THÉRAPIES INNOVANTES DANS LES MALADIES NEUROMUSCULAIRES

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DÉCLARATION LIENS D'INTÉRÊTS

- Je déclare avoir des liens d'intérêts ponctuels avec les laboratoires ALNYLAM

THÉRAPIES INNOVANTES DANS LES MALADIES NEUROMUSCULAIRES

- Nombreux progrès ces dernières années dans la compréhension du déterminisme génétique des maladies neuromusculaires
- Meilleure compréhension des conséquences des mutations retrouvées : perte de fonction et/ou gain de fonction toxique
- Développement de nouvelles thérapeutiques ciblant le gène ou la protéine mutante, comme médiateur précoce de la pathogénèse

THÉRAPIES INNOVANTES DANS LES MALADIES NEUROMUSCULAIRES DE L'ADULTE

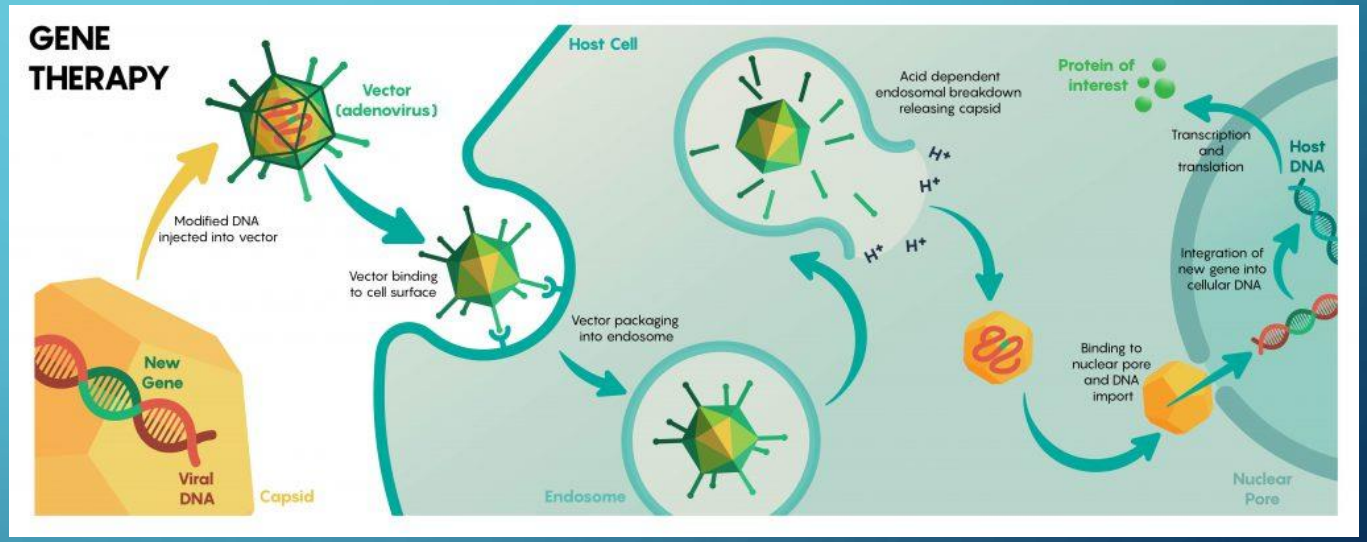
- Amylose TTR
- Sclérose latérale amyotrophique
- Amyotrophie spinale proximale
- Maladie de Charcot-Marie-Tooth

THERAPIES INNOVANTES

- Thérapies nouvelles pour toutes les maladies neuromusculaire à déterminisme génétique.
- 2 types d'approche :
  - Thérapie génique : modification du gène anormal par un vecteur viral (AAV)
  - Silençage génique : suppression ou modification d'une protéine synthétisée par un gène anormal.

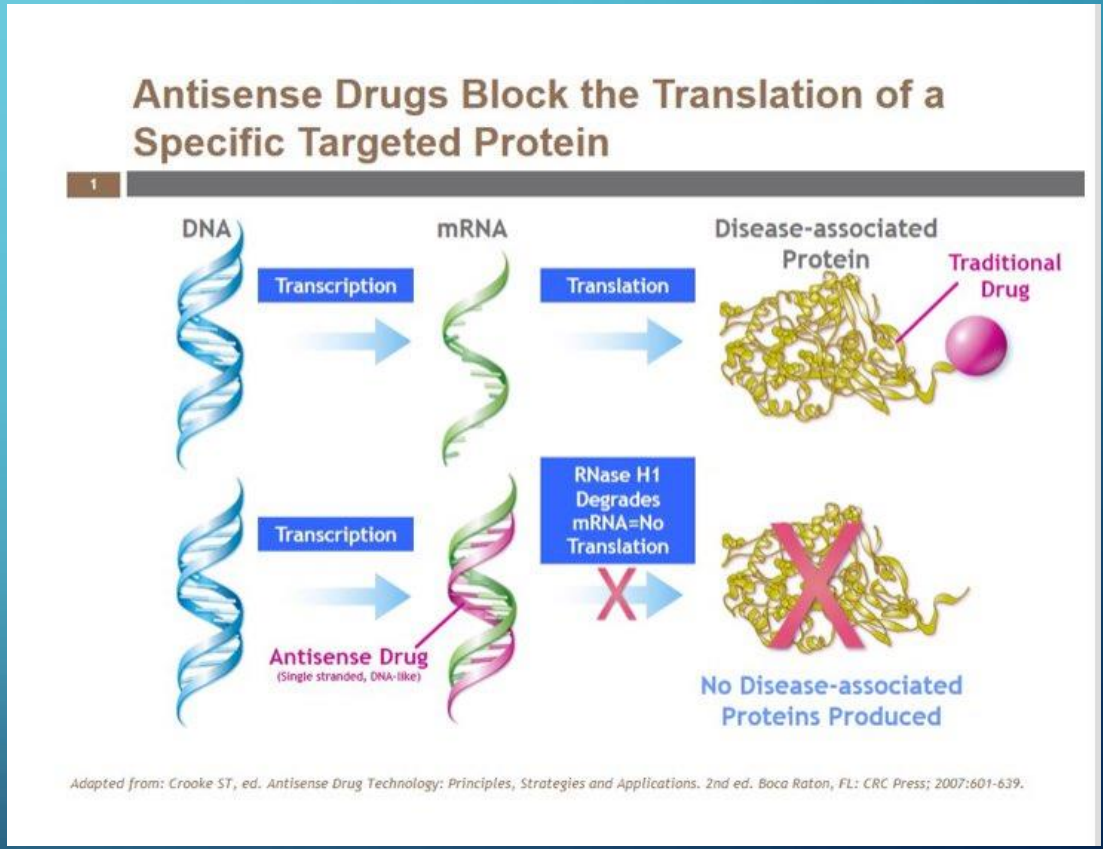
THÉRAPIE GÉNIQUE

- AAV (adeno-associated virus) : vecteur de petite taille, bonne diffusion tissulaire, résistance à des conditions extrêmes de pH et de température. Peuvent infecter des cellules d'origine tissulaires diverses et stabilisent leur génome par intégration dans un chromosome.



“SILENÇAGE” GÉNIQUE

- ASO (antisense oligonucleotide) : séquence d’acide nucléique destinée à se fixer à l’ARNm pour inactiver le gène ou modifier la protéine correspondante.
- Peut affecter aussi l’épissage du pré-ARN, changeant le contenu en exons de l’ARNm.



