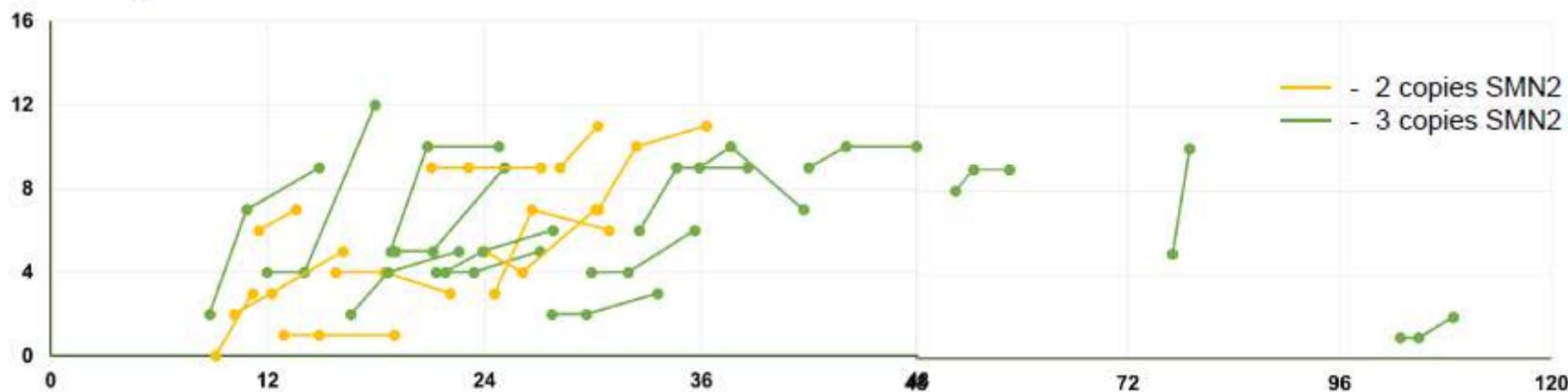
Grand Total : 104 patients

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## Longitudinal HINE Motor Milestones scores, according to age at first injection



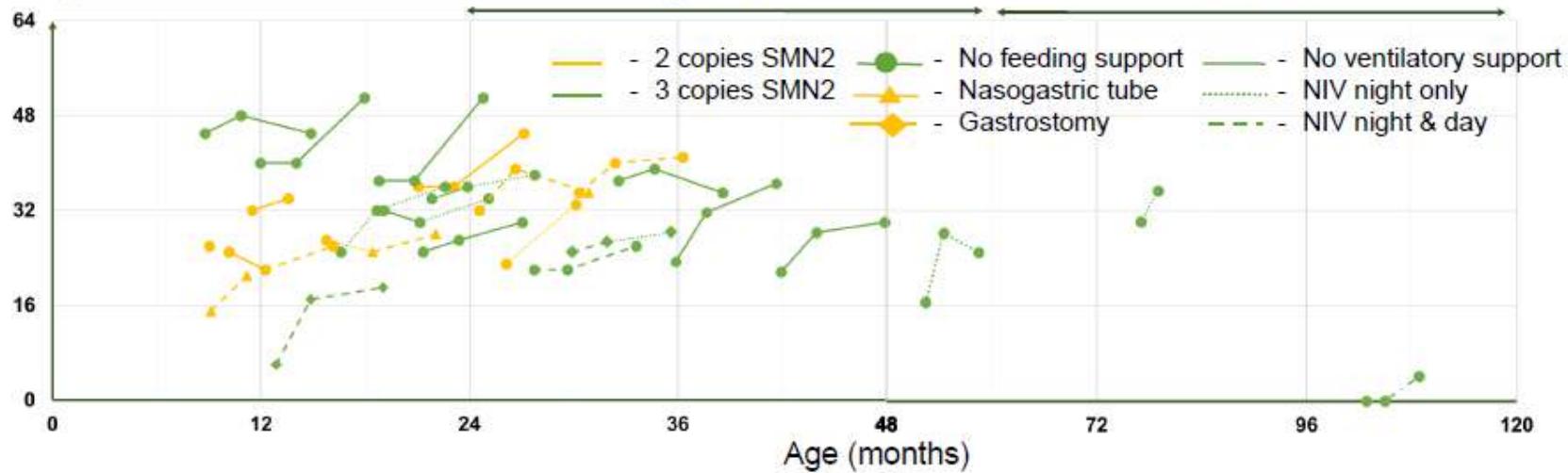
## Longitudinal HINE Motor Milestones scores



