HỘI THẢO KHOA HỌC
BỆNH VIỆN NHI ĐỒNG 1

TRƯỜNG HỢP LÂM SÀNG
ĐIỀU TRỊ BỆNH TEO CƠ TỦY SỐNG TYPE 1 BẰNG AVXS-101 (ZOLGENSMA)

Nguyễn Lê Trung Hiếu,
Bệnh viện Nhi Đồng 1,
27 - 28.11.2020

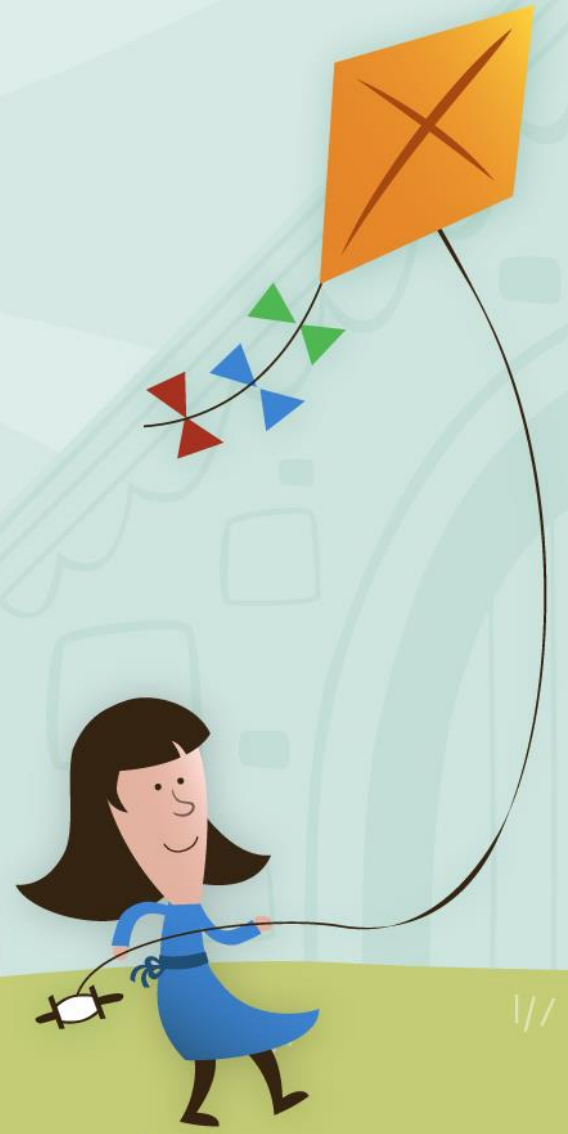
