

PTC Therapeutics, Inc.

January 2015

Forward-Looking Statements

This presentation includes ‘‘forward-looking statements’,’ within the meaning of the Private Securities Litigation Reform Act of 1995, that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words ‘‘anticipate,’’ ‘‘believe,’’ ‘‘estimate,’’ ‘‘expect,’’ ‘‘intend,’’ ‘‘may,’’ ‘‘might,’’ ‘‘plan,’’ ‘‘predict,’’ ‘‘project,’’ ‘‘target,’’ ‘‘potential,’’ ‘‘will,’’ ‘‘would,’’ ‘‘could,’’ ‘‘should,’’ ‘‘continue,’’ and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. The forward-looking statements in this presentation include, among other things, statements about: (i) the timing and conduct of our clinical trials of Translarna (ataluren) for the treatment of nmDMD, nmCF and nmMPS I, as well as our trials in spinal muscular atrophy and BMI1, including statements regarding the timing of initiation, enrollment and completion of the trials and the period during which the results of the trials will become available; (ii) our plans to pursue development of Translarna for additional indications other than nmDMD, nmCF and nmMPS I; (iii) our ability to advance our earlier stage programs, including our antibacterial program; (iv) our plans to pursue research and development of other product candidates; (v) the potential advantages of Translarna; (vi) the rate and degree of market acceptance and clinical utility of Translarna; (vii) our ability to maintain the conditional marketing authorization of Translarna for the treatment of nmDMD in the European Economic Area; (viii) the timing of and our ability to obtain additional marketing approvals of Translarna and our other product candidates, and the ability of Translarna and our other product candidates to meet existing or future regulatory standards; (ix) our estimates regarding the potential market opportunity for Translarna, including the size of eligible patient populations and our ability to identify such patients; (x) our ability to expand the approved product label of Translarna for the treatment of nmDMD; (xi) our ability to commercialize Translarna, including our ability to successfully negotiate favorable pricing and reimbursement processes in the countries in which we may obtain regulatory approval; (xii) the timing and scope of our commercial infrastructure expansion, including the growth of our international presence in Europe and in other territories; (xiii) the potential receipt of revenues from future sales of our product candidates, including our ability to earn a profit from sales or licenses of Translarna for the treatment of nmDMD; (xiv) our sales, marketing and distribution capabilities and strategy; (xv) our ability to establish and maintain arrangements for the manufacture of Translarna and our other product candidates that are sufficient to meet clinical trial and commercial launch requirements; (xvi) our estimates regarding expenses, future revenues, capital requirements and needs for additional financing; (xvii) our intellectual property position; (xviii) the impact of government laws and regulations; (xix) our competitive position; and (xx) our expectations with respect to the development and regulatory status of our program directed against spinal muscular atrophy in collaboration with Roche and the Spinal Muscular Atrophy Foundation. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Our actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements we make as a result of a variety of risks and uncertainties, including those described in the ‘‘Risk factors’’ section of our most recent Form 10-Q. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

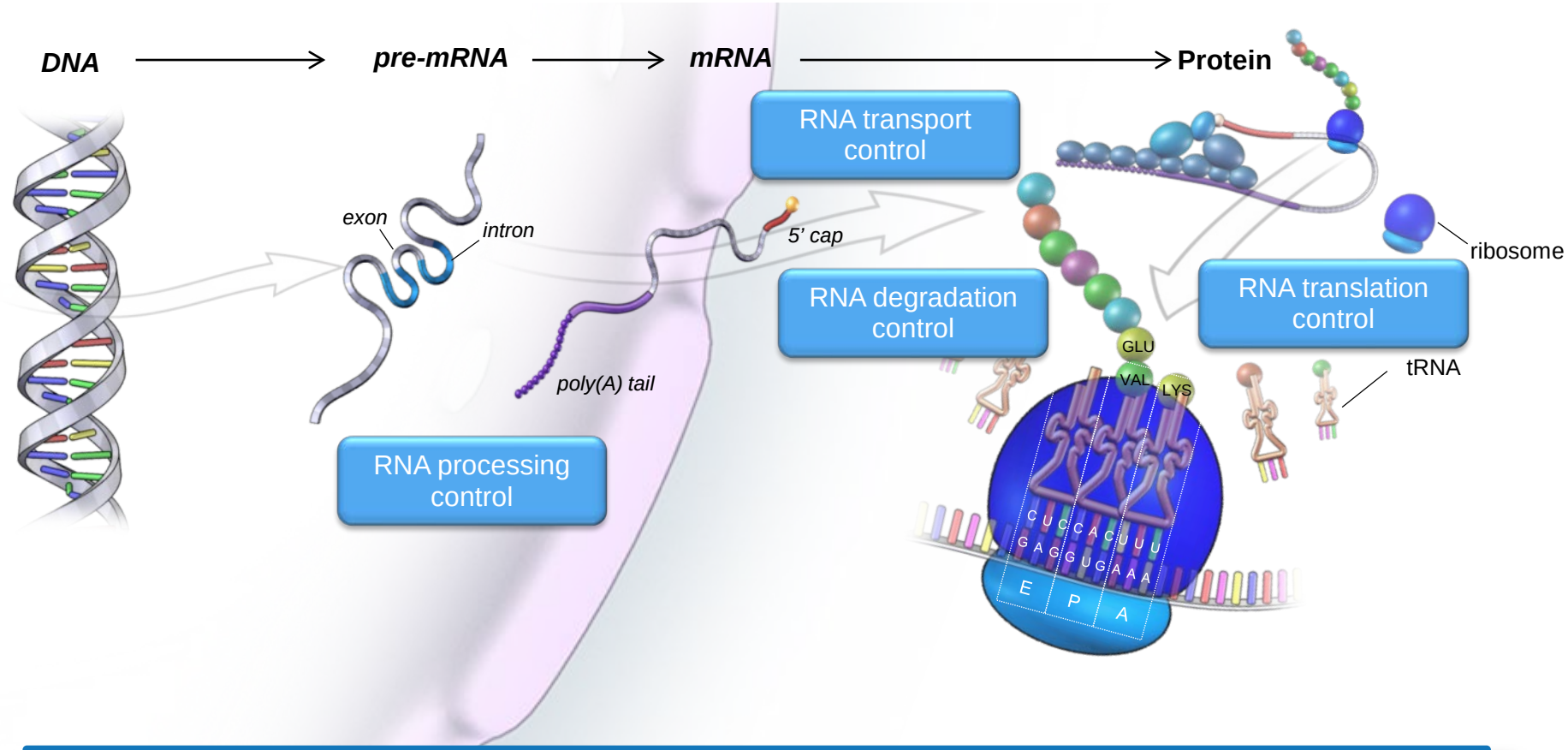
Our mission

To leverage our knowledge
of **RNA biology** to bring
novel therapeutics to patients affected
by **rare and neglected disorders**

Executing on PTC's strategy

- **Focus on the development and commercialization of Translarna™ (ataluren) in nmDMD, nmCF, nmMPS I and additional indications**
- **Expand PTC's clinical stage pipeline using our scientific expertise to develop novel compounds for unmet medical needs**
- **Foster relationships with strong strategic partners to further leverage PTC's discovery and development capabilities**

PTC's RNA-focused small molecule technology platform



PTC's Platform Technologies

- Nonsense Readthrough
- Alternative Splicing
- Nucleotide Repeat
- Protein Modification
- Transcript Regulators

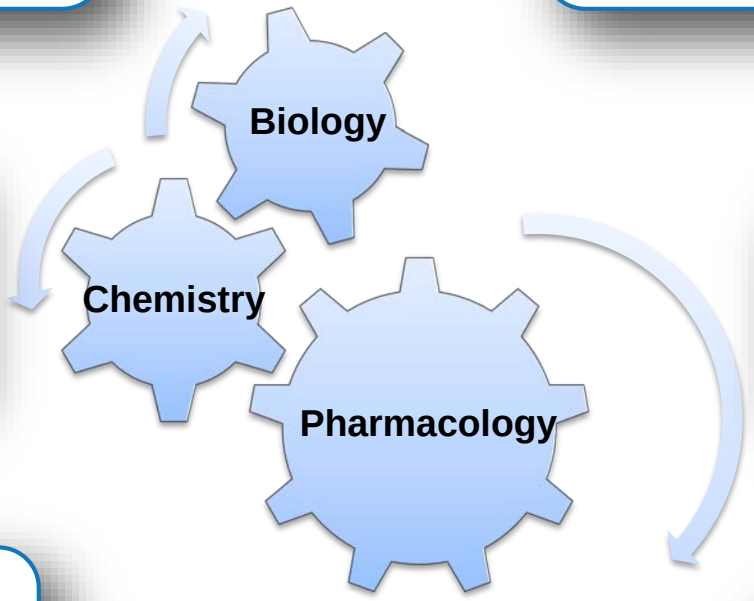
PTC's innovative discovery platform has produced multiple drug candidates

RG7800

Alters SMN2 splicing to produce functional protein

Translarna™ (ataluren)

Enables ribosomal read-through of premature termination codons



PTC596

Inhibits cancer stem cells through BMI1

PTC672

Inhibits resistant *N. gonorrhoeae*

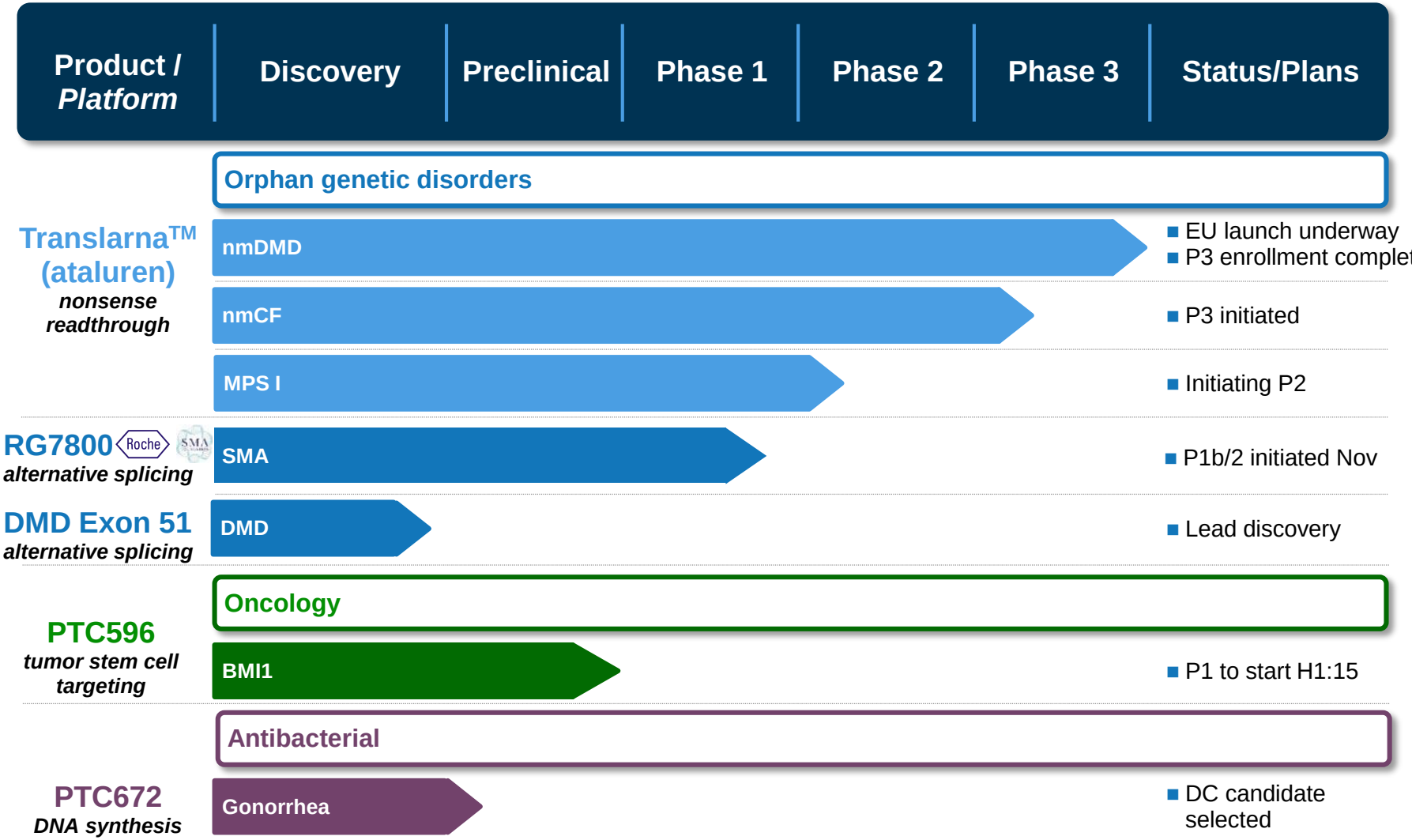
PTC299

Selectively inhibits stress-induced protein synthesis (VEGF)

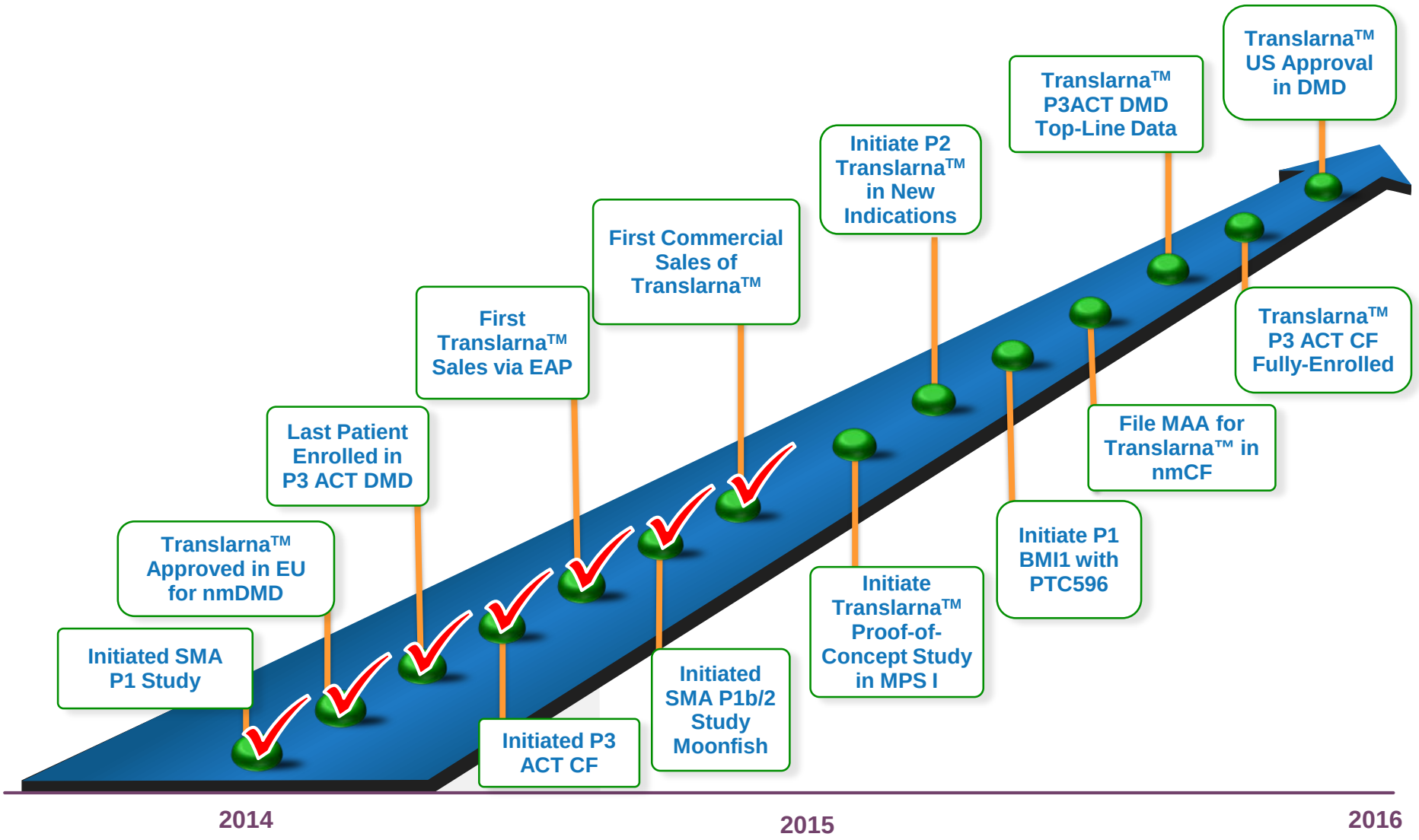
PTC725

Inhibits g1 HCV

Pipeline summary



PTC value drivers

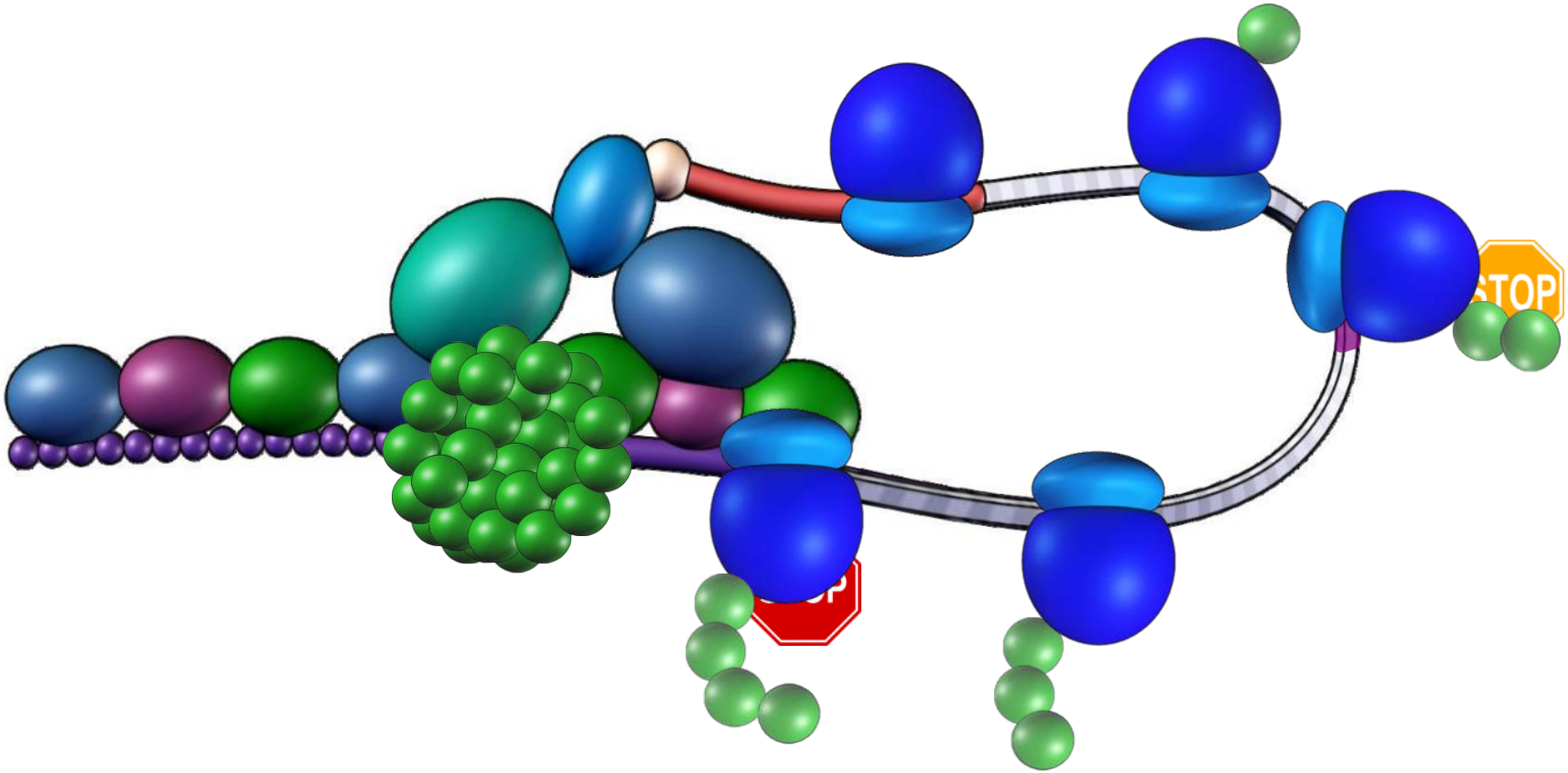




Translarna ™

Nonsense mutation readthrough

Translarna binds to the ribosome and enables readthrough of nonsense mutation to produce functional protein



- Potentially treats any nonsense mutation across multiple orphan disorders
- High specificity for nonsense readthrough without affecting normal termination codons
- Nonsense mutations are routinely identified by genetic testing

Translarna™: Potential across multiple rare disorders

Muscle disorders

- DMD (Welch 2007; Kayali 2012; Finkel 2013; Li 2014; Bushby 2014)
- Miyoshi myopathy/ Dysferlin (Wang 2010)

Neurological disorders

- Infantile Neuronal Ceroid Lipofuscinoses (INCL) (Sarkar 2011; Miller 2013)
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Ion channel disease

- Cystic fibrosis (CF) (Du 2008; Kerem 2008; Sermet-Gaudelus 2010; Wilshanski 2011; Gonzalez-Hilarion 2012; Johansonn 2014; Kerem 2014; Pibiri 2014)
- Long QT syndrome (Yu 2014)

Skin disease

- Pseudoxanthoma elasticum (Zhou 2013)
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- Choroideremia (Moosajee 2014)
- Aniridia (Gregory-Evans 2014)

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- Hurler's syndrome (MPS I) (Keeling, unpublished)

Genetically defined epilepsy

- CDLK5
- Rett Syndrome
- Dravet Syndrome

(independent investigators)

Translarna™:
First approved therapy for Duchenne muscular dystrophy

Characteristics

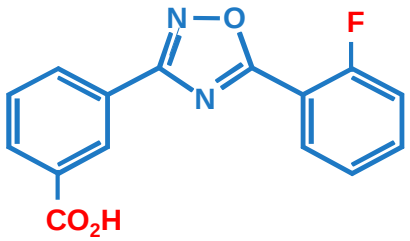
- Orally bioavailable
- Reliable manufacturing
- Pediatric-friendly formulation
- Generally well tolerated >750 individuals dosed to date

Market Potential

- ~11% of patients across all monogenic disorders have a nonsense mutation
- Potential disease modifying therapy
- Orphan designation EU & US
- PTC retains worldwide commercial rights
- Patents until 2024-2027 (composition & method of use)

Status

- EU approval for nmDMD ambulatory patients 5 yrs and older
- Confirmatory Phase 3 nmDMD trial - enrollment complete
- Phase 3 nmCF trial initiated
- Phase 2 in MPS I initiating





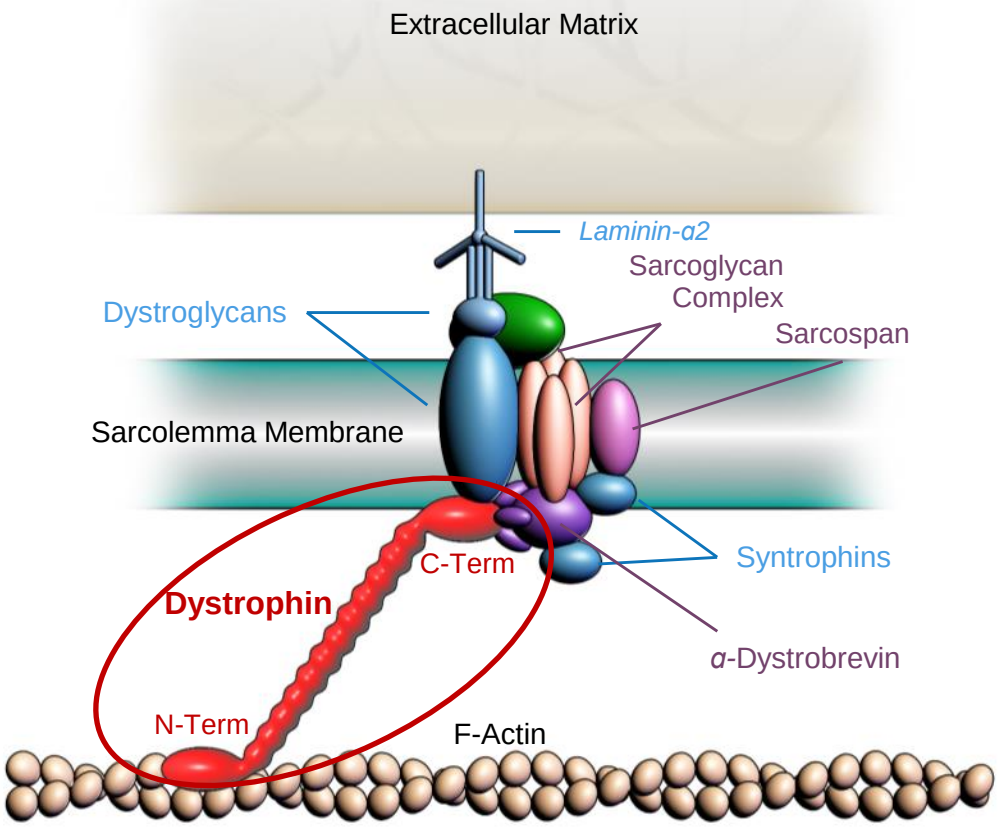


Translarna™

Nonsense mutation Duchenne Muscular Dystrophy

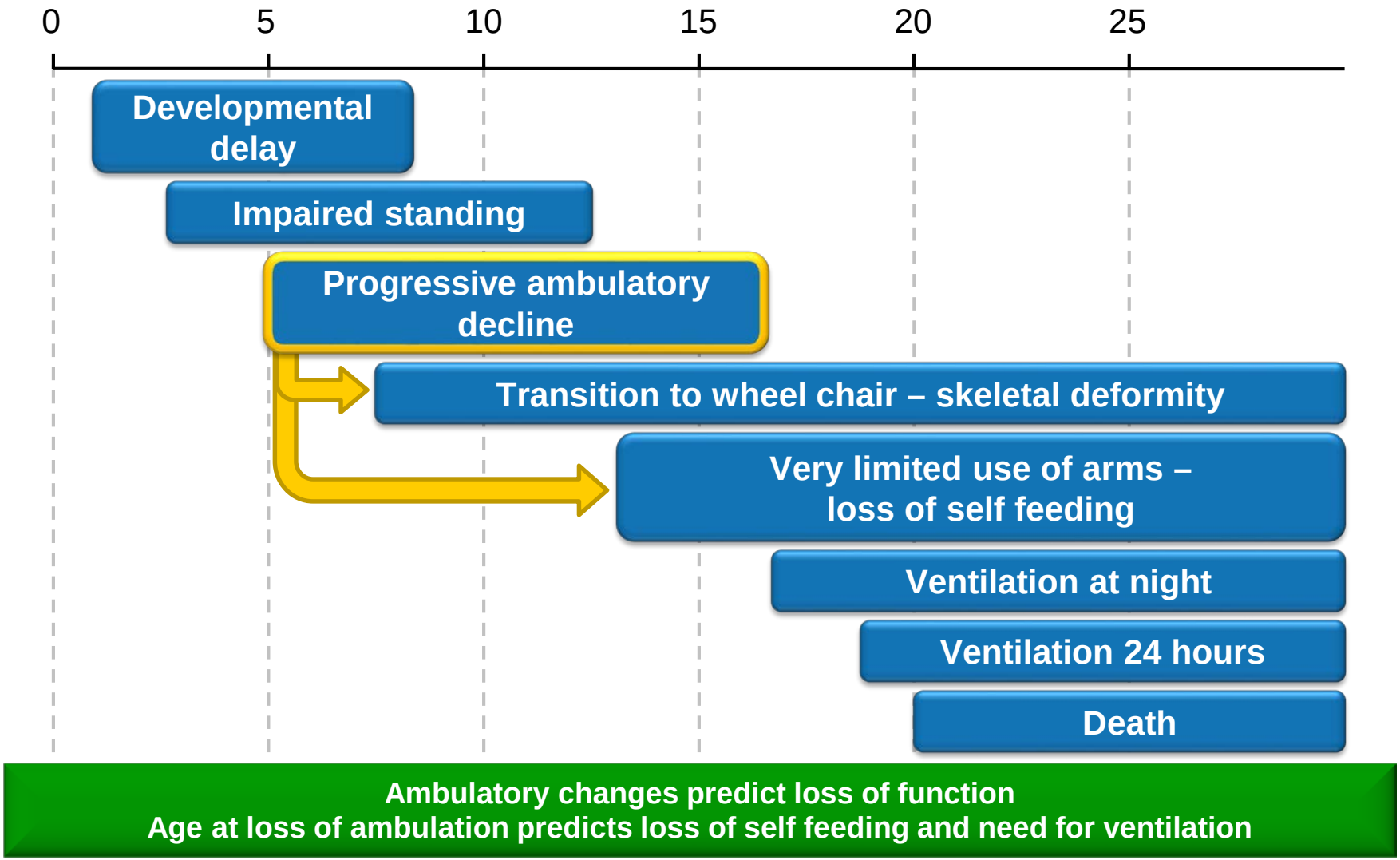
Duchenne muscular dystrophy (DMD) is a progressive and fatal genetic disorder due to the loss of dystrophin protein