CHOP Intend

MFM 20

MFM 32





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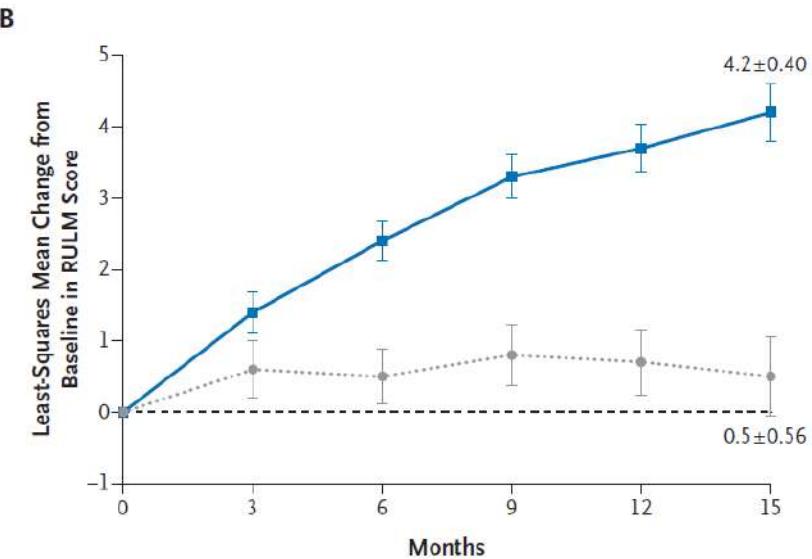
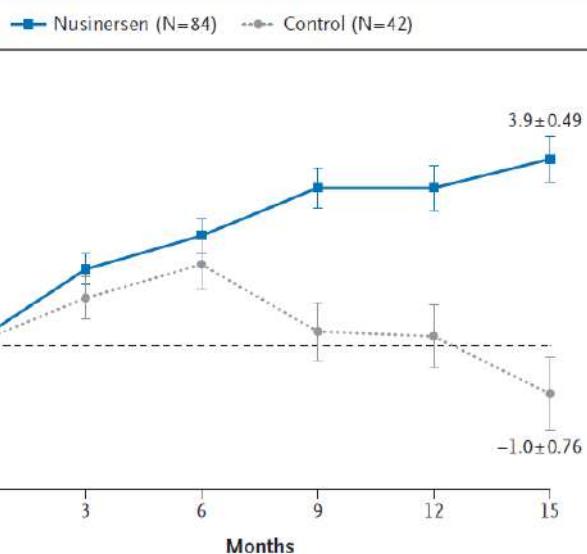
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ORIGINAL ARTICLE

## Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

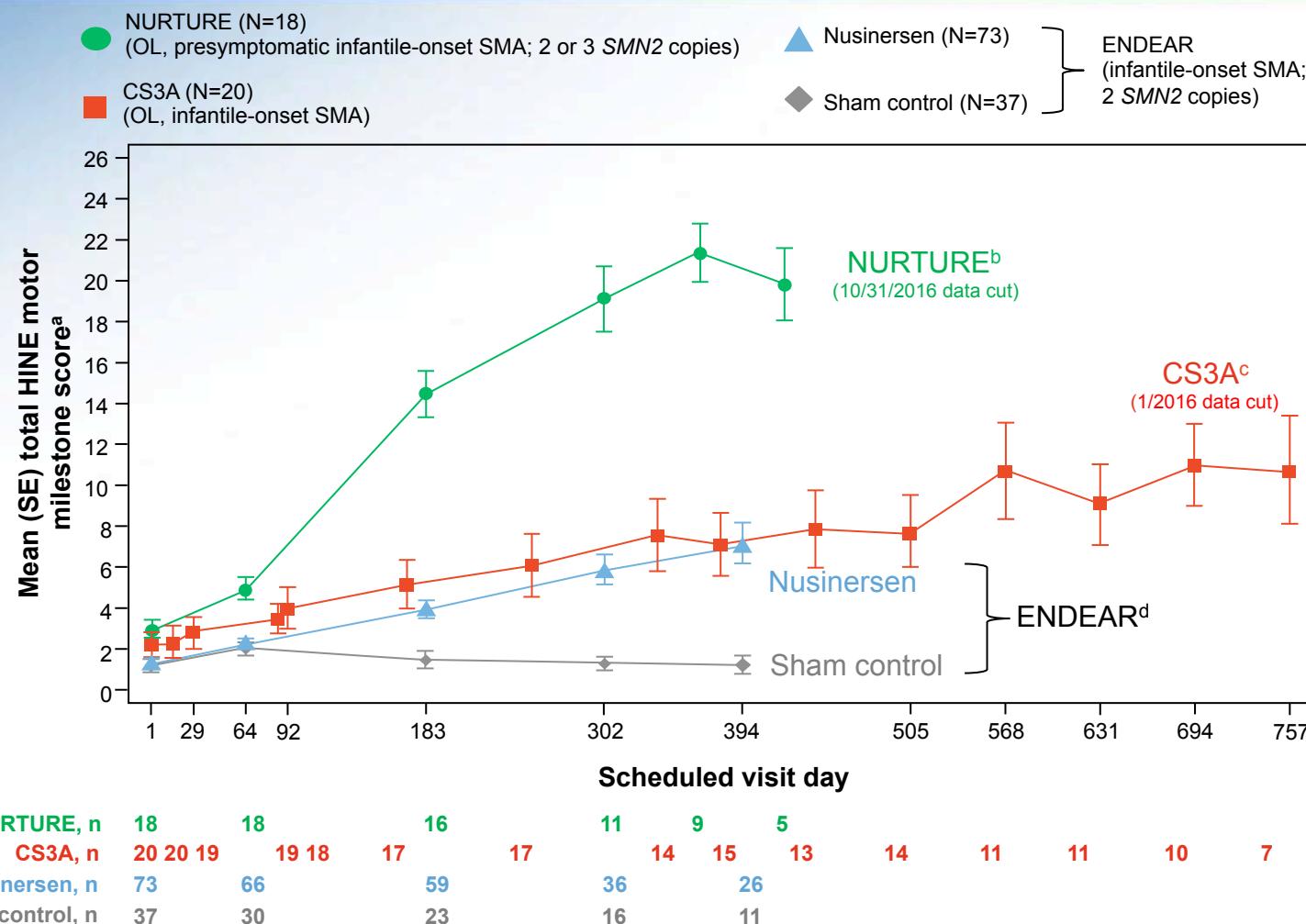
E. Mercuri, B.T. Darras, C.A. Chiriboga, J.W. Day, C. Campbell, A.M. Connolly, S.T. Iannaccone, J. Kirschner, N.L. Kuntz, K. Saito, P.B. Shieh, M. Tulinius, E.S. Mazzone, J. Montes, K.M. Bishop, Q. Yang, R. Foster, S. Gheuens, C.F. Bennett, W. Farwell, E. Schneider, D.C. De Vivo, and R.S. Finkel,  
for the CHERISH Study Group\*