1. Tình huống lâm sàng

Đã xin phép Ba Mẹ bệnh nhi,

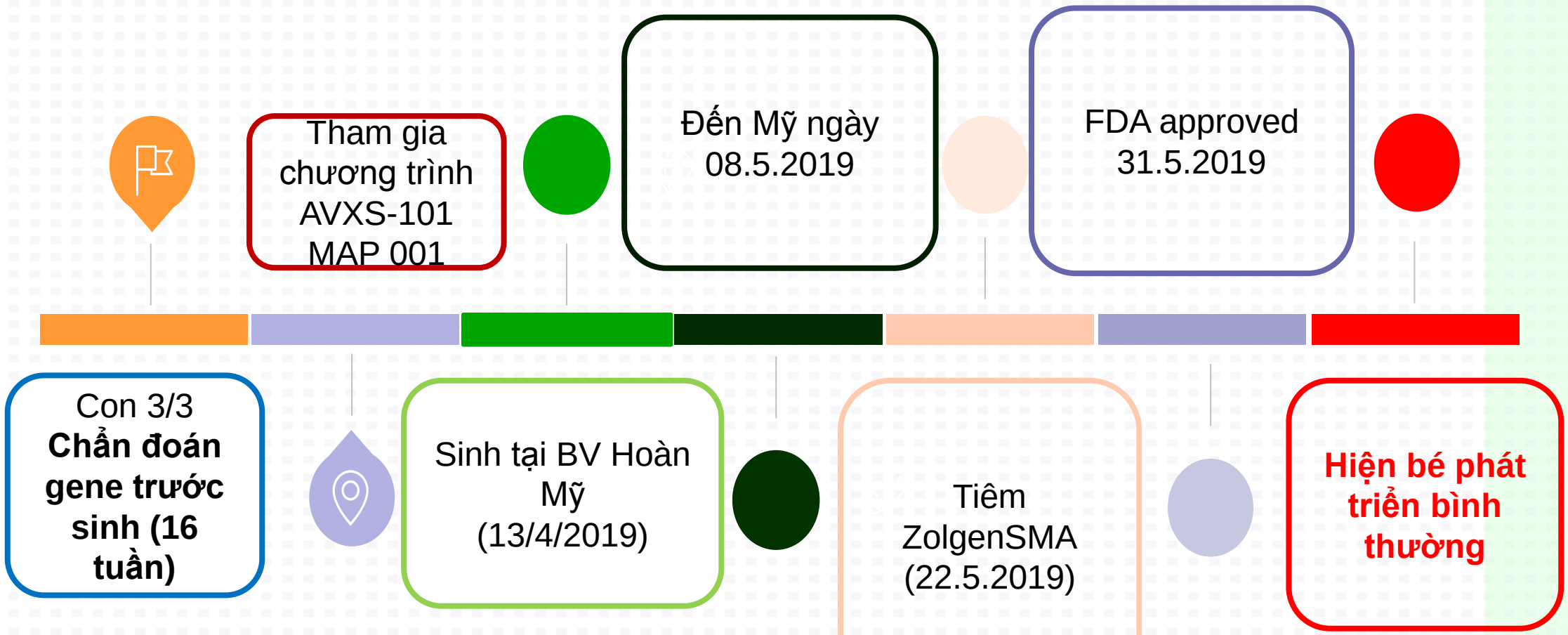
Chỉ trình chiếu,

Không in thành tài liệu,

Không quay phim, chụp hình.



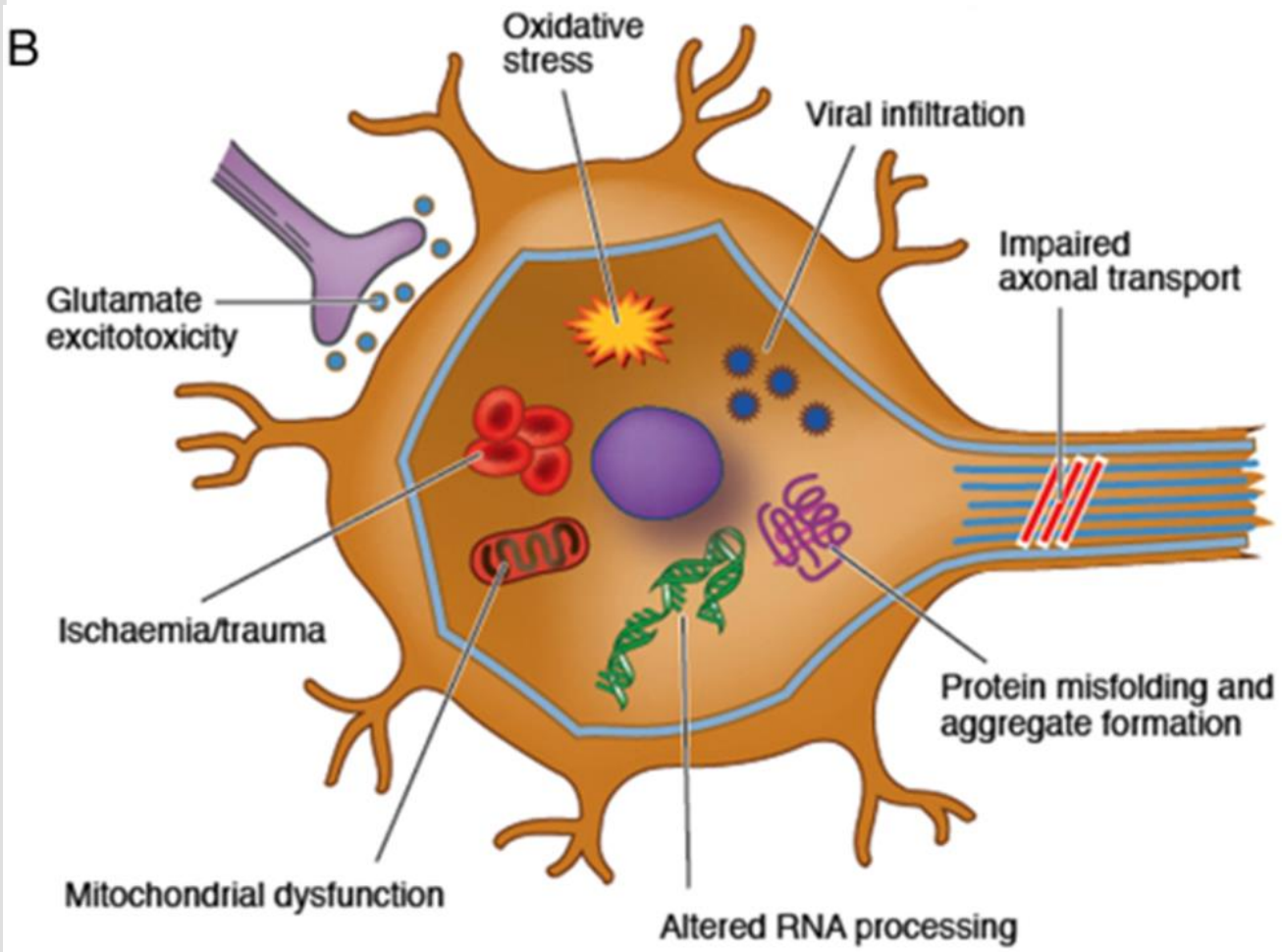
Bé gái sinh 13/4/2019 (19 tháng)



