The narrow gap
when research becomes clinical treatment and vice versa. Experiences from the SMA and DMD fields

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Disclosures

- Advisory Board Meetings for PTC, BioMarin, AveXis
- Lectures for PTC
- Clinical trials for:

  PTC 2008 – 2017

  Prosensa/BioMarin 2008 – 2016

  Ionis 2014 – 2017

  Roche 2017

RÖRELSE
Nr 5 • 2008

Forskning för barnens bästa

Temanummer om forskning kring barn med rörelsehinder

Hopp om bot för Måns svåra sjukdom sidan 4

Måns Rundqvist, 5, deltar i en viktig studie om Duchennes muskeldystrofi.

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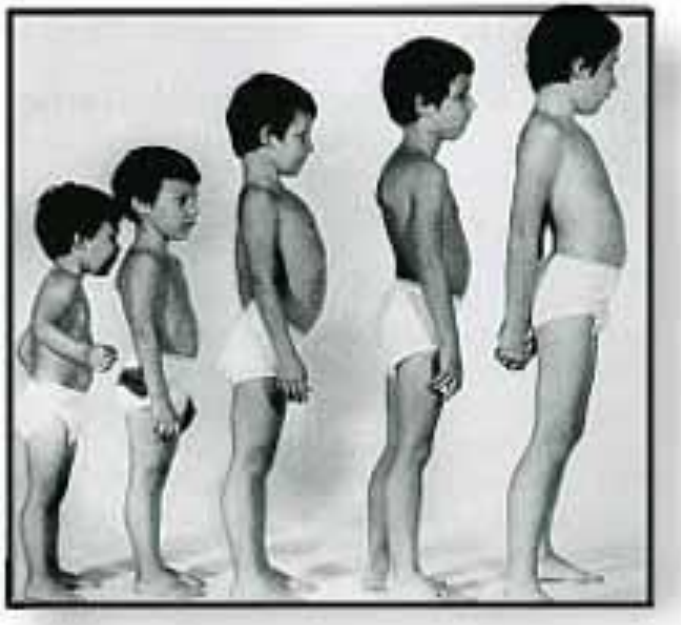
Experiences from the SMA and DMD fields

Duchenne Muscular Dystrophy

PTC Therapeutics – Translarna/Ataluren – Premature stop-codon readthrough

Spinal Muscular Atrophy

IONIS/Biogen – Spinraza/Nusinersen - SMN2 upregulation



Cell. 1987 Jul 31;50(3):509-17.

Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals.

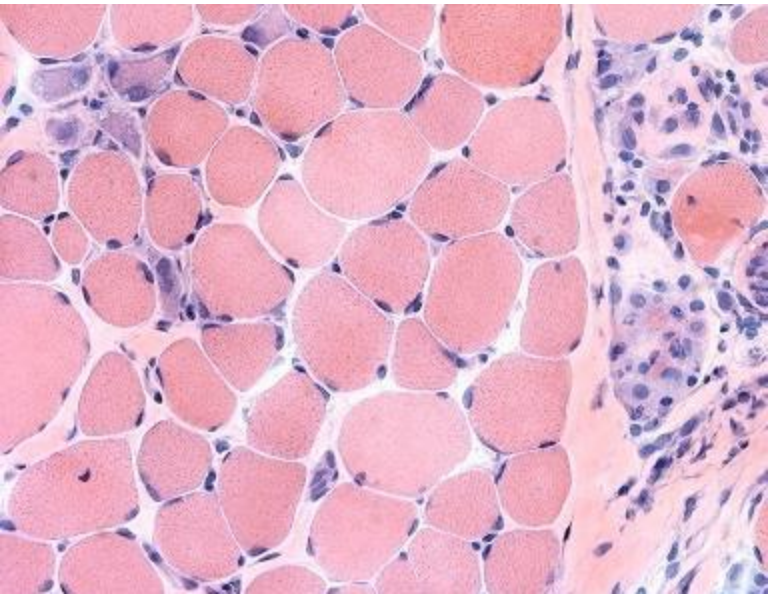
Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, Kunkel LM.

