santhera Pharmaceuticals

Efficacy of Raxone® (idebenone) on respiratory outcome in patients with DMD

Dr. Thomas Meier

5. April 2016

Agenda

- Raxone® (idebenone) - development pipeline
- Medical need for treatment of respiratory function loss in DMD
- Mitochondrial impairment in dystrophin-deficient muscle
- Idebenone - mode of action in DMD
- Clinical development program with Raxone®: DELOS Phase 3 trial
- Positioning of Raxone® in the treatment of DMD
- SIDEROS trial in patients on glucocorticoids

Pipeline with Raxone® (idebenone) in three indications with high unmet medical need

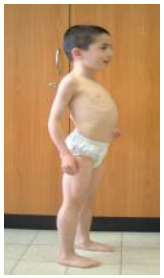
Leber's Hereditary Optic Neuropathy (LHON):
Approved in EU

Duchenne Muscular Dystrophy (DMD):
Positive Phase 3 study outcome,
NDA/MAA filing in preparation

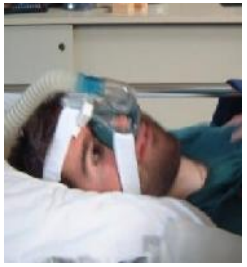
Primary progressive MS (ppMS):
Phase 2 study in collaboration with NIH

Clinical progression of DMD

Courtesy: Nathalie Goemans.
University Hospitals Leuven, Belgium

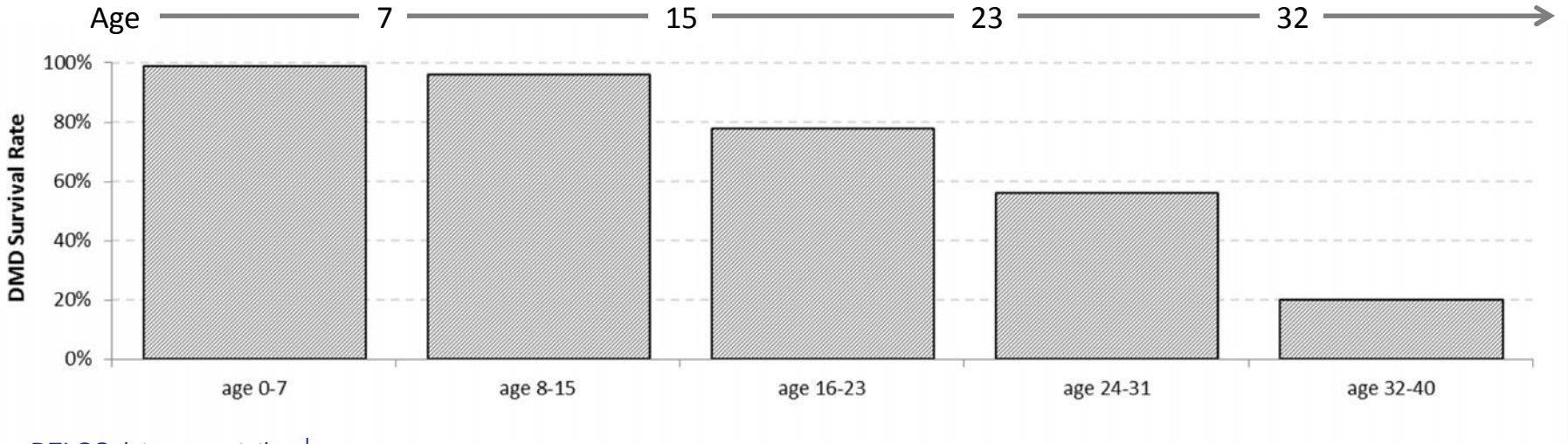






Loss of ambulation

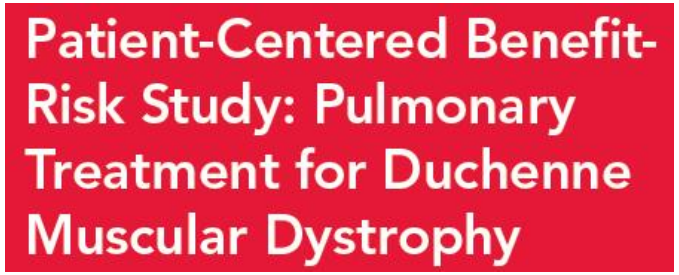
Loss of respiratory function
Assisted ventilation
Nocturnal ventilation



Medical need for effective treatment of respiratory illness in DMD

- Progressive weakness of respiratory muscles leads to a loss of respiratory function (restrictive pulmonary syndrome).
- Medical complications include ineffective cough, nocturnal hypoventilation, sleep disordered breathing, and ultimately daytime respiratory failure.
- DMD patients develop cardiac and respiratory complications that typically lead to early morbidity and mortality.

Patients' treatment preference of pulmonary function



Parent Project Muscular Dystrophy

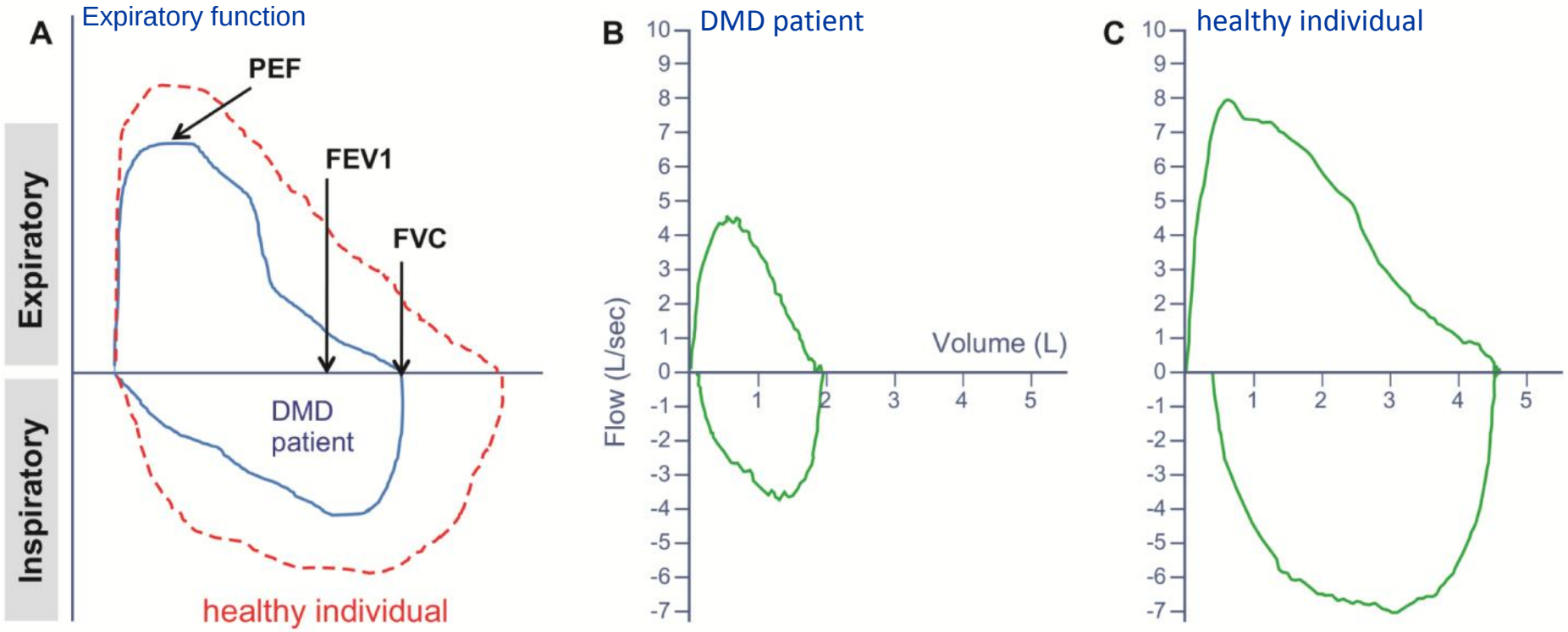
LEADING THE FIGHT TO END DUCHENNE

PPMD study team: Holly Peay, Caroline Young, Ryan Fischer, Pat Furlong
JHU study team: John F P Bridges, Ilene Hollin, Caroline Hansen

Sponsored by Santhera Pharmaceuticals

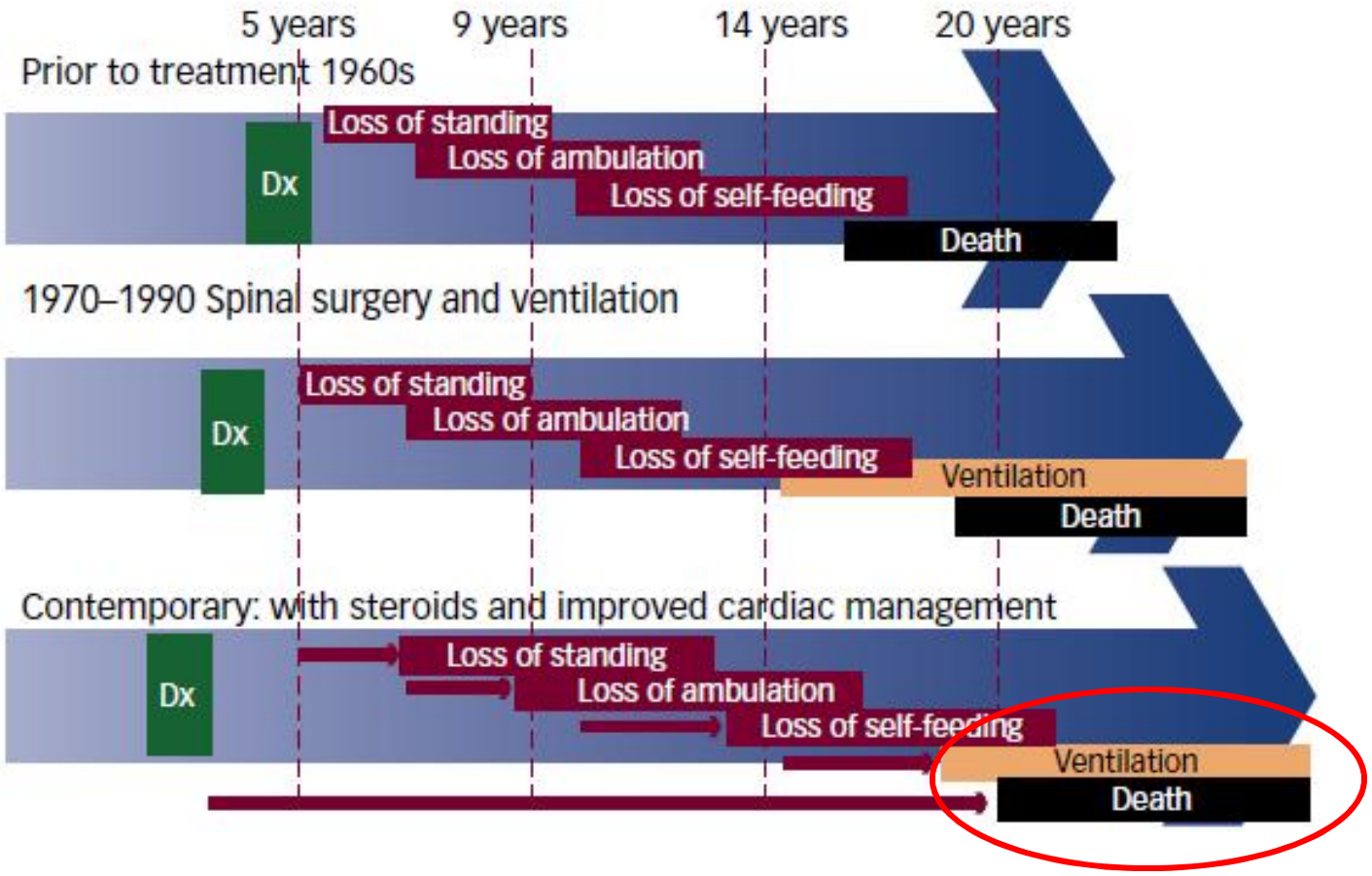
- Patient-centered benefit-risk survey conducted by PPMD in a community engaged approach
- Focus on treatment priorities for disease aspects not directly related to skeletal muscle function (best-worst scaling methodology, 4 different survey activities)
- 155 participants (85% patients/caregivers with DMD)
- **Treatment of pulmonary disease (cough, prevention of airway infections) was highly prioritized as patient/caregiver preference**