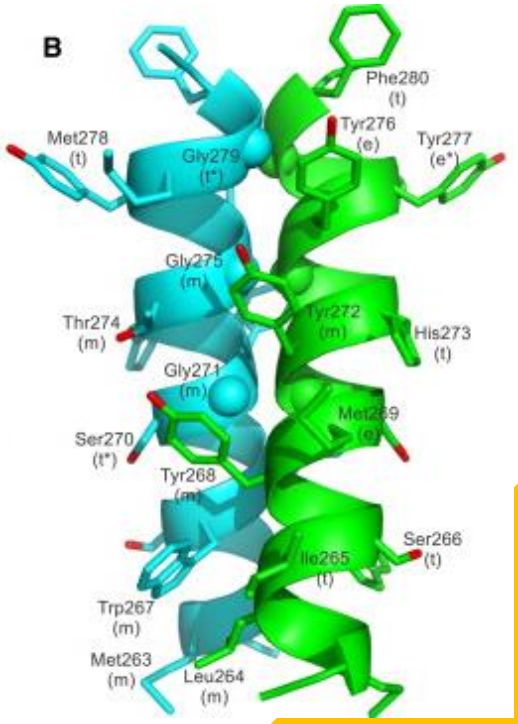
2. Tổng quan tài liệu

CÁ THỂ BỆNH SMA

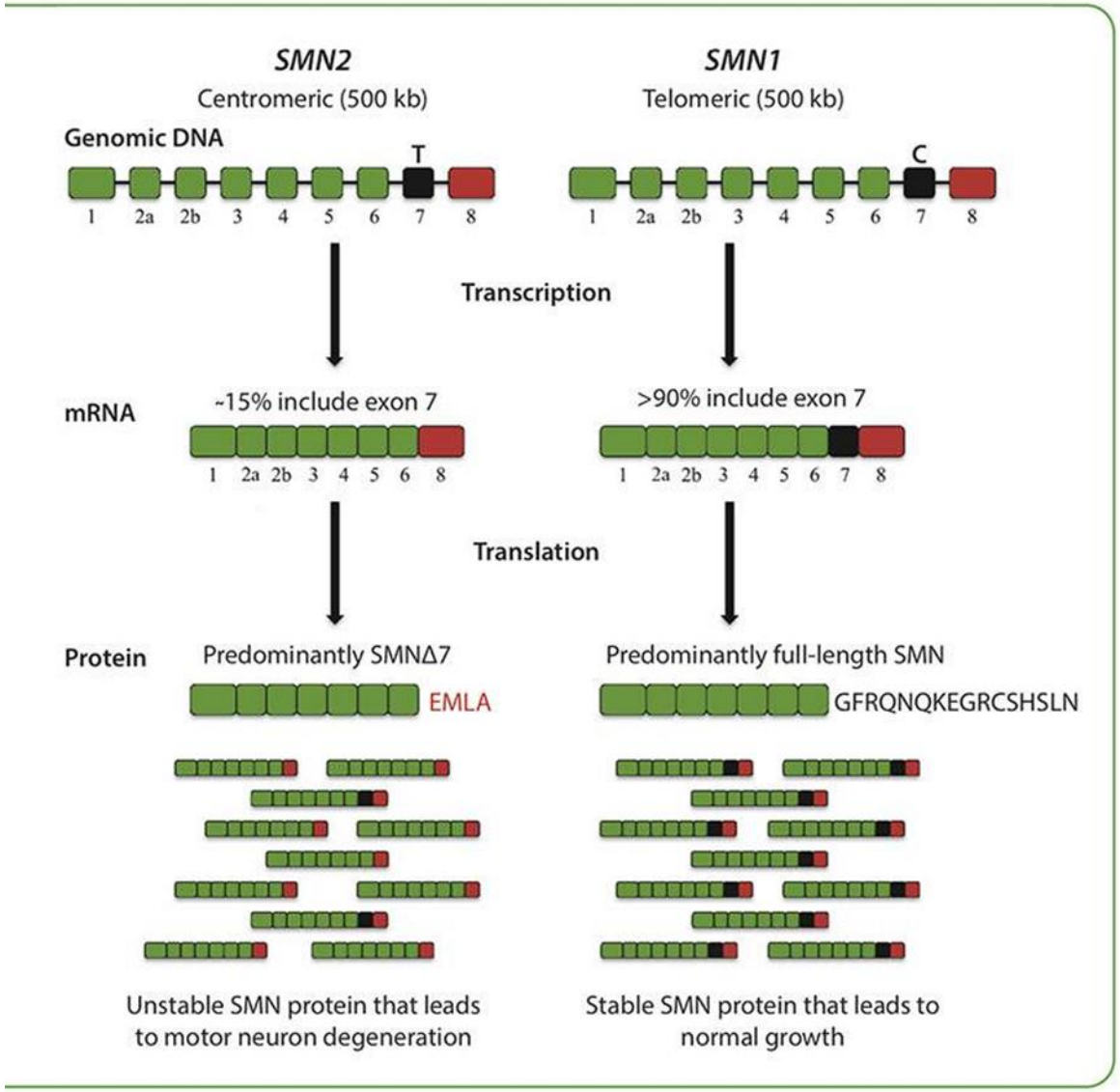
Type	Frequency (%)	*SMN2* Copy	Age Onset	Max Motor	Survival	Comorbidities
0	<1	1	Prenatal	Never sit	<6 months	Respiratory failure Dysphagia Contractures Decreased fetal movement
1	50–60	2,3	0–6 months	Never sit	<2 years	Respiratory failure Dysphagia Weak cough Paradoxical breathing Contractures Severe weakness
2	30	2,3,4	<18 months	Sit	>2 years/ adult	Respiratory insufficiency Weak cough Tremor Scoliosis Contractures Weakness
3	10	3–4	18 months-21 years	Walk	Adult	Variable weakness Joint contractures Scoliosis
4	1	4+	Late childhood–adult	Walk	Adult	Mild weakness



- SMN, NST 5
- Liên quan mRNA
- Ngoài SMN:
  - NAIP
  - BTF
  - CAG



Garg N, et al. Differentiating lower motor neuron syndromes, J Neurol Neurosurg Psychiatry 2016;0:1–10