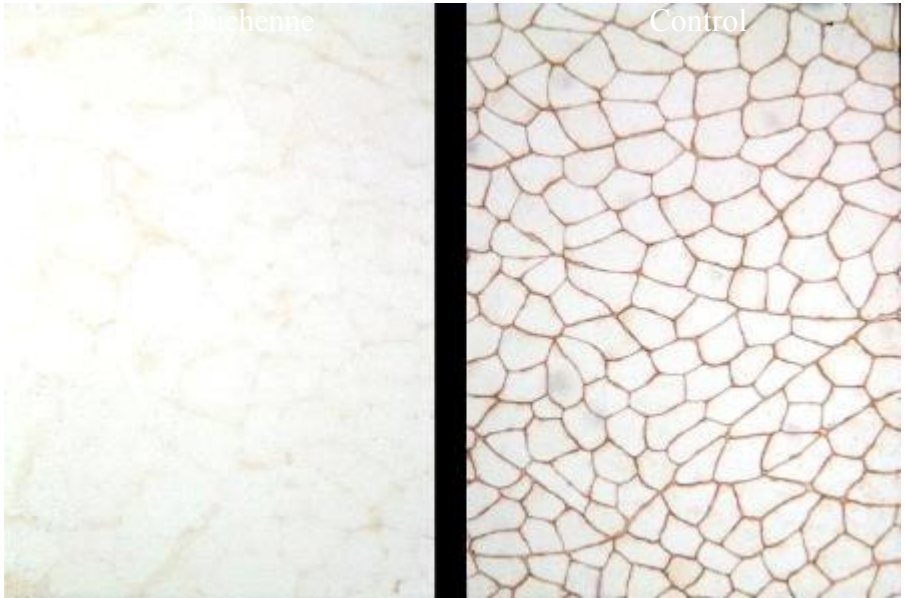
Cell. 1987 Dec 24;51(6):919-28.

Dystrophin: the protein product of the Duchenne muscular dystrophy locus.

Hoffman EP, Brown RH Jr, Kunkel LM.

We have named the protein dystrophin because of its identification via the isolation of the Duchenne muscular dystrophy locus.





Duchenne Muscular Dystrophy

- Steady decline in strength with increasing motor difficulties
- Lose walking ability from 7 - 13 years
- Contractures and Scoliosis
- Respiratory failure from 16 years
- Cardiomyopathy
- Mean age of death 25 years (range 12 – 45 years)

DMD is caused by a variety of different mutations:
10-15% of DMD cases are caused by nonsense mutations

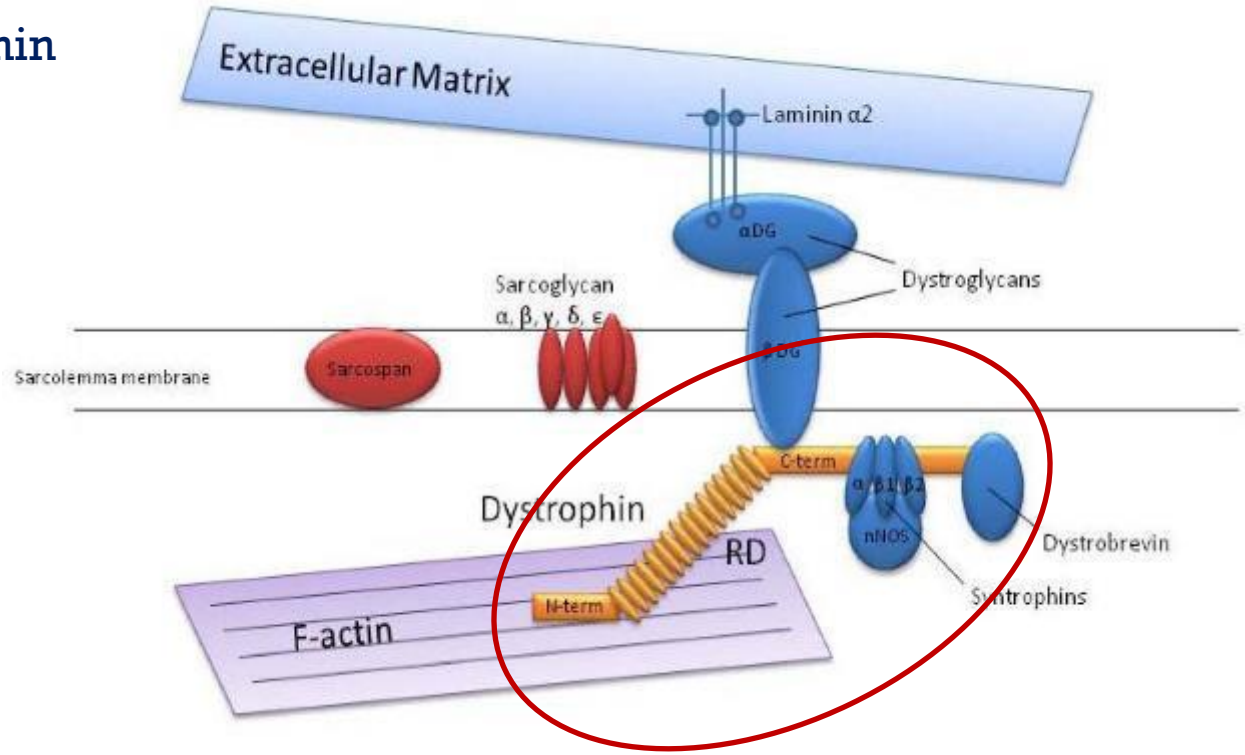
DMD causing mutations in the dystrophin gene	Mutation frequency in males with DMD
Deletion of one or more exons[1]	~65%
Duplication of one or more exons[1]	7–10%
Other mutations, e.g. insertion or missense mutations	15–30%
Nonsense mutations[2]	10–15%