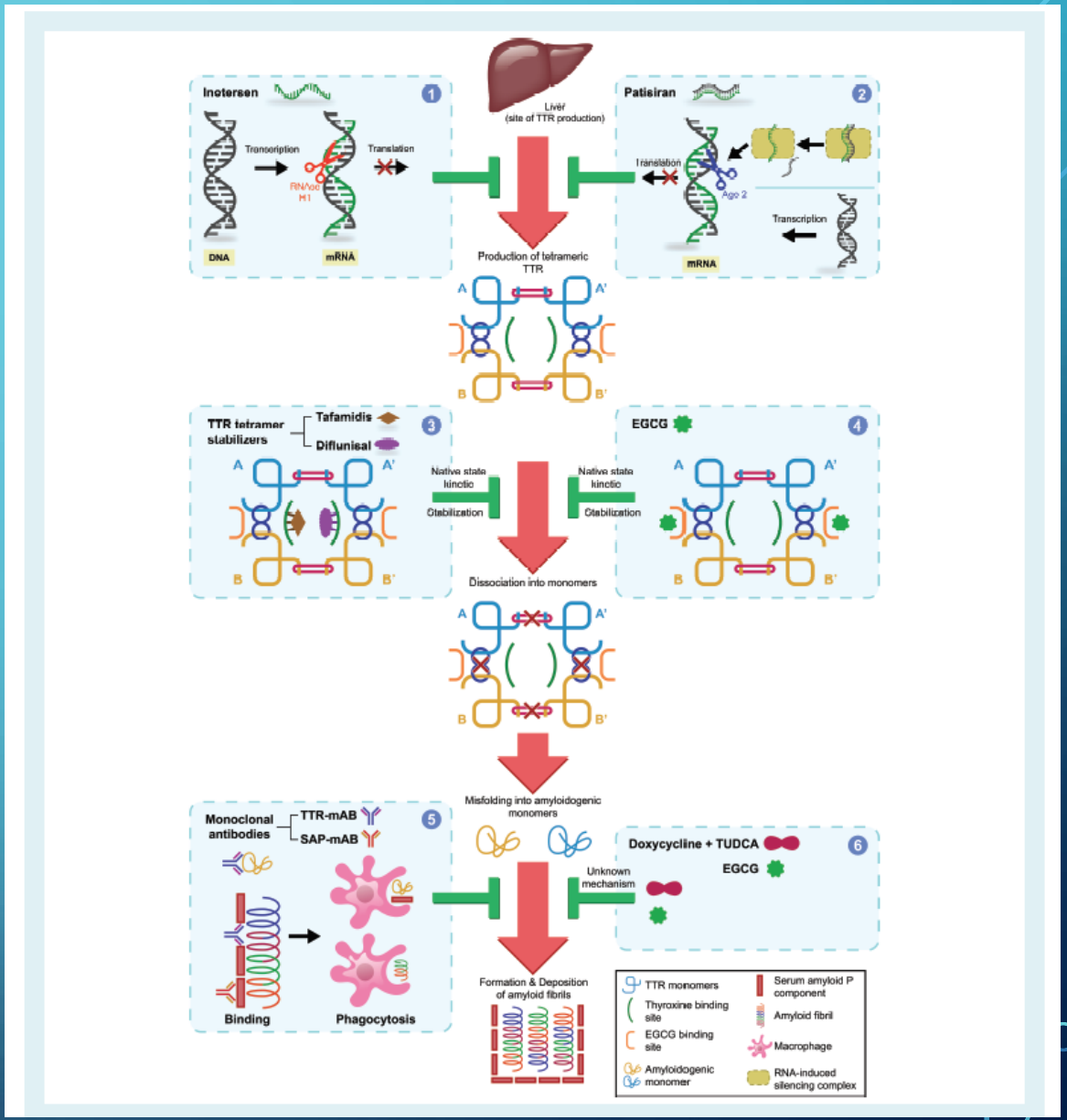
C. Frank Bennett, Ph.D.
Executive Vice President,
Chief Scientific Officer

Ionis' Neurological Disease Pipeline

MEDICINES	INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Tominersen (IONIS-HTT$_{Rx}$)	Huntington's disease	Roche				
Tofersen (IONIS-SOD1$_{Rx}$)	ALS	Biogen				
TTR-L$_{Rx}$	TTR Amyloidosis	Ionis				
IONIS-MAPT$_{Rx}$	Alzheimer's disease	Biogen				
IONIS-C9$_{Rx}$	ALS	Biogen				
ION859	Parkinson's disease	Biogen				
IONIS-DNM2-2.5$_{Rx}$	Centronuclear myopathy	Dynacure				
ION464	Multiple System Atrophy	Biogen				
ION541	ALS	Biogen				
ION581	Angelman syndrome	Biogen				
ION260	Undisclosed	Biogen				
ION363	ALS	Ionis				
ION716	Prion diseases	Ionis				
ION373	Alexander disease	Ionis				
ION283	Lafora disease	Ionis				
Numerous development candidates						

AMYLOSE TTR

- Neuropathie amyloïde familiale
- Protéine TTR (pré-albumine)
- 2 principaux niveaux d'action :
  - Synthèse : Patisiran, Inotersen
  - Stabilisation : Tafimidis



European Journal of Heart Failure (2020) 22, 39–53

AMYLOSE TTR

Table 1 **Overview of pharmaceuticals used for the treatment of transthyretin amyloidosis (status as of November 2019)**

Pharmaceutical (trade name)	Mechanism	Approval		
		By	Indication	In
Tafamidis (Vyndaqel)	TTR tetramer stabilizer	EMA	Polyneuropathy (Stage I)	ATTRv & -wt
		FDA	Cardiomyopathy	ATTRv & -wt
Inotersen (Tegsedi)	TTR silencer	EMA	Polyneuropathy (Stage I and II)	ATTRv
		FDA	Polyneuropathy (any Stage)	ATTRv
Patisiran (Onpattro)	TTR silencer	EMA	Polyneuropathy (Stage I and II)	ATTRv
		FDA	Polyneuropathy (any Stage)	ATTRv
		Current use		
Diflunisal	TTR tetramer stabilizer	Off-label		
EGCG	TTR tetramer stabilizer; Fibril disruptor	Natural compound in green tea		
Doxycycline and TUDCA	Fibril disruptors	Off-label		
Monoclonal antibodies	Fibril disruptors	Pre-clinical (phase 1)		

ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; EGCG, epigallocatechin-3-gallate; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; TTR, transthyretin; TUDCA, tauroursodeoxycholic acid.

European Journal of Heart Failure (2020) 22, 39–53

PRINCIPAUX TRAITEMENTS AMYLOSE TTR

- Tafamidis (VYNDAQEL) : stabilisateur spécifique de la TTR, AMM chez patients présentant une forme de stade 1, voie orale
- Patisiran (ONPATTRO) : nanoparticule entrainant dans le foie une interférence avec ARN, AMM stades 1 et 2, voie IV toutes les 3 semaines, risque réactions immuno-allergiques
- Inotersen (TEGSEDI) : ASO anti-TTR, AMM stade 1 et 2, voie SC hebdomadaire, risque neutropénie et glomérulonéphrite

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

- Phase 3, agent interférent avec l'ARN
- 225 patients, 148 sous Patisiran
- Amélioration de multiples manifestations cliniques de la maladie.