- Muscles lacking dystrophin are more susceptible to muscle damage
- Dystrophin replacement is expected to prevent muscle damage
- ~34,000 boys & young men in US/EU
  - ~13% caused by nonsense mutations



Dystrophin stabilizes, but does not increase muscle strength

DMD is a progressive and fatal genetic disorder



Ambulatory changes predict loss of function
Age at loss of ambulation predicts loss of self feeding and need for ventilation

First drug approved for the underlying cause of DMD

Primary	Secondary	Tertiary
Positive 6MWT results ■ 31.3 m in overall population ■ 49.9 m in ambulatory decline group ■ 68.2 m in <350 m group	Improvement seen in TFTs ■ 10 m walk- run ■ Stair climb ■ Stair descend ■ All phases of disease	Better outcomes observed ■ Myometry – in 5&6 year olds ■ Quality of life ■ Fewer falls ■ Step activity ■ Less time in wheelchair
Natural History independently confirmed and consistent	Safety: Generally well tolerated	Confirmatory Trial: Well underway

EU Approval

Ongoing confirmatory Phase 3 ACT DMD clinical trial targeting patients in the ambulatory decline phase

Double-blind placebo-controlled study

Length of Trial	Translarna™ (n)	Placebo (n)
48 weeks	110	110

Primary outcome measure:

- 6MWD (change from baseline)

Secondary outcome measure:

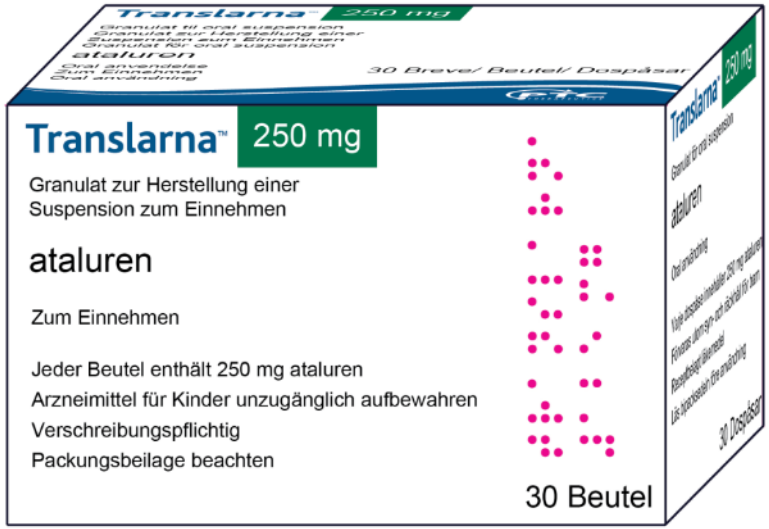
- Timed-function tests
- North Star
- PODCI QoL

Eligibility Criteria	Stratification
≥7 years & ≤16 years Steroid use 6MWD ≥150 m ≤80% of predicted for age and height	≥350 m vs <350 m ≥9 years vs <9 years

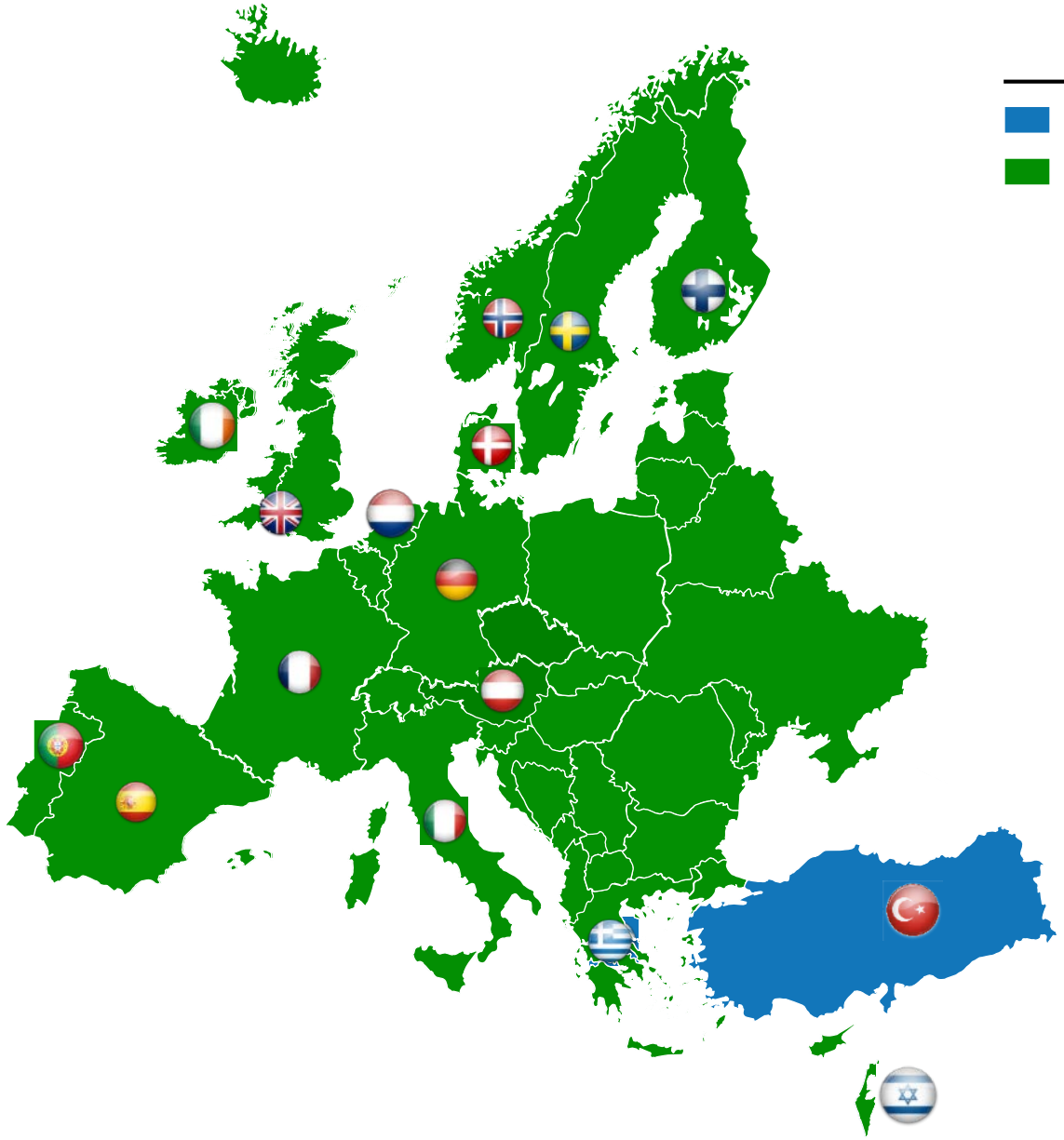
Enrollment complete - Top-line data Q4 2015

Commercial launch activities are well underway

- ✓ Senior commercial leadership team in place and international organization established
- ✓ Supply chain and distribution processes in place
- ✓ Early Access Programs authorized in France, Italy, Spain, Turkey and Israel
- ✓ Market Access Dossiers in key launch countries submitted
- ✓ First commercial sales began in Germany



Translarna access expanding rapidly: Focusing first on fastest access geographic areas



Translarna access expanding rapidly: Focusing first on fastest access geographic areas

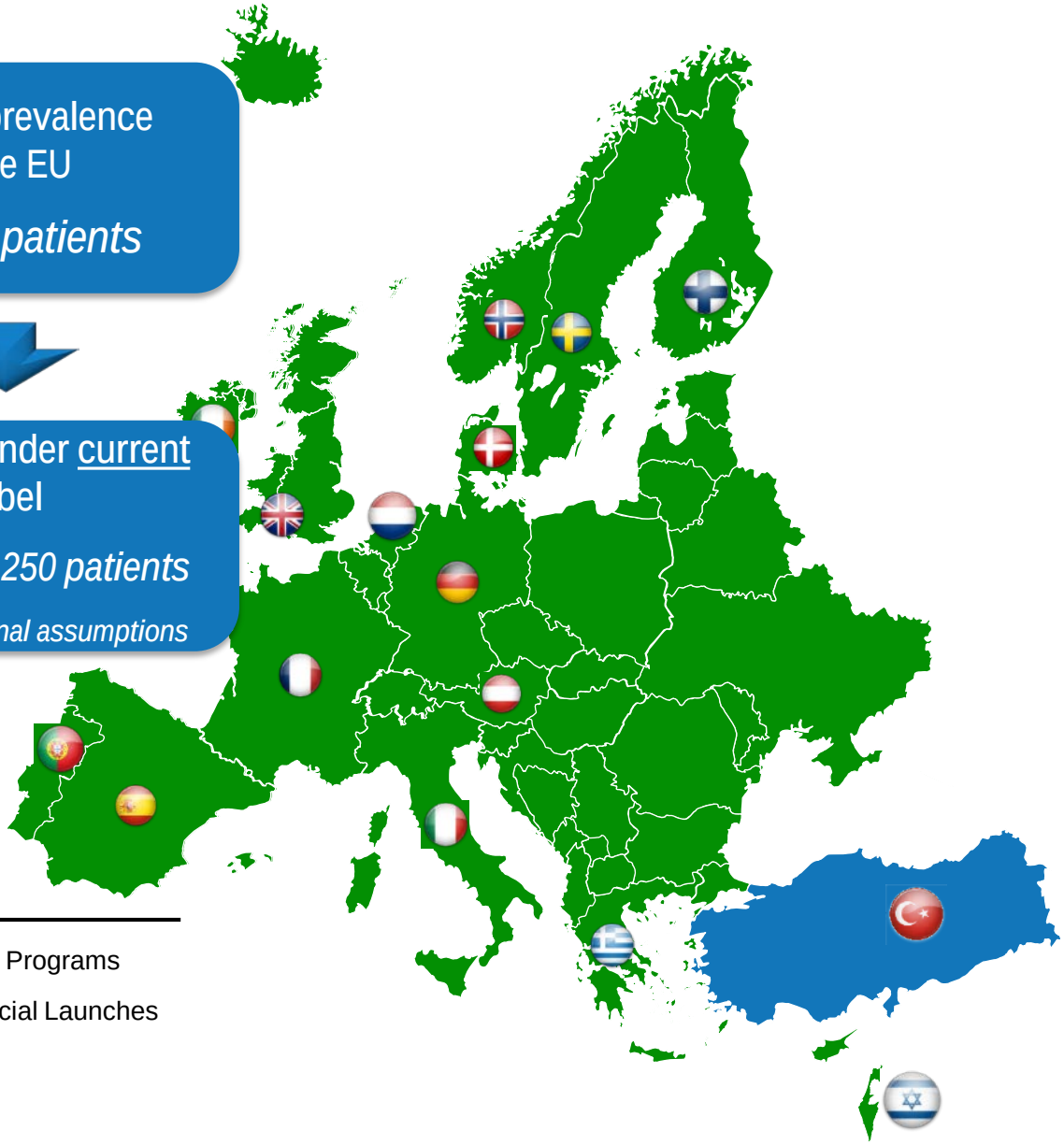
nmDMD prevalence in the EU

~ 2,500 patients

~ 40-50% under current label

~ 1,000 – 1,250 patients

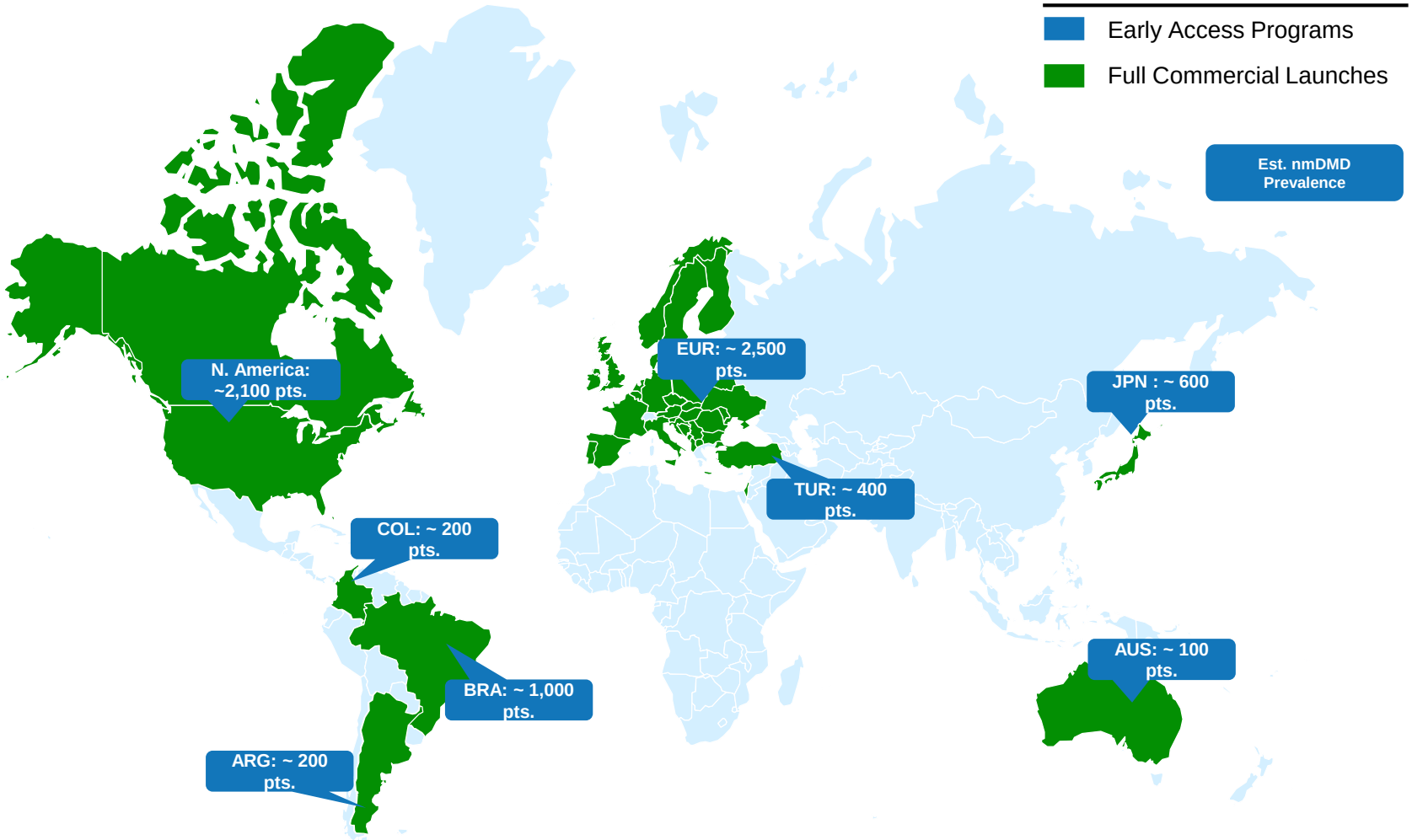
Based on internal assumptions



Early Access Programs

Full Commercial Launches

Global concurrent expansion process



Maximizing access to patients in markets with successful orphan drug history

Identifying and mapping patients: Germany example

Estimated nmDMD prevalence in Germany ~400 pts.

↓

~ 40-50% under current label
~ 160-200 patients

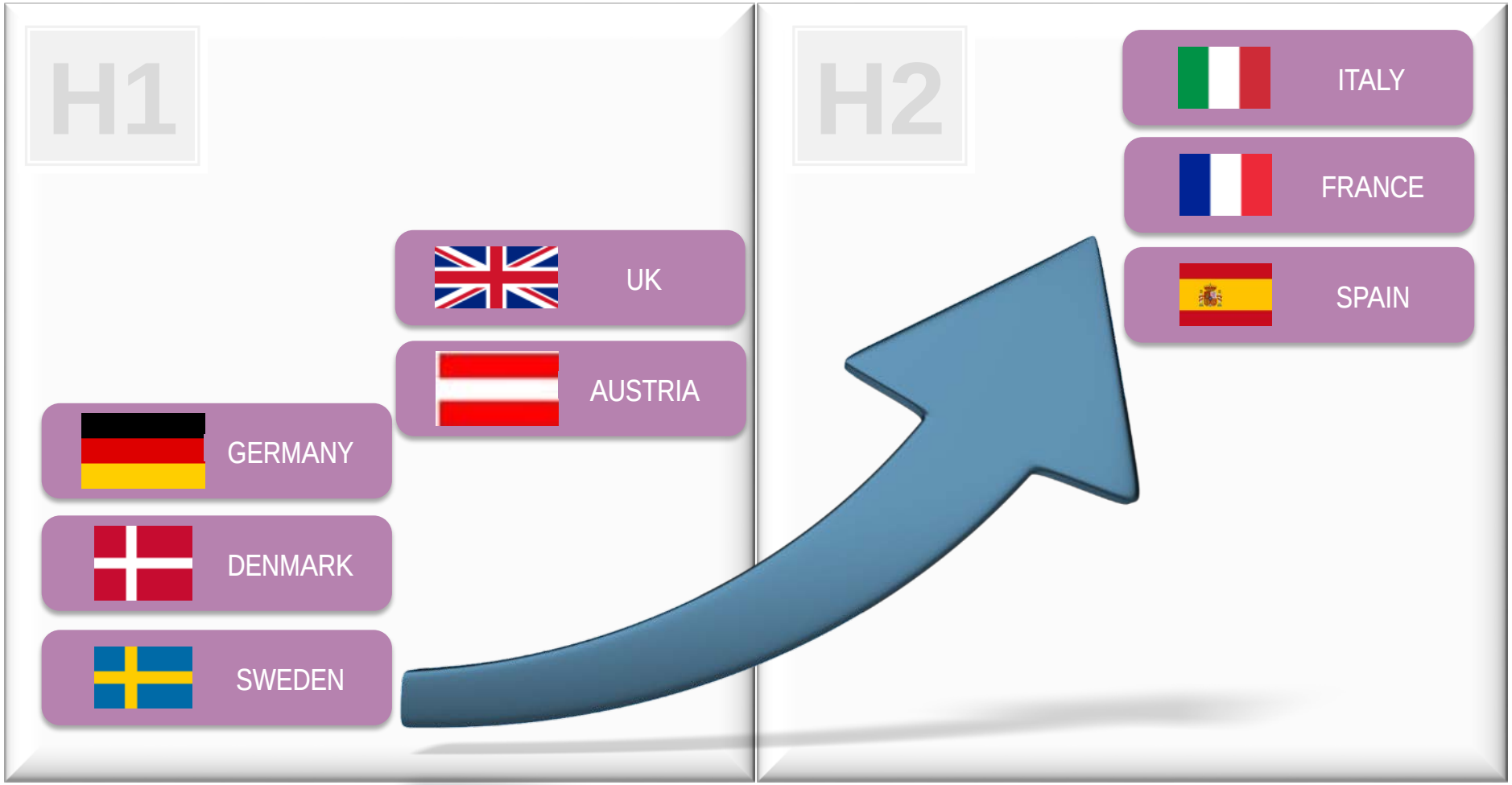
↓

Known identified patients on label (50%)
~ 90 patients



Patient #s based on internal assumptions

Positioned to maximize the commercial launch in 2015



EU launches on track pending pricing negotiations



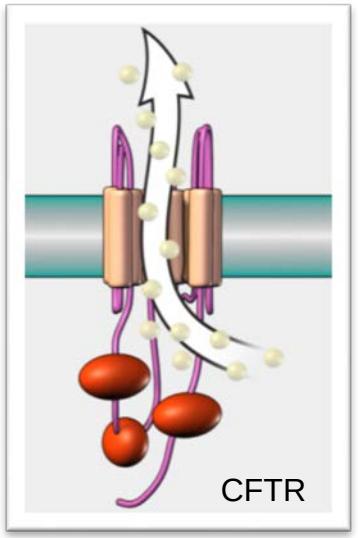
Translarna™

Nonsense mutation Cystic Fibrosis

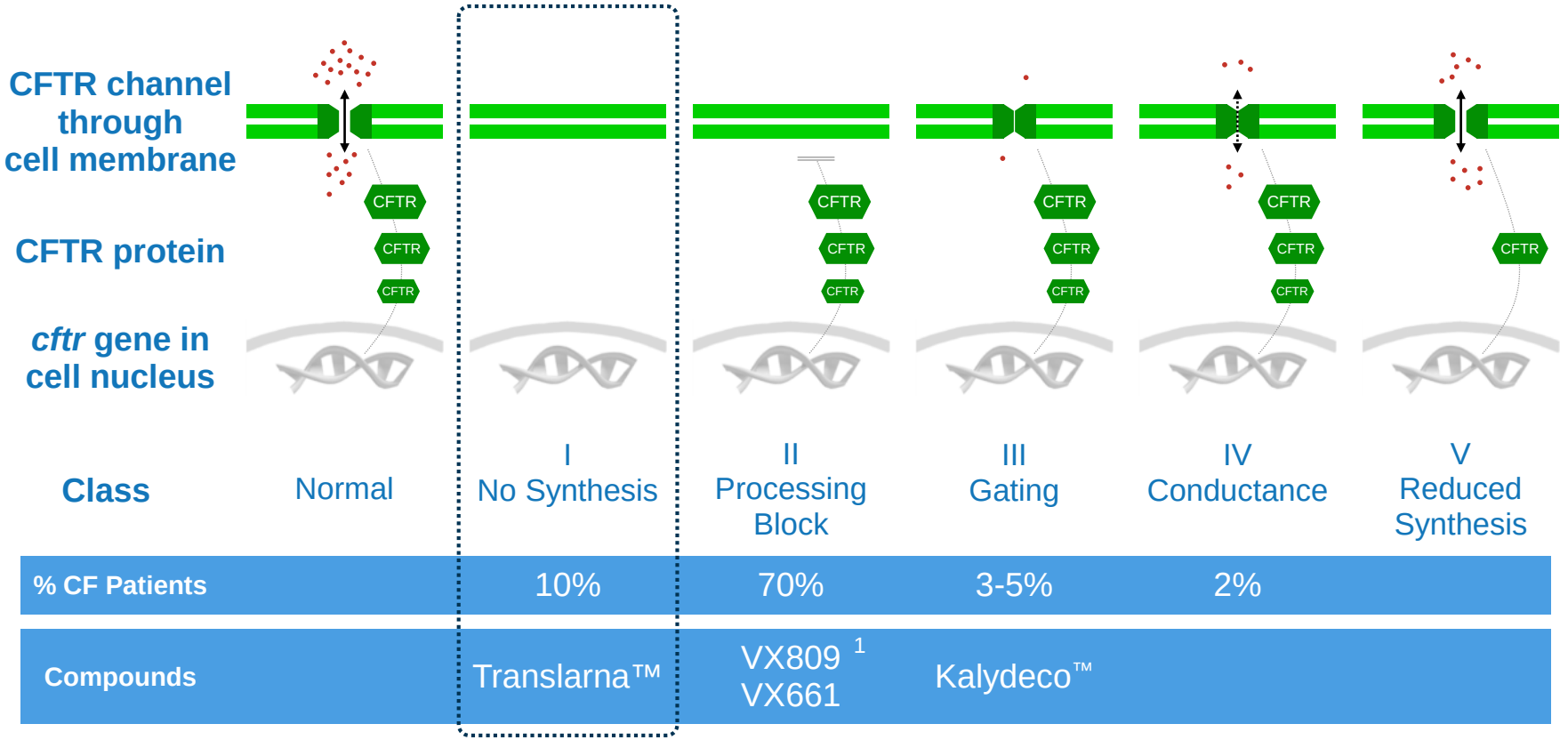
Cystic fibrosis is a progressive and fatal genetic disease