1. Abbs S *et al. Neuromuscul Disord* 2010;20:422–7; 2. Prior TW *et al. Am J Hum Genet* 1995;57:22–33

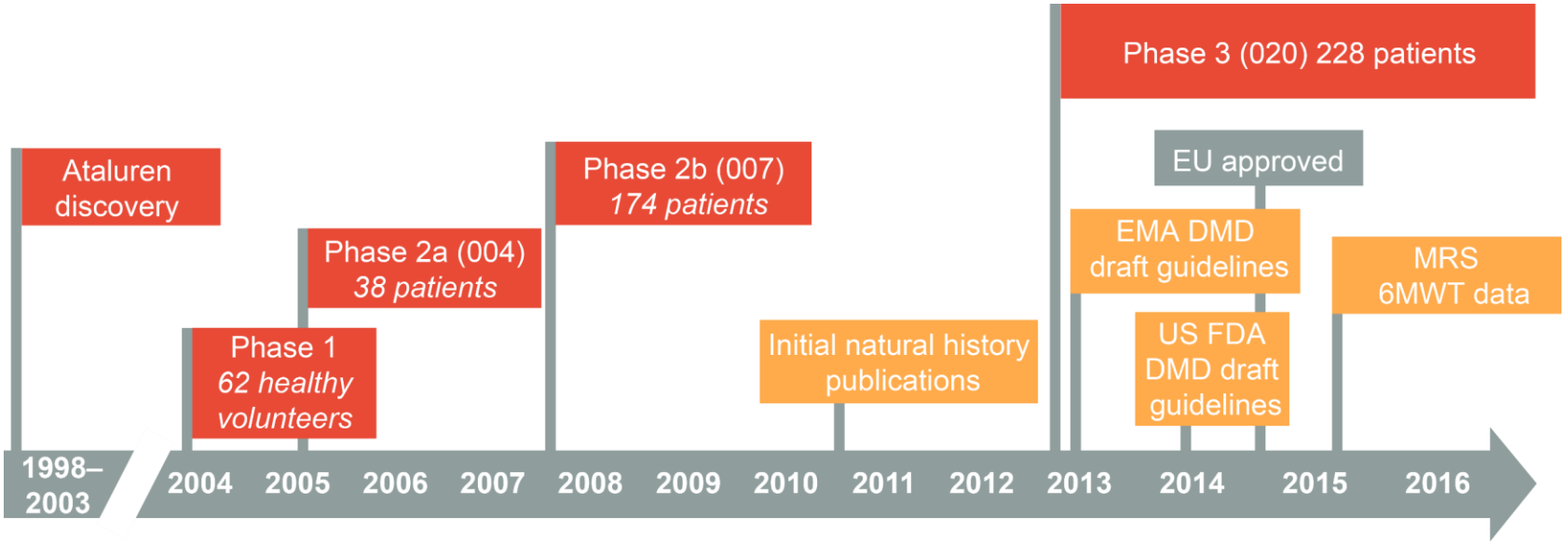
DMD is due to the loss of dystrophin which acts as a shock absorber in muscle cells

- Muscles lacking dystrophin are more susceptible to muscle damage
- Dystrophin restoration is expected to prevent muscle damage