Measures of pulmonary function loss in DMD



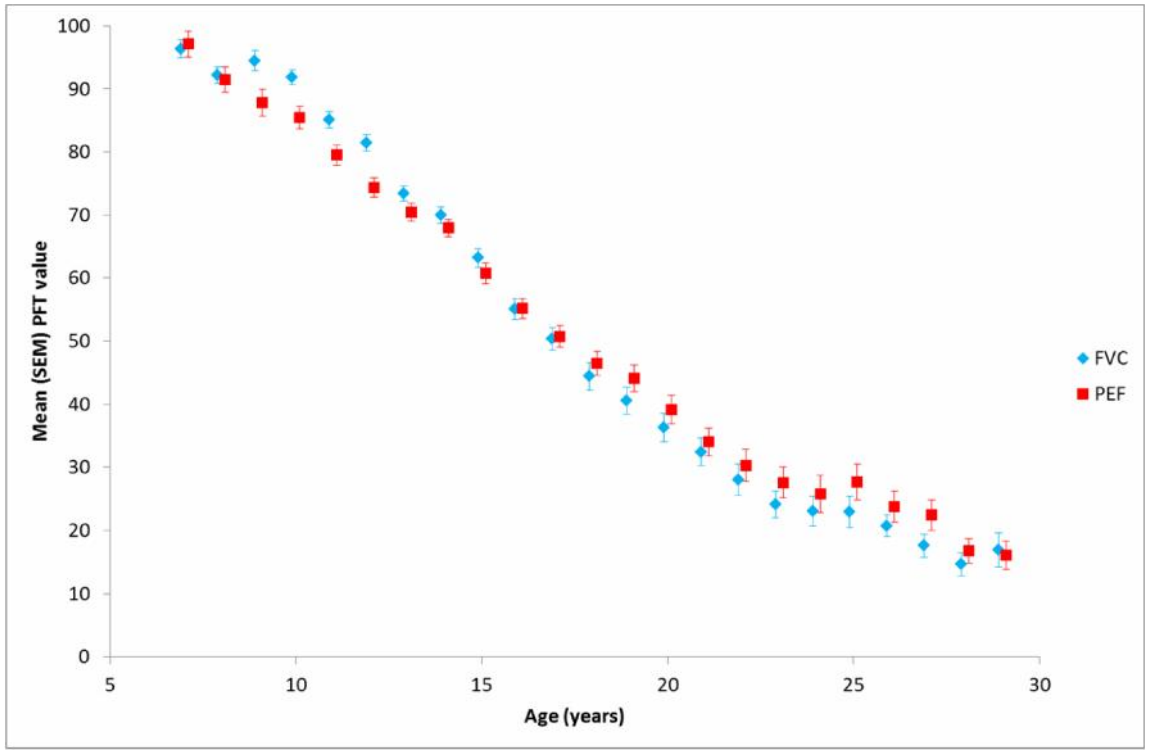
Figures (B) and (C) courtesy of Dr. Oscar H. Mayer, Division of Pulmonology, The Children's Hospital of Philadelphia, USA.

Use of glucocorticoid steroids and assisted ventilation increase life expectancy in DMD



taken from Goemans et al. (2014) European Neurological Review, 9(1):78–82

Progressive decline in PEF%p and FVC%p between 10 and 20 years of age

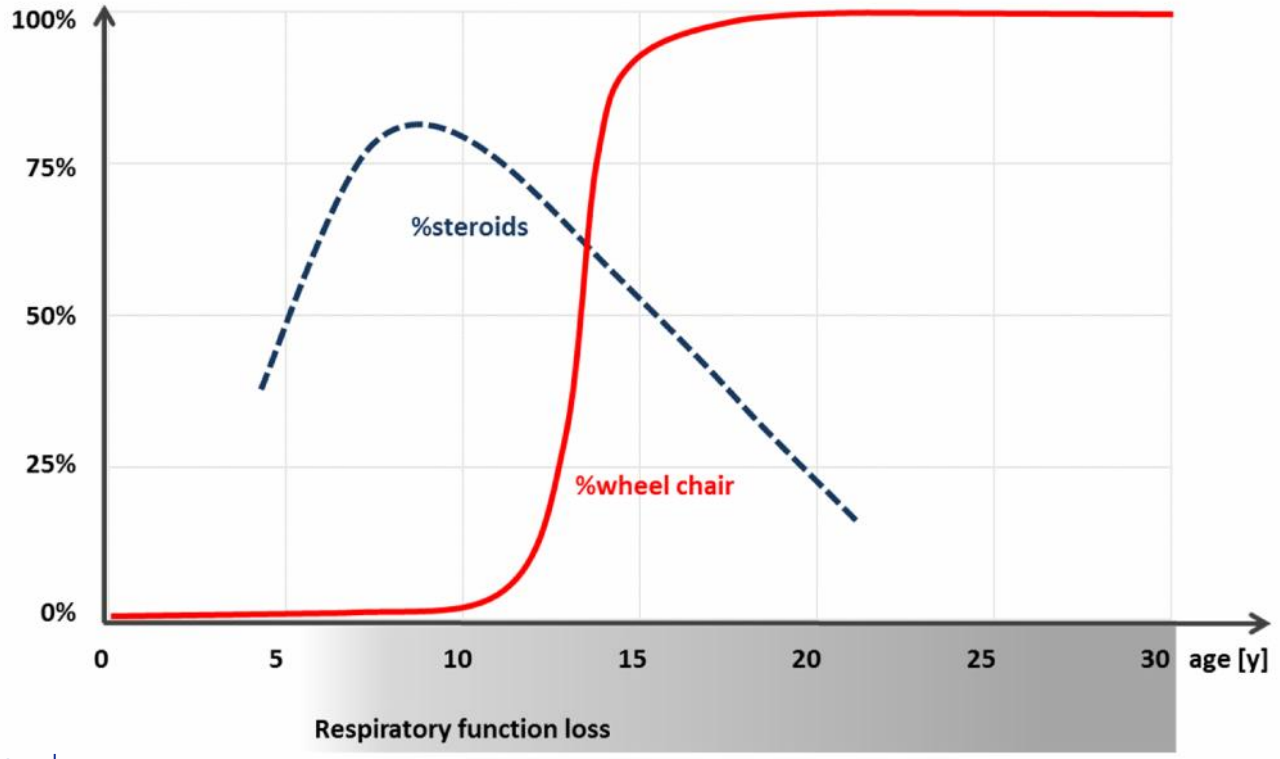


Source: Natural history data base from Cooperative International Neuromuscular Research Group (CINRG) ; N= 334 patients

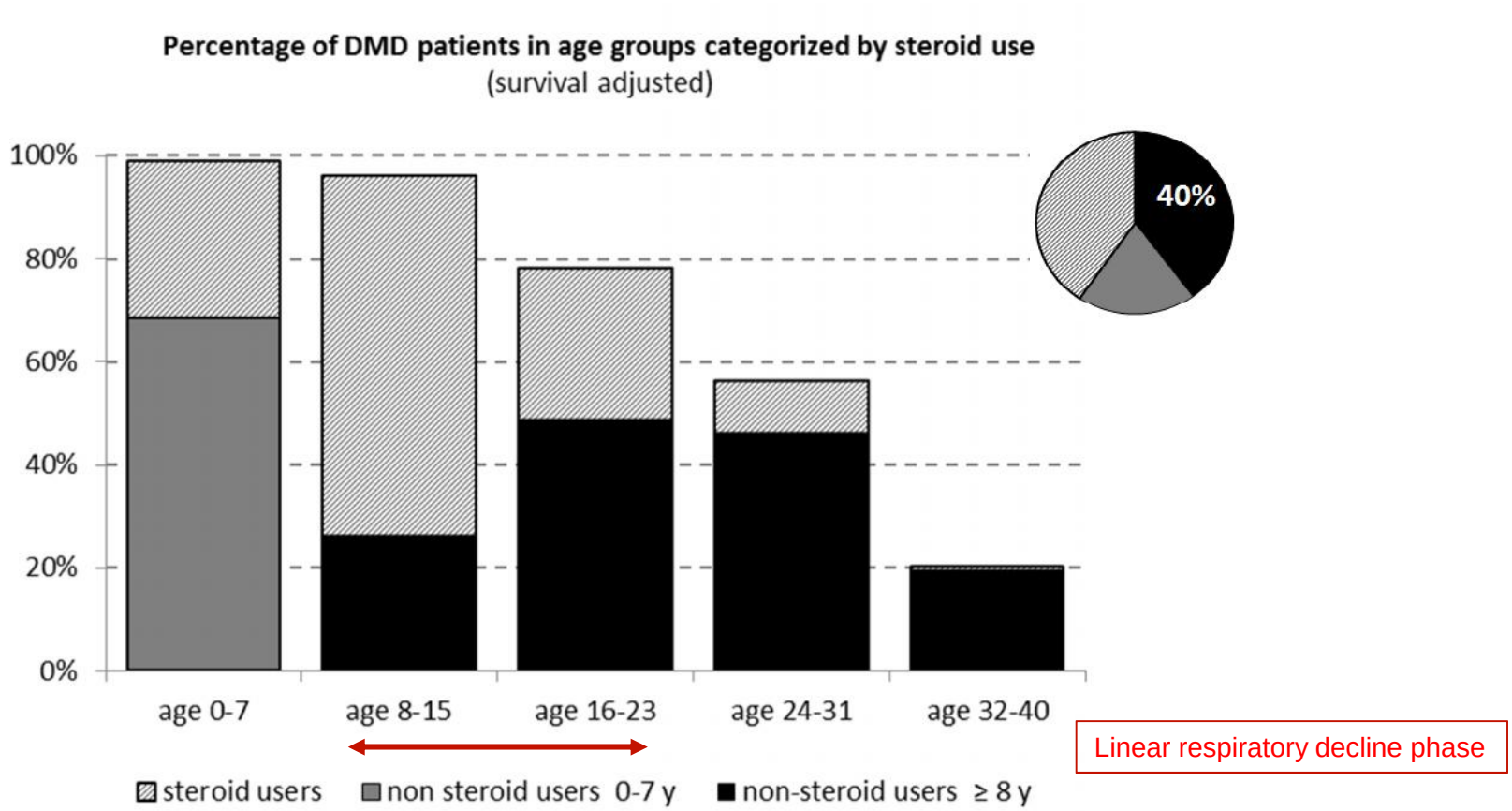
- Almost linear decline in respiratory function from age ~10 years
- PEF%p and FVC%p follow parallel/overlapping trajectories
- Decline established at ~80%p
- Decline in expiratory function predicts morbidity (e.g. need for assisted ventilation) and mortality
- PEF selected as primary endpoint of pivotal DELOS trial