# NURTURE study pre-symptomatic SMA patients

# HINE motor milestone scores across studies

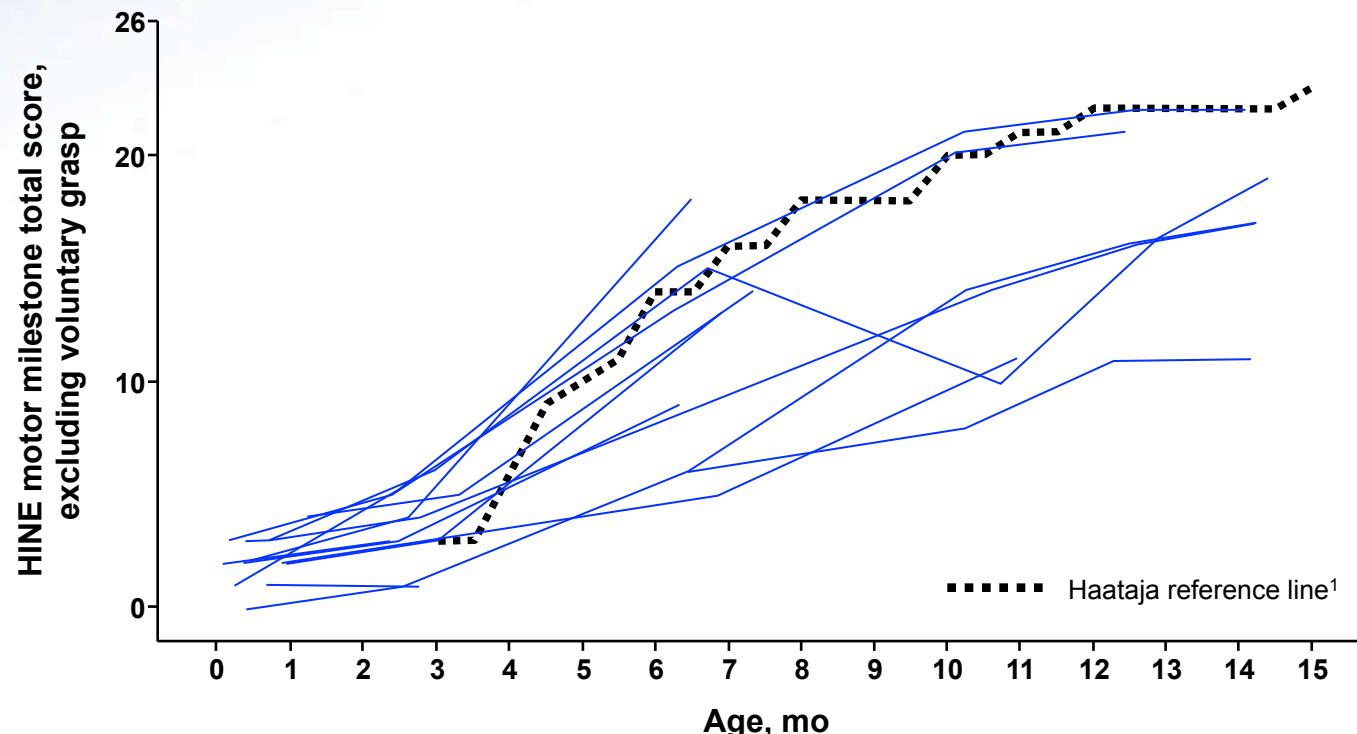


OL = open label. Populations : NURTURE (232SM201) = interim efficacy set; CS3A = all dosed infants ; ENDEAR (CS3B) = interim efficacy set. For each study, visits with n < 5 are not plotted. <sup>a</sup>Maximum total milestone score = 26. <sup>b</sup>Median (range) age at first dose : 19.0 (3-42) days. <sup>c</sup>Median (range) age at enrollment : 155 (36-210) days. <sup>d</sup>Median (range) age at first dose: 175.0 (30-262) days.