Dystrophin stabilizes, but does not increase muscle strength



Ataluren in nmDMD: Development history



- 15 years of research and development
- Over 650 healthy volunteers/patients exposed/treated
- Generally well-tolerated
- Phase 2a: dystrophin expression demonstrated; Finkel et al Plos One 2013
- Phase 2b: clinical efficacy versus placebo demonstrated/natural history established; Bushby et al Muscle & Nerve 2014
- Phase 3: ACT DMD top-line results available; Submitted
- **EMA granted marketing authorization approval for ambulatory patients with nmDMD aged 5 years and older: July 2014, renewed January 2017**

Phase 3 Ataluren/Translarna results

In the overall Intent-to-Treat (ITT) population, Translarna™ (ataluren) demonstrated a 15m benefit in the six minute walk test (6MWT) which was not statistically significant (p=0.213, n=228)

Translarna demonstrated a highly significant 47m benefit observed in 6MWT for the pre-specified 300m – 400m baseline six minute walk distance (6MWD) patients (nominal p=0.007, n=99)

Pre-specified meta-analysis of combined ACT DMD and Phase 2b ambulatory decline phase show statistically significant 6MWT benefit of 22m (p=0.015, n=291)

Key secondary endpoints favored Translarna including Time Function Tests (TFTs) across ACT DMD as well as the pre-specified meta-analysis

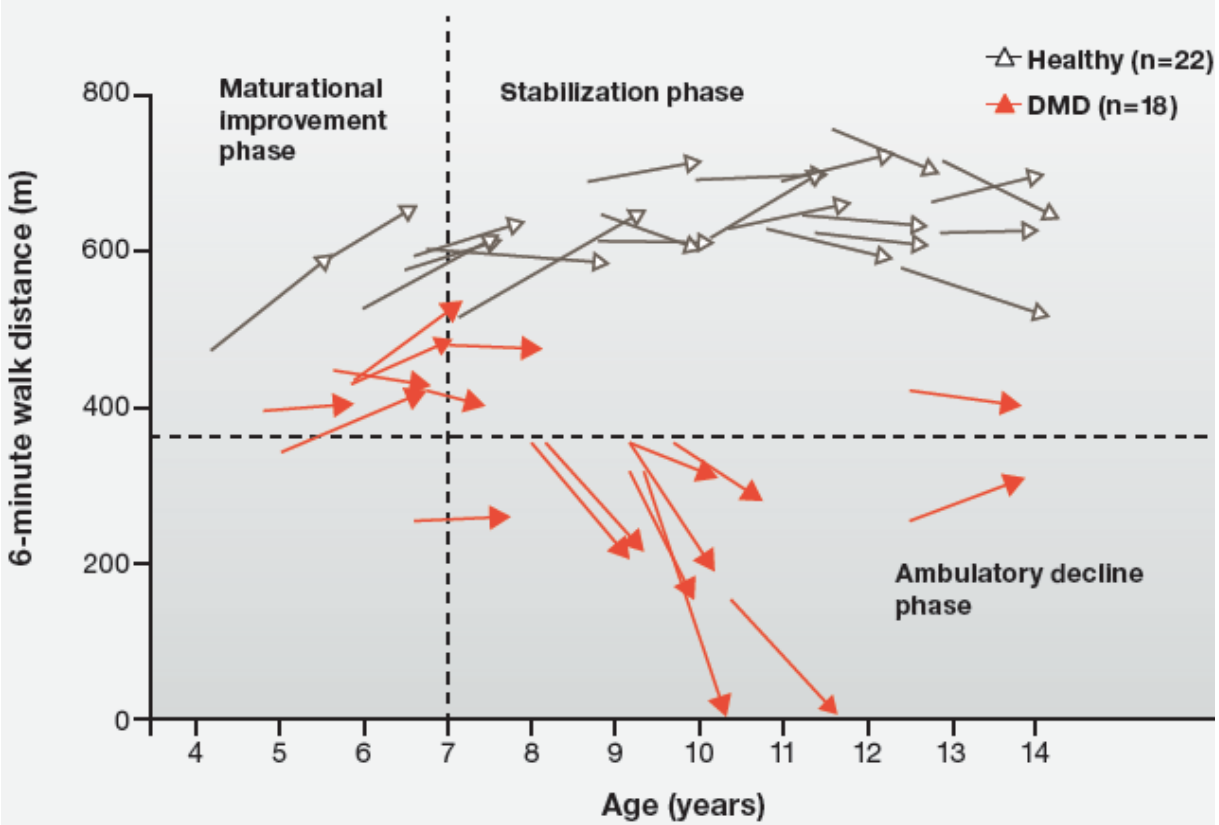
North Star Ambulatory Assessment demonstrated benefit for Translarna

No Translarna treated patients lost ambulation in the 300m – 400m baseline 6MWD group (0 / 47) vs four placebo patients in the same group (4 / 52)

Translarna demonstrated a strong safety profile, consistent with previous studies

Boys with DMD have a significantly decreased ambulatory capacity compared with healthy controls[1]

Ambulatory capacity of patients and healthy controls with DMD



1. McDonald *et al. Muscle Nerve*. 2010;42(6):966–74. Figure adapted with permission from McDonald *et al*.
DMD, Duchenne muscular dystrophy.