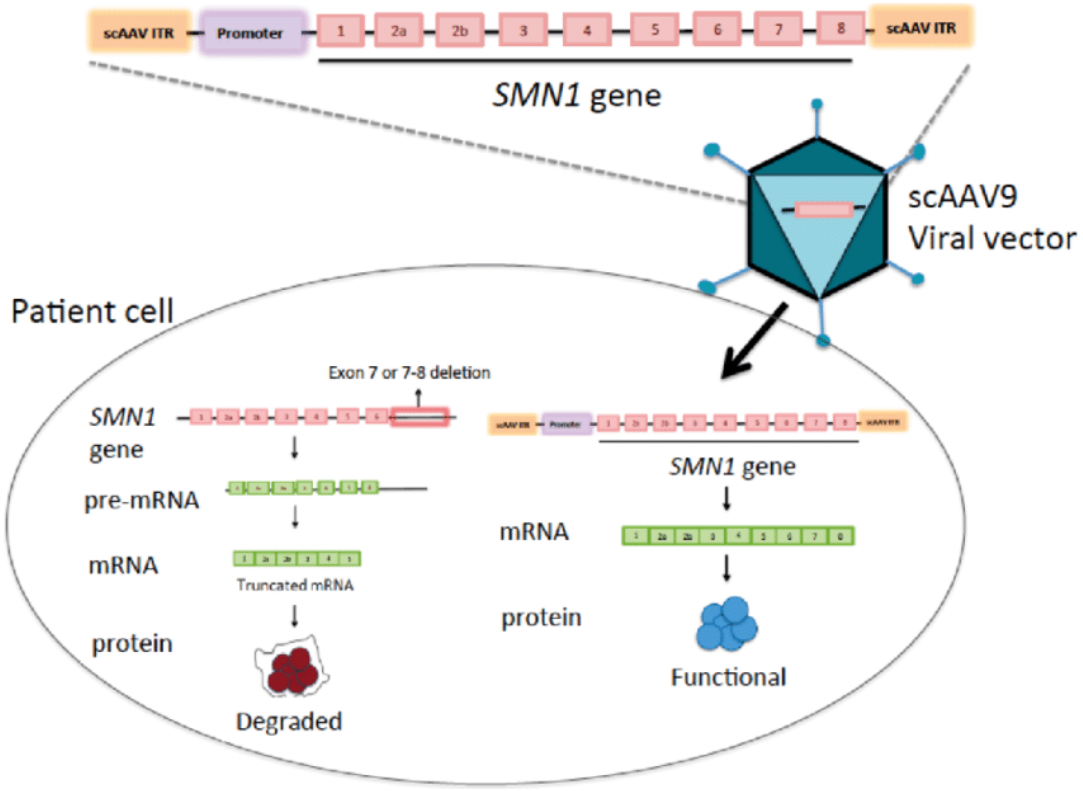

SMN2
Centromeric (500 kb)
SMN1
Telomeric (500 kb)
Genomic DNA
T
C
1 2a 2b 3 4 5 6 7 8
1 2a 2b 3 4 5 6 7 8
Transcription
mRNA
~15% include exon 7
>90% include exon 7
1 2a 2b 3 4 5 6 8
1 2a 2b 3 4 5 6 7 8
Translation
Protein
Predominantly SMNΔ7
EMLA
Predominantly full-length SMN
GFRQNQKEGRCSHSLN
Unstable SMN protein that leads to motor neuron degeneration
Stable SMN protein that leads to normal growth

SMN1 và SMN2

Spinal Muscular Atrophy

	Drug	Delivery route	Target of treatment	Study design	Planned sample size	Primary outcome
Spinal muscular atrophy						
NCT02594124 (SHINE)	Nusinersen (antisense oligonucleotide)	Intrathecal	*SMN2* splicing	Phase 3	292	Safety: adverse events, serious adverse events, or both; and other safety parameters
NCT02386553 (NURTURE)	Nusinersen	Intrathecal	*SMN2* splicing	Phase 2, open-label	25 with presymptomatic SMA	Time to death or respiratory intervention
NCT02908685	RO7034067 (small molecule)	Oral	*SMN2* splicing	Phase 2/3, two-part, seamless, randomised, placebo-controlled, double-blind	219 with SMA type 2 and 3	Change from baseline of total MFM-32 score after 12 months of treatment; recommended dose for part 2 of the study
NCT02913482	RO7034067	Oral	*SMN2* splicing	Phase 2/3, open-label	48 with SMA type 1	Percentage of infants who are sitting without support at 12 months of treatment; recommended dose for part 2 of the study
NCT03032172	RO7034067	Oral	*SMN2* splicing	Phase 2, open-label	24 previously enrolled in a study of SMN2-targeting therapy	Safety, tolerability, pharmacokinetics
NCT02268552	Branaplam (LMI070; small molecule)	Oral	*SMN2* splicing	Phase 1/2, open-label	44 with SMA type 1	Safety at 13 weeks and 52 weeks
NCT03421977	AVXS-101 (self-complementary AAV9 vector carrying *SMN*)	Intravenous	Gene replacement	Phase 1/2, open-label	15 with SMA type 1	Long-term safety (15 years)
NCT03306277	AVXS-101	Intravenous	Gene replacement	Phase 3, open-label	15	Sitting without support at age 18 months; event-free survival at age 14 months