- Life-threatening disease with average age of death in the mid-twenties
- Death typically due to respiratory failure
- Caused by defects in the CFTR gene
- ~70,000 patients in US/EU
  - ~10% caused by nonsense mutations
- Nonsense mutations are the most severe form
- For patients with a nonsense mutation only palliative treatments are available





Nonsense mutations cause the most severe form of CF



Translarna is only compound in development for the most severe form (Class 1)

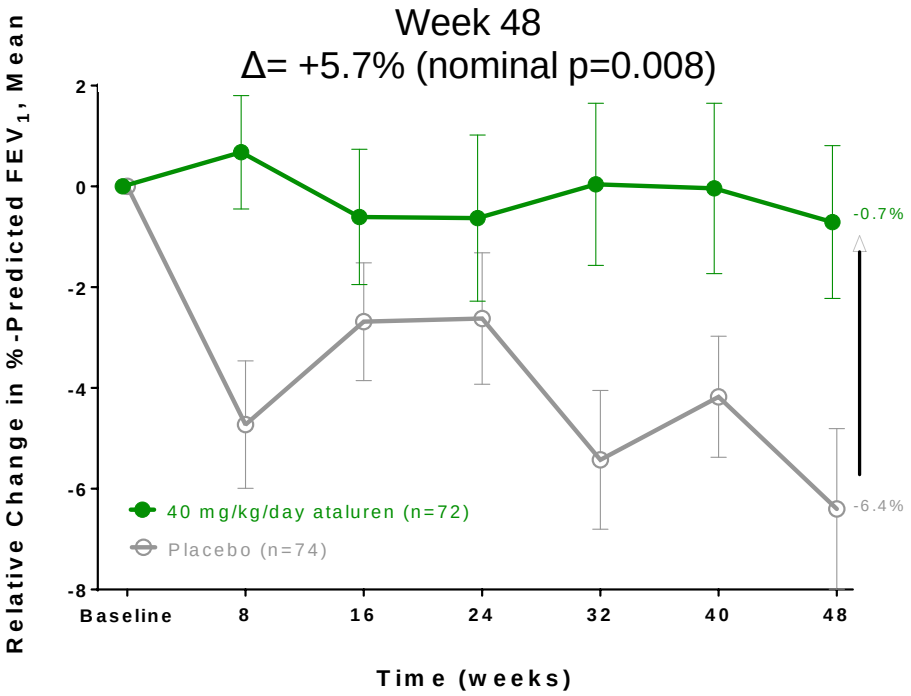
JAN 2015

1. VX809 and VX661 are only for homozygote, 45-55%

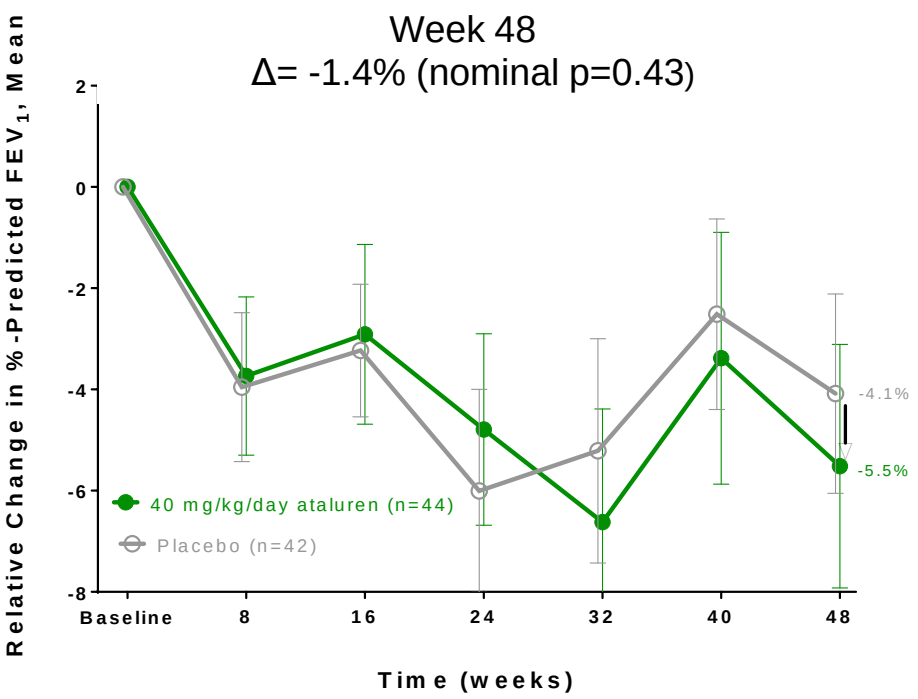
Translarna had a clinically meaningful benefit (ΔFEV_1 +5.7%) in the ~65% of nmCF patients not on inhaled TOBI®

Based on Phase 3 post-hoc analysis

Without Inhaled TOBI®[1]



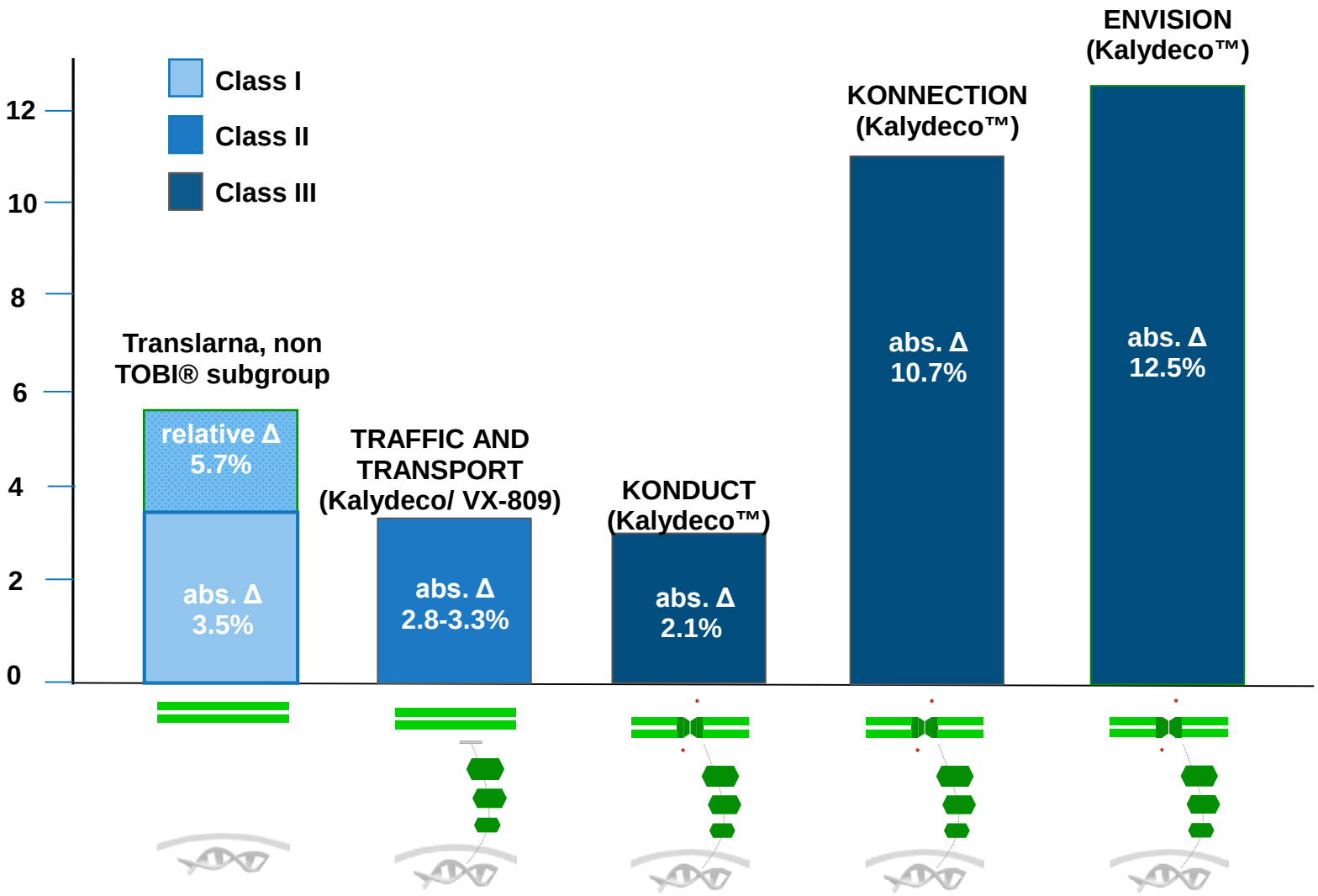
With Inhaled TOBI®[2]



Translarna decreased pulmonary exacerbation rates in Non-TOBI® patients by 41% vs. placebo nominal p=0.005[3]

1. No antibiotics or use of non-aminoglycoside antibiotics
2. Alone or with other antibiotics
3. Overall population decreased 23% (n=226, p=0.0992)

Significant FEV_1 changes seen in recent CF trials vs. Translarna™



*Measured in separate trials

ACT CF (Ataluren Confirmatory Trial) study design

Length of Trial	Translarna™ (n)	Placebo (n)
48 weeks	104	104

Primary outcome measure:

- % predicted FEV1

Secondary outcome measure:

- Pulmonary exacerbation rate
- CFQ-R
- BMI and LFTs

Eligibility Criteria	Stratification
■ Nonsense mutation CF ■ ≥6 years ■ FEV1 ≥40% and ≤90% predicted ■ No chronic inhaled TOBI	■ Age: <18 vs ≥18 years ■ Inhaled antibiotic use (yes vs no) ■ Baseline FEV1: ≥65% vs <65% of predicted

On-track to complete enrollment in H2 2015

MPS 1: Next Proof-of-Concept Study for Translarna™

Muscle disorders

- ✓ DMD (Welch 2007; Kayali 2012; Finkel 2013; Li 2014; Bushby 2014)
- Miyoshi myopathy/ Dysferlin (Wang 2010)

Neurological disorders

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Ion channel disease

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Skin disease

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Genetically defined epilepsy

- CDLK5
- Rett Syndrome
- Dravet Syndrome

(independent investigators)

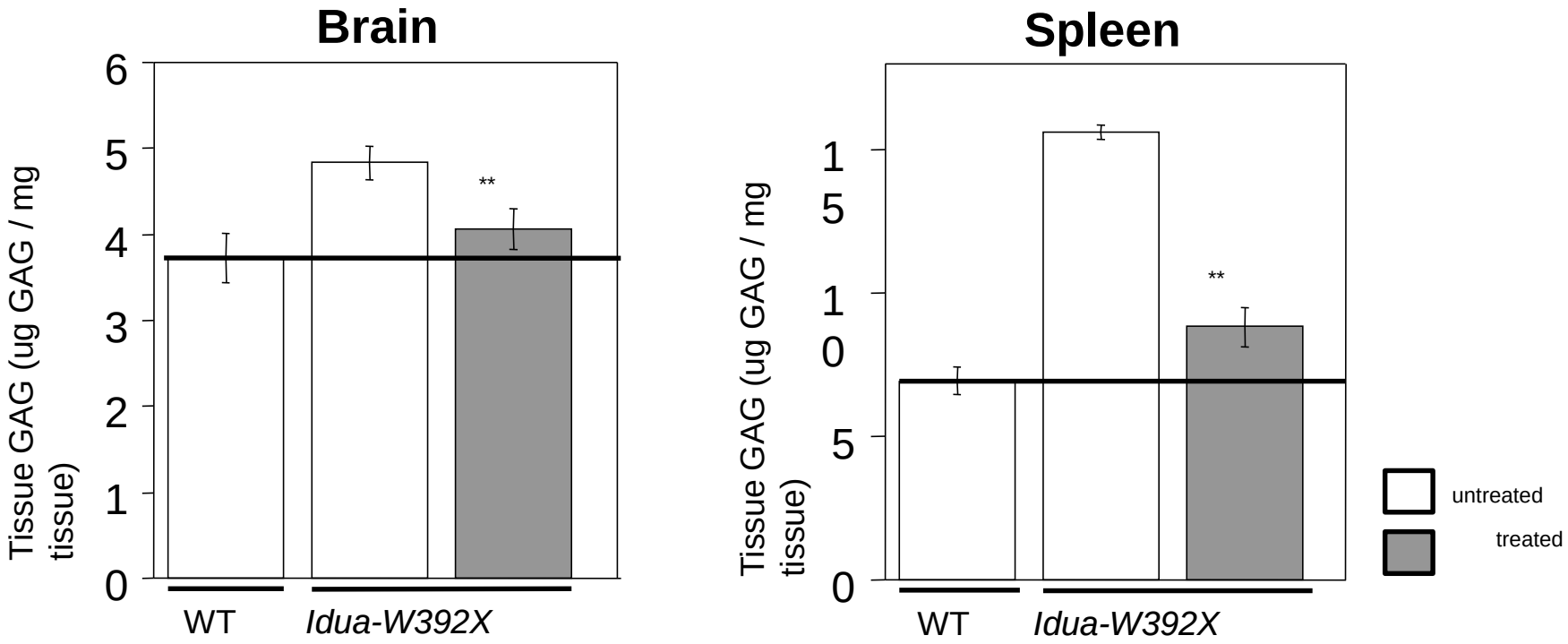
MPS 1 CNS effects are not addressed by existing therapy

- Enzyme replacement therapy has limited efficacy in addressing the CNS pathology of MPS I [1]
- CNS involvement in MPS I can result in a wide range of developmental delay
  - Most severe cases result in severe retardation
  - Brain compression seen as a secondary CNS effect
  - Cardiac and bone/joint-related abnormalities may not be corrected by either Bone marrow transplant/HSCT or ERT

Translarna crosses BBB & penetrates other key tissues

1. Kakkis E, McEntee M, Vogler C, Le S, Levy B, Belichenko P, et al. Intrathecal enzyme replacement therapy reduces lysosomal storage in the brain and meninges of the canine model of MPS I. Mol Genet Metab. 2004;83:163–174.

Translarna treatment reduces GAG levels in multiple tissues in an MPS I (Hurler) nonsense-mutation mouse model



**p<0.01
(t-test, compared to Idua-W392X vehicle)

Neufeld and Muenzer, The Mucopolysaccharidoses, in The Metabolic and Molecular Bases of Inherited Disease, 2001

Keeling et al unpublished data

Translarna™: Potential across multiple rare disorders

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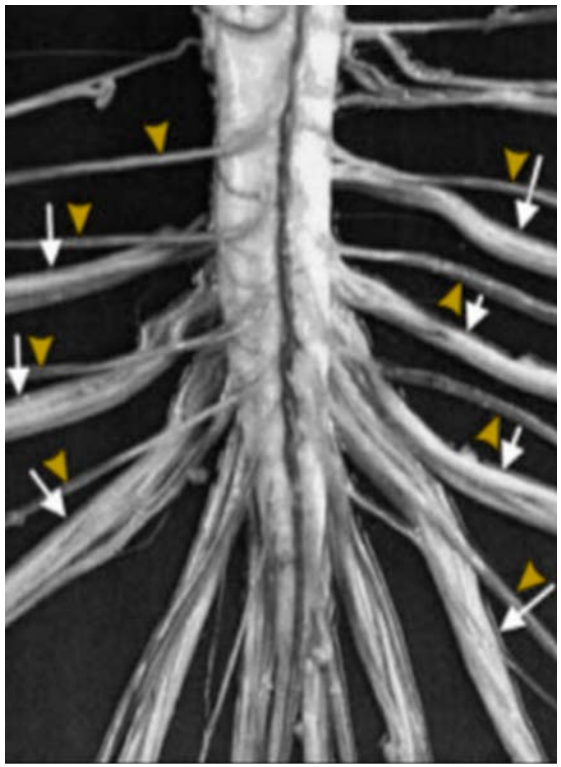


Spinal Muscular Atrophy

Discovery of a small molecule therapeutic

Spinal Muscular Atrophy:
The leading genetic cause of mortality in infants

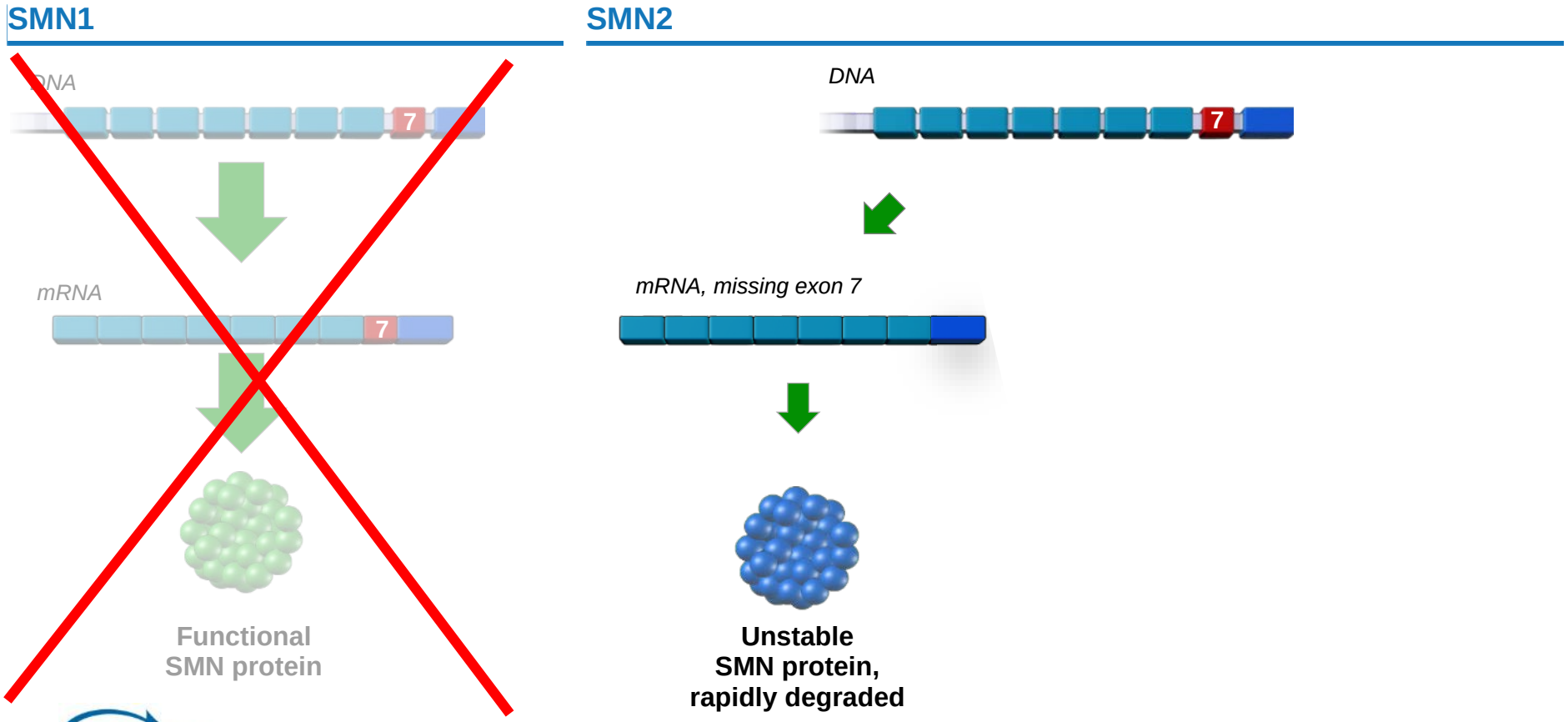
- Spinal muscular atrophy (SMA) is caused by the loss of a SMN-1 gene
- Low expression of SMN protein leads to the loss of motor neurons in the spinal cord
- Low levels of SMN lead to the death of motor neurons in the spinal cord and muscle atrophy
- One in every 10,000 children born is affected with the disorder
- No marketed therapies for SMA, only palliative treatments
- SMA program partnered with Roche and the SMA Foundation



Dorsal Root
Ventral Root

Targeting alternative splicing in SMA

- SMA patients rely on a related SMN2 gene which produces only low levels of SMN protein due to a splicing defect
- Small molecule selectively targets SMN splicing to include exon 7 and produce functional SMN



The Spinal Muscular Atrophy program validates PTC's splicing platform

- Highly active, orally bioavailable compounds
- SMN splicing correction and protein induction in cells from SMA patients
- SMN splicing correction and protein induction in mouse models of SMA
- Significant improvement in survival, body weight gain and motor behavior in mouse model of severe SMA
- Currently in clinical development
- PTC's splicing platform may be broadly applicable to many biological targets



MOTOR NEURON DISEASE

SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy

MOLECULAR BIOLOGY

A splicing magic bullet

Drugs that modulate RNA splicing are potential therapeutics for spinal

NEUROMUSCULAR DISORDERS

Beefing up the right splice variant to treat spinal muscular atrophy

Spinal muscular atrophy (SMA), the leading genetic cause of infant mortality, is characterized by progressive degeneration of motor neurons in the anterior horn of the

compounds that alter *SMN2* splicing, thereby increasing the production of full-length *SMN2* transcripts. By screening a library of ~200,000 compounds and performing further chemical optimization for molecules

SMN-C3, protein levels were partially restored in the brain and spinal cord, and fully restored in muscle to those levels observed in unaffected heterozygous *Smn1*$^{+/-}$ mice.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Romancing the Spliceosome to Fight Spinal Muscular Atrophy

Kathryn J. Swoboda, M.D.

Every scientist, clinician, and patient seeks that holy grail that will cure disease. Nowhere is this need more acute than in the field of neurodegeneration. In neurogenetic diseases, in the large majority of cases, aberrant code is embedded in the DNA in every cell, and the blood–brain bar-

cies from a single pre-mRNA template. Alternative splicing results in the exclusion of one or more exons from the mature mRNA and facilitates the expression of different protein isoforms (all derived from the same gene) at different stages of development, in different tissues, and in

P1a showed no S.A.Es
Demonstrated proof of mechanism

MOONFISH enrolling- completion expected Jan 2016

Double-blind placebo-controlled study

Dosing	(n)
12 week cycles Multiple doses	48

Primary outcome measure:

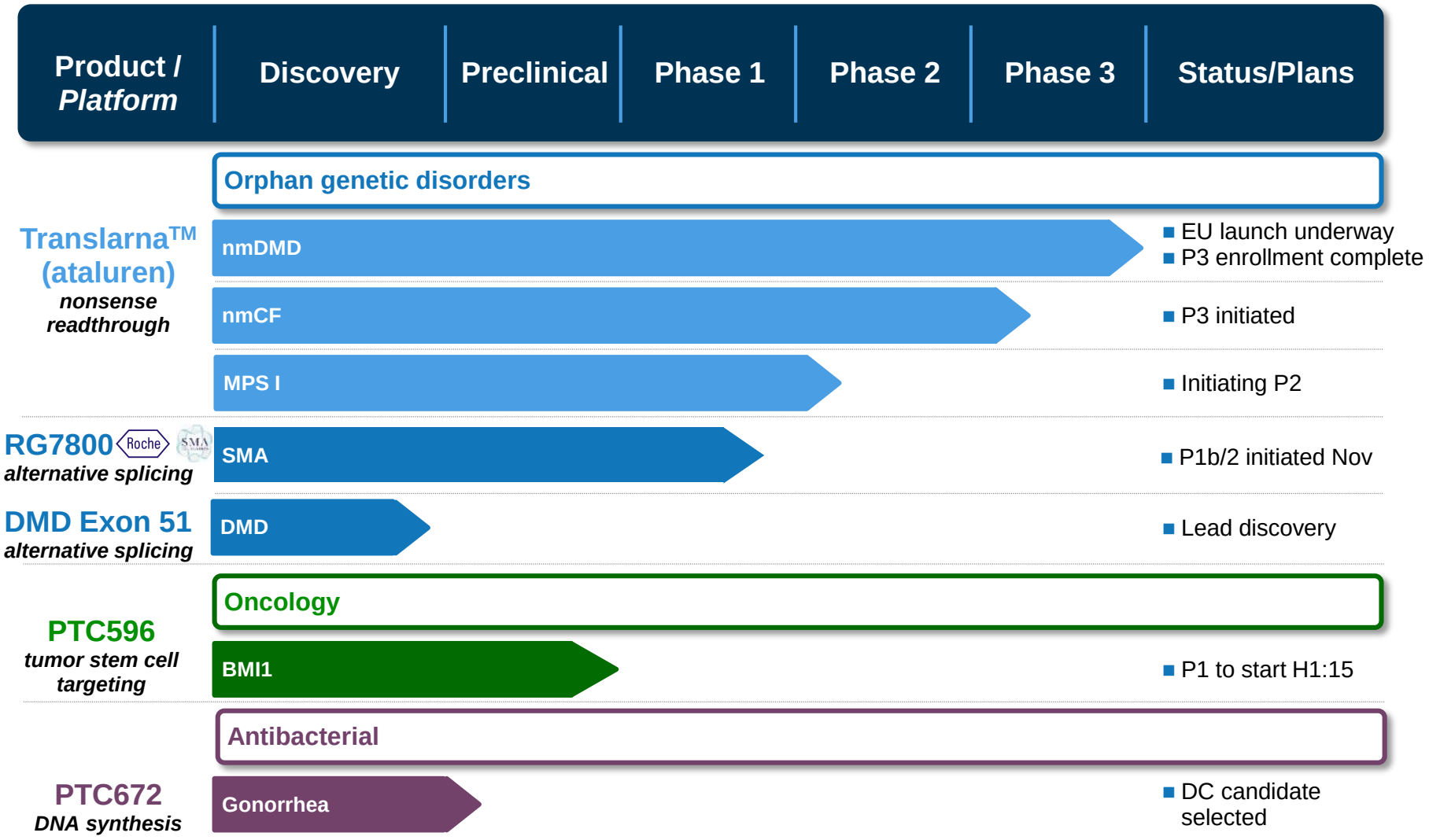
- Safety and tolerability

Enrollment Criteria
≥2 years & ≤55 years Primarily SMA types 2 & 3

Secondary outcome measure:

- Plasma concentration & AUC
- SMN protein and SMN2 mRNA levels in blood
- Nerve and muscle function

Pipeline summary





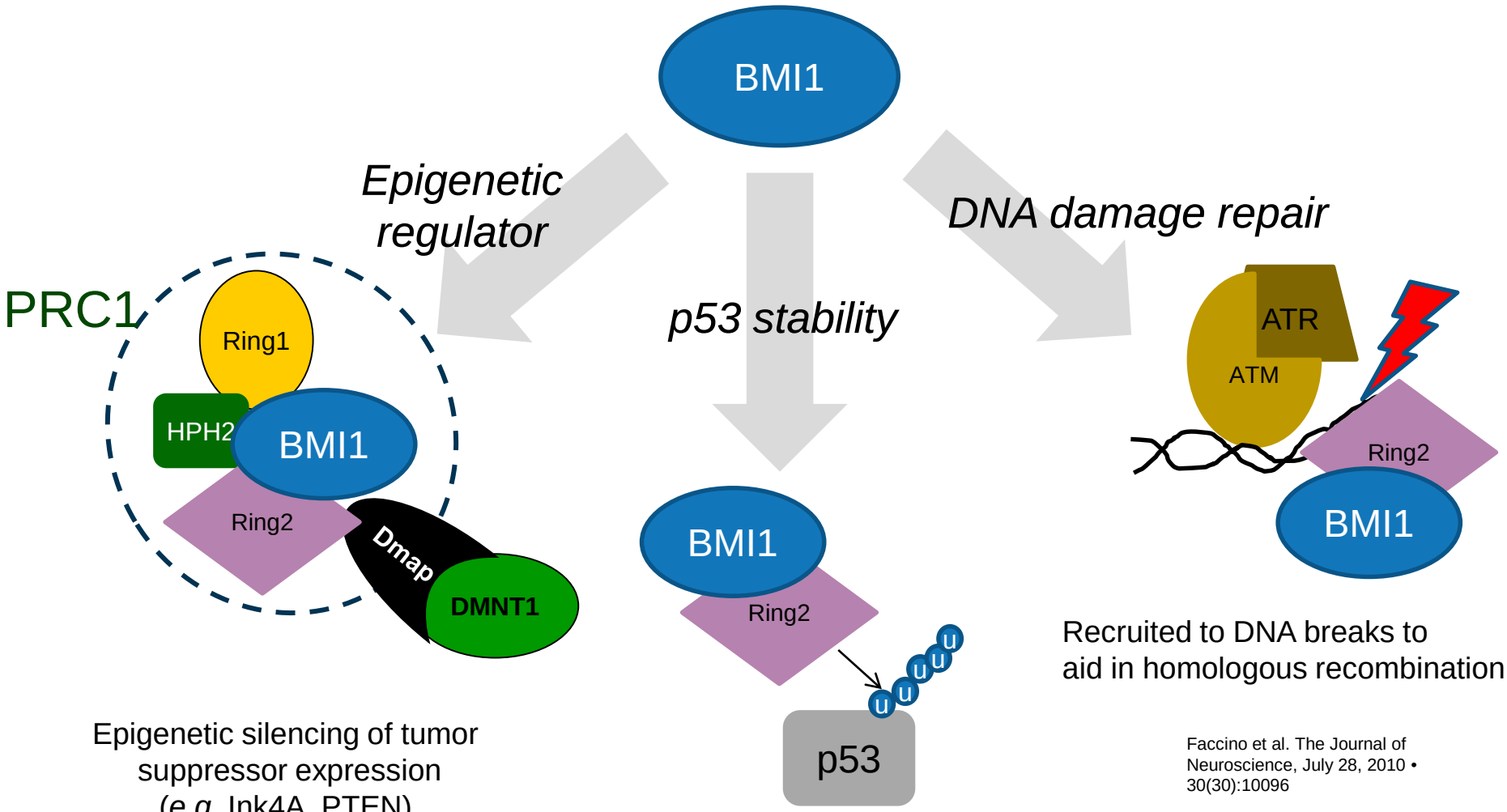
www.ptcbio.com



PTC596

BMI1 Tumor target

BMI1 imparts both immortality and resistance to tumor cells



Epigenetic silencing of tumor suppressor expression (*e.g.* Ink4A, PTEN)

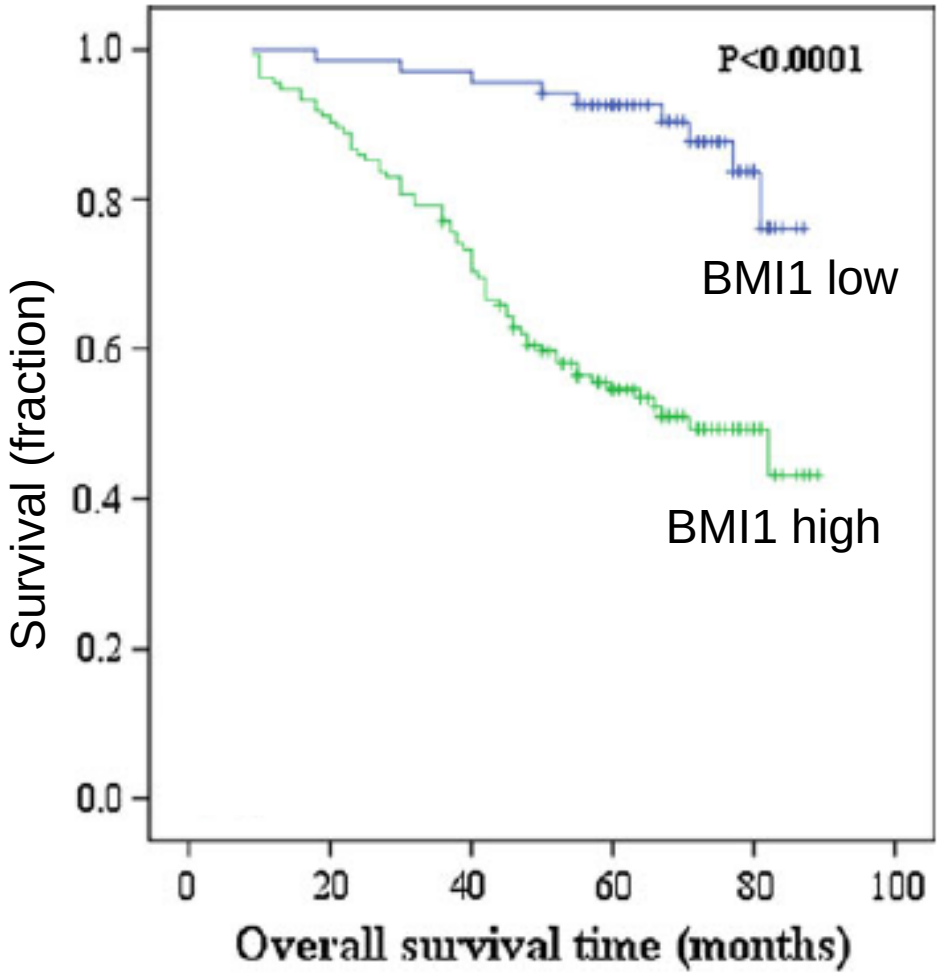
Agherbi et al. PLoS One. 2009 May 20;4(5):e5622

Mediates poly-ubiquitylation and degradation of p53

Recruited to DNA breaks to aid in homologous recombination

Faccino et al. The Journal of Neuroscience, July 28, 2010 • 30(30):10096

High BMI1 protein expression predicts poor overall survival in the clinic: Colorectal cancer



J Cancer Res Clin Oncol (2010) 136:997–1006

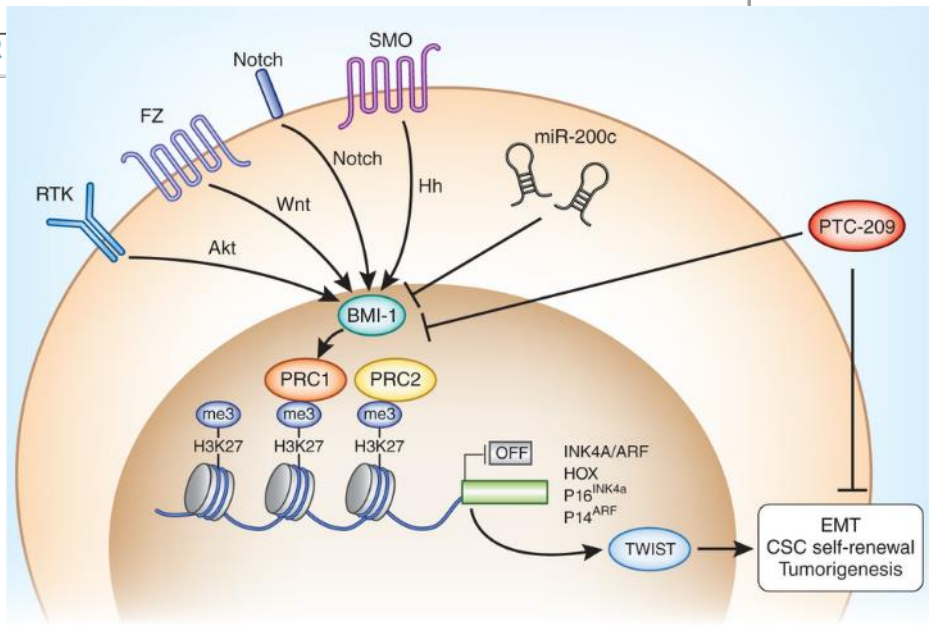
PTC compounds reduce the expression of BMI1 and deplete tumor stem cell populations within model systems

nature medicine

Self-renewal as a therapeutic target in human colorectal cancer

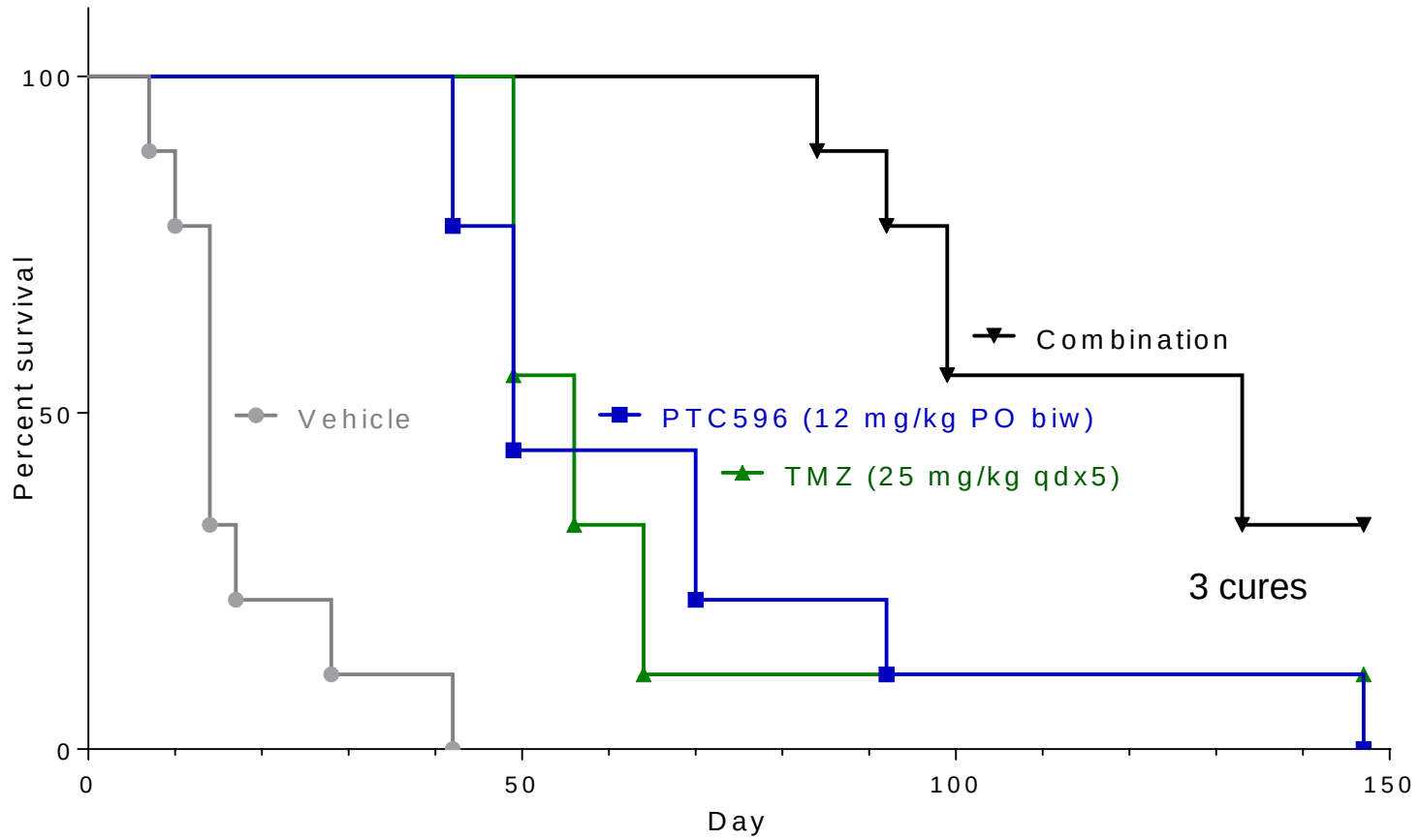
Antonija Kreso[1,2], Peter van Galen[1], Nicholas M Pedley[1,3], Evelyne Lima-Fernandes[4], Catherine Frelin[1,5], Thomas Davis[6], Liangxian Cao[6], Ramil Baiazitov[6], Wu Du[6], Nadiya Sydorenko[6], Young-Choon Moon[6], Lianne Gibson[1,3], Yadong Wang[1,3], Cherry Leung[1,3], Norman N Iscove[1,5,7], Cheryl H Arrowsmith[1,4,5], Eva Szentgyorgyi[8], Steven Gallinger[9,10], John E Dick[1,2,11] & Catherine A O'Brien[1,3,9,11]

NATURE MEDICINE VOLUME 20 | NUMBER



From: "Targeting self-renewal, an Achilles' heel of cancer stem cells" MS Wicha, Nature Medicine 20, 14–15 (2014)

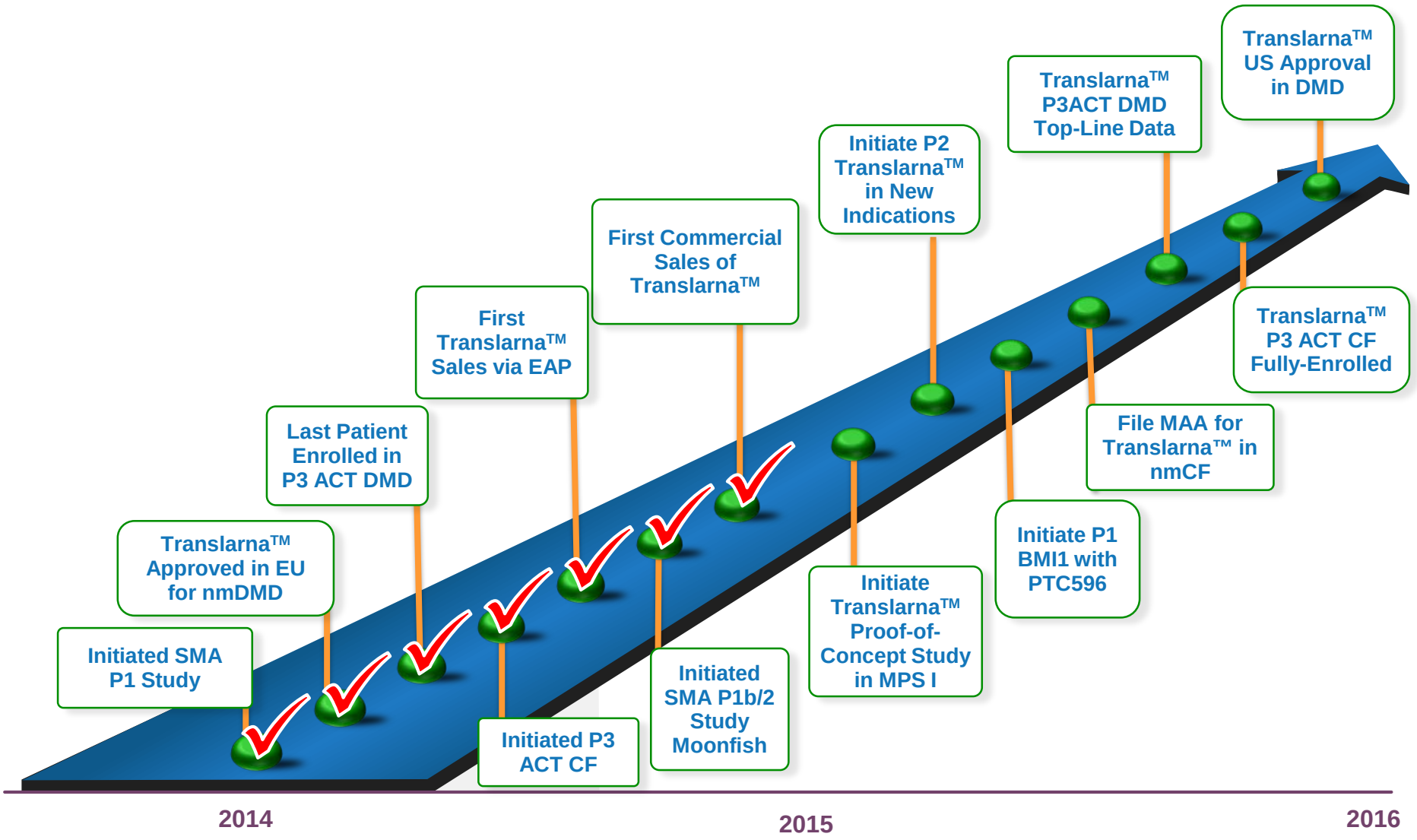
The combination of PTC596 and standard-of-care extends survival of mice with patient-explant GBM tumors



*p<0.05, ANOVA, multiple pairwise comparisons (PTC596 vs. combination, and temozolomide vs combination)

S Keir, 2014 (unpublished)

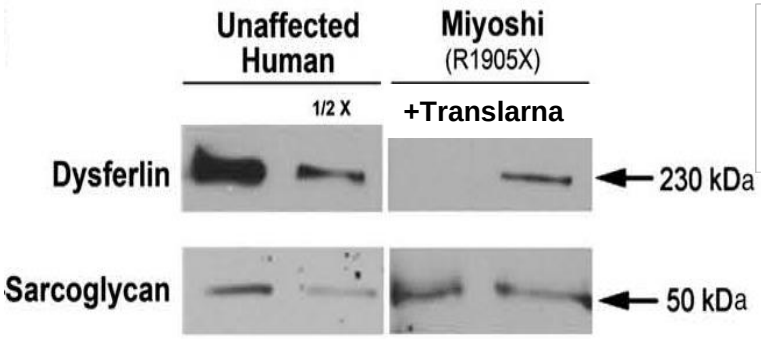
PTC value drivers



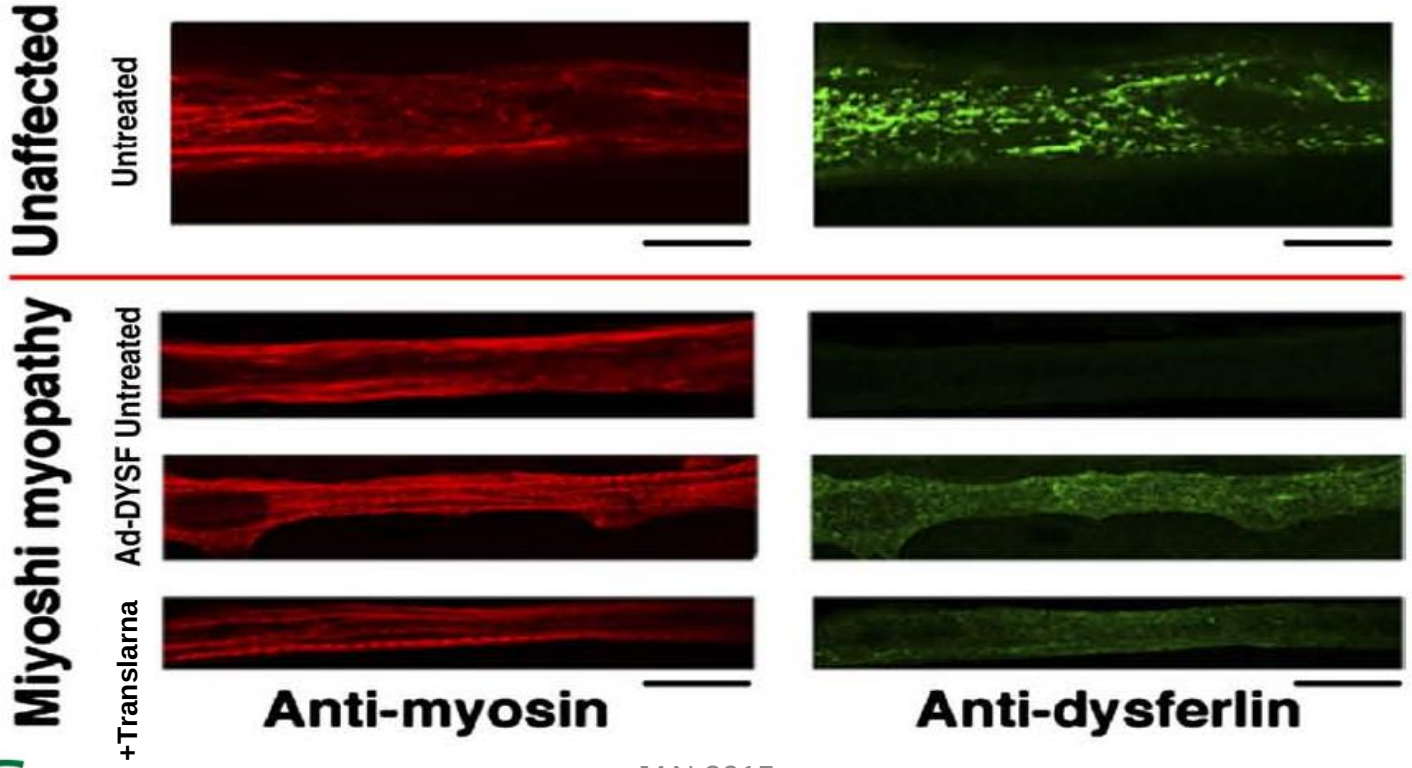


Appendix slides

Miyoshi myopathy: Translarna treatment of nmMyoshi myopathy patient myotubes increases dysferlin expression

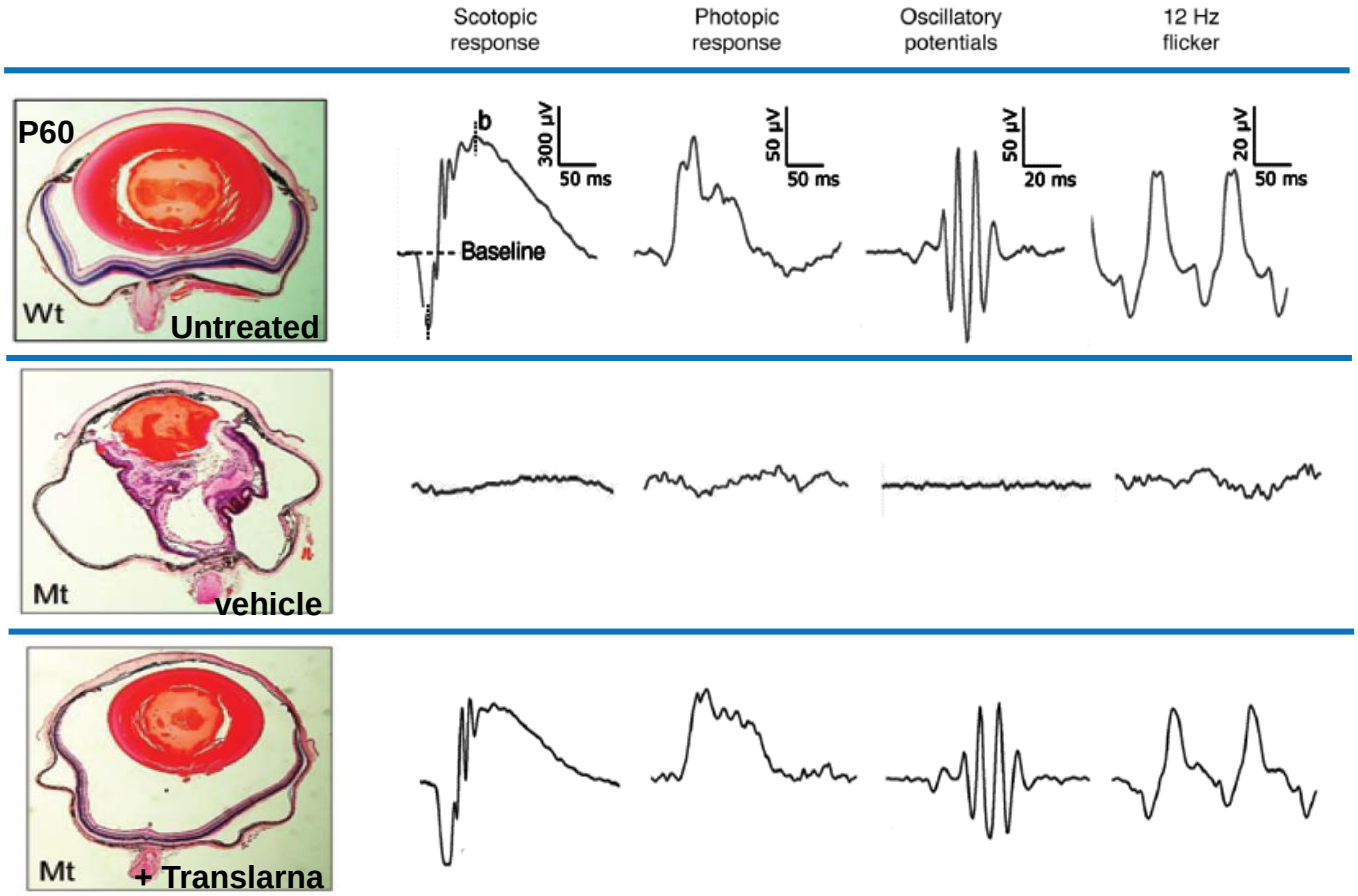


- Muscle wasting disorder in early adults
- Caused by mutations of the DYSF/ANOS genes
- In Japan incidence is 1/440,000