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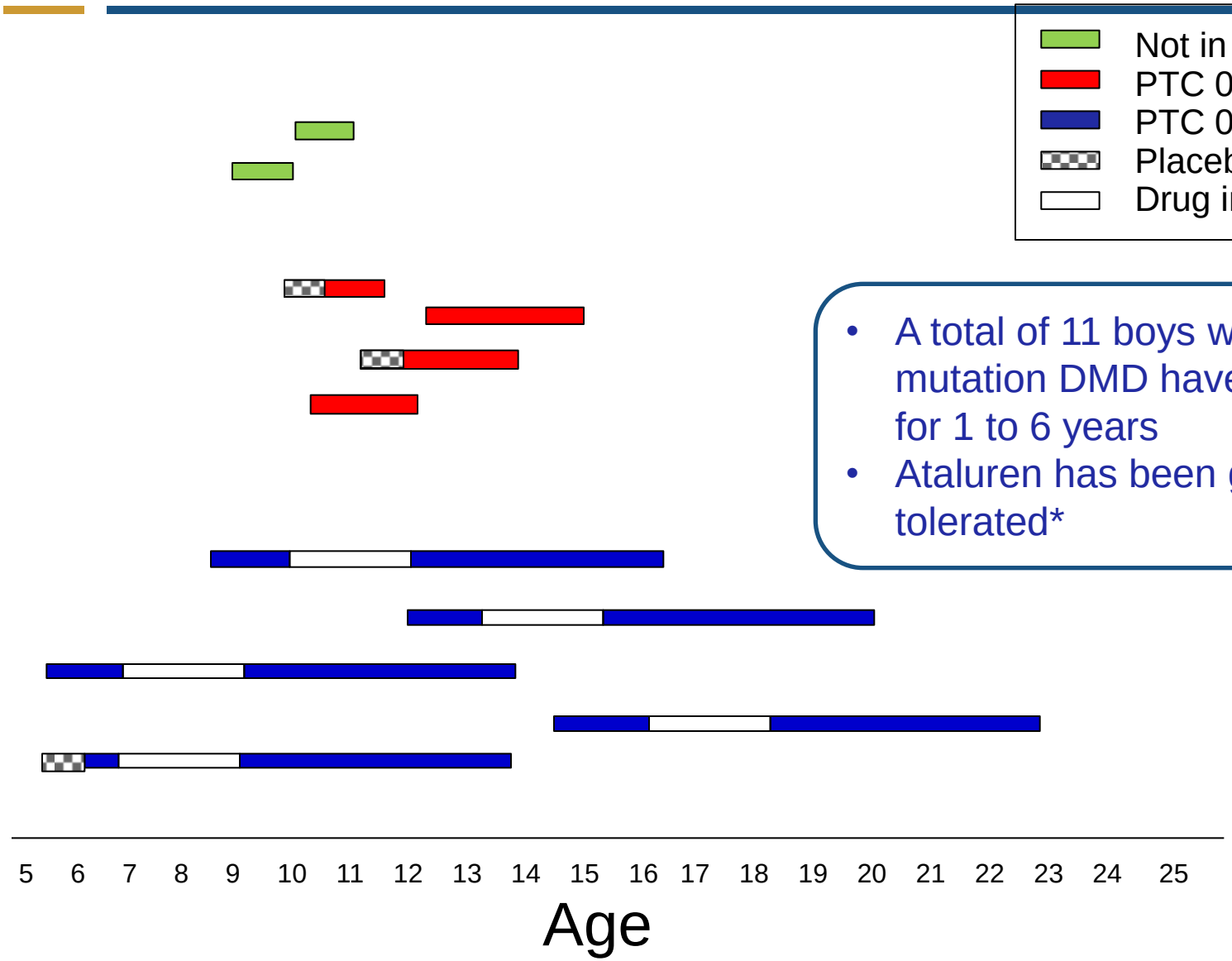
Patients treated with ataluren in Gothenburg