Urgent medical need for patients unable to take glucocorticoid steroids

- With increasing age, fewer patients tolerate glucocorticoid steroids (side effects)
- Loss of respiratory function enters critical stage in early teenage years
- There is currently no treatment available for this group of DMD patients



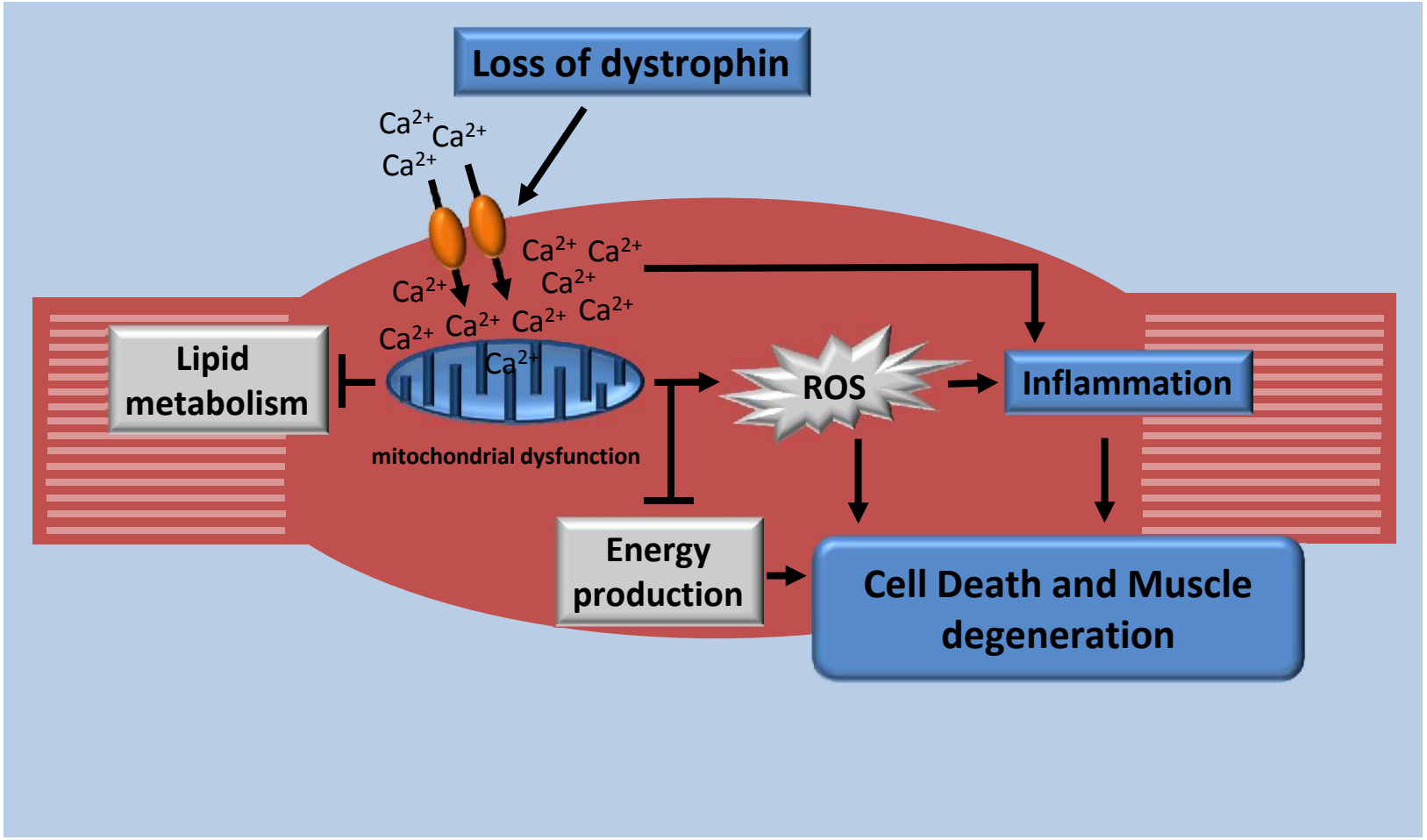
40% of prevalent cases are not using glucocorticoid steroids



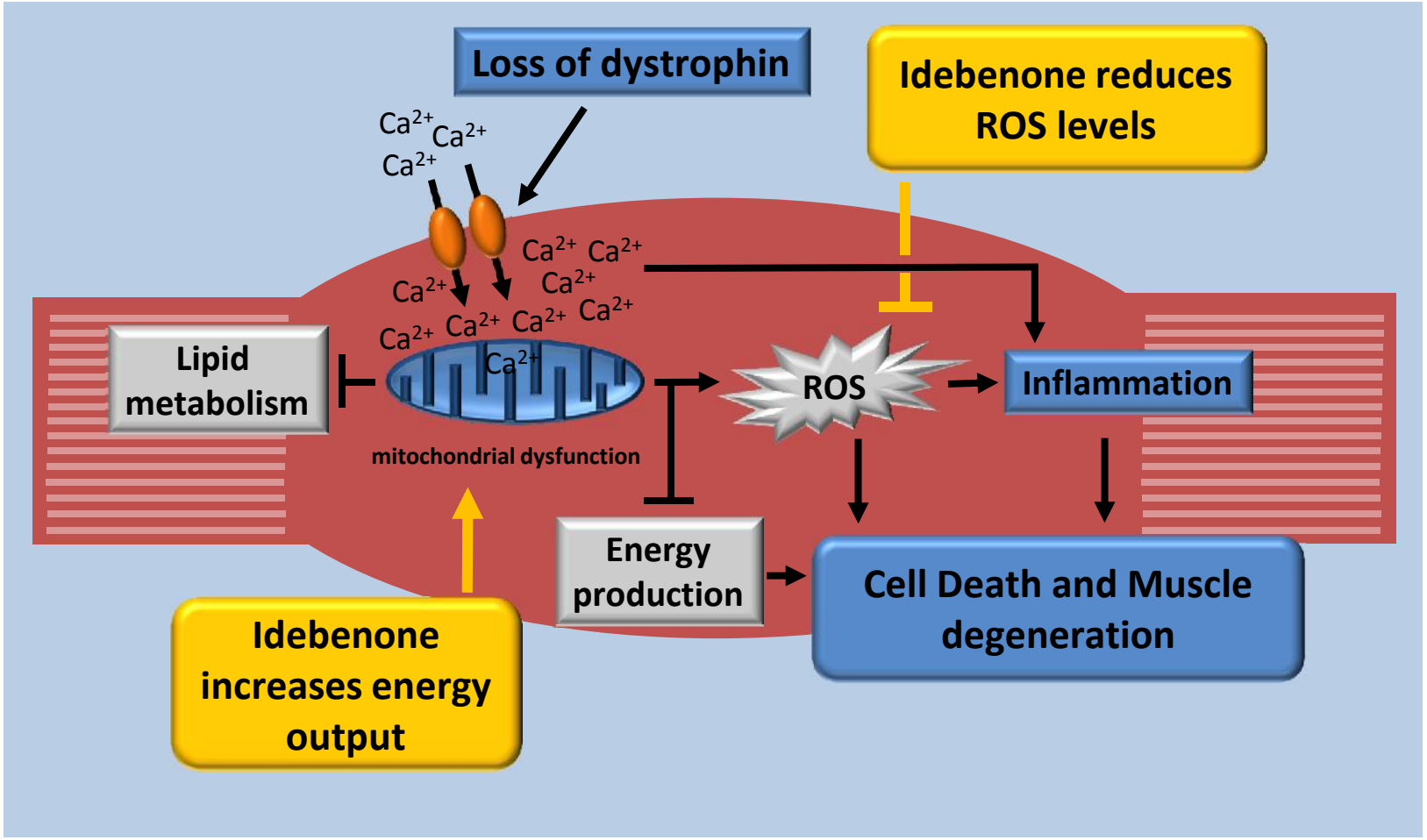
Santhera model based on survival data[1] and reported steroid use[2]

1) *Passamano et al., Acta Myol. 2012. Rall et al., Acta Myol. 2012*
2) *2) Henricson et al ., Muscle Nerve 2013*