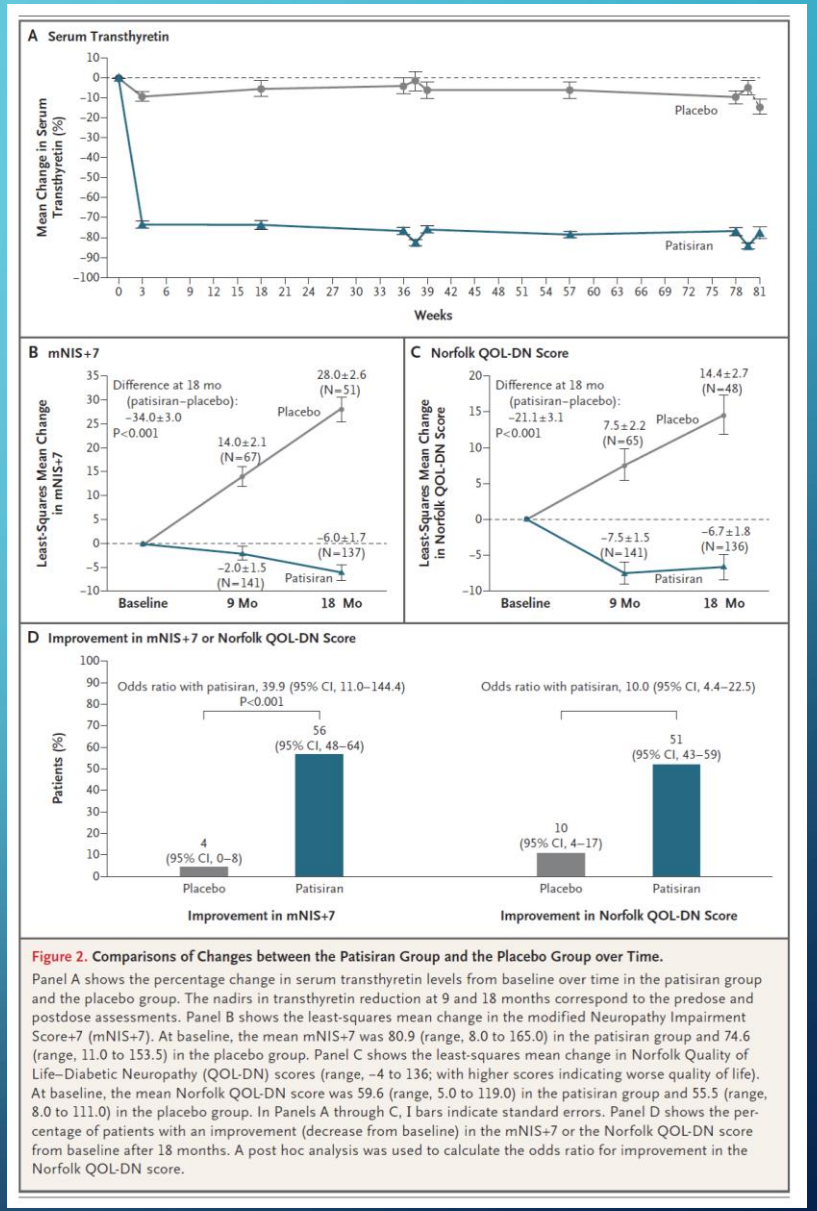


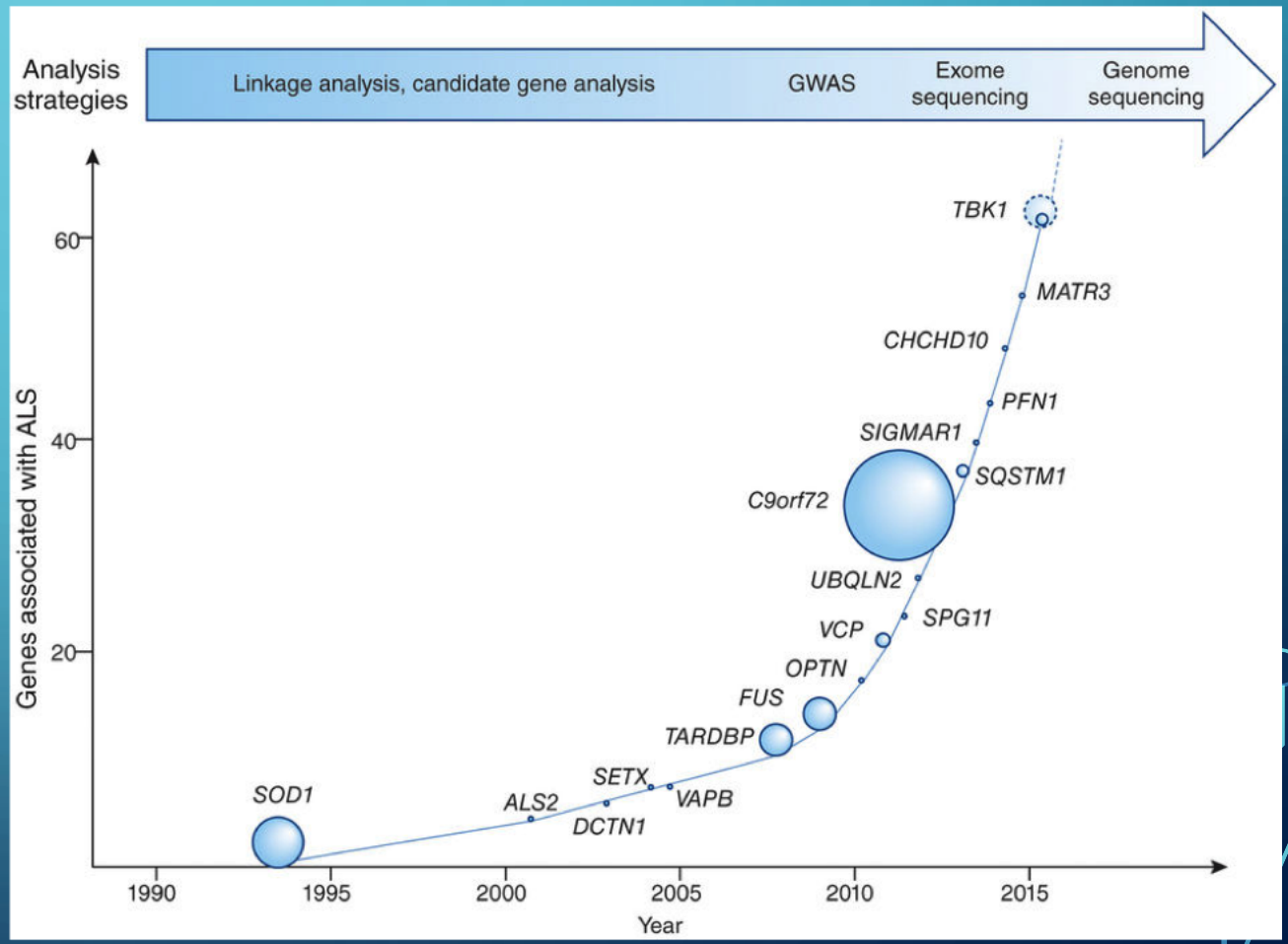
Figure 2. Comparisons of Changes between the Patisiran Group and the Placebo Group over Time.

Panel A shows the percentage change in serum transthyretin levels from baseline over time in the patisiran group and the placebo group. The nadirs in transthyretin reduction at 9 and 18 months correspond to the predose and postdose assessments. Panel B shows the least-squares mean change in the modified Neuropathy Impairment Score+7 (mNIS+7). At baseline, the mean mNIS+7 was 80.9 (range, 8.0 to 165.0) in the patisiran group and 74.6 (range, 11.0 to 153.5) in the placebo group. Panel C shows the least-squares mean change in Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) scores (range, −4 to 136; with higher scores indicating worse quality of life). At baseline, the mean Norfolk QOL-DN score was 59.6 (range, 5.0 to 119.0) in the patisiran group and 55.5 (range, 8.0 to 111.0) in the placebo group. In Panels A through C, I bars indicate standard errors. Panel D shows the percentage of patients with an improvement (decrease from baseline) in the mNIS+7 or the Norfolk QOL-DN score from baseline after 18 months. A post hoc analysis was used to calculate the odds ratio for improvement in the Norfolk QOL-DN score.

N Engl J Med 2018;379:11-21.

SCLÉROSE LATÉRALE AMYOTROPHIQUE

- 5-10 % de formes familiales
- Anomalie génétique retrouvée chez 70 à 75 % des formes familiales
- Principaux gènes : SOD1, C9ORF72, FUS, TDP43



ASO ET SCLÉROSE LATÉRALE AMYOTROPHIQUE :