Translarna restores morphology and sight in Aniridia mouse model

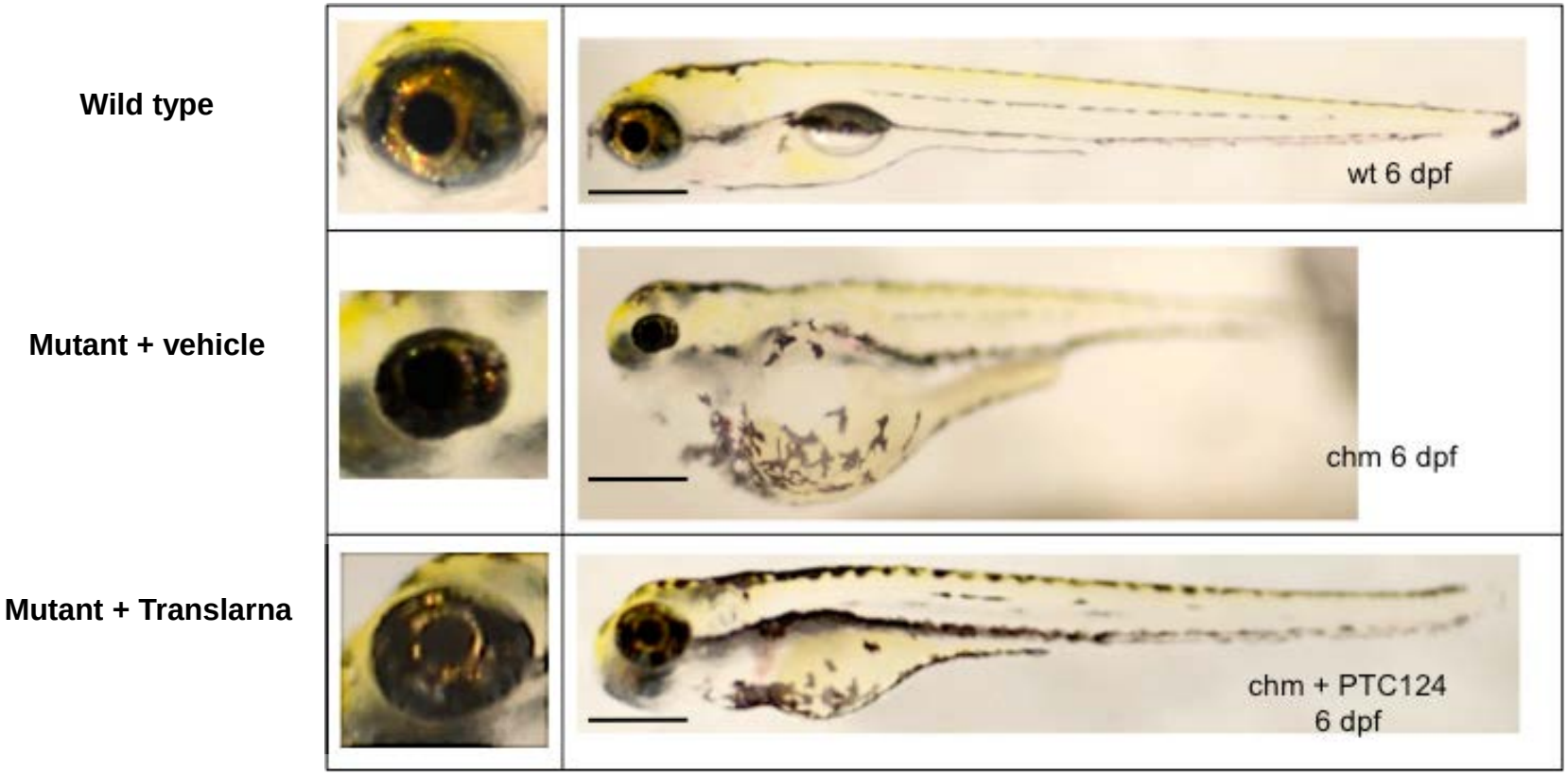
- Aniridia caused by mutations in the paired box 6 gene (PAX6)
- Incidence is 1 in 60,000 births, 20% have nonsense mutations
- Treatment methods used today are mostly surgical and ineffective



Gregory-Evans 2014 JCI

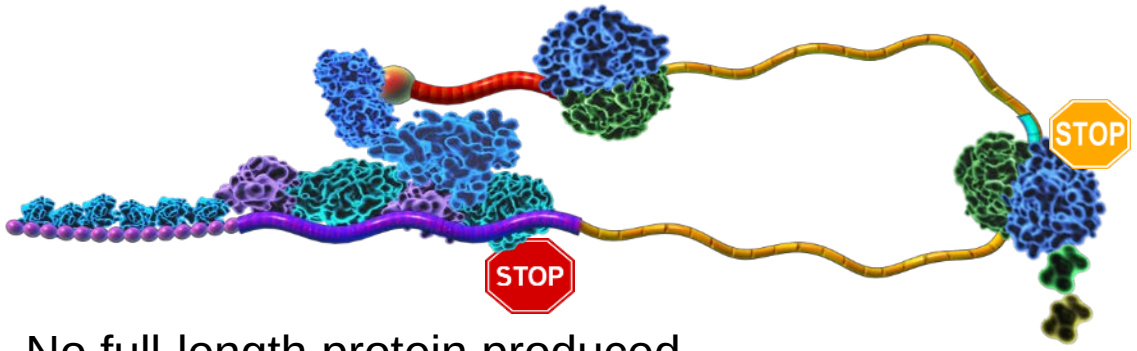
Efficacy of Translarna in nonsense mutation choroideremia

- X-linked recessive chorioretinal disease resulting in blindness in patients
- Caused by mutations in the REP1 gene
- Nonsense mutations account for over 33% of patients

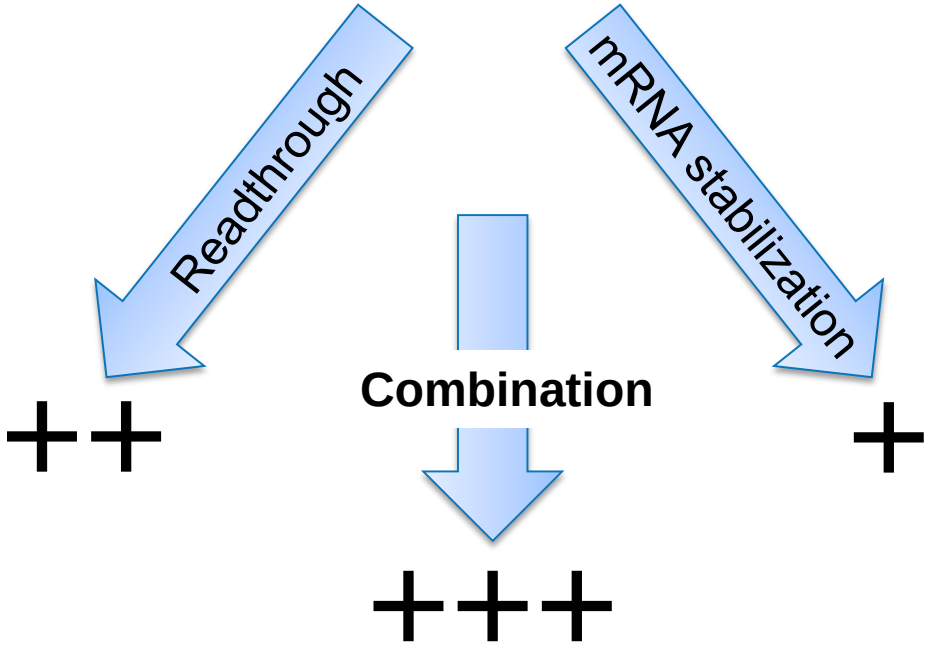


Moosajee et al. unpublished data

Two potential points of intervention at a nonsense codon



- No full-length protein produced
- Reduced mRNA abundance due to accelerated decay

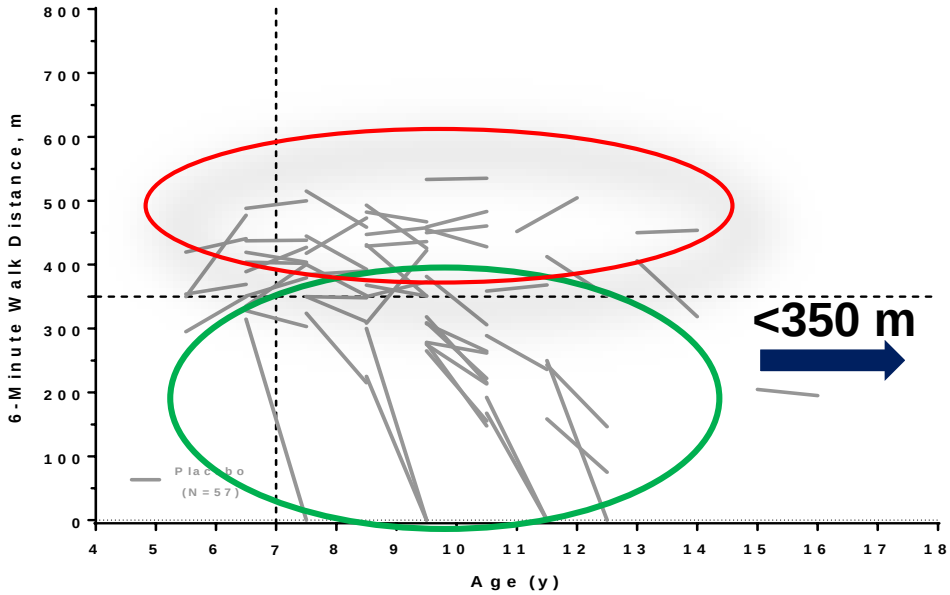


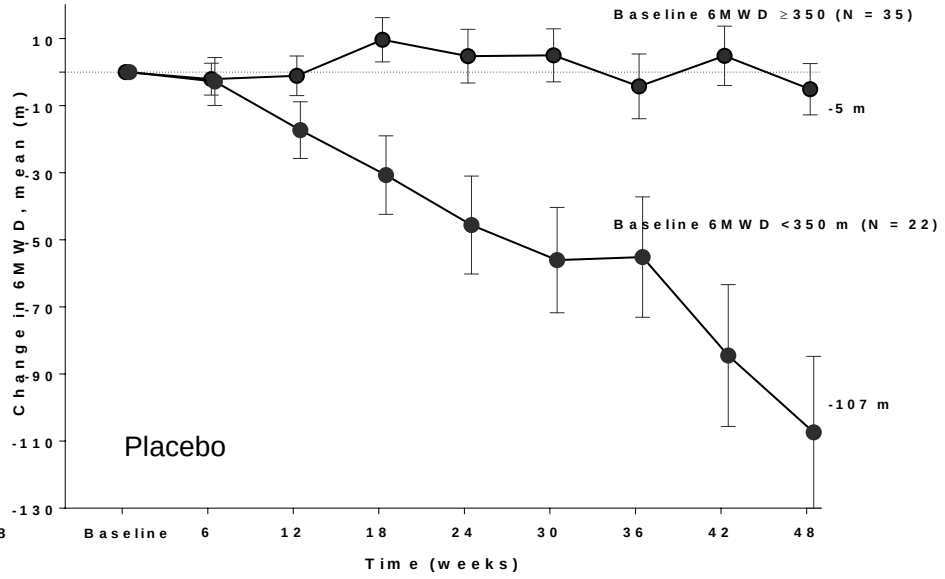


Translarna™

Nonsense mutation Duchenne Muscular Dystrophy

Phase 2b placebo-control data defined natural history of 6MWD

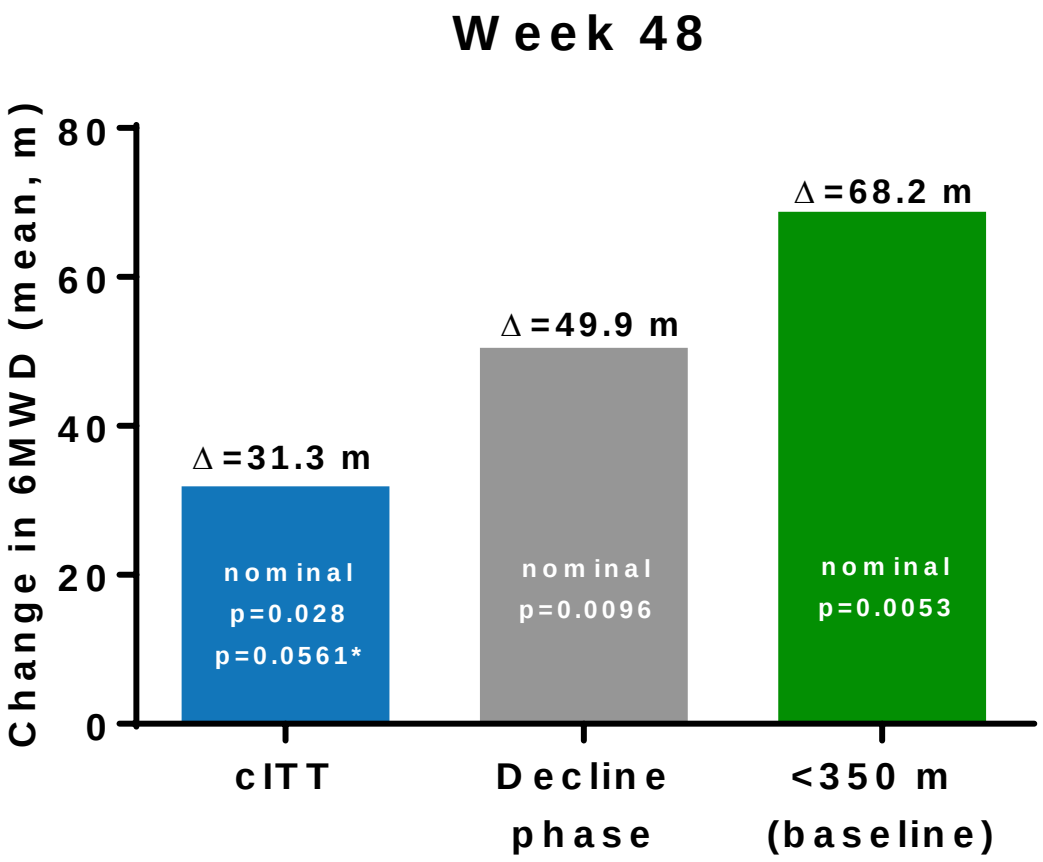




Lessons learned

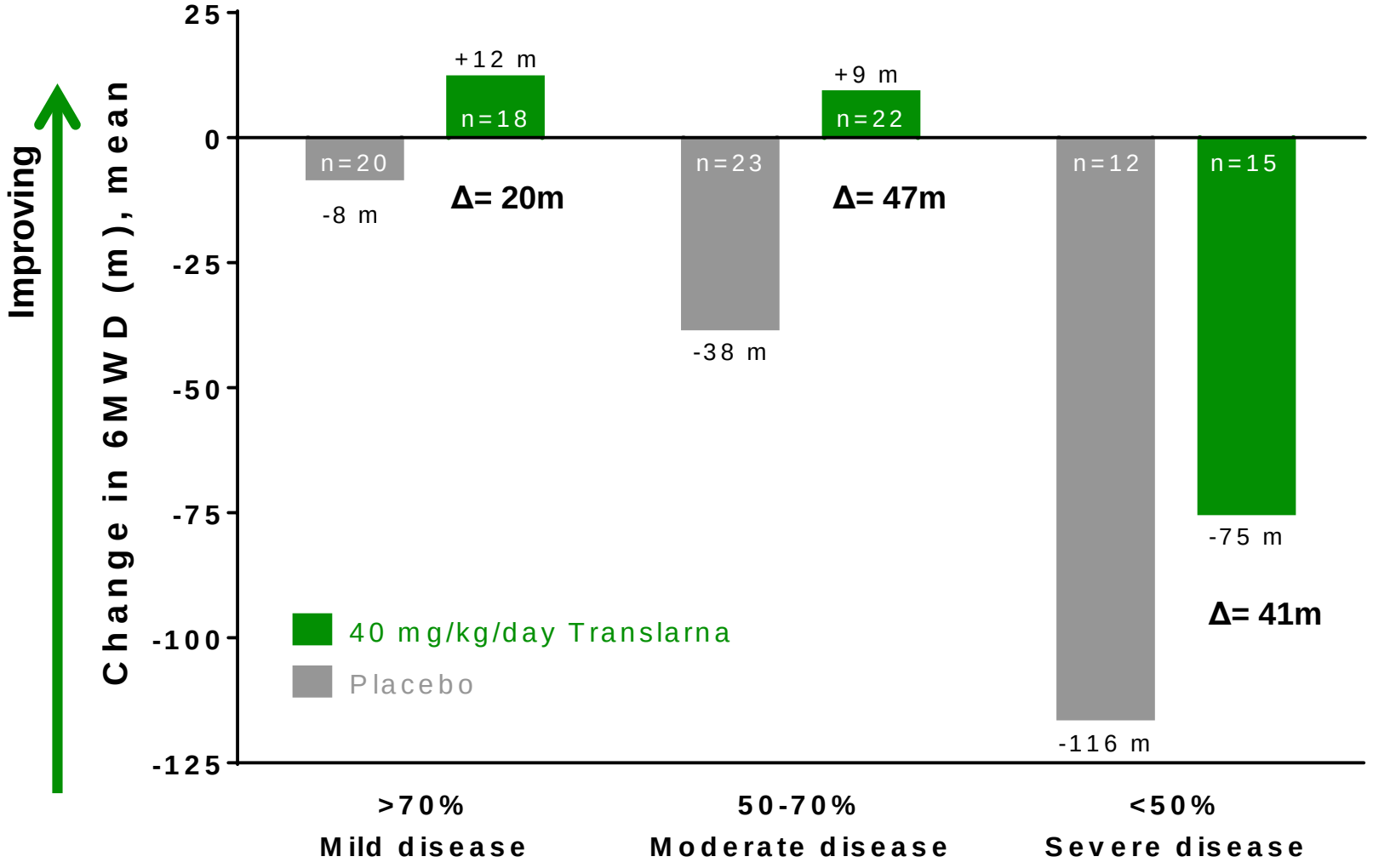
- **Baseline 6MWD is a key factor in determining whether DMD patients decline**
- **The mean ∆6MWD in >350 meter population was relatively stable**
  - Difficult to demonstrate a drug effect over a 48-week study
- **The mean ∆6MWD in <350 meter population show a large decline**
  - Best population to demonstrate an effect in ambulation in a 48-week study
- **Confirmatory trial has inclusion criteria to enrich patients in the decline phase**

Translarna™ treatment effect increases in the decline subgroup and in the pre-specified baseline 6MWD <350 m subgroup

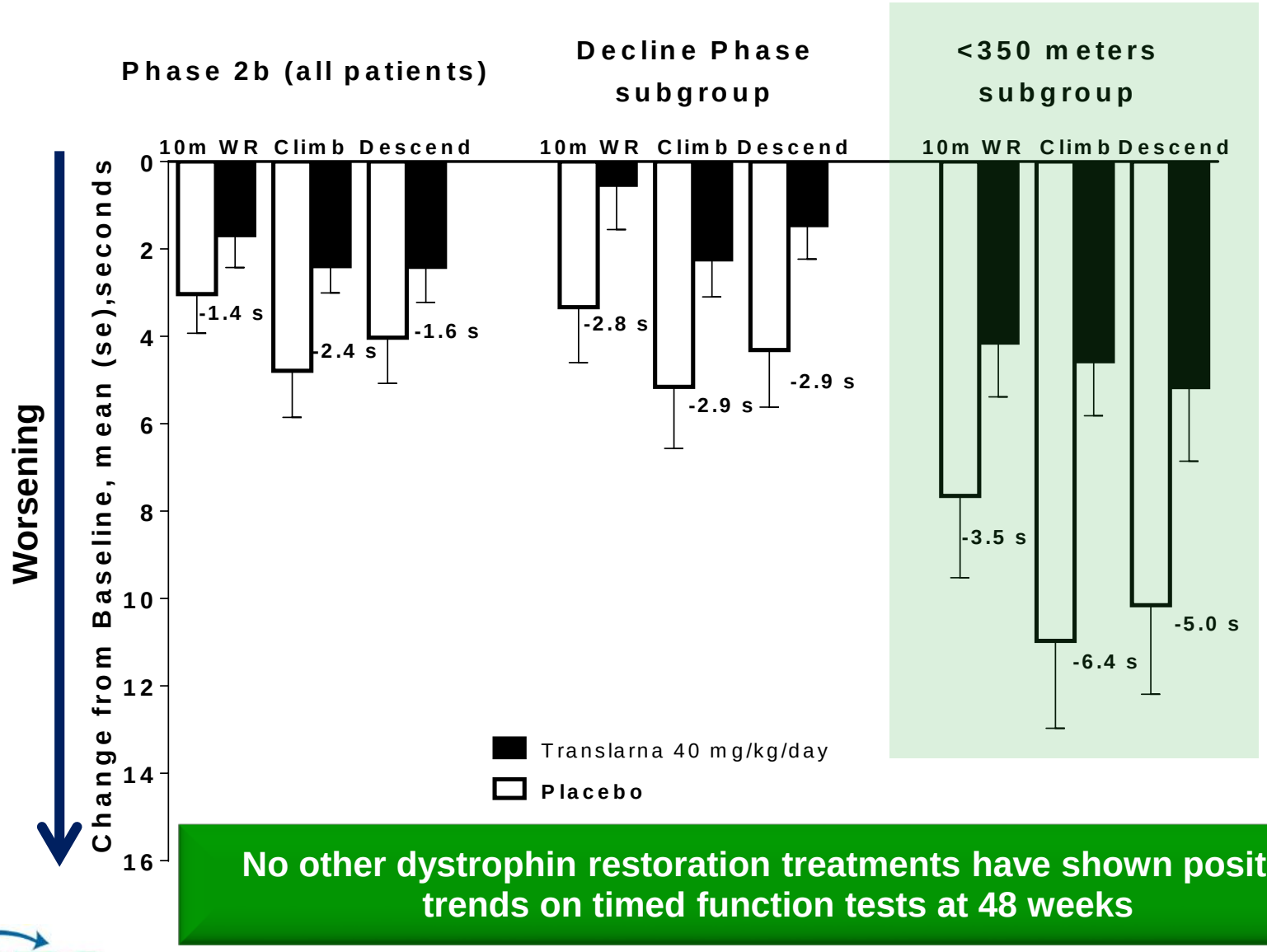


*MMRM analysis adjusted for multiplicity
Post-hoc analysis on cITT population

Translarna™ treatment effect seen in all disease stages studied



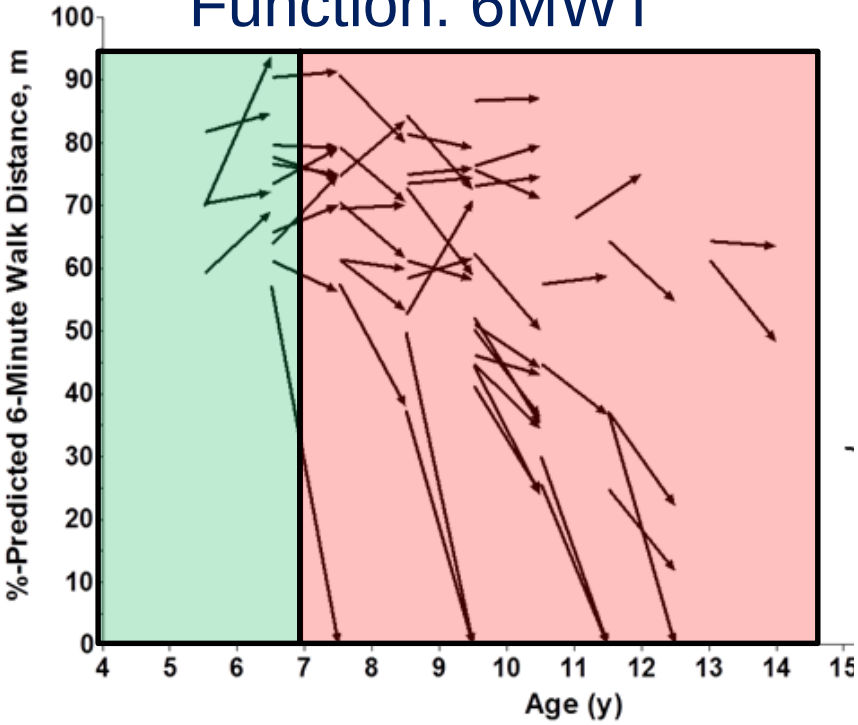
Phase 2b demonstrated activity in timed function tests: Overall population and decline subgroups



No other dystrophin restoration treatments have shown positive trends on timed function tests at 48 weeks

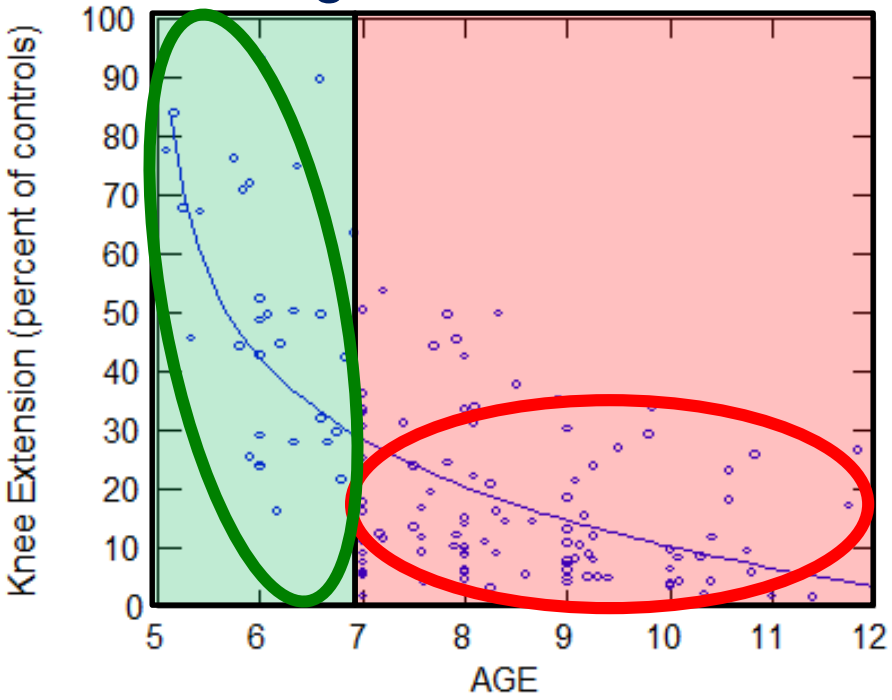
Myometry is only sensitive in young patients: Strength vs. Function