Mariacristina Scoto, Richard Finkel, Eugenio Mercuri, Francesco Muntoni (2018), Genetic therapies for inherited neuromuscular disorders, Lancet Child Adolesc Health.



Gamze BORA, Recent therapeutic developments in spinal muscular atrophy, Turk J Med Sci (2018) 48: 203-211

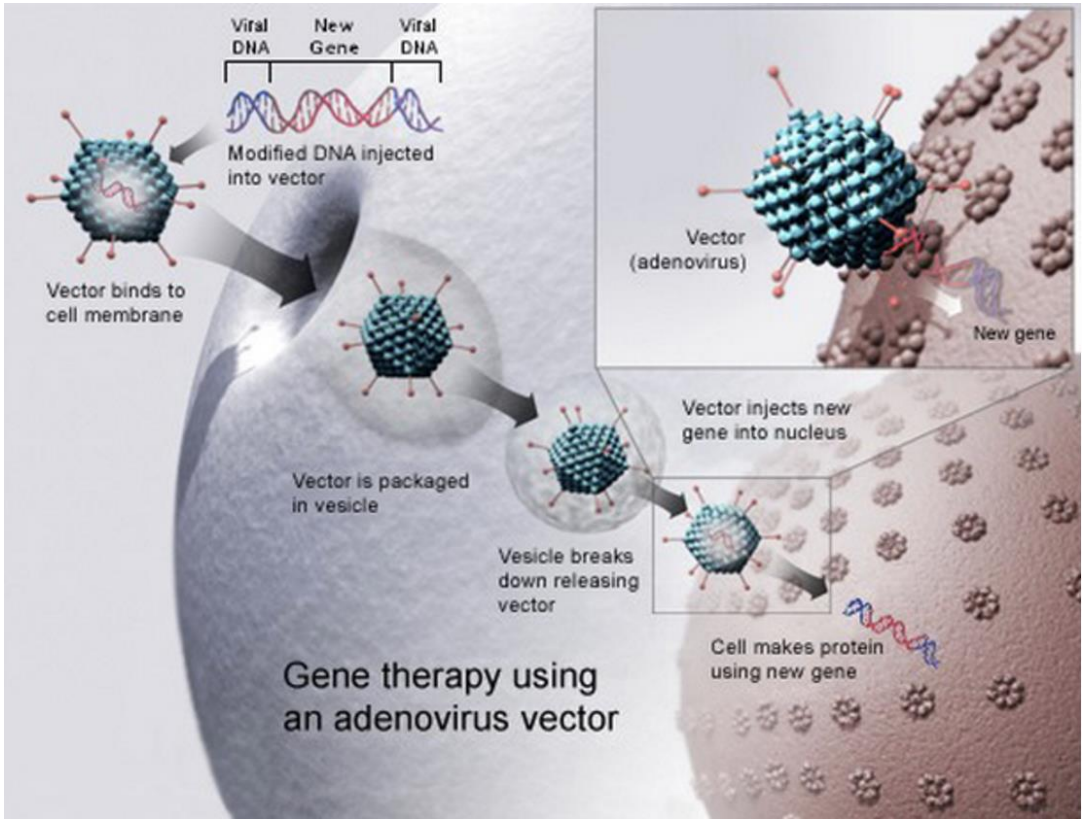
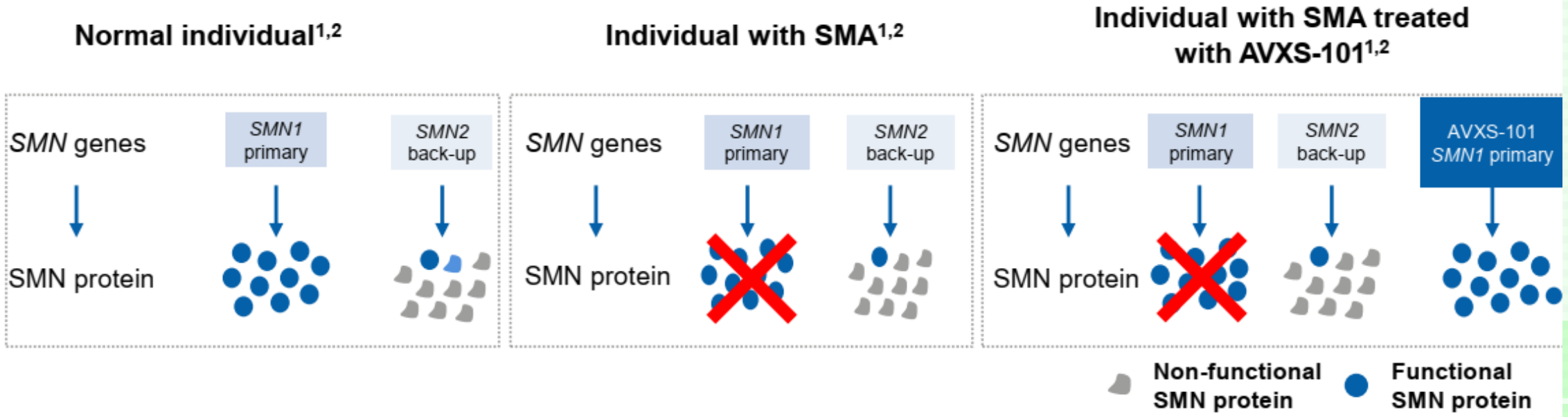