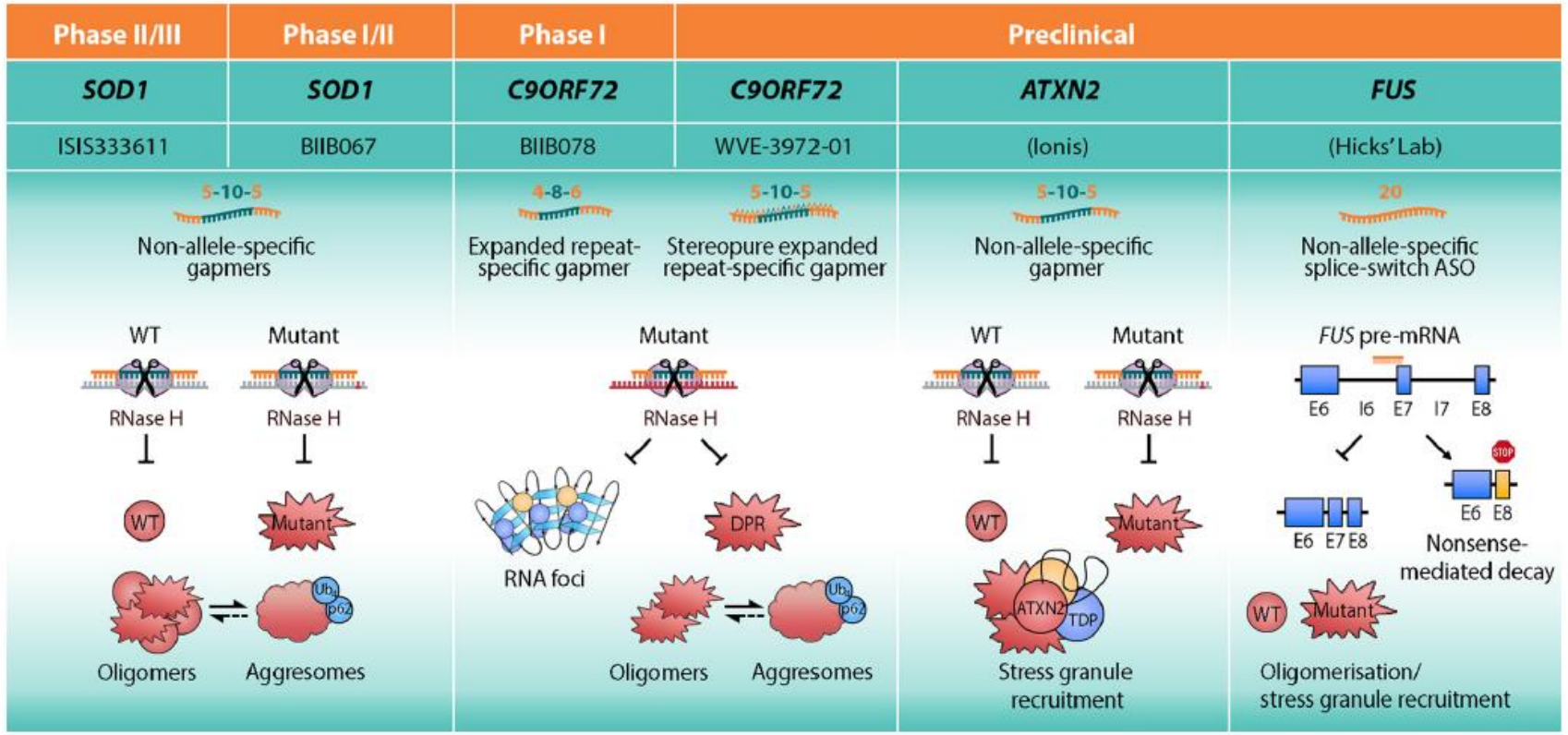


Fig. 2. Selected antisense oligonucleotide therapies in trial or development for ALS.
Three ASO-based therapies for ALS are currently in clinical trials with several more in development. *SOD1* ISIS333611, *SOD1* BIIB067, *C9ORF72* BIIB078, *C9ORF72* WVE-3972-01, and the *ATXN2* ASO are phosphorothioate (PS)- or mixed PS/phosphodiester-backbone gapmers with 2'-O-methoxyethyl-modified ribonucleotides flanking a central unmodified ribonucleotide stretch. For *C9ORF72* WVE-3972-01, the chirality of each phosphorothioate linkage is controlled. All five stimulate RNase H cleavage, of either the mutant transcript alone or of both wildtype and mutant transcripts, to mitigate gain-of-toxic-function; SOD1 or *C9ORF72* dipeptide repeat (DPR) polymers, *C9ORF72* RNA foci formation, or aberrant recruitment of TDP-43 to stress granules by ATXN2. The FUS splice-switching ASO has a PS-linked backbone with 2'-O-methyl-modified ribonucleotides, which targets the intron 6/ exon 7 junction to sterically block binding of auto-regulatory FUS protein and induce exon 7 skipping. The resulting frameshift produces a premature stop codon in exon 8, inducing nonsense-mediated decay of FUS transcript and decreased FUS protein.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2020 VOL. 383 NO. 2

Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T. Miller, M. Cudkowicz, P.J. Shaw, P.M. Andersen, N. Atassi, R.C. Bucelli, A. Genge, J. Glass, S. Ladha, A.L. Ludolph, N.J. Maragakis, C.J. McDermott, A. Pestronk, J. Ravits, F. Salachas, R. Trudell, P. Van Damme, L. Zinman, C.F. Bennett, R. Lane, A. Sandrock, H. Runz, D. Graham, H. Houshyar, A. McCampbell, I. Nestorov, I. Chang, M. McNeill, L. Fanning, S. Fradette, and T.A. Ferguson

- Phase 1-2, ASO anti-SOD1
- Voie intra-thécale, 5 doses en 12 semaines
- 4 doses étudiées : 20, 40, 60 et 100 mg
- Critères principaux : sécurité et pharmacocinétique
- Critère secondaire : concentration SOD1 LCR à 85 jours

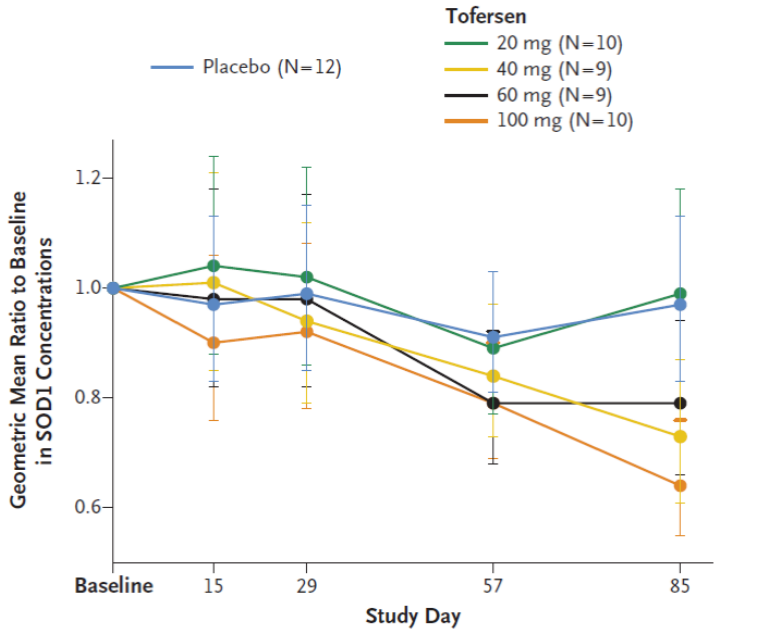
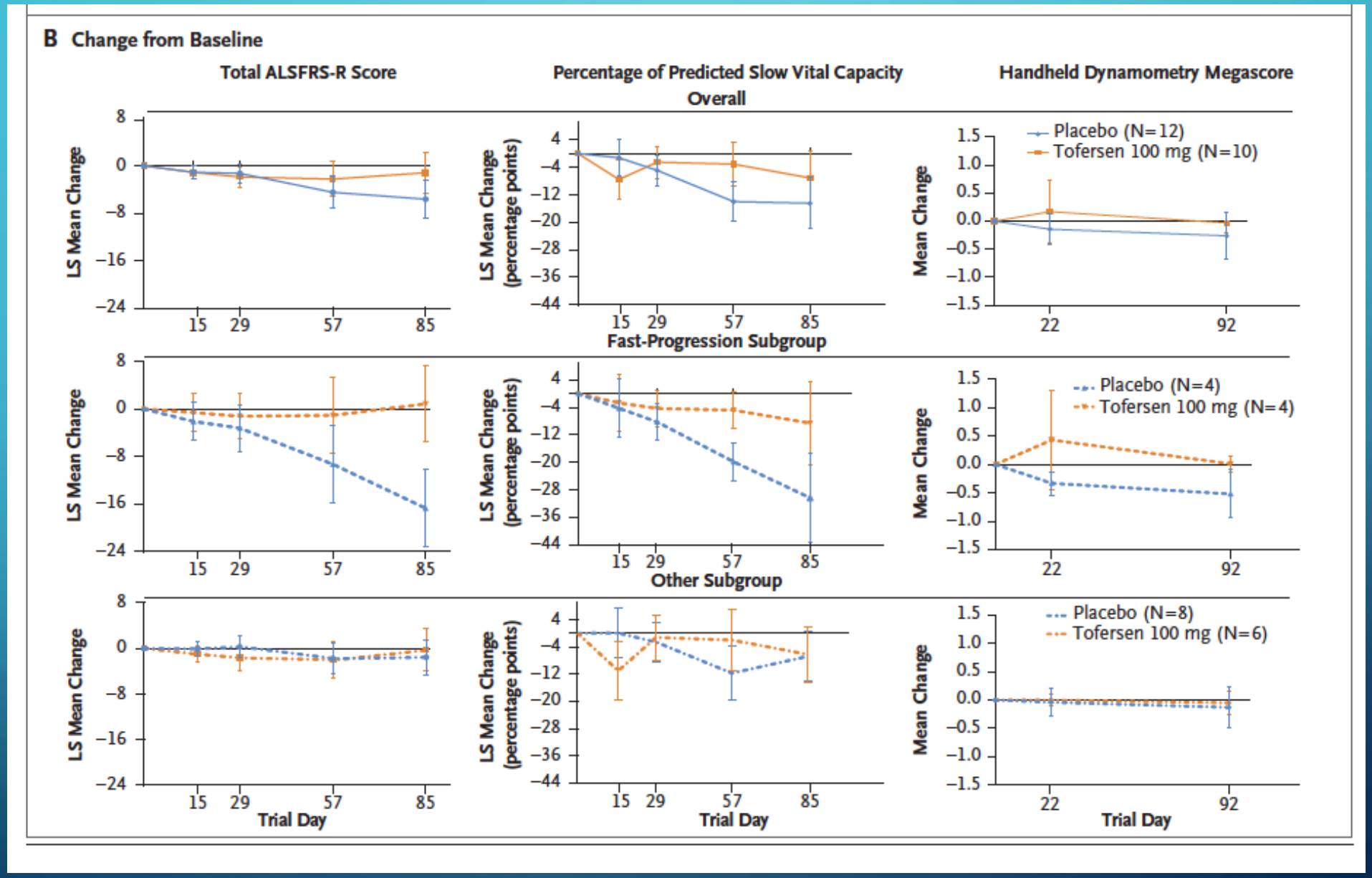