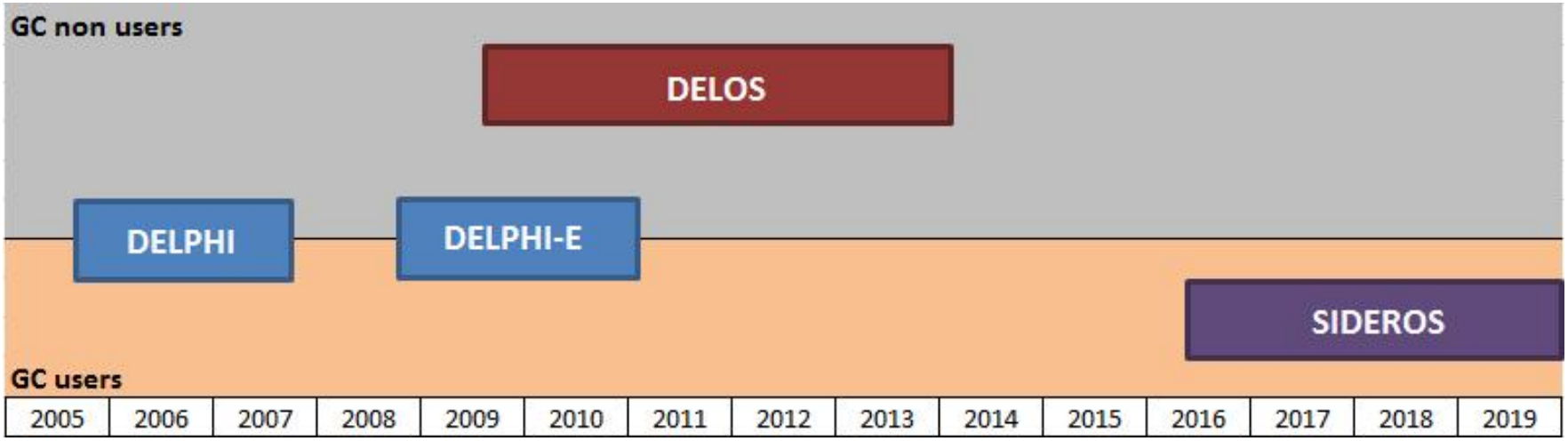
Mitochondrial impairment in DMD



Idebenone mode of action in dystrophic muscle



Clinical development program with Raxone®



Clinical development program with Raxone®

Phase 2:
DELPHI
(2005-2007)

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 21 (2011) 396–405

NMD
www.elsevier.com/locate/nmd

Idebenone as a novel, therapeutic approach for Duchenne muscular dystrophy: Results from a 12 month, double-blind, randomized placebo-controlled trial

Gunnar M. Buyse [a,*], Nathalie Goemans [a], Marleen van den Hauwe [a], Daisy Thijs [b], Imelda J.M. de Groot [c], Ulrike Schara [d], Berten Ceulemans [e], Thomas Meier [f], Luc Mertens [b]

Phase 3:
DELOS
(2009-2014)

Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial

Gunnar M Buyse, Thomas Voit, Ulrike Schara, Chiara S M Straathof, M Grazia D'Angelo, Günther Bernert, Jean-Marie Cuisset, Richard S Finkel, Nathalie Goemans, Craig M McDonald, Christian Rummey, Thomas Meier, for the DELOS Study Group

The Lancet 2015; 385:1748-57

Phase 3 DELOS trial – patients and treatment

Patients:

- Age 10-18 years
- No selection for mutational status
- Patients had to be off chronic steroids
- 92% of patients were non-ambulatory
- Established respiratory function decline (< 80% PEF%p)

Randomized treatment:

- Raxone® (900 mg/d): N=31
- Placebo: N=33
- Mean Age: 14.3 y
- Treatment duration: 12 months

Respiratory function was assessed by:

- spirometry at hospital visits (every 3 months)
- at weekly intervals with portable device used at the patient's home

Assessment of respiratory function

Spirometer – At Hospital Visit Only

Test performed with physiotherapist

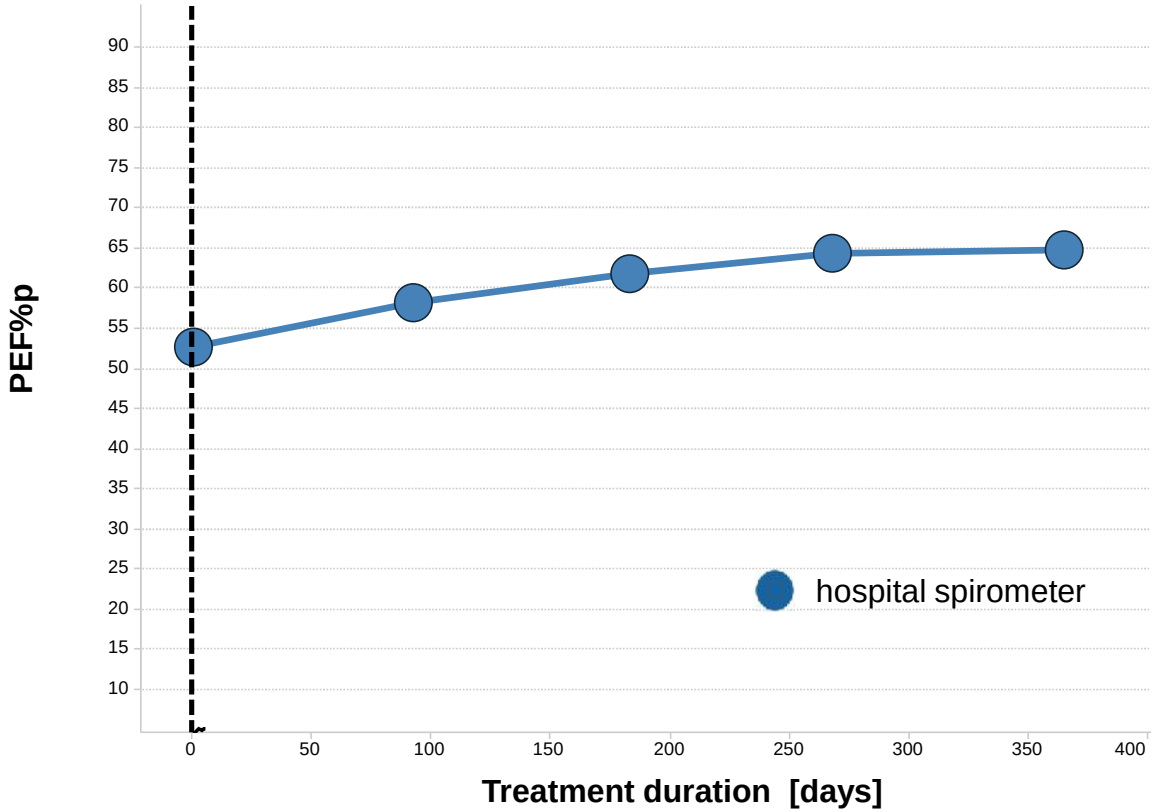
- Peak Expiratory Flow (PEF)
- Forced Vital Capacity (FVC)
- Peak Cough Flow (PCF)
- Inspiratory Flow Reserve (IFR)

ASMA-1™ - Hospital Visit & Weekly Home Testing

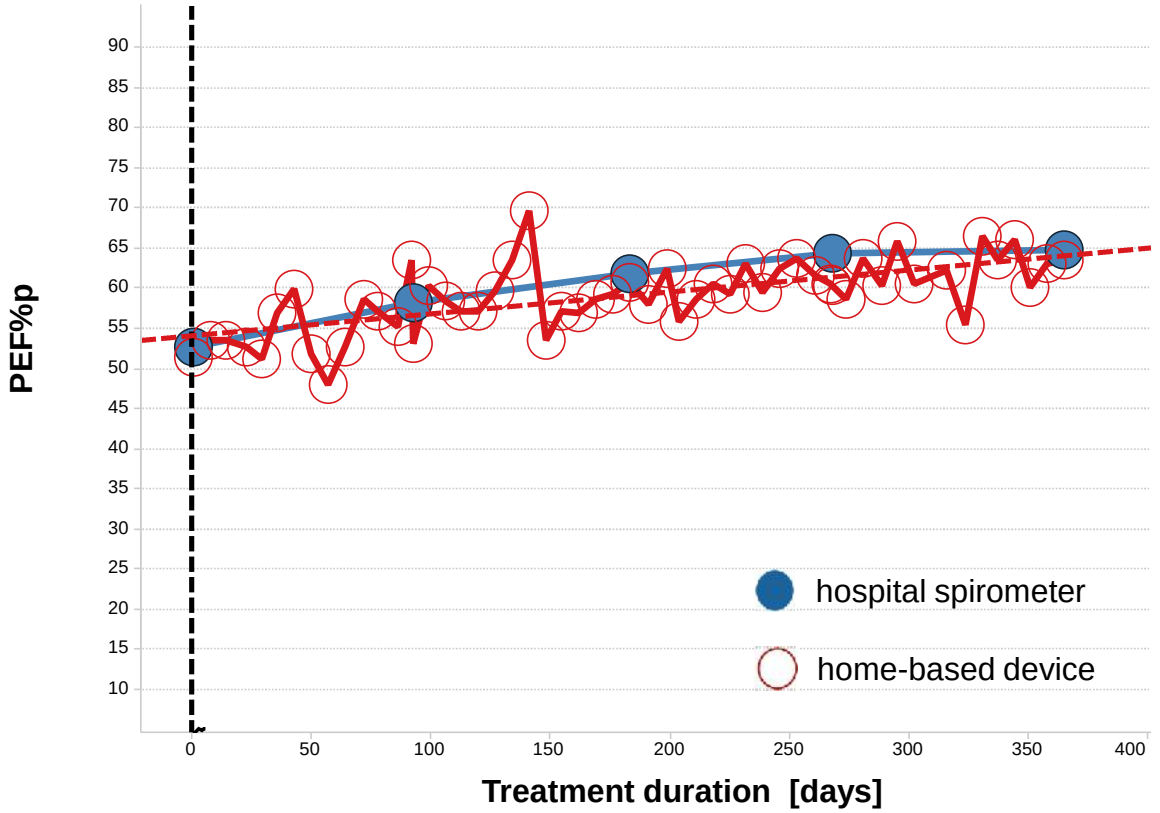
- Peak Expiratory Flow (PEF)
- Forced Expiratory Volume (FEV1)

At each clinic visit, the patient returns the device, the physiotherapist downloads, saves and prints all the stored readings from the home testing