# HINE motor milestone total score (excluding voluntary grasp)

Infants with 2 *SMN2* copies

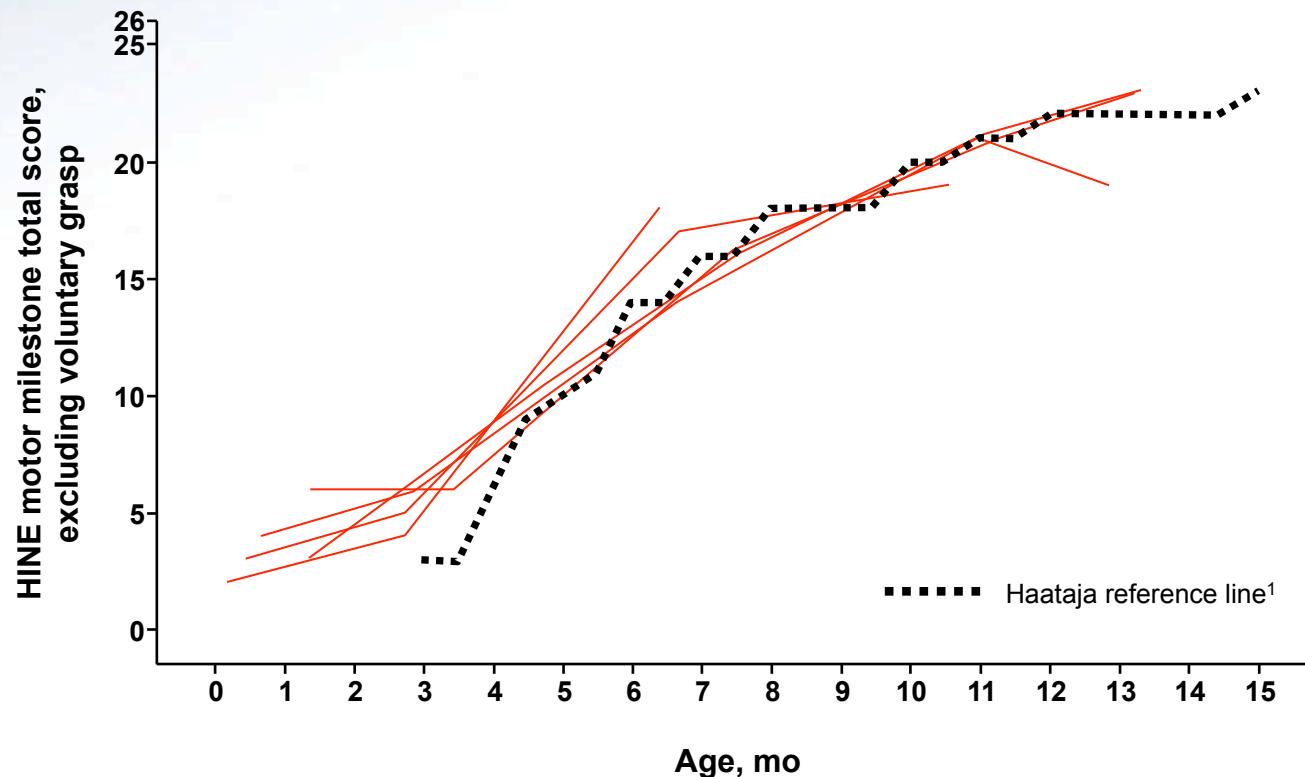
- Some infants are achieving motor milestones along timelines consistent with normal development
- Among those who are not, the infants are trending up and achieving new motor milestones along timelines near normal development



# HINE motor milestone total score (excluding voluntary grasp)

Infants with 3 *SMN2* copies

- Most infants are achieving motor milestones along timelines consistent with normal development



One infant attended the day 64 assessment on study day 98. NURTURE study interim analysis data cut-off date : october 31, 2016.

1. Haataja L et al. J Pediatr. 1999;135(2 pt 1):153-161.







A Liège, il  
reste 102  
heures....

<https://www.facebook.com/sunmayariseonsma/>



# Remerciements