Function: 6MWT



[McDonald 2013]

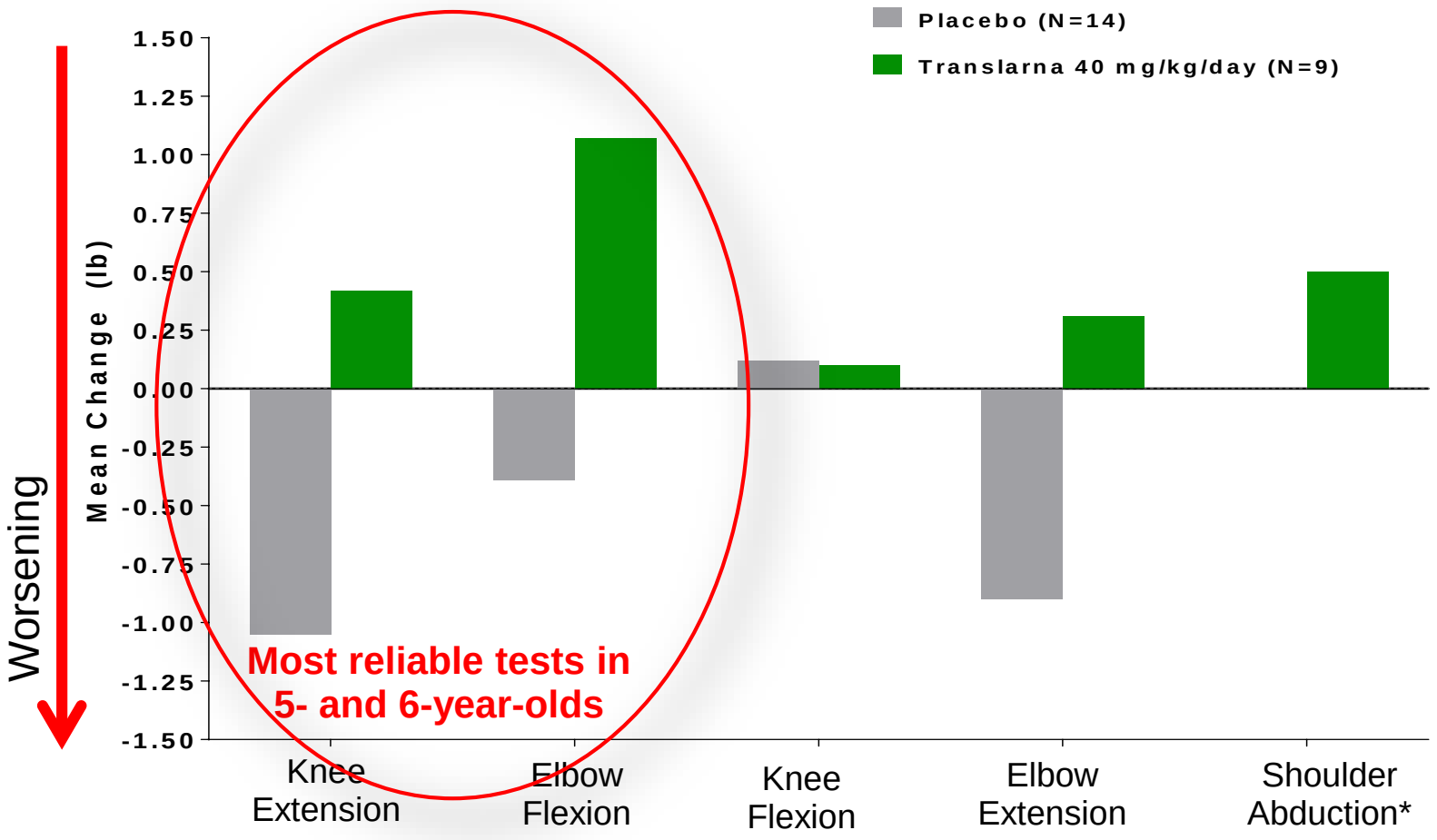
Strength: Knee Extension



[Abresch 2011 – American Academy of Neurology presentation]

Largest improvements in 6MWT up to age 7
Largest decline in strength up to age 7 followed by floor effect

Mean change from baseline in muscle strength evaluated by myometry (patients 5-6 years old)

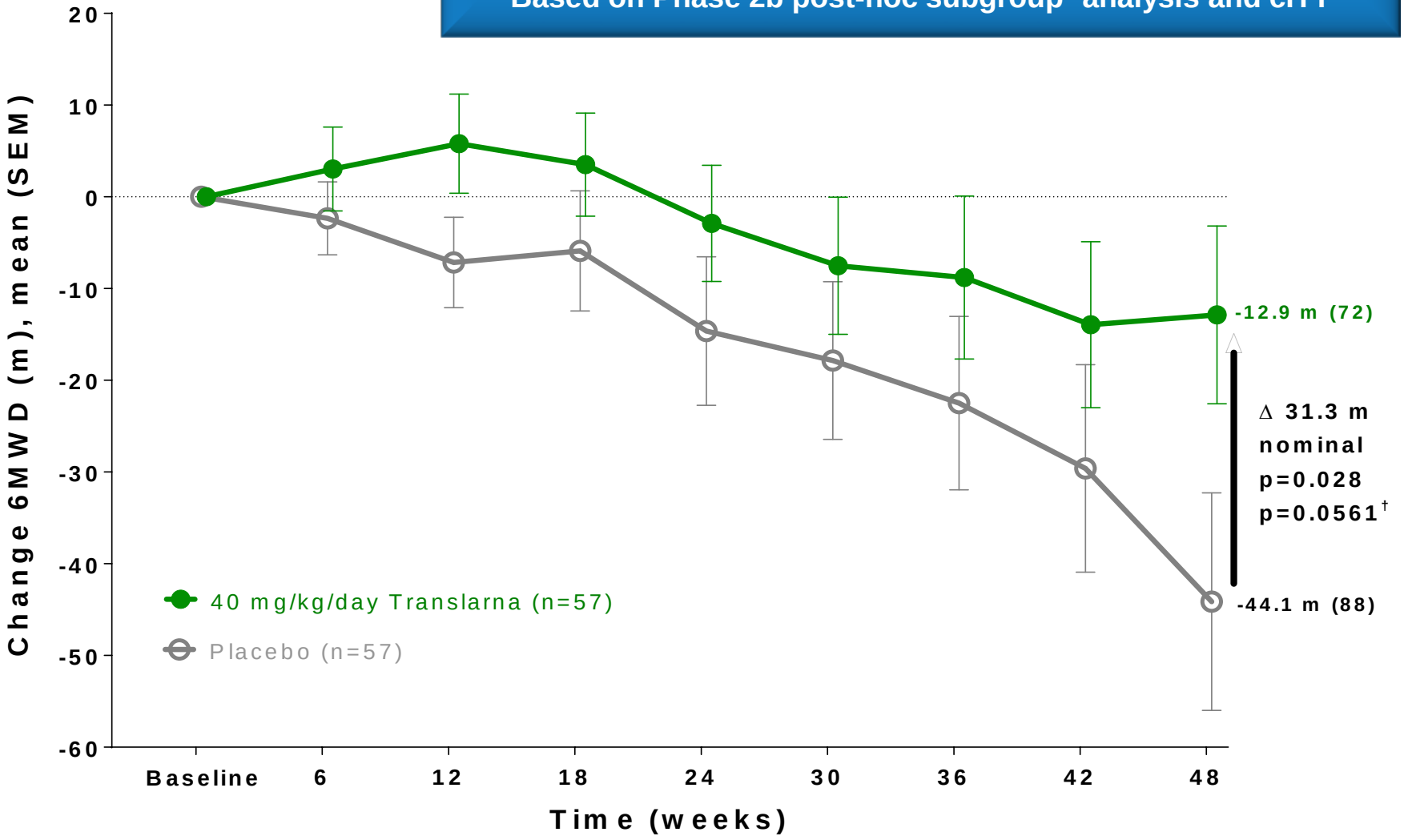


No other dystrophin restoration treatments have shown positive trends in strength

* For shoulder abduction, the mean change in the placebo arm was 0.0 lbs

Translarna™ slowed disease progression in nmDMD patients

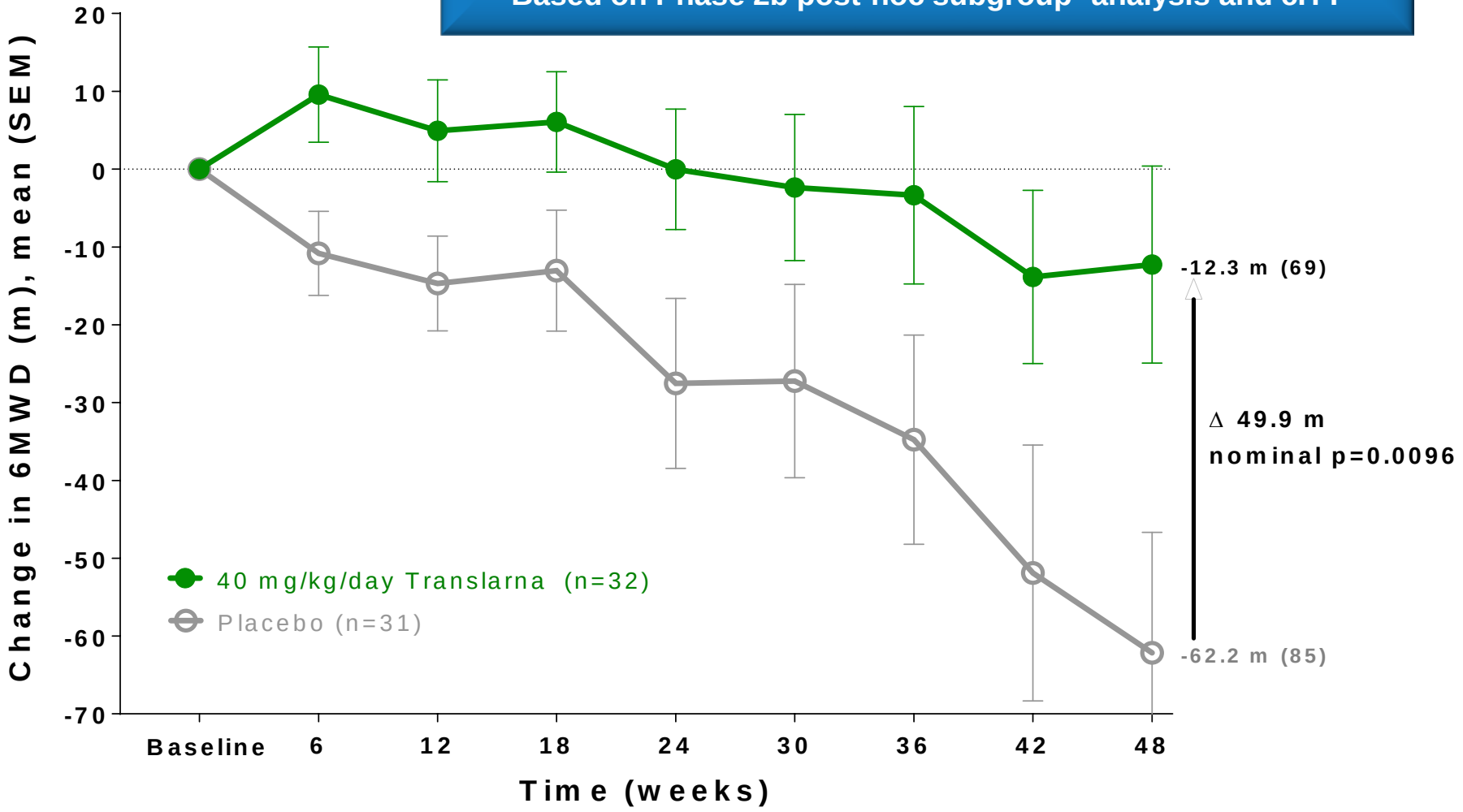
Based on Phase 2b post-hoc subgroup[1] analysis and cITT



*cITT= Corrected intent to treat population
† = MMRM analysis adjusted for multiplicity

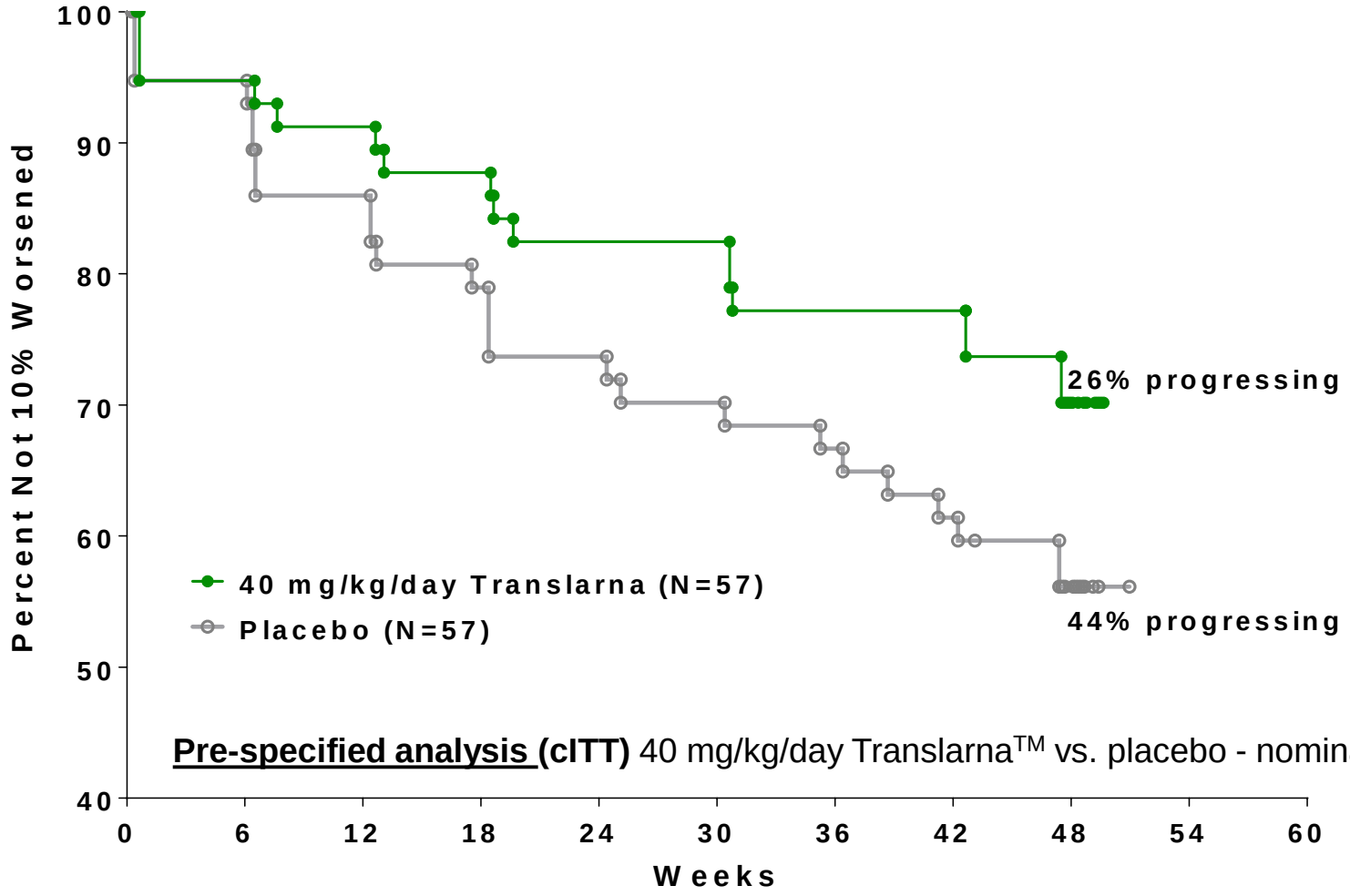
Translarna™ demonstrated the greatest benefit over 48 weeks with patients in the ambulatory decline phase

Based on Phase 2b post-hoc subgroup[1] analysis and cITT



1. In patients on corticosteroids, between 7 and 16 years of age, with baseline 6MWD ≥150m and ≤80% of predicted

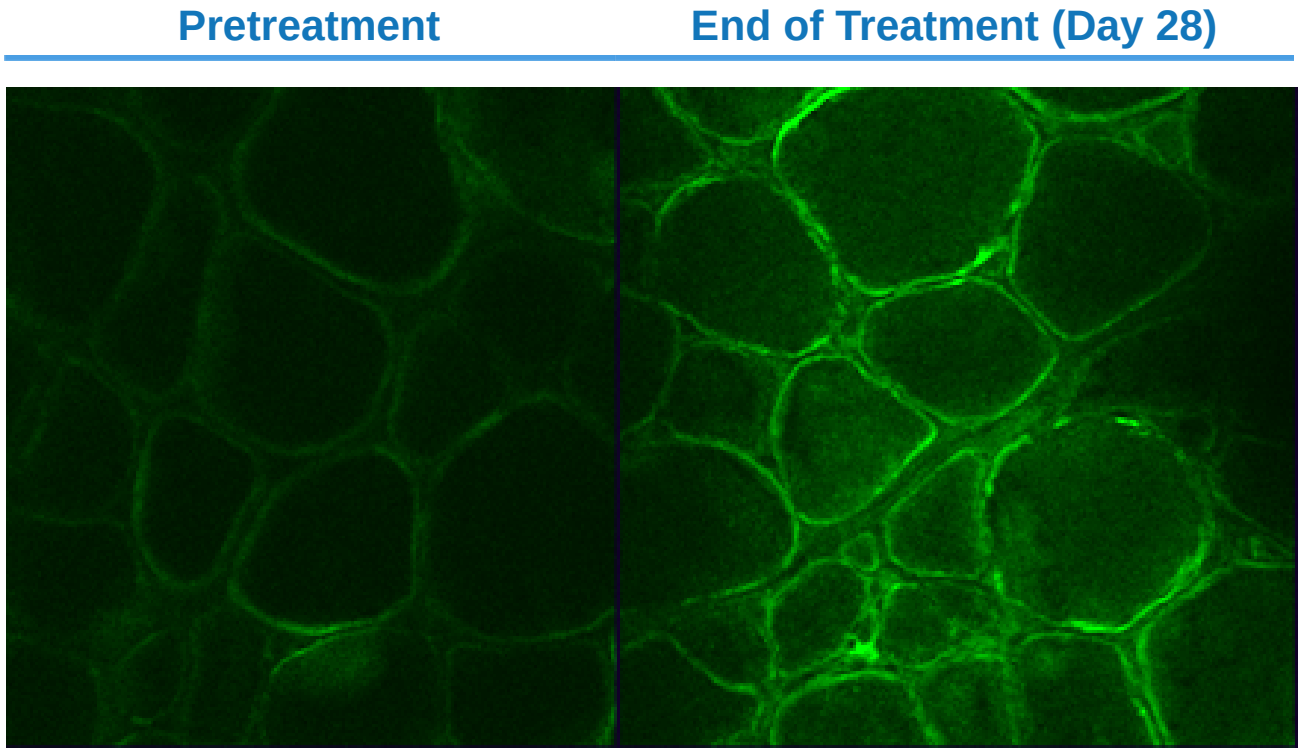
Translarna™ slowed disease progression in nmDMD patients



Pre-specified analysis (cITT) 40 mg/kg/day Translarna™ vs. placebo - nominal p=0.039

Separation between treated and placebo patients occurred early

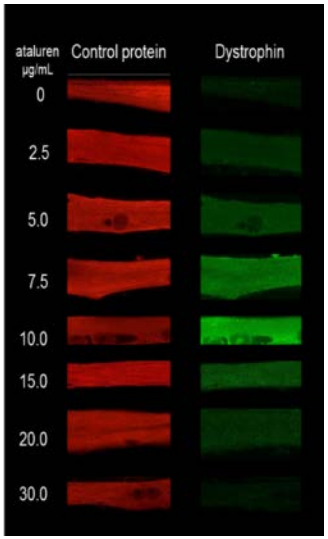
Translarna treatment was associated with improvements in dystrophin expression in Phase 2a nmDMD clinical trial

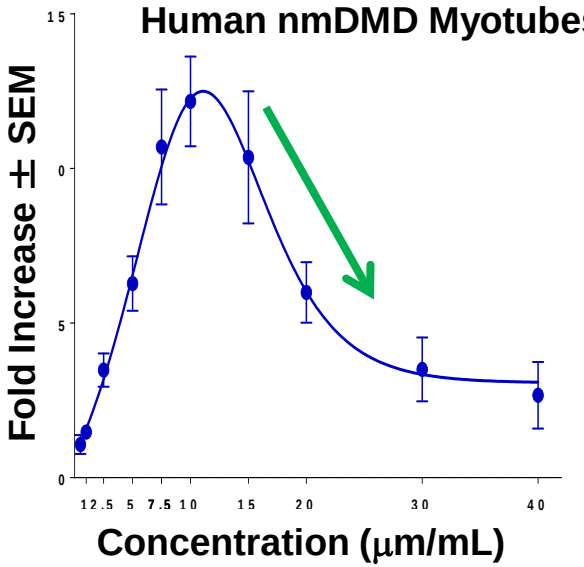


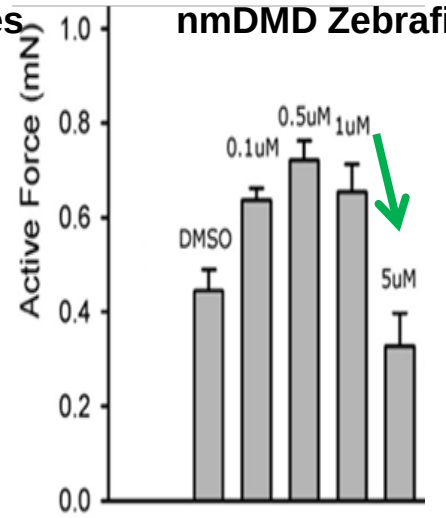
Over 28 days, improvements were seen in ~60% of patients

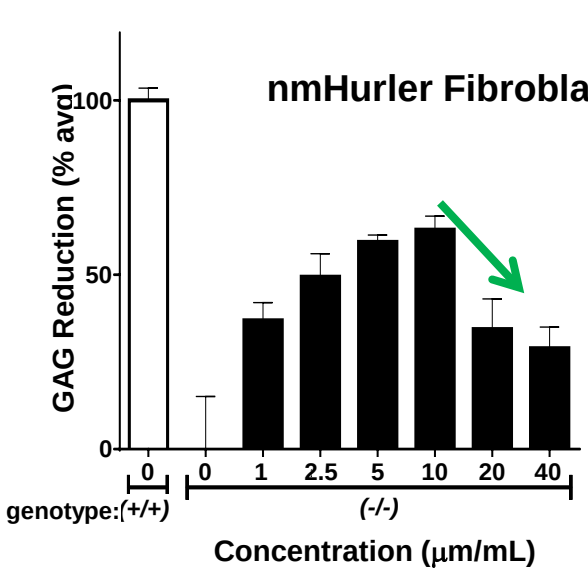
Phase 2a study; Bönnemann et al, Neuromusc. Disord. 2007

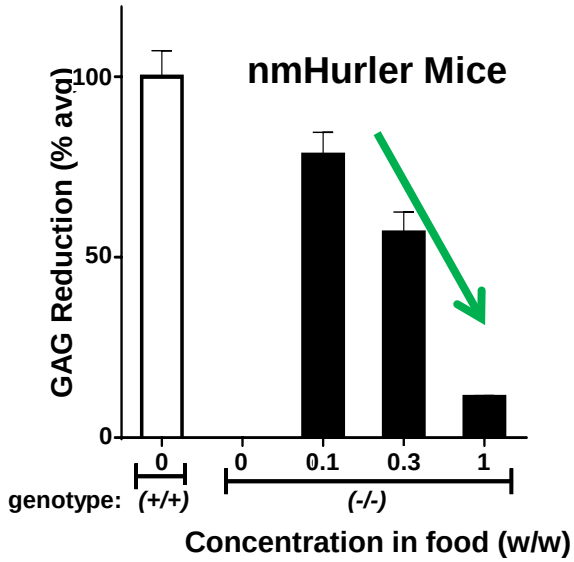
Bell-Shaped Concentration-Responses to Translarna Are Observed in Cells, Fish, and Mice