Assessment of pulmonary function in DELOS



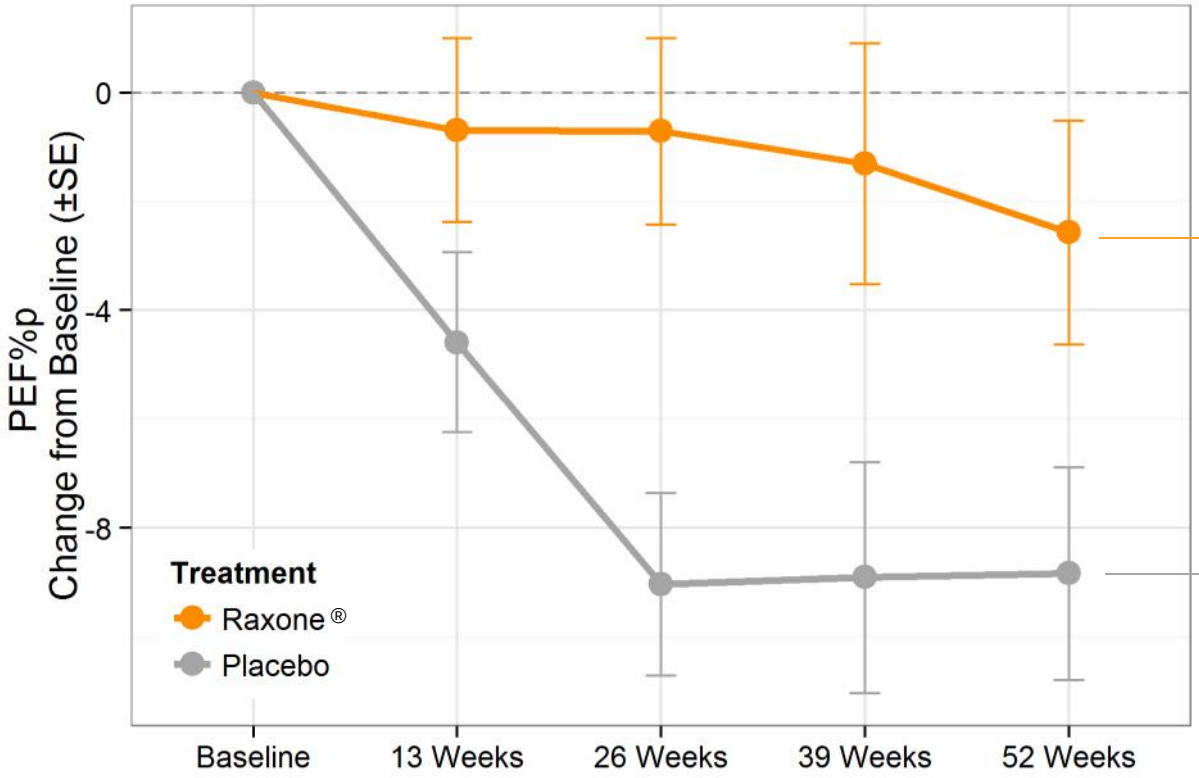
Assessment of pulmonary function in DELOS

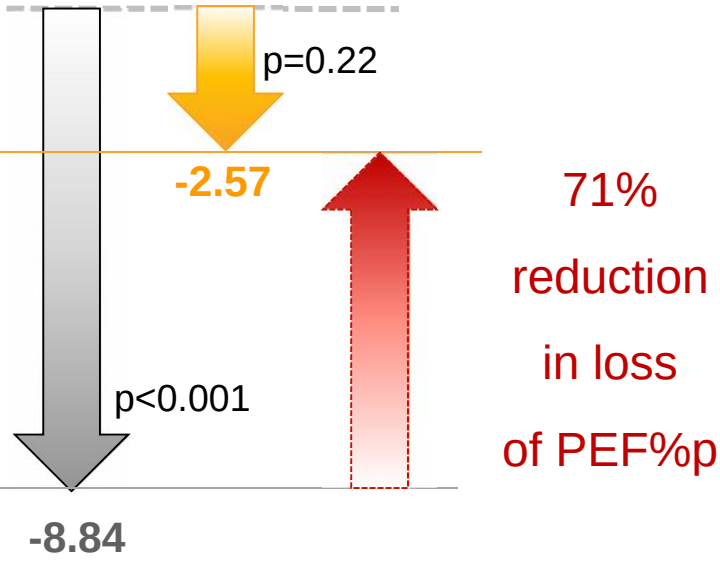


Primary analysis in patients with <20% difference between both measurements for PEF:

mITT: N=57 (30 Catena®/Raxone®; 27 Placebo)

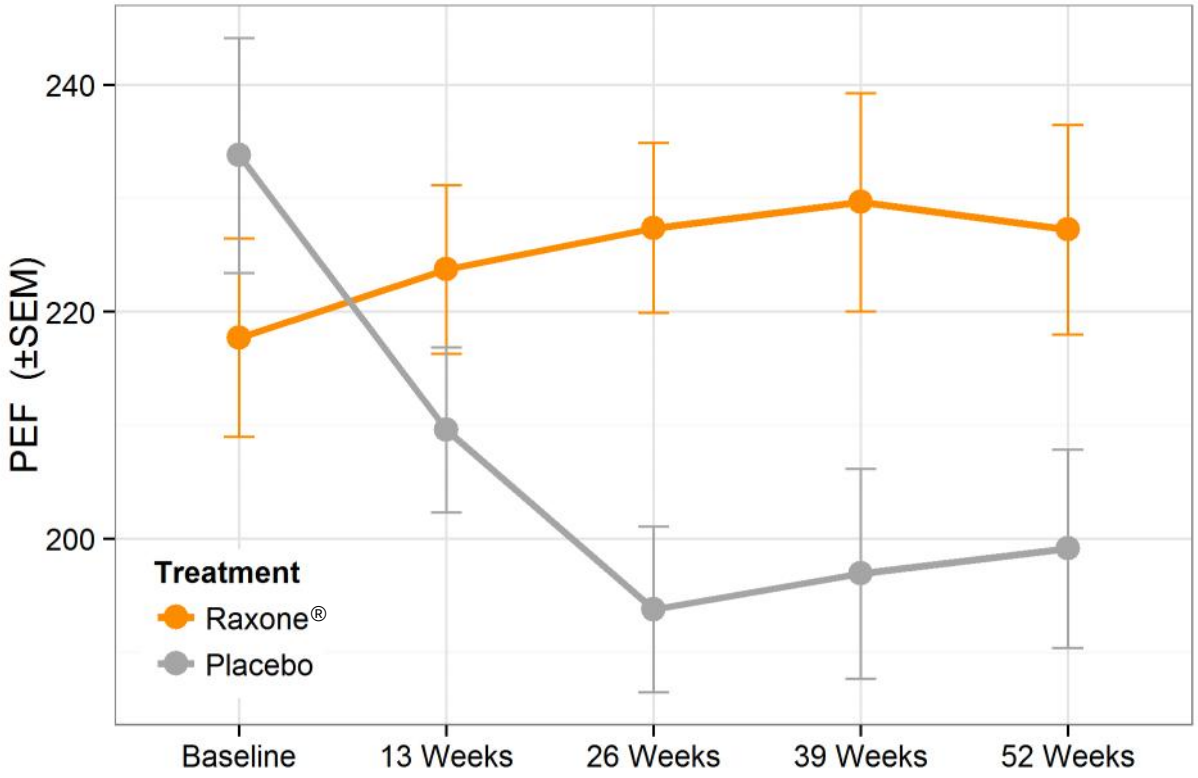
Primary endpoint: Change in PEF%p
(hospital-based spirometry)





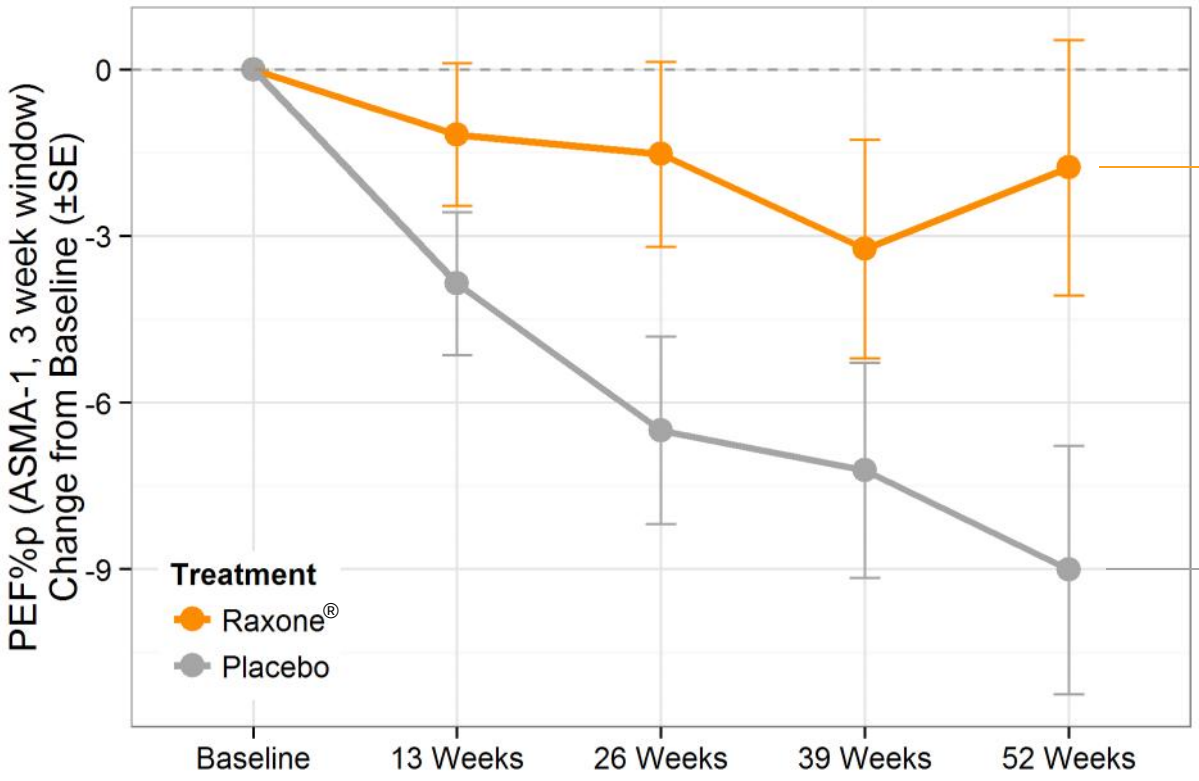
Difference	3.90	8.32	7.60	6.27
p-value	**0.10**	**<0.001**	**0.02**	**0.03**

Progression in absolute PEF [L/min]
(hospital-based spirometry)