Figure taken from U.S. National Library of Medicine, 2014

AVXS-101 replaces defective *SMN1* gene

AVXS-101 replaces defective *SMN1* gene, restoring SMN protein production



FDA APPROVAL

Summary Basis for Regulatory Action

Date: May 24, 2019

From: Andrew Byrnes, PhD

BLA STN#: 125694/0

Applicant Name: AveXis, Inc

Date of Submission: October 1, 2018

Goal Date: May 31, 2019

Proper Name: onasemnogene abeparvovec-xioi

Proprietary Name: ZOLGENSMA

Indication: Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1* (*SMN1*) gene

Recommended Action: The Review Committee recommends approval.

2. Chương trình điều trị mở rộng toàn cầu cho AVXS-101-MAP-002

January 22th, 2020

Treatment Plan for a Managed Access Program (MAP) for AVXS-101-MAP-002

BV NĐ 1, 2 và Nhi TW đã ĐĂNG KÝ

Treating Institution

Treatment Institution Registration Form ✓**AVXS_INS_00065T**

- Prior to approval and shipment of AVXS-101, this one-time form is to be completed by the treatment institution, usually by the hospital pharmacy. Each institution where AVXS-101 is ordered or re-ordered must be registered.

Treating Physician

Treating Physician Registration Form ✓**AVXS_PHY_00070T**

- To be able to obtain AVXS-101, the treating physician must first register with the program. This is a one-time registration that each treating physician must complete.
- The physician must be suitably qualified and experienced in order to administer this therapy for the treatment of Spinal Muscular Atrophy.

Registration of Patient

Registration of Patient

- This form will be provided to the treating physician upon their registration. This form must be completed by the treating physician.
- This form must be completed prior to supply.
- All patients registered with this form must be able to return to the required institution(s) for all testing, treatment and monitoring.

For more information on how to register to the Global MAP or for other inquiries please contact Durbin at AveXisMAP@DurbinGlobal.com.