Figure 1. Effect of Tofersen Treatment on Total Superoxide Dismutase 1 (SOD1) Protein Concentrations in Cerebrospinal Fluid.

The geometric mean ratio between the baseline value and the values at the specified time points are shown. Geometric mean ratios were calculated with the use of the least-squares method. I bars indicate 95% confidence intervals. In the combined placebo group, there was one anomaly for a cerebrospinal fluid sample obtained at day 15; the result was below the limit of quantitation and was noted as being missing data. All missing data were imputed with the use of a mixed model for repeated measures.

N Engl J Med 2020;383:109-19.

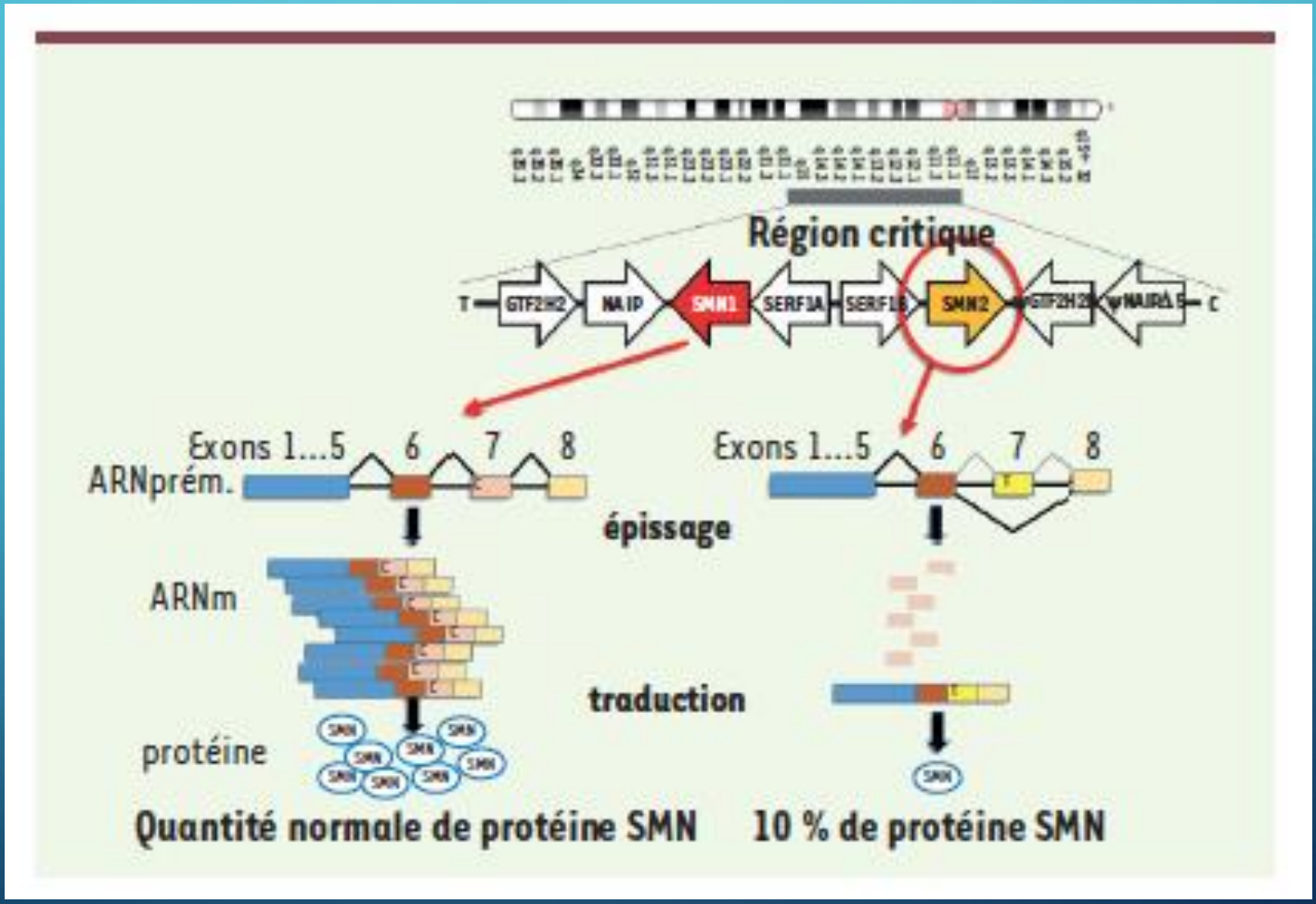


N Engl J Med 2020;383:109-19.