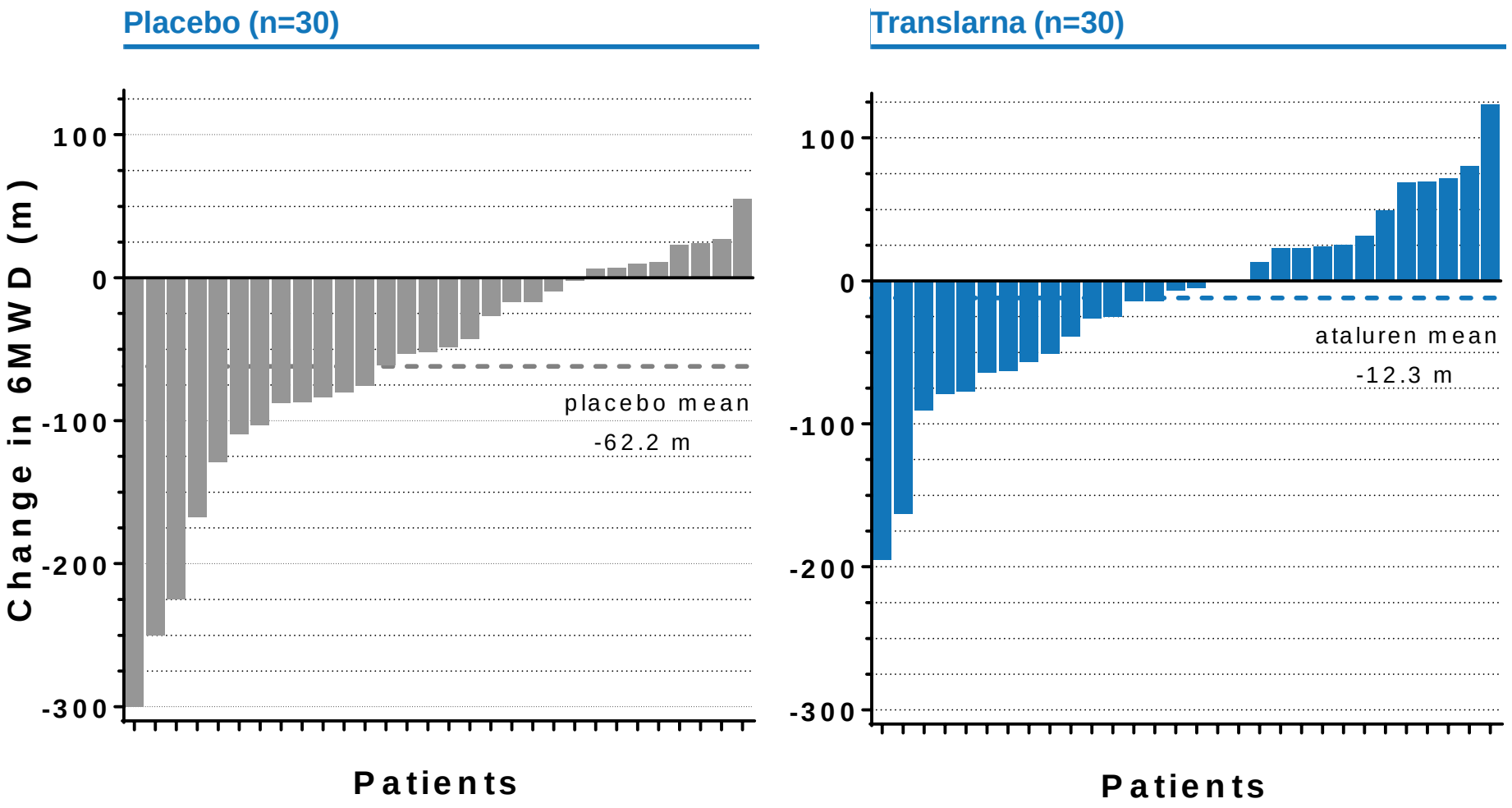






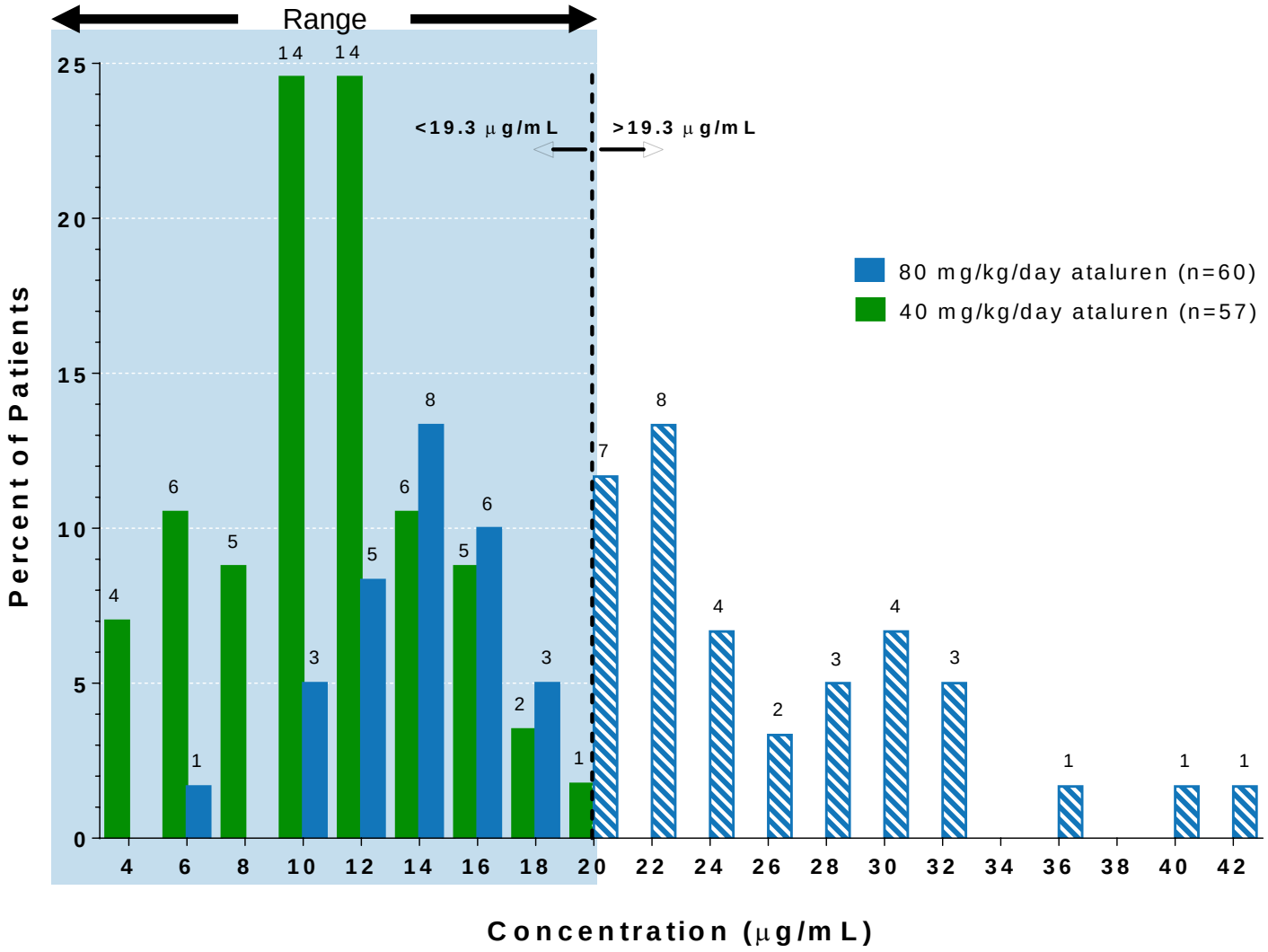


Individual change in 6MWD for patients meeting confirmatory Phase 3 nmDMD clinical trial entry criteria

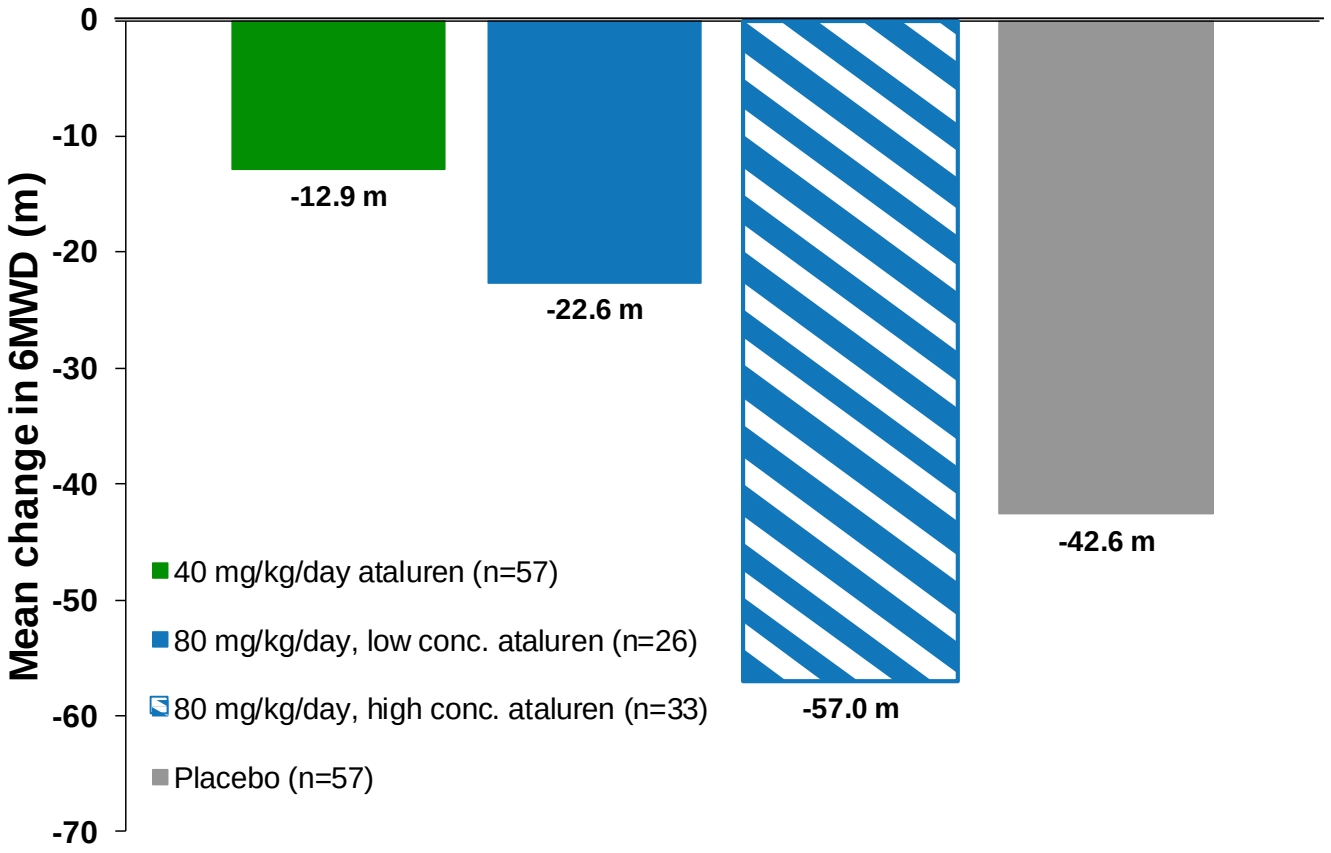


Patients from Phase 2b study: on steroids, age 7-16 y, baseline 6MWD ≥150 m, and baseline 6MWD <80%-predicted

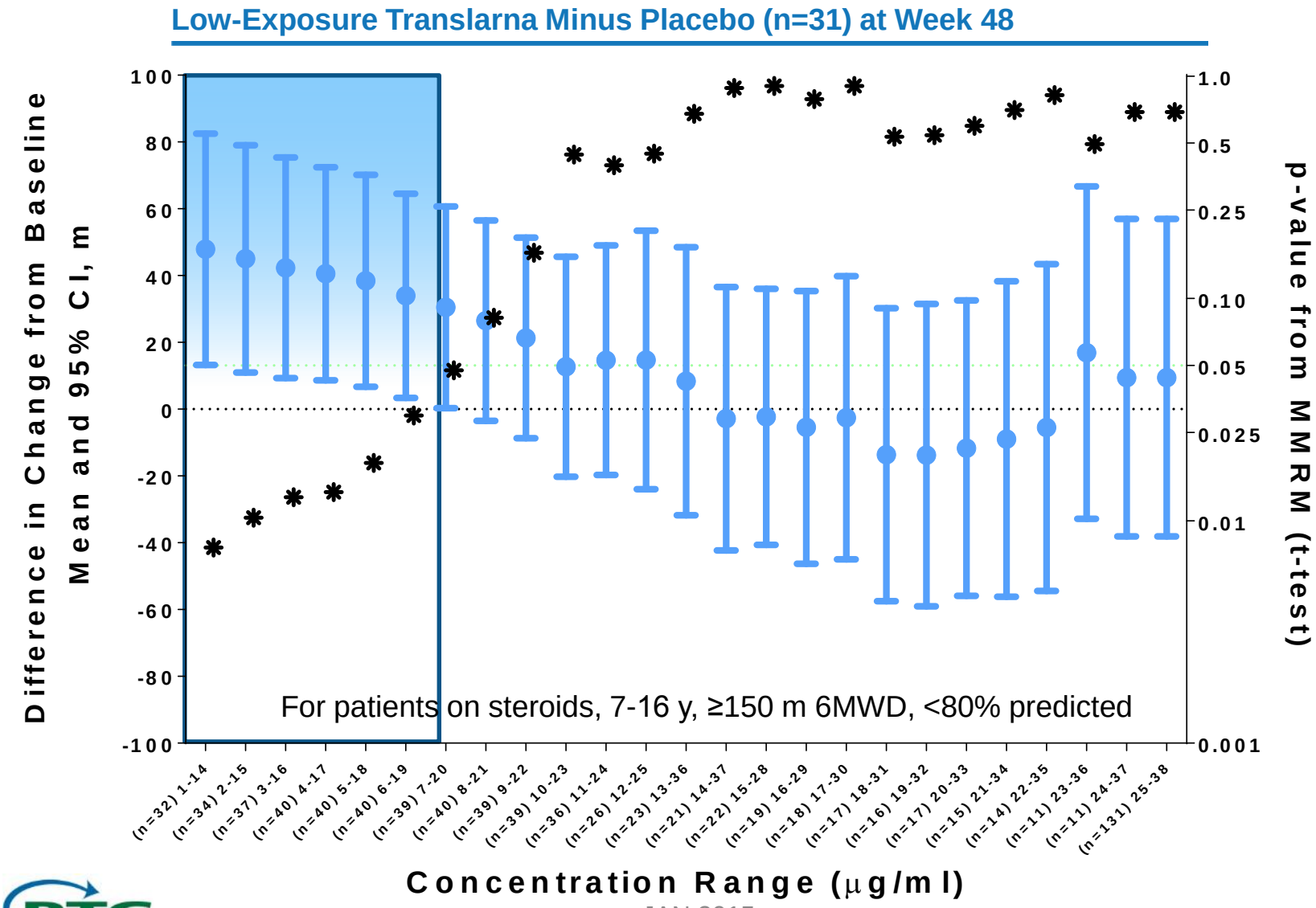
All low-dose Translarna subjects had mean ataluren concentrations <19.3 μg/mL 2 hours after the morning dose



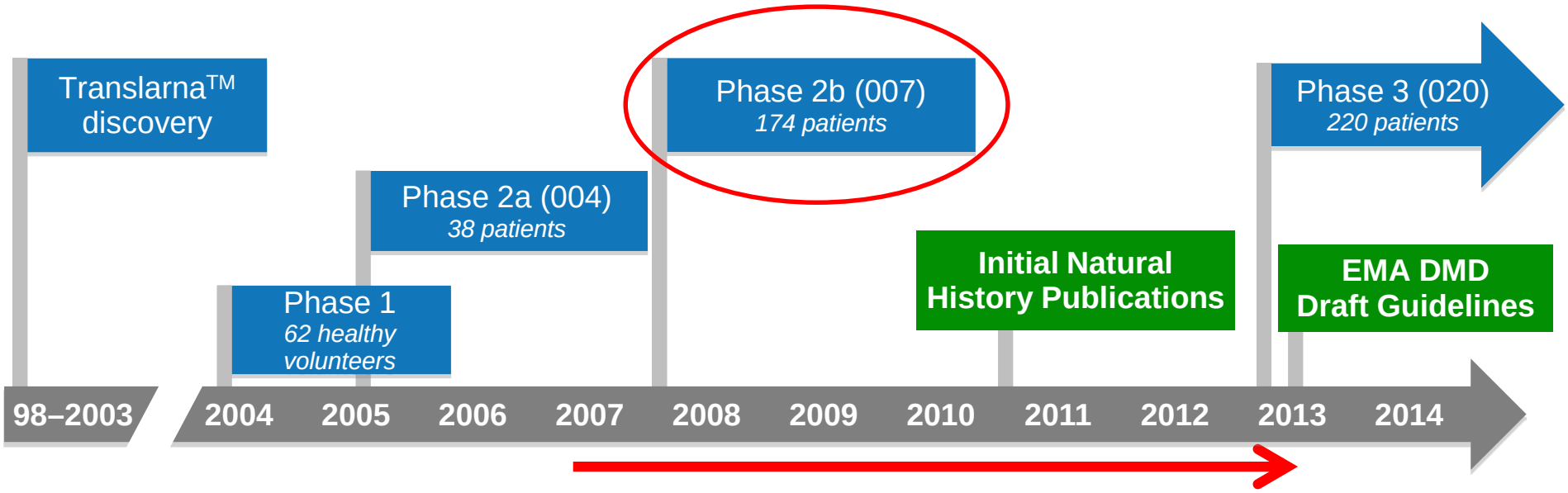
6MWT results were better in the low concentration group of the 80 mg/kg/day group in the Phase 2b nmDMD trial



Mean and significance levels for change in 6MWD by 2-hour plasma concentrations ranges confirmed better outcomes at lower exposures



PTC: The pioneer in DMD trial development



- ✓ 15 years of research & development
- ✓ 650+ healthy volunteers/patients exposed/treated
- ✓ **Safety profile:** Generally well tolerated
- ✓ **Phase 2a:** Dystrophin expression demonstrated
- ✓ **Phase 2b:** Clinically meaningful benefit in 6MWT/Natural History data
- ✓ **Phase 3:** ACT DMD fully enrolled with data expected Q4 2015



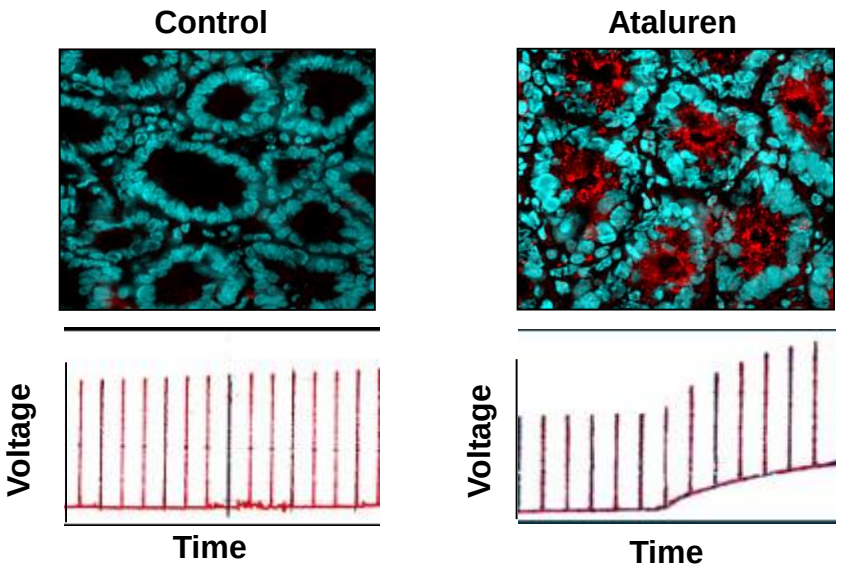
Translarna™

Nonsense mutation Cystic Fibrosis

Ataluren mechanism of action has been demonstrated in preclinical and clinical studies in nmCF

nmCF mouse model

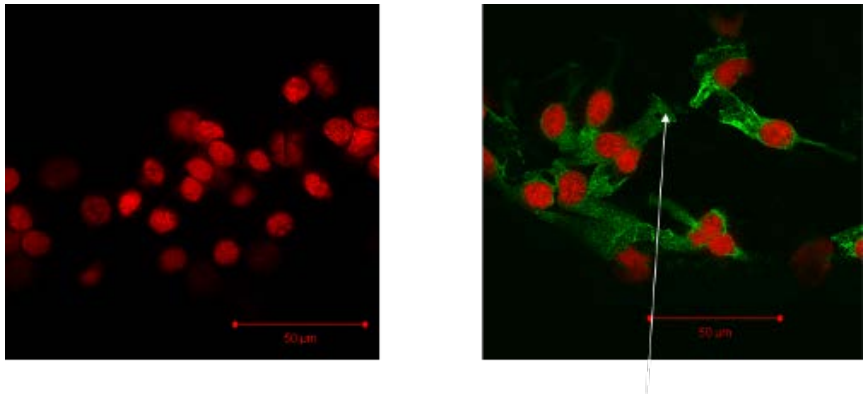
- Increased CFTR expression in intestine
- CFTR chloride channel activity



Du et al, PNAS, 2008

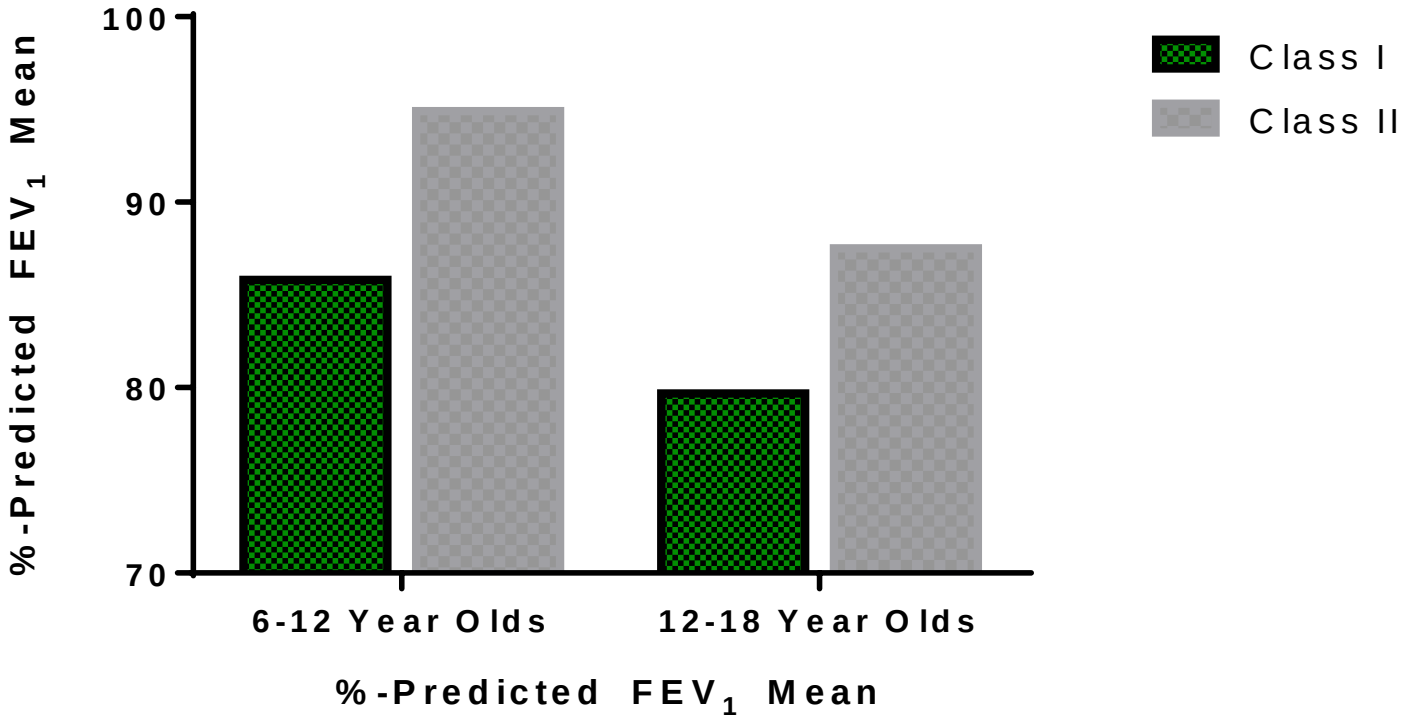
Phase 2a nmCF clinical trial

- Increased CFTR production after ataluren treatment
- Demonstrated CFTR chloride channel activity
- Trends in improvement in pulmonary function
- Reduction in cough



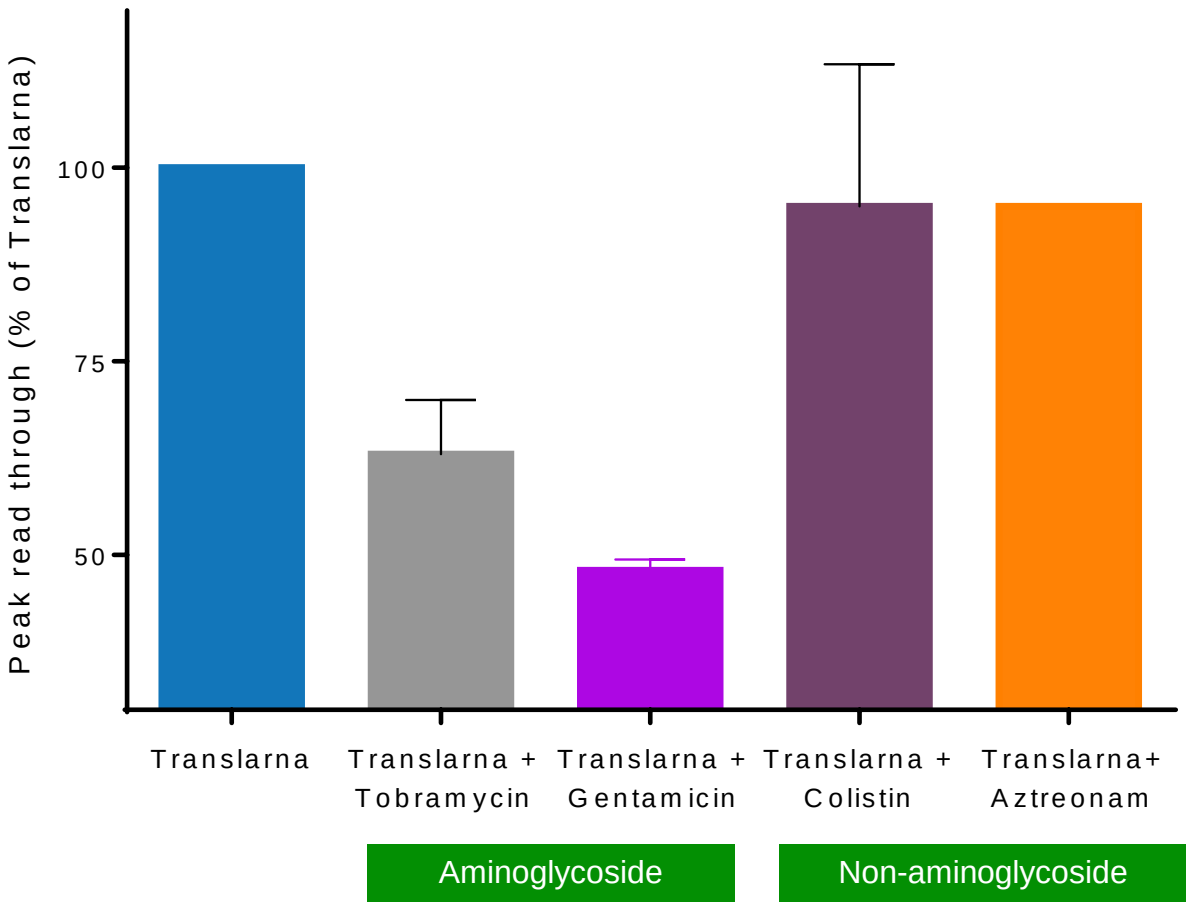
Sermet et al, Ped Pulm, 2008

Class I cystic fibrosis patients have a more rapid decline in lung function than patients with Class II mutations