Difference	14.1	33.6	32.7	28.1
p-value	**0.18**	**0.002**	**0.02**	**0.03**

Change in PEF%p
(measured by ASMA-device)



p=0.45

-1.77

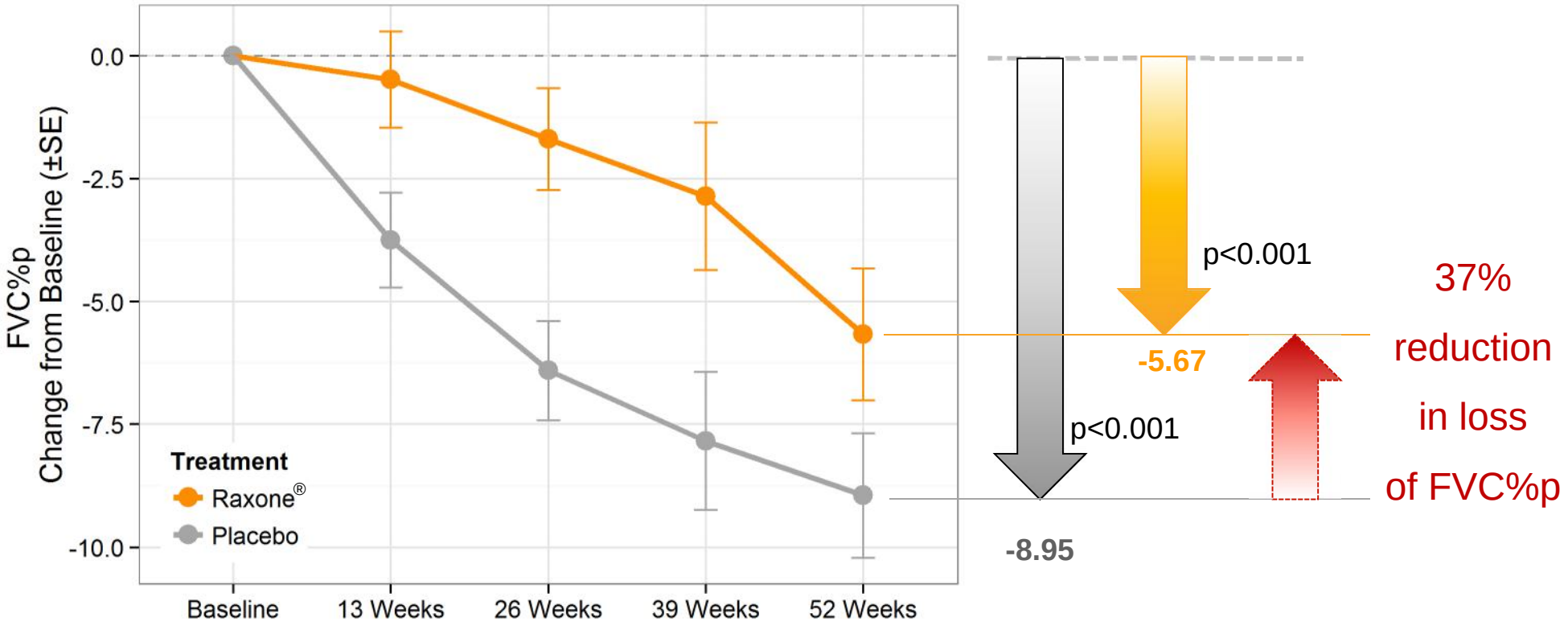
p<0.001

-9.01

80% reduction in loss of PEF%p

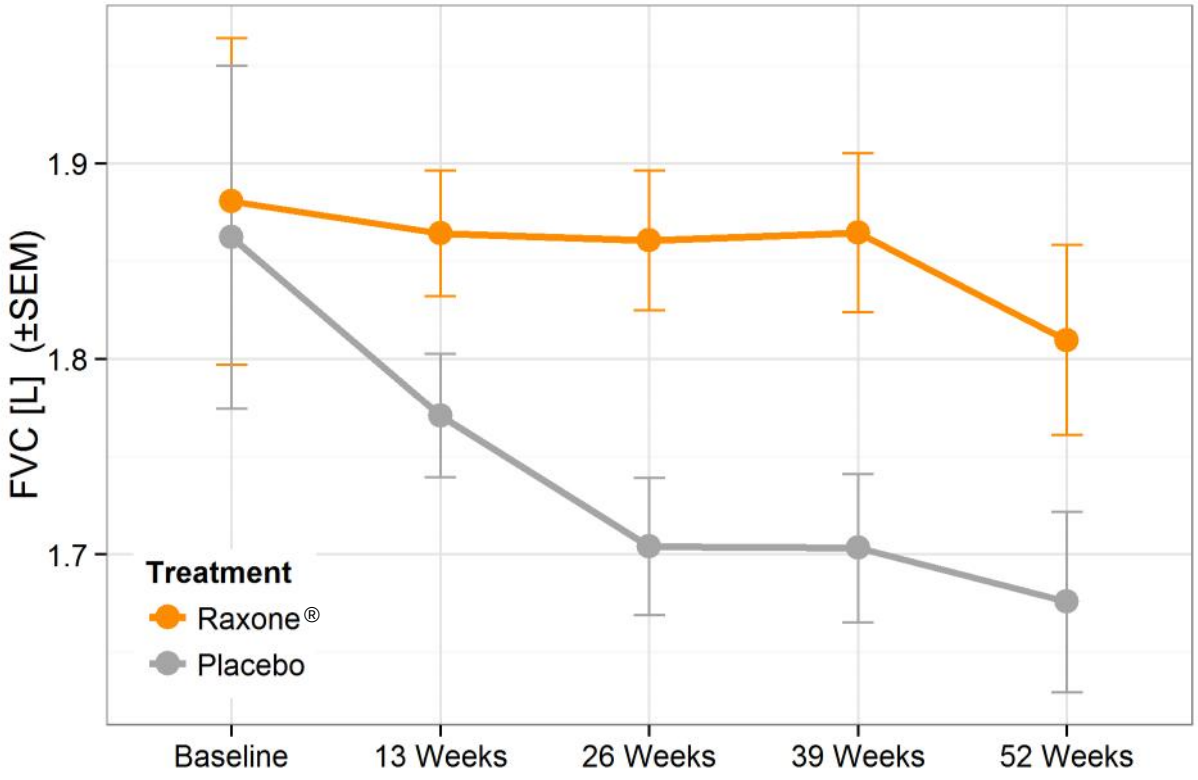
Difference	2.68	4.97	3.98	7.24
p-value	**0.15**	**0.04**	**0.15**	**0.03**

Change in FVC%p



Difference	3.27	4.72	4.97	3.27
p-value	**0.02**	**0.002**	**0.02**	**0.08**

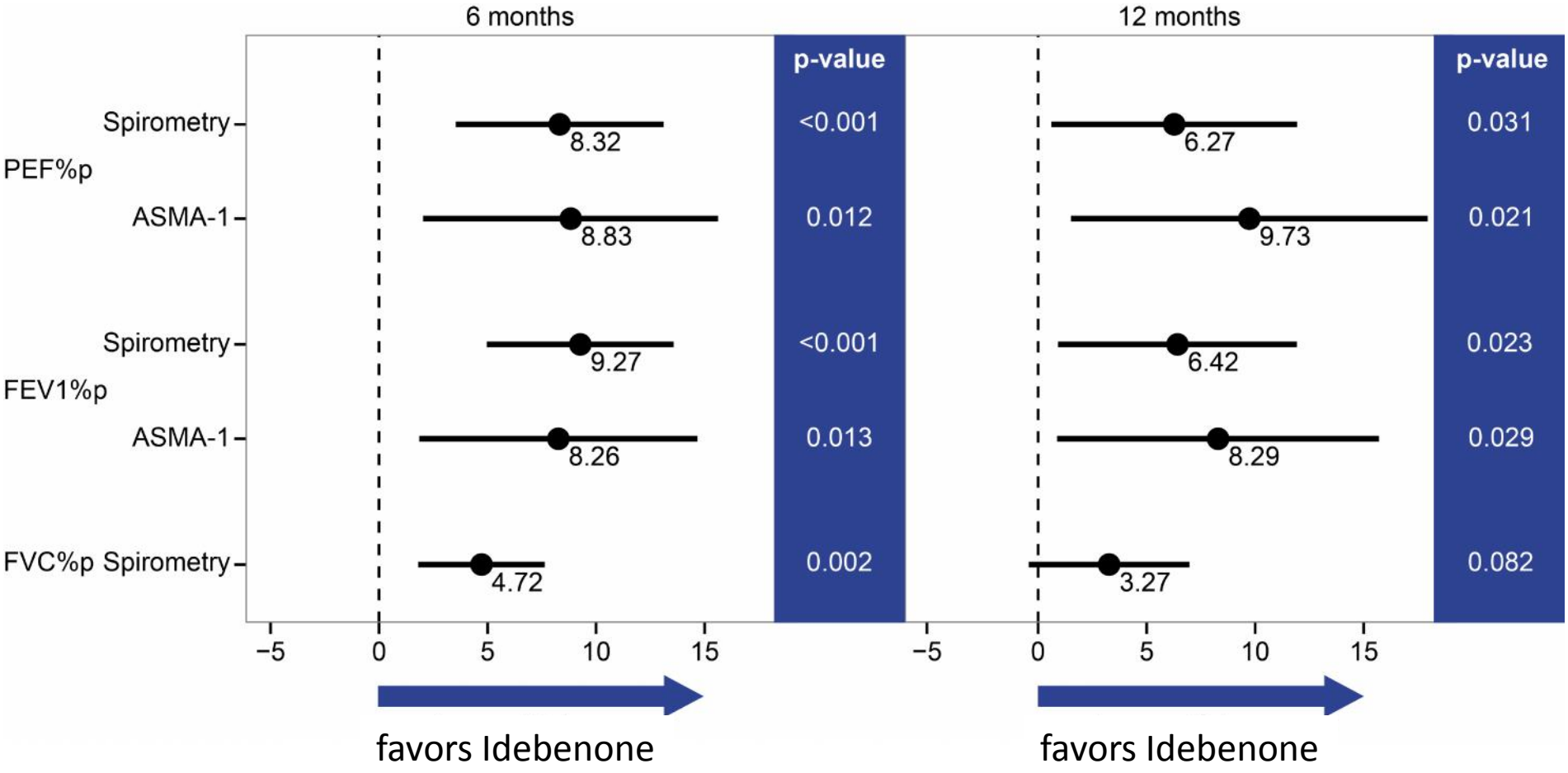
Progression in absolute FVC [L]