AMYOTROPHIE SPINALE PROXIMALE

- Incidence 1 à 2 naissances pour 10 000
- France : 120 nouveaux cas par an, 1500 patients tous stades confondus
- Gène responsable localisé sur le chromosome 5 : 2 copies sur le même chromosome, SMN 1 et SMN 2 (substitution C-T exon 7)
- Maladie : altération homozygote du gène SMN1 dans les cellules empêchant la production de la protéine Smn.
- SMN 2 : peut contrôler la sévérité de la maladie par l'expression d'une quantité variable de faible niveaux de protéine Smn fonctionnelle. Relation inverse entre le nombre de copies de SMN2 et la sévérité de la maladie.
- 4 types selon l'âge de début

ASP : GÈNES SMN 1 ET SMN 2



AMYOTROPHIE SPINALE PROGRESSIVE

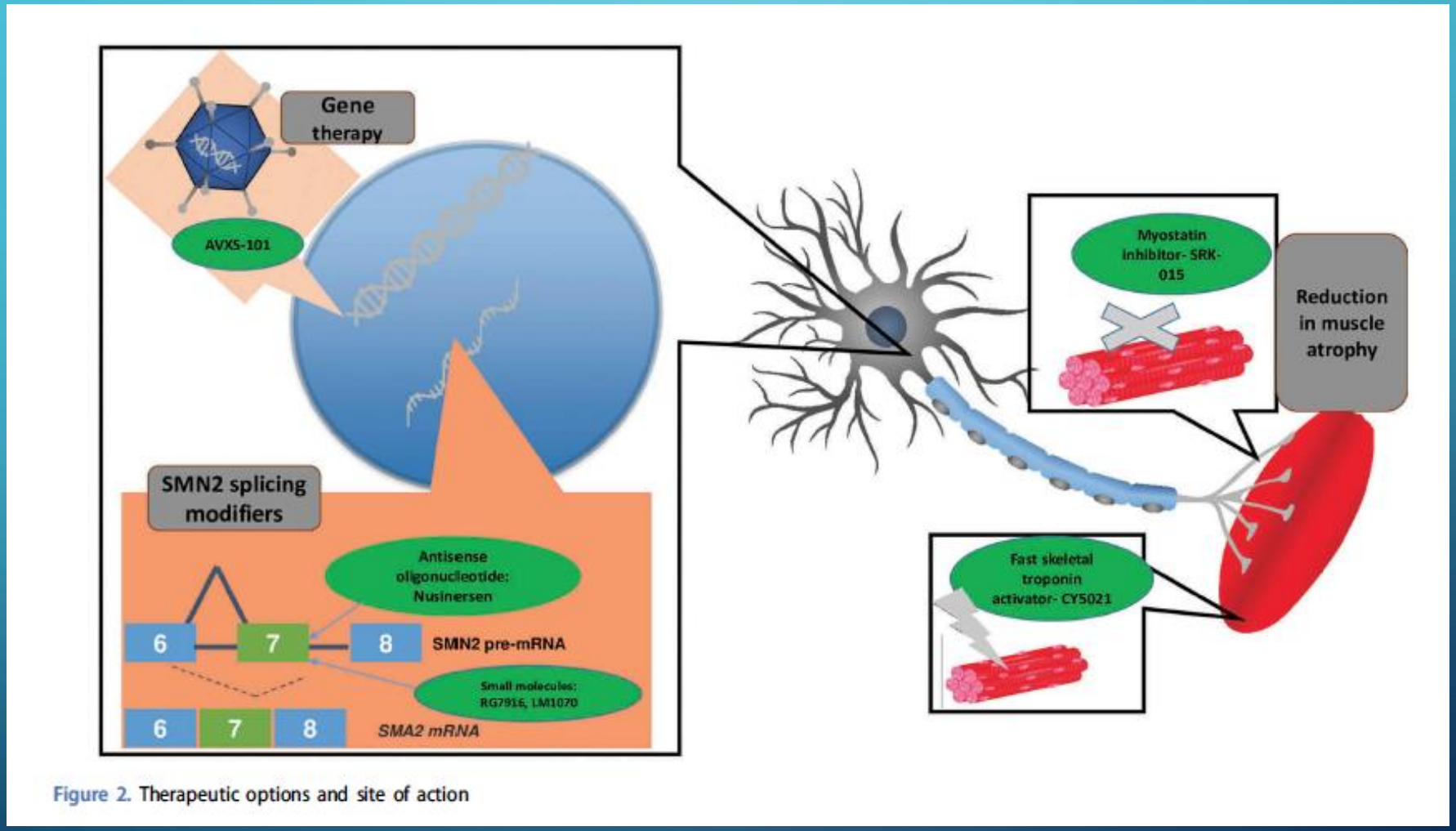


Figure 2. Therapeutic options and site of action

EXPERT OPINION ON PHARMACOTHERAPY
2020, VOL. 21, NO. 3, 307–315

AMYOTROPHIE SPINALE PROGRESSIVE

Table 1. Current clinical developments in Spinal Muscular Atrophy.

Primary targeted cell	Motor neurons					Muscle		
Mechanism	*SMN* gene replacement	SMN2 splicing modification				Antimyostatin		Troponin activation
Pharmacological class	AAV9	Antisens	Splicing modifiers		β-adrenergic agonist	Recombinant protein	Monoclonal antibody	Heteroarylpyrimidine
Product name	Zolgensma	Nusinersen	Risdiplam	Branaplam	Albuterol	RO7239361	SRK-105	Reldesemtiv
Company	Avexis (Novartis)	Biogen	Roche	Novartis		Roche	Scholar Rock	Cytokinetics
Route of administration	IV (IT)	IT	Oral	Oral	Oral	SC	IV	Oral
Approval status	FDA	FDA/EMA			Off label			
Phase completed in patients	I	III in SMA1, III in SMA2, I in SMA3						II
Current studies	III in type 1, I in type 2		III in SMA1, III in SMA2/3	I/II	II		II	

SMN, survival motor neuron; AAV, Adeno associated virus; IT, intrathecal; IV, intravenous; SC, subcutaneous.

EXPERT OPINION ON PHARMACOTHERAPY
2020, VOL. 21, NO. 3, 307–315

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

- Etude phase 1
- 15 patients SMA1
- Dose unique AAV9 pour remplacer le gène muté SMN1
- Objectif primaire : sécurité
- Objectifs secondaires : temps jusqu'au décès ou ventilation permanente

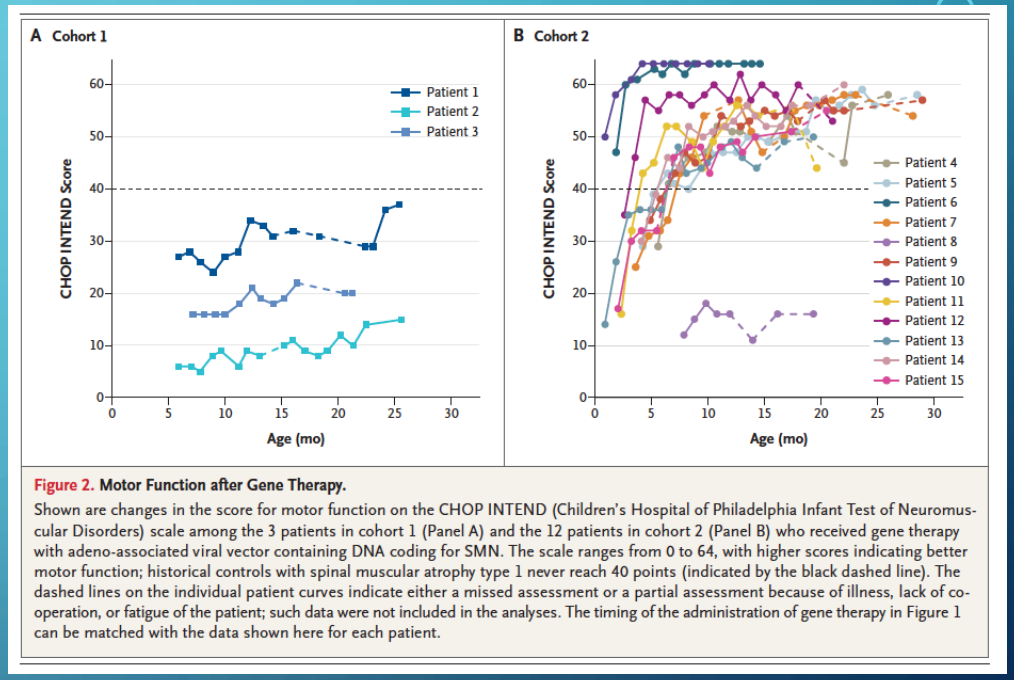


Figure 2. Motor Function after Gene Therapy.

Shown are changes in the score for motor function on the CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale among the 3 patients in cohort 1 (Panel A) and the 12 patients in cohort 2 (Panel B) who received gene therapy with adeno-associated viral vector containing DNA coding for SMN. The scale ranges from 0 to 64, with higher scores indicating better motor function; historical controls with spinal muscular atrophy type 1 never reach 40 points (indicated by the black dashed line). The dashed lines on the individual patient curves indicate either a missed assessment or a partial assessment because of illness, lack of cooperation, or fatigue of the patient; such data were not included in the analyses. The timing of the administration of gene therapy in Figure 1 can be matched with the data shown here for each patient.