Inclusion criteria

Patients must meet all of the following inclusion criteria:

1. Patients under the age of two with genetically confirmed SMA, regardless of type, symptom onset or prior treatment;
2. Patients are a citizen or legal resident of a country where the therapy is not approved by local health authorities;
3. Patients must have a pre-treatment swallowing evaluation test performed prior to administration of onasemnogene abeparvovec;
4. Patients must have a formal pulmonary evaluation including documentation of non-invasive ventilatory use prior to administration of onasemnogene abeparvovec. Ventilation should be actively managed by an appropriately trained specialist per the published standard of care;[1,2]
5. Patient need to be up-to-date on childhood vaccinations. Seasonal vaccinations and palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections must have been administered.
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule.

Exclusion Criteria:

Patients must **not** meet any of the following exclusion criteria:

1. Tracheostomy or >=16 hours per day of non-invasive ventilatory support
2. Contraindication to receiving glucocorticosteroids or their excipients.
3. Anti Adeno Associated Virus Serotype 9 (AAV9) antibody titer > 1:50 (or any value reported as elevated for the laboratory) as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate anti-AAV9 antibody titer > 1:50, he or she may be retested and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is < 1:50.
4. Clinically significant abnormal laboratory values (especially troponin-I, platelets, ALT, AST, bilirubin or gamma glutamyl transferase (GGT) >2 x the upper limit of normal (ULN) prior to gene replacement therapy that in the judgment of the treating physician would create too great a risk for the patient to be treated with onasemnogene abeparvovec or prophylactic prednisolone.
5. Medical conditions, diagnoses (especially cardiac), or on concurrent medications prior to gene replacement therapy that in the judgment of the treating physician would create too great a risk for the patient to be treated with onasemnogene abeparvovec or prophylactic prednisolone.
6. Participation or expected participation in current treatment clinical study (with the exception of observational cohort studies or non-interventional studies) for an unapproved or approved investigational agent (e.g., Nusinersen).

SỐ BỆNH NHÂN NĐ 2

- 2.2020:
  1. **AVXS_PAT_T00066 (DOB: 28.10.2018)**
  2. AVXS_PAT_T00067 (DOB:31.3.2018)
- 3.2020:
  3. AVXS_PAT_T000151(DOB: 18.8.2018) (ND91)
- 4.2020:
  4. **AVXS_PAT_T00185**
  5. **AVXS_PAT_T000186**
  6. AVXS_PAT_T000187 (Thở máy)
  7. AVXS_PAT_T000188 (Mất)
  8. AVXS_PAT_T000189 (Thở máy)
- 5.2020
  9. AVXS_PAT_T000227 (AVV9 (+))
  10. **AVXS_PAT_T00228**
- 7.2020:
  11. **AVXS_PAT_T00263**
  12. AVXS_PAT_T00264 (Mất)
- 8.2020:
  13. **AVXS_PAT_T00273**
- 9.2020:
  14. **AVXS_PAT_T00289**
- 10.2020
  15. **AVSX_PAT_T00318**

Báo cáo số liệu đến 28.11.2020

Loại (7/15)

- 2/15: Quá 2 tuổi
- 2/15: Tử vong
- 1/15: Đang thở máy
- 1/15: Dương tính AAV9
- 1/15: Loại sau khi được chọn vì thở máy

Nhận thuốc 5/15

- 2/15: Đã được truyền thuốc ngày 22.10
- 3/15: Đã được truyền thuốc ngày 19 và 20/11

Chờ quay số 3/15

- 3/15: Chờ quay số (23.11)

Approved SMA products			
Product	**Patient population**	**Annual/total list cost**	**2026e sales ($m)**
Evrysdi	All SMA types, all ages	Up to $340,000 pa	1,545
Spinraza	All SMA types, all ages	$750,000 in first year, then 375,000 pa	1,174
Zolgensma	Type 1/2 children aged two or under	$2.1m one-off cost	1,872
Source: EvaluatePharma and company documents.			

TAKE HOME MESSAGES

1. SMA là một bệnh do mất đoạn gene SMN1
2. Nusinersen, AVXS-101, Risdiplam
3. BV Nhi Đồng 2: 2 trường hợp đầu tiên

Treating pediatric neuromuscular disorders: The future is now

James J. Dowling[1,2,3] | Hernan D. Gonorazky[1] | Ronald D. Cohn[2,3] | Craig Campbell[4]

Am J Med Genet. 2017;1–38.

Chân thành cảm ơn!