Difference	0.09	0.16	0.16	0.13
p-value	**0.04**	**0.003**	**0.005**	**0.05**

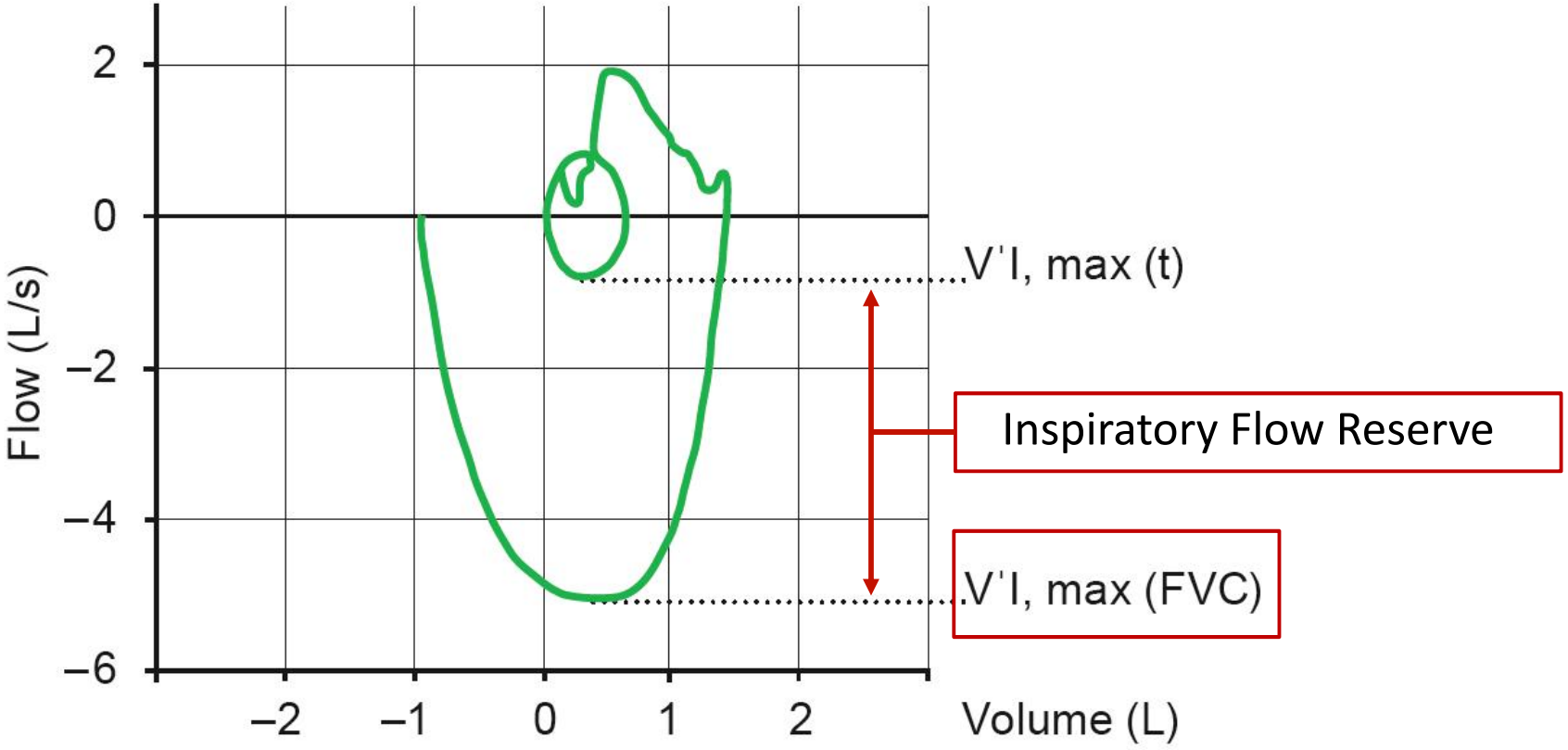
Idebenone slows the loss of respiratory function

Consistency of results



Inspiratory function is impaired in DMD patients

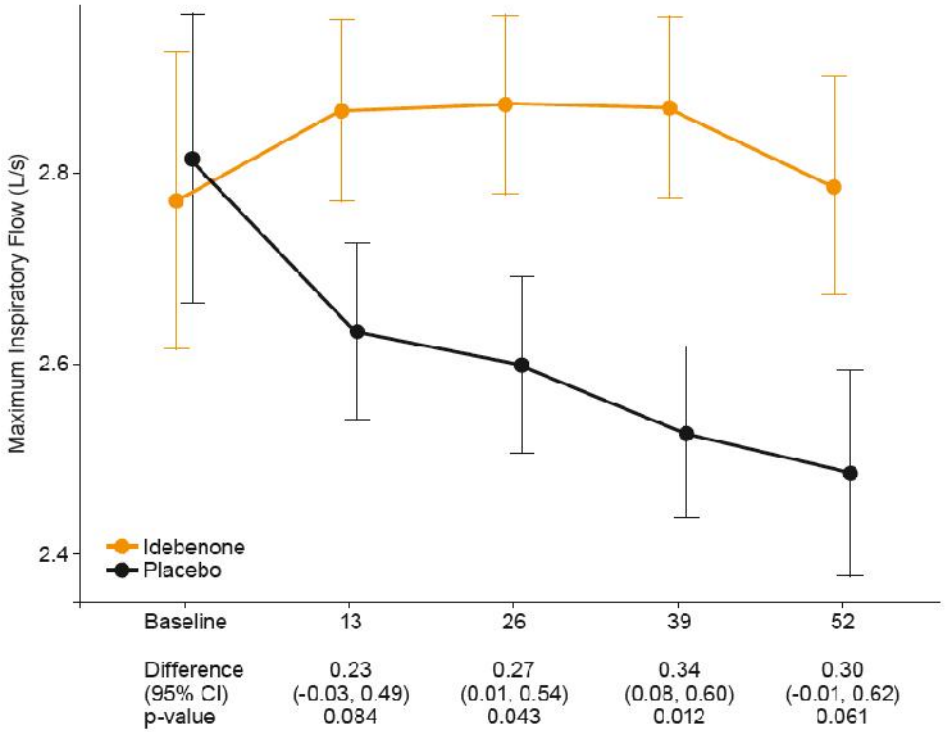
- Reduced V'I, max (FVC)
- Reduced inspiratory flow reserve (IFR)



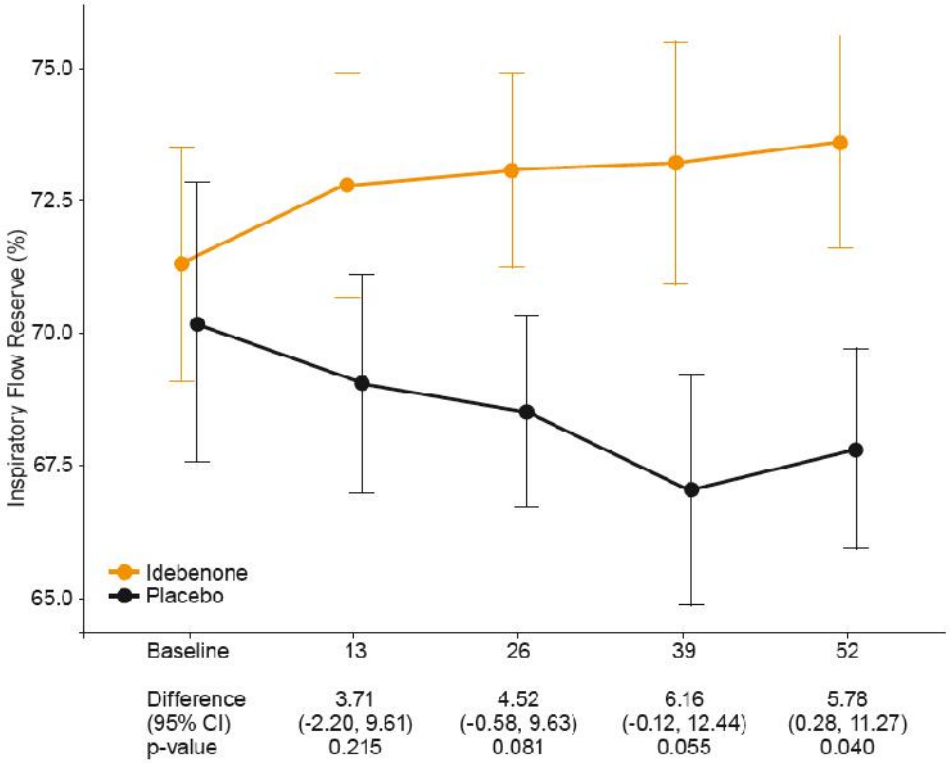
De Bruin et al., 2001. Inspiratory low reserve in boys with DMD. Pediatric Pulmonology 31:451-457

Raxone®also preserves inspiratory function

Maximum Inspiratory Flow: V'I,max (FVC)



Inspiratory Flow Reserve (IFR, %)



Fewer patients on Raxone® fell below critical thresholds for Peak Cough Flow (PCF)

"When the PCF falls below **160 L/min**, the cough is no longer effective enough to provide adequate mucociliary clearance“ [1,2,3]

Pre-specified analysis

No. of Patients	Raxone®	Placebo
PCF at BL: >160 L/min	26	33
Patients with PCF < 160L/min during 1y	1	6

Analysis of ITT population

1. Gauld LM et al., Ped Pulmonol (2005), 39:457-460
2. Bach JR et al., Chest (1997), 112:1024-1028
3. Tzeng AC et al., Chest (2000), 118: 1390-1396

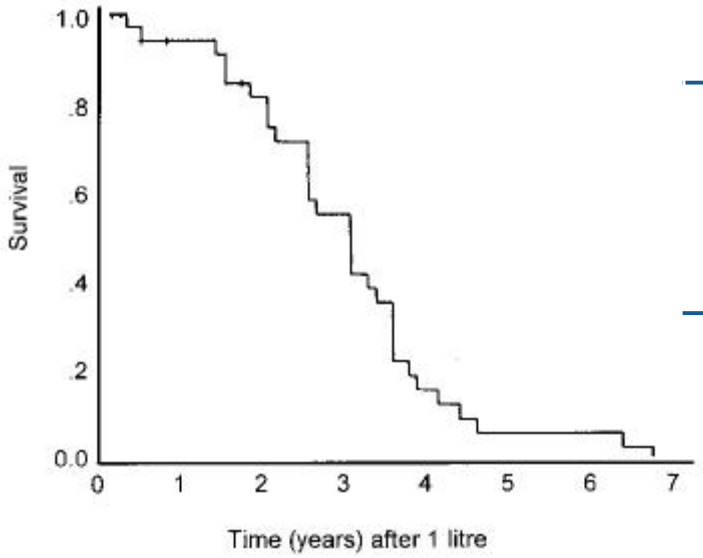
Fewer patients on Raxone® fell below critical 1 L-threshold in FVC

Changes in Spirometry Over Time as a Prognostic Marker in Patients with Duchenne Muscular Dystrophy

MARGARET F. PHILLIPS, ROSALINE C. M. QUINLIVAN, RICHARD H. T. EDWARDS, and PETER M. A. CALVERLEY

Pulmonary and Rehabilitation Research Group, University Hospital Aintree, Fazakerley, Liverpool; Muscle Clinic, Robert Jones and Agnes Hunt Orthopaedic and District Hospital, Oswestry, Shropshire, United Kingdom