N Engl J Med 2017;377:1713-22.

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*

- Phase 3, 126 enfants
- Administration intra-thécale de 12 mg de nusinersen
- Amélioration HFMSE groupe traité vs déclin groupe placebo : arrêt prématuré de l'étude

N Engl J Med 2018;378:625-35.

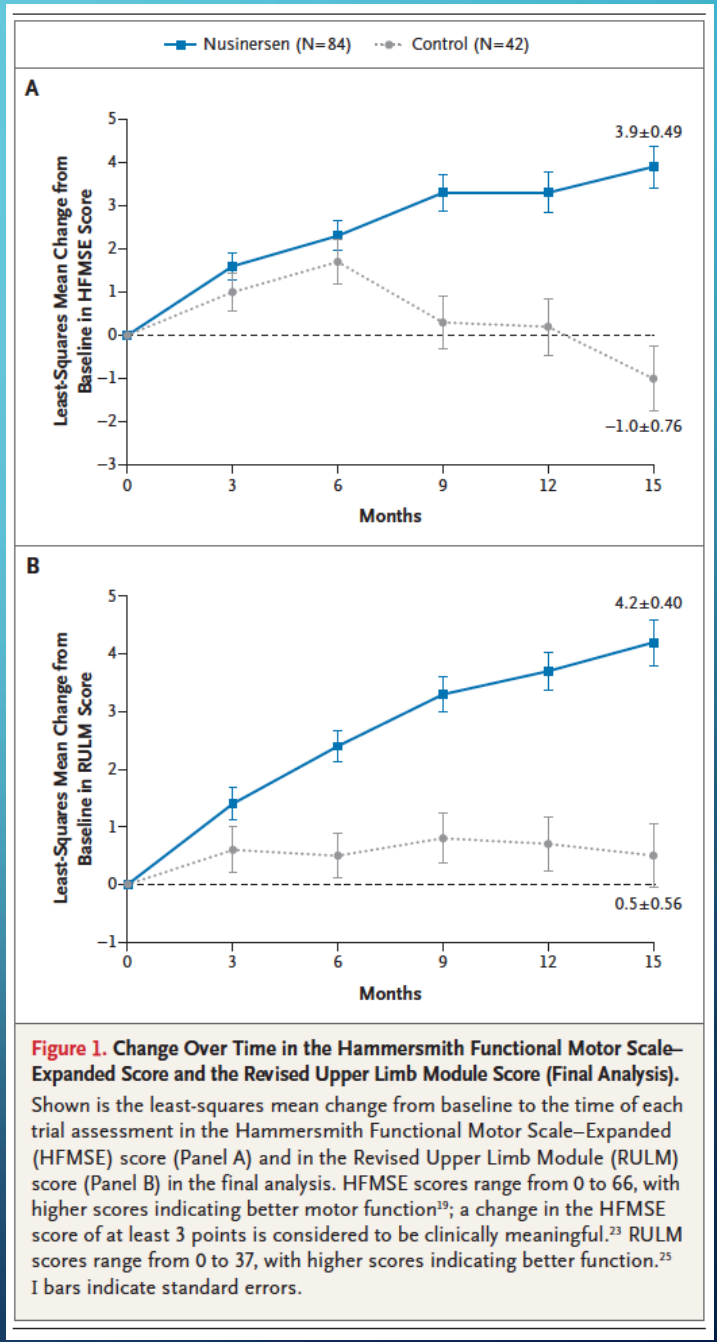


Figure 1. Change Over Time in the Hammersmith Functional Motor Scale–Expanded Score and the Revised Upper Limb Module Score (Final Analysis).

Shown is the least-squares mean change from baseline to the time of each trial assessment in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score (Panel A) and in the Revised Upper Limb Module (RULM) score (Panel B) in the final analysis. HFMSE scores range from 0 to 66, with higher scores indicating better motor function[19]; a change in the HFMSE score of at least 3 points is considered to be clinically meaningful.[23] RULM scores range from 0 to 37, with higher scores indicating better function.[25] I bars indicate standard errors.

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) 85 181–193

A phase 1 healthy male volunteer single escalating dose study of the pharmacokinetics and pharmacodynamics of risdiplam (RG7916, RO7034067), a *SMN2* splicing modifier

Stefan Sturm[1], Andreas Günther[1], Birgit Jaber[1], Paul Jordan[1], Nada Al Kotbi[2], Nikhat Parkar[3], Yumi Cleary[1], Nicolas Frances[1], Tobias Bergauer[1], Katja Heinig[1], Heidemarie Kletzl[1], Anne Marquet[1], Hasane Ratni[1], Agnès Poirier[1], Lutz Müller[1], Christian Czech[1] and Omar Khwaja[1]

Roche's risdiplam meets primary endpoint in pivotal SUNFISH trial in people with type 2 or 3 spinal muscular atrophy

- Study demonstrated statistically significant improvements in the overall study population with Type 2 or 3 SMA
- No treatment related safety findings leading to withdrawal seen in any risdiplam trial to date
- Data will be shared with health authorities globally, including the U.S. Food and Drug Administration (FDA)

AMYOTROPHIE SPINALE PROGRESSIVE

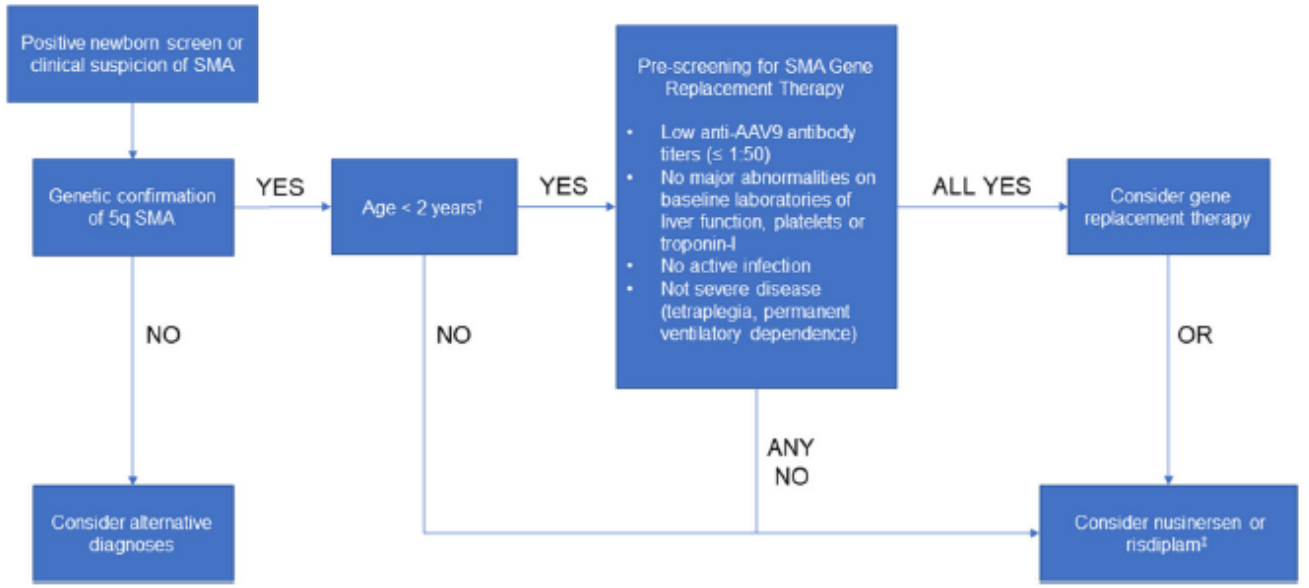


FIGURE 1 Clinical decision-making algorithm for the use of gene replacement therapy in spinal muscular atrophy. §Evaluation for *SMN2* copy number should be conducted during genetic confirmation to inform prognosis and aid in conversations about medical decision-making even though treatments in the United States are not currently limited by *SMN2* copy number. †Approved for use in Europe for children with SMA less than 21 kg (~under 5 years of age) and up to three *SMN2* copies. ‡Nusinersen is available for all ages and the recently approved splicing modifier risdiplam is available if the child is 2 months of age or older. SMA, spinal muscular atrophy [Color figure can be viewed at wileyonlinelibrary.com]

Pediatric Pulmonology. 2020;1–11.