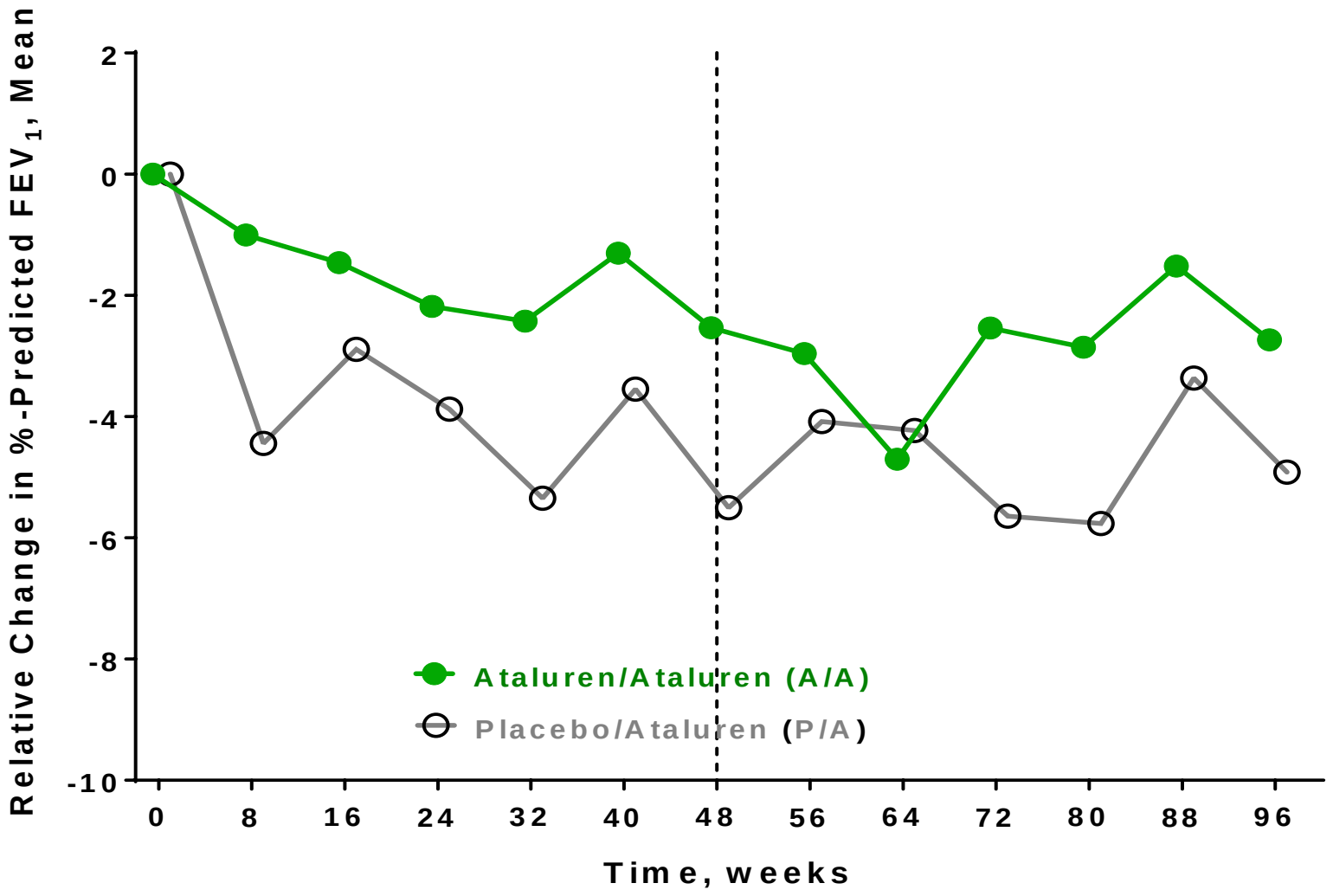
Cystic Fibrosis Foundation Registry Data

Impact of antibiotics on Translarna activity: in vitro reporter system*



*Results from 2 independent experiments

Relative Change in %-Predicted FEV_1 (ITT; Observed Data) in Study 009 and 009e





Spinal Muscular Atrophy

Discovery of a small molecule therapeutic

Severity of SMA determined by % functional SMN

Type	Disease Severity	% Functional SMN[1]
I	Most severe, infants have trouble breathing and don't usually live past 2 years of age	**25 – 40%**
II	Onset at 6-18 months, patient may walk briefly, death likely in early adulthood	**~60% (+/- 5%)**
III	Patients may walk into early adulthood	**~70% (+/- 5%)**

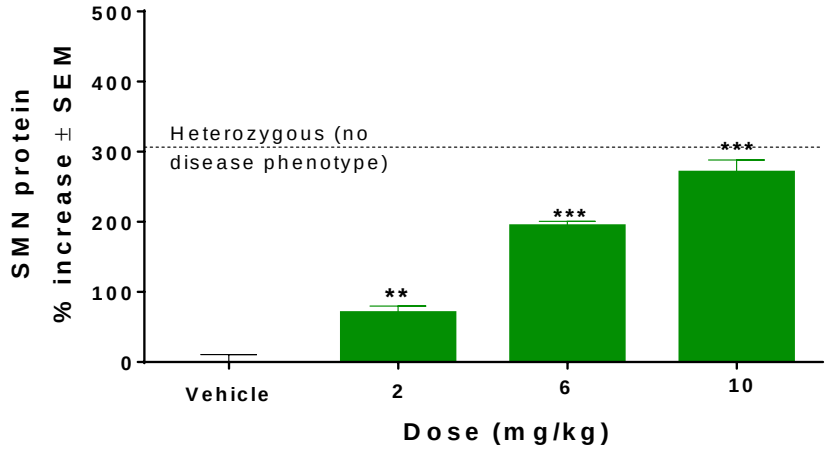
Incremental increases in SMN protein levels create meaningful clinical improvements

1. Protein levels measured in vitro fibroblast cells as a percent of heterozygous levels

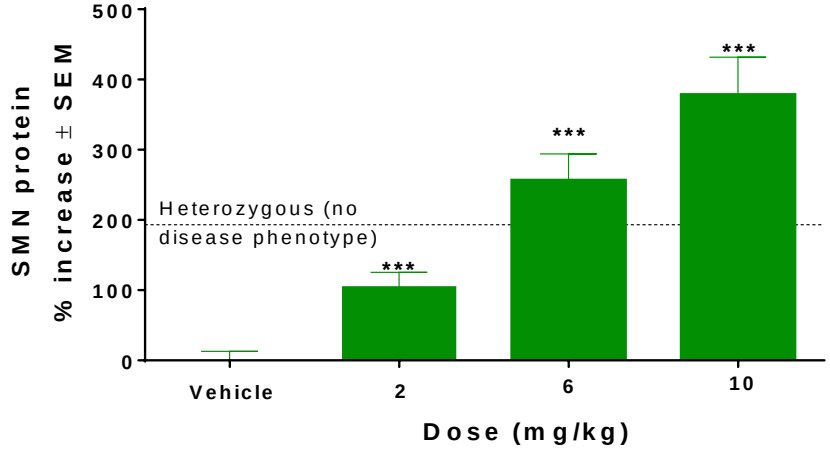
PTC compounds increase SMN protein in multiple tissues to near or above heterozygous levels

- Oral dosing for 10 days in SMA Type 3 mouse model

Brain



Peripheral Blood Mononuclear Cells

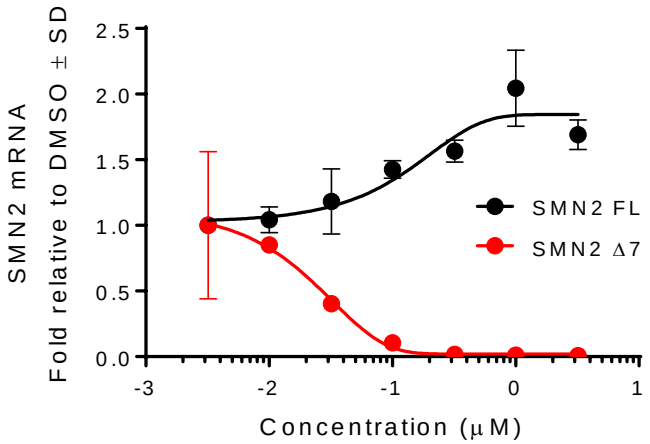


- SMN protein levels in peripheral blood cells correlate to those in brain
- Similar increases in SMN observed in spinal cord, muscle, heart, liver, skin
- Crosses blood brain barrier for pan-tissue distribution

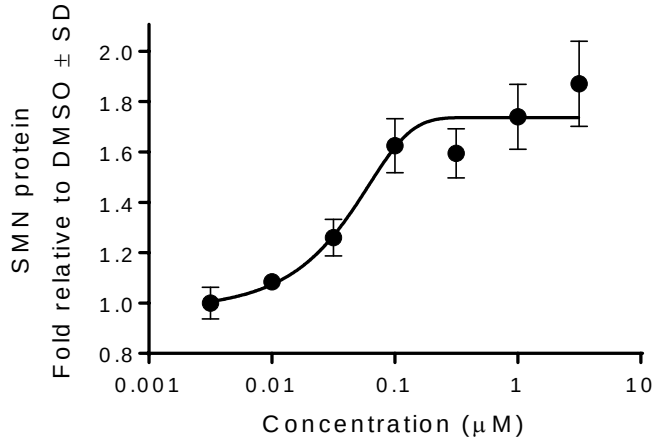
Naryshkin *et al.*, 2014 Science, 345:688

Compound modifies SMN2 alternative splicing and increases SMN protein in vitro in SMA patient cells

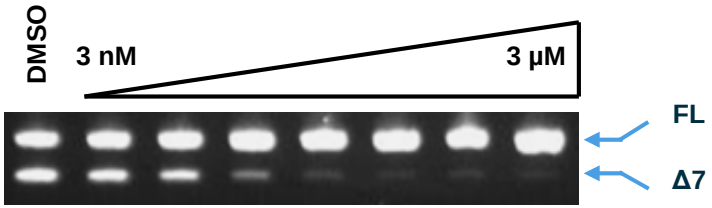
SMN2 alternative splicing correction (RT-qPCR)



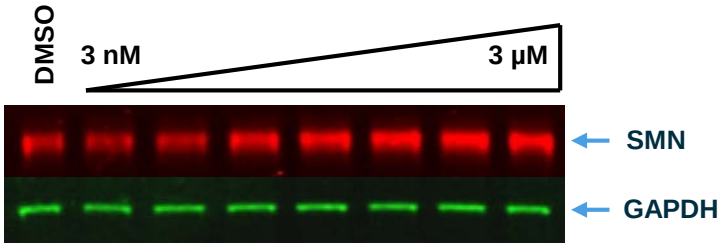
SMN protein increase (HTRF)



SMN2 alternative splicing correction (end-point RT-PCR)



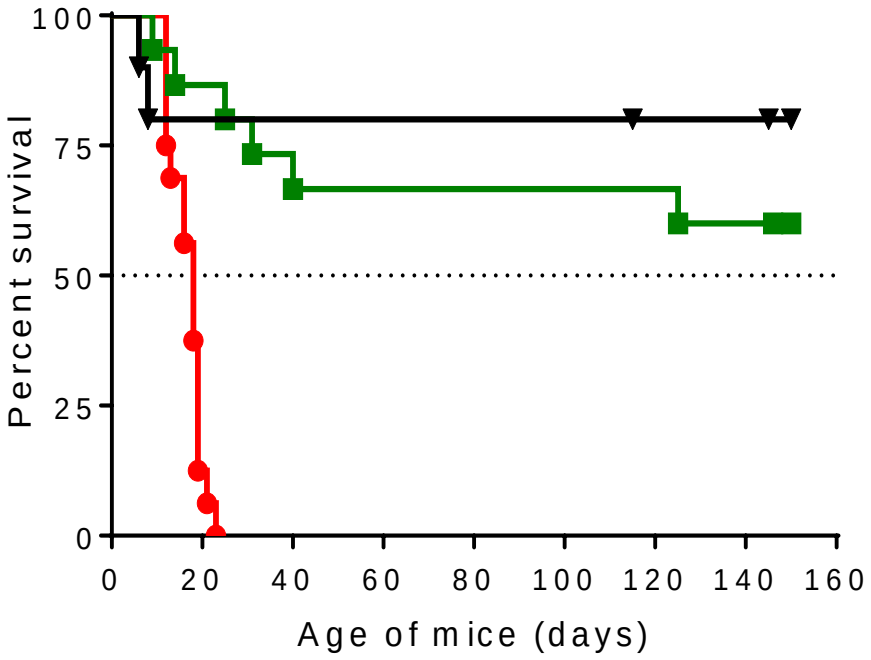
SMN protein increase (Western blot)



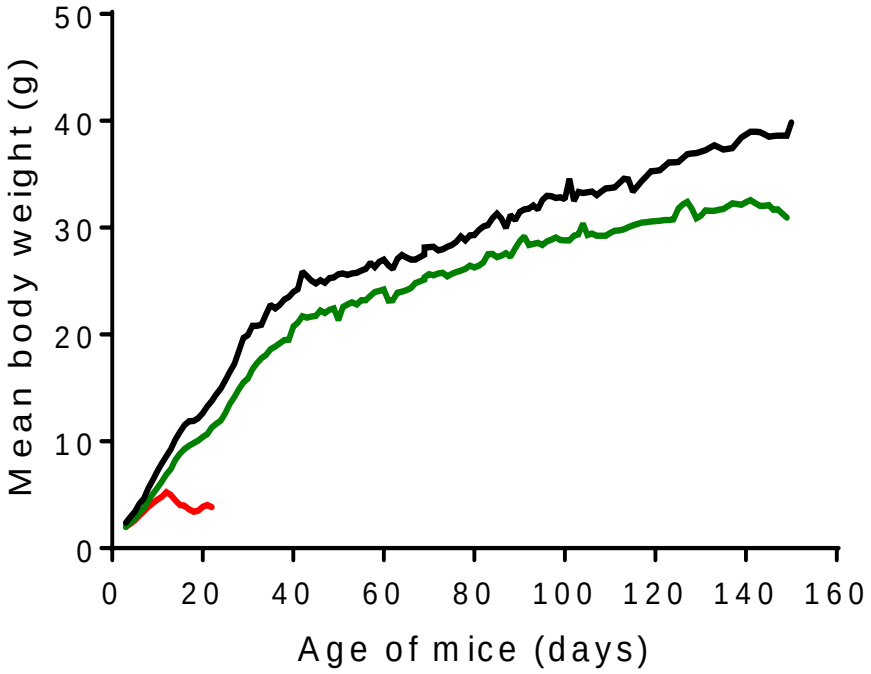
Naryshkin *et al.*, 2014 Science, 345:688

PTC compounds confer long term survival and prevent body-weight loss in Type I SMA mice

Prolonged Survival



Body Weight Gain

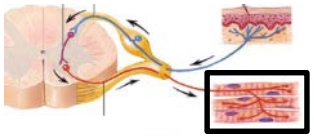


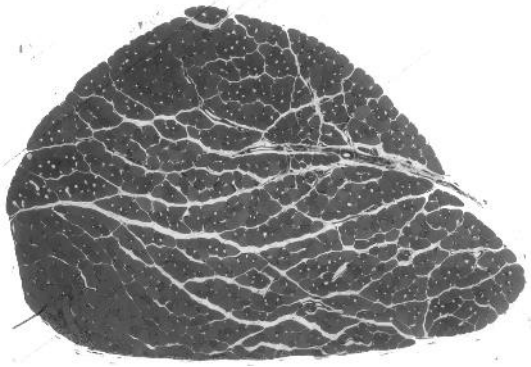
Heterozygous (n=10), Placebo (n=15), 6 mg/kg PO (n=15)

Pre-clinical data demonstrated improved phenotype and survival

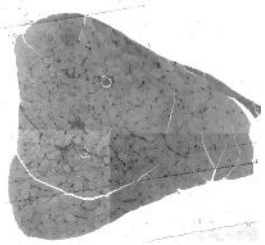
Naryshkin *et al.*, 2014 Science, 345:688

Prevention of muscle atrophy in severe Type I SMA mice

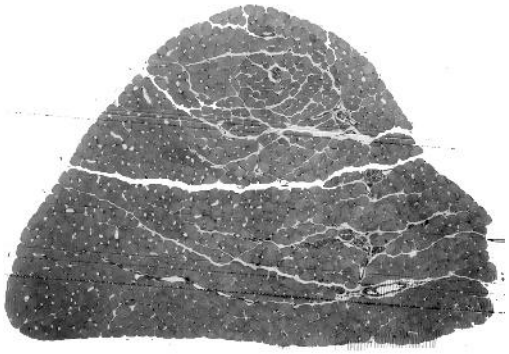




Wild type



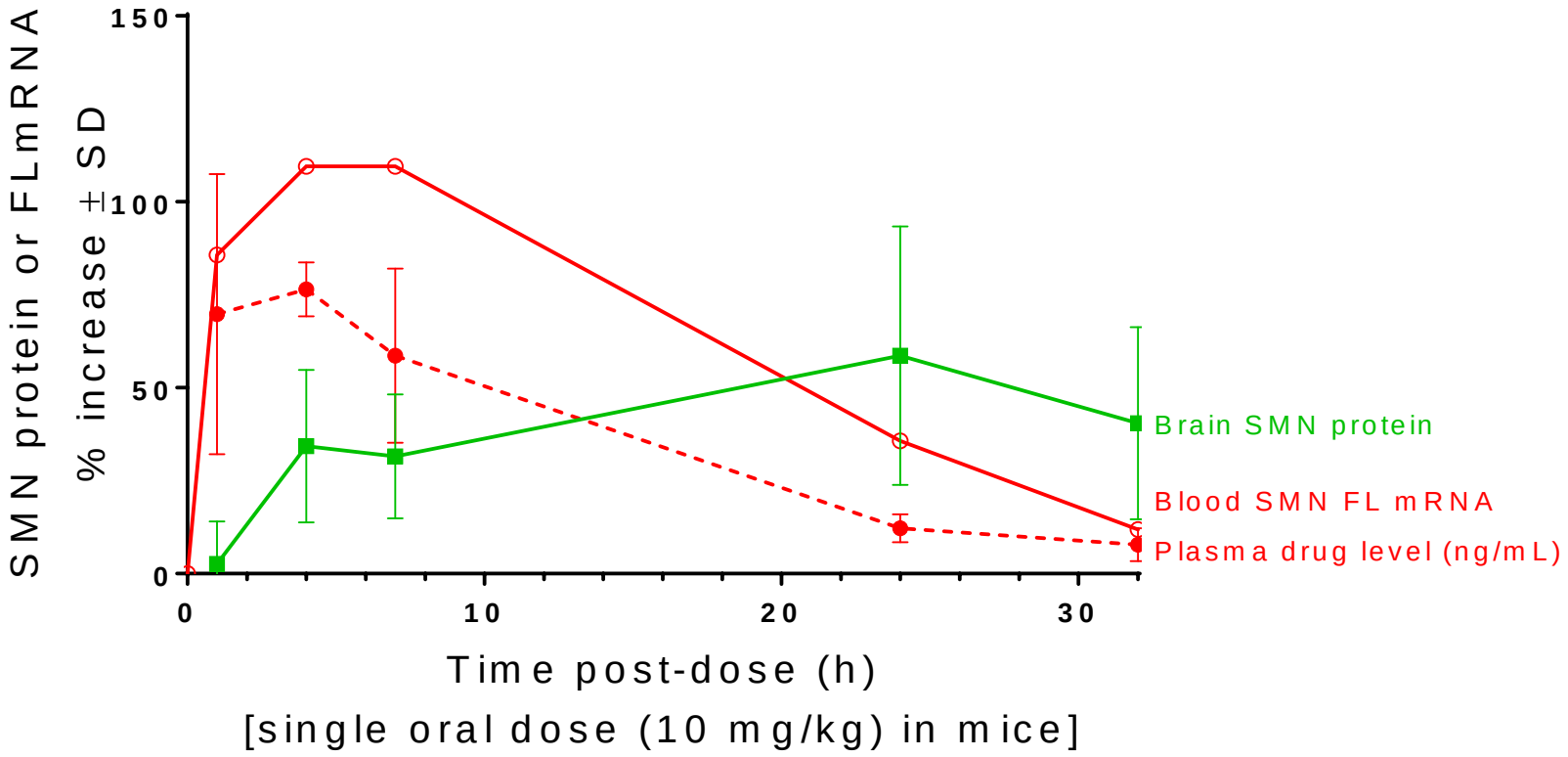
SMA mouse



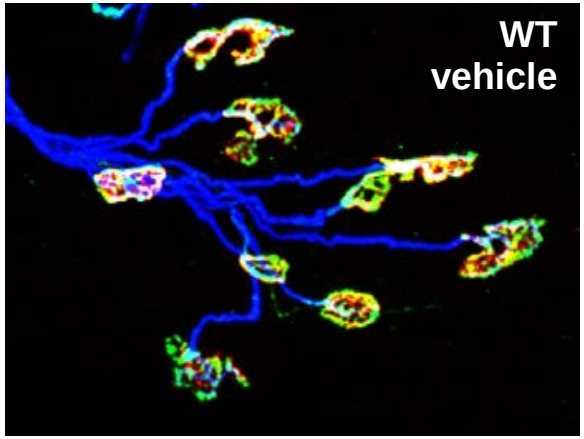
Treated SMA mouse

Mice were treated from 3-days old through 14-days old with Compound (3 mg/kg IP)

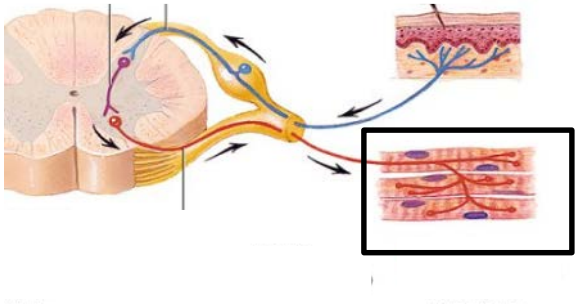
SMN protein can be monitored as a biomarker

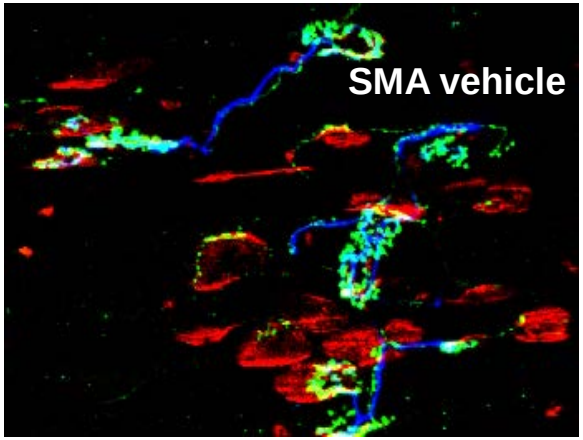


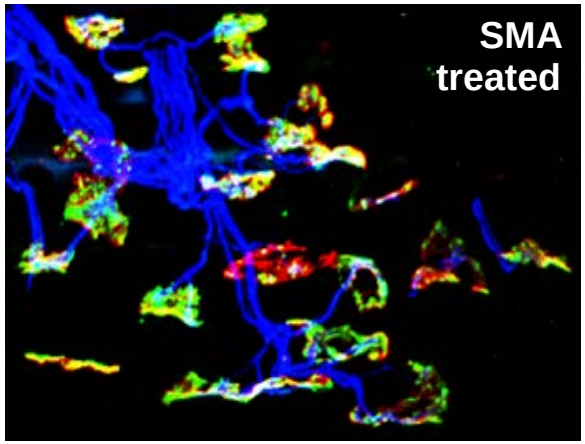
Protection from neuromuscular junction denervation

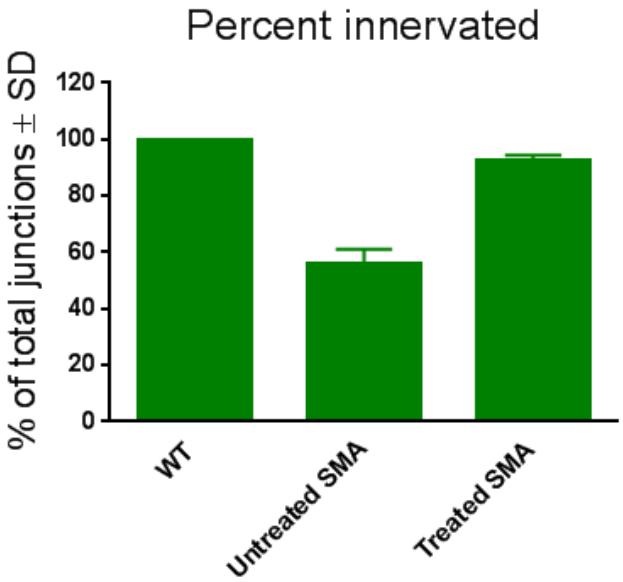


Blue = neuronal axon
Green = NMJ, neuron
Red = NMJ, muscle









Courtesy of Dr. Ko (USC)