- A total of 11 boys with nonsense mutation DMD have been treated for 1 to 6 years
- Ataluren has been generally well tolerated*

*One patient was included in the sibling programme in 2015, but had to stop treatment because of urticaria

Nonsense mutation DMD – experience of treatment with ataluren in Gothenburg

- All boys and their parents report that ”nothing much happens” while on treatment, meaning that the disease is not progressing as fast as without the drug. The lack of disease progression (not losing function) is of utmost importance for these boys.
- The boys and their parents report that they have more energy and less tiredness and fatigue.
- All boys who have had to stop treatment have reported that they have a feeling that the disease progresses more rapidly when not on the drug.
- The drug is taken orally three times a day and compliance is very good. It is mainly the afternoon dose which can be forgotten but this rarely happens.
- All patients/families are very afraid of having to stop treatment, especially the non-ambulant boys.

Duchenne Muscular Dystrophy

Translarna/Ataluren – Premature stop-codon readthrough

EMA granted marketing authorization approval for ambulatory patients with nmDMD aged 5 years and older in July 2014 which means that Translarna/Ataluren is an approved drug within the EU – accordingly 85% of nmDMD boys in Europe who fulfill the indication are on the drug

In Sweden it is approved since August 2016 for boys who have participated in clinical trials, but not for others. There are at least 6 boys who were too young to participate in studies or have been diagnosed later who do not receive the drug. From a medical perspective these boys should be on treatment as they still have muscles to save

A question regulatory authorities are asking and which needs to be answered concerns how long do we treat patients with Translarna. When to stop treatment? When do the patients no longer gain from the treatment?? This will have to be dealt with on an individual basis. From a medical perspective and from the experience we have this occurs at the time the patients develop a need for mechanical ventilation (late non-ambulatory phase). A national group of neuromuscular experts should be formed to discuss on a case by case basis indication to start and stop treatment. This group could also be used in decisions regarding Nusinersen and other similar drugs

Spinal Muscular Atrophy

Spinraza/Nusinersen - SMN2 upregulation

RNA-modulating treatment which corrects the splicing disorder in SMN2

Was approved by FDA for treatment of children and adults with SMA on December 23 2016

Application to EMA submitted in October 2016 and approval may come as early as April 2017 and at the latest July 2017

SMA/Nusinersen – What happens now?

Await approval by European Medicines Agency (EMA)

Expanded access program ongoing for patients with SMA type 1 at centers which participated in clinical trials

In Gothenburg we have 3 patients with SMA type 1 in Shine and have started treatment in 4 patients with SMA type 1 who were between the ages of 3 and 18 months at start of treatment

We have 2 infants recently diagnosed with SMA type 1 and 7 patients who are older than 2 years and who have been referred for treatment

SMA/Nusinersen – What happens now?

SMA type 1

More or less all patients have Cough Assist and BiPap and have or will receive Percutaneous Endoscopic Gastrostomy

Two patients have tracheostomy and very little muscle function and relatively severe contractures, but as one of the mothers put it; ”Just a little bit of muscle strength would help him alot”

SMA type 2

We have two patients with SMA type 2 in Shine and follow 12 patients below age 18 years at the regional rehabilitation clinic in Gothenburg

SMA type 3

We follow nine patients with SMA type 3 below age 18 years at the regional rehabilitation clinic in Gothenburg

Orphan drug development has been encouraged by governments and led to real investment and innovation by the pharmaceutical industry

Regulation (year)	1983	2000	1993
Prevalence (to define if a medicine can be designated as an orphan)	<200,000 (<6.25/10,000)	<5/10,000 (England / Wales: "ultra-orphan" disorders, prevalence <1/50,000)	<50,000 (<4.7/10,000)
Market exclusivity	7 years	10 years	10 years
Tax credits	Yes (50% of clinical investigation expenses)	Yes (6% for any type of study + limited to 10% of the company's corporation tax)	Yes
Lower filing fees/ Grant funding	Yes (exemption of application/ filing fee	Yes (fee reductions for regulatory activities)	Yes
Protocol assistance	Yes	Yes	Yes

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Summary

This has been a long and winding road

Patients should not have to wait because of long bureaucratic processes where a multitude of committees at different national, regional and hospital levels have opinions when the European Medicines Agency has approved a drug

Hopefully, the path for Nusinersen/Spinraza will be quicker than what we have experienced for Translarna/Ataluren