MALADIE DE CHARCOT-MARIE-TOOTH

- CMT : la plus fréquence des neuropathies héréditaires
- Prévalence : 1 pour 2500
- 3 formes EMG : démyélinisante (CMT 1), axonale (CMT 2) et intermédiaire (CMT X).
- Plus de 90 gènes décrits, forme la plus fréquente : CMT1a (60 %)

MALADIE DE CHARCOT MARIE TOOTH

Table 2. Therapy investigations CMT.

PMP22	GJB1	MPZ	MFN2	Other
PXT3003 (3) [66–69] *ClinicalTrials.gov* NCT03023540	CAMKII inhibitors (p) [81–83,116]	Curcumin (p) [89,90,92]	Coenzyme Q10 [99]	Follistatin-based therapy (2) [115] *ClinicalTrials.gov* NCT03124459
Vitamin C (P, 1–3) [6,58,61–63,117–120]	Cx32 gene therapy (p) [85,86]	Sephin 1 (p) [94]	Mitofusion agonists (p) [100]	Stem cell research (p) [104,105]
Progesterone Antagonists (p) [59,121]				Gene therapy (p) [85,86,107,108,122,123]
siRNA (p) [60]				HDAC6 Inhibition (p) [101–103]
Antisense Oligonucleotides(p) [74]				NT-3 (p) [106–108]
Lipid supplementation (p) [75]				Nrg-1Type III (p) [109,110]
Schwann cell differentiation (p) [50,77]				TACE modulation (p) [111,112]
Curcumin (p) [89,90,92]				CSF1R inhibition (p) [114]
				Intermittent Fasting (p) [46]

(p) = Preclinical; (0) = Phase 0 clinical trial; (1) = Phase 1; (2) = Phase 2; (3) = Phase 3.

Int. J. Mol. Sci. **2019**, *20*, 3419

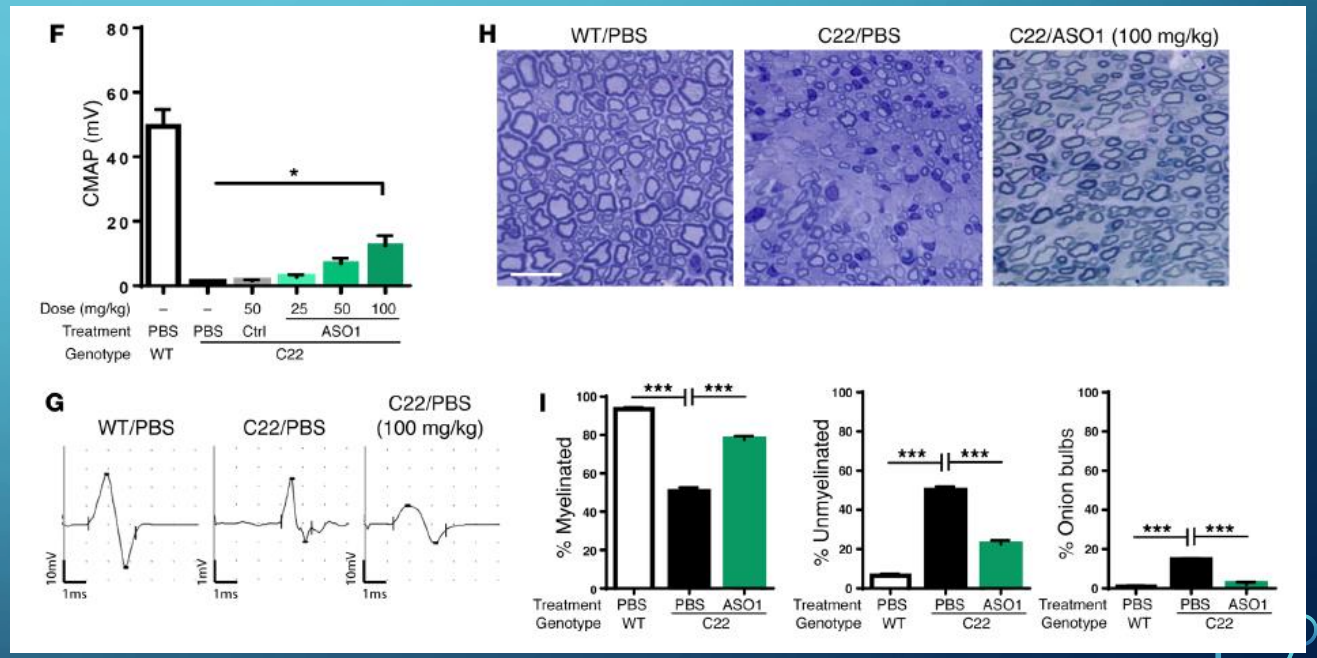
The Journal of Clinical Investigation RESEARCH ARTICLE

PMP22 antisense oligonucleotides reverse Charcot-Marie-Tooth disease type 1A features in rodent models

Hien Tran Zhao,[1] Sagar Damle,[1] Karli Ikeda-Lee,[1] Steven Kuntz,[1] Jian Li,[2] Apoorva Mohan,[1] Aneeza Kim,[1] Gene Hung,[1] Mark A. Scheideler,[3] Steven S. Scherer,[2] John Svaren,[4] Eric E. Swayze,[1] and Holly B. Kordasiewicz[1]

[1]Ionis Pharmaceuticals Inc., Carlsbad, California, USA. [2]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [3]HumanFirst Therapeutics LLC, Silver Spring, Maryland, USA. [4]Waisman Center and Department of Comparative Biosciences, University of Wisconsin-Madison, Madison, Wisconsin, USA.

- Etude ASO anti-PMP22 chez 2 modèles de rongeurs
- Etude de 3 doses (25, 50 et 100 mg/kg)
- Amélioration des paramètres neurographiques sur des formes modérées à sévère de la maladie



J Clin Invest. 2018;128(1):359–368.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Status

Recruitment :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Expanded Access :

Eligibility Criteria

Age :

years OR

Age Group:

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Terminated	Ulipristal Acetate in Disease Charcot-Marie-Tooth Type of 1A	• CMT1A	• Drug: EllaOne • Drug: EllaOne placebo	• Département de Neurologie Centre de Référence des Maladies Neuromusculaires Grand Est (OERNEST) Hôpital de Hautepierre Strasbourg, France
2	☐	Not yet recruiting	Phase I/IIa Trial of scAAV1.tMCK.NTF3 for Treatment of CMT1A	• Charcot-Marie-Tooth Neuropathy Type 1A	• Drug: scAAV1.tMCK.NTF3	• Nationwide Children's Hospital Columbus, Ohio, United States
3	☐	Active, not recruiting	Central and Peripheral Nervous System Changes as Markers of Disease Progression in Multiple Sclerosis	• Multiple Sclerosis • Neurodegeneration • Central Nervous System Lesion • (and 5 more...)		• Department of Neurology (Sklerosklinikken), Sygehus Sønderjylland Sønderborg, Jylland, Denmark
4	☐	Completed	High Dose Ascorbic Acid Treatment of CMT1A	• Charcot-Marie-Tooth Disease, Type Ia	• Drug: Ascorbic acid (Vitamin C) • Drug: placebo	• Johns Hopkins University, Dept of Neurology Baltimore, Maryland, United States • Wayne State University, Dept of Neurology Detroit, Michigan, United States • University of Rochester Medical Center, Dept of Neurology Rochester, New York, United States

CONCLUSION

- Nombre considérable de traitements déjà commercialisés ou en cours de développement pour les maladies neuromusculaires héréditaires
- Question des formes sporadiques de certaines maladies neuromusculaires : ex. SLA sporadique avec SOD1 misfoldée
- Question du coût de ces nouveaux traitements ? Accessibilité ? Prise en charge financière ?
  - Nusinersen : 70 000 € le flacon, 420 000 € la première année
  - ZolgenSMA : 1,9 millions d'euros !

JE VOUS REMERCIE POUR VOTRE ATTENTION