Am J Respir Crit Care Med Vol 164. pp 2191–2194, 2001



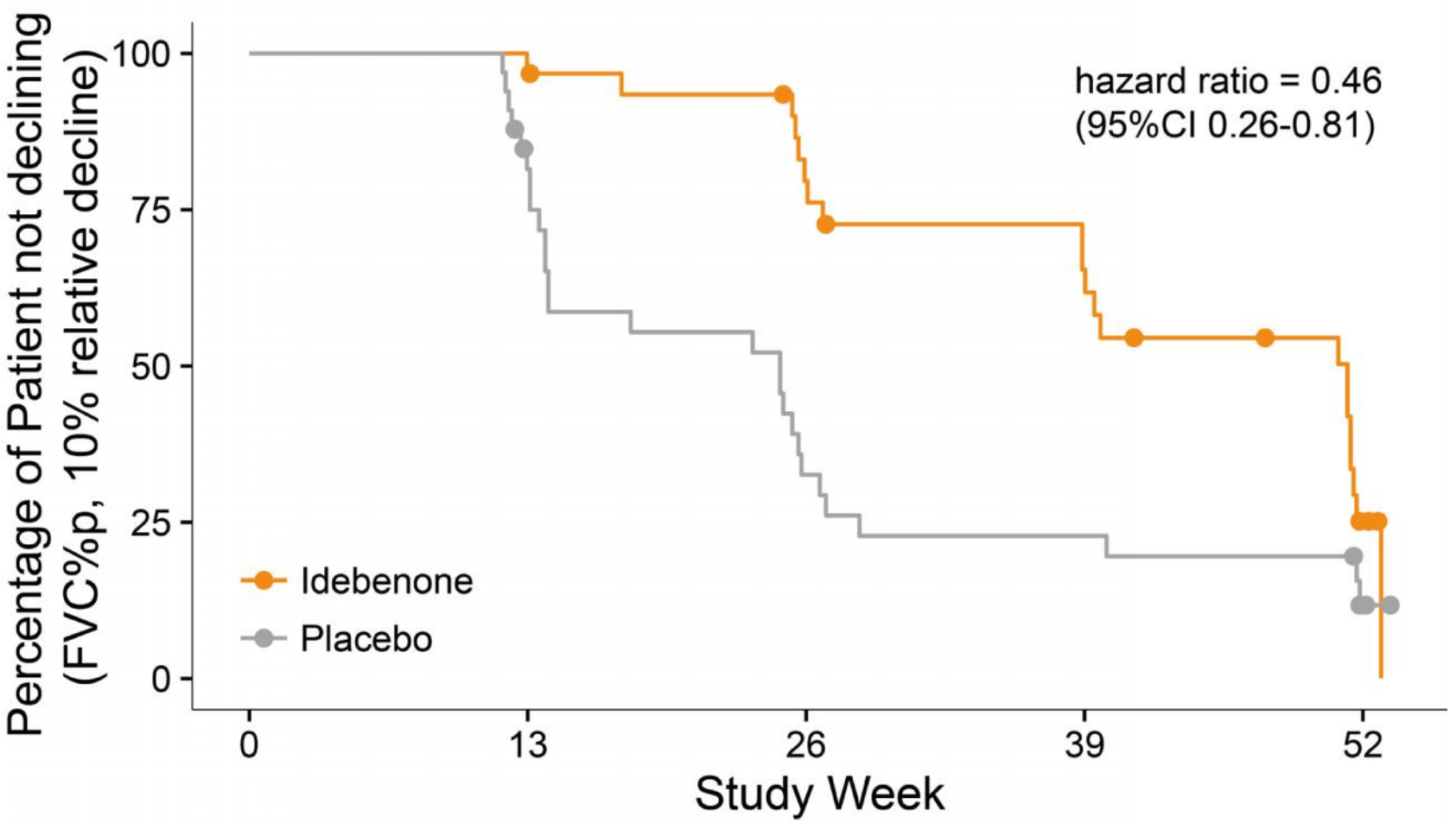
Post-hoc analysis

No. of Patients	Raxone®	Placebo
BL FVC: > 1L but < 1.5 L	6	9
Patients with FVC < 1L during 1y	1	5

Analysis of ITT population

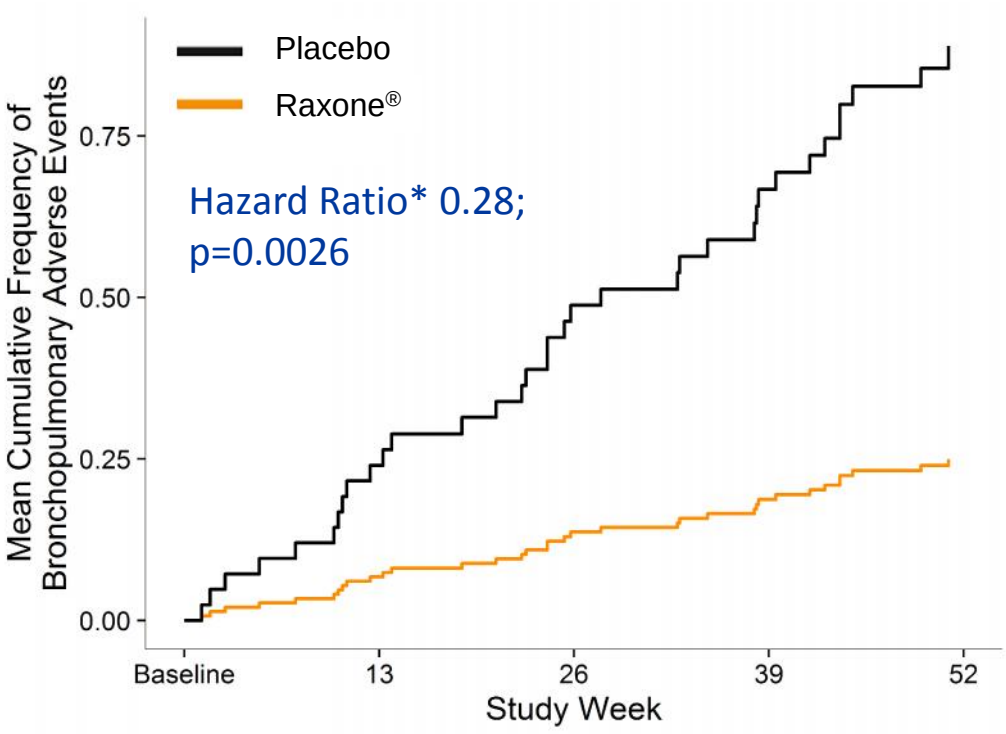
The time when FVC falls below 1 L is a strong marker of subsequent mortality (5-yr survival 8%).

Raxone® delays time to 10% relative decline in FVC%p



Fewer patients on Raxone® experience bronchopulmonary disease (e.g. airway infections)

	Raxone®	Placebo
Subjects (%)	6 (19.4%)	17 (51.5%)
Events	7	28
Duration of antibiotic use (d)		
Mean	11.7	7.9
Median	9	8
Total Days	**82**	**222**



*proportional means regression analysis

Bronchopulmonary disease classified as treatment emergent adverse events:

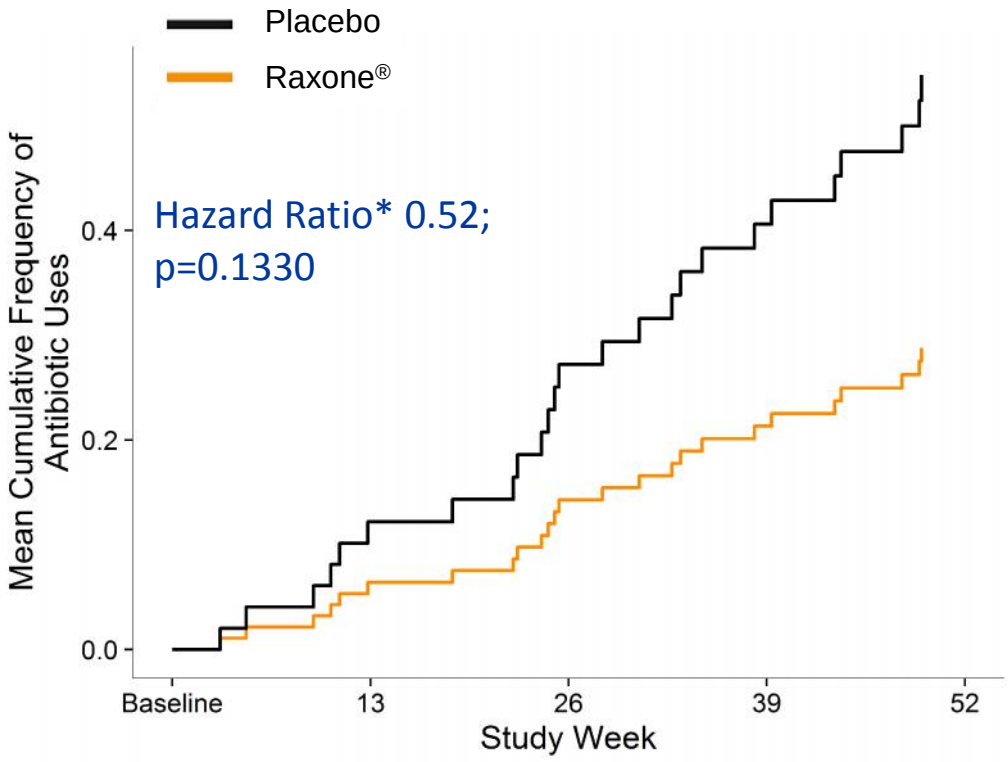
Included: larynx, airways, alveoli (bronchitis, influenza, laryngitis, pneumonia, upper respiratory tract infection, viral infection, respiratory failure, cough, dyspnoea);

Excluded: pharynx and nose (influenza like illness, pyrexia, otitis media, rhinitis allergic, rhinorrhea, sleep apnoea syndrome)

Patients on Raxone® use less antibiotics for the treatment of bronchopulmonary disease

	Raxone®	Placebo
Subjects (%)	7 (22.6%)	13 (39.4%)
Events	8	17
Duration of antibiotic use (d)		
Mean	8.1	6.2
Median	8	6
Total Days	**65**	**105**

*proportional means regression analysis



Summary of DELOS outcome

- The Phase 3 trial met its primary and secondary endpoints
- Demonstrated a consistent treatment effect for Raxone® on expiratory and inspiratory function
- Provides supportive evidence for efficacy in clinically relevant responder analyses
- Demonstrates clinically relevant impact of bronchopulmonary disease and antibiotic use

Positioning of Raxone® in the treatment of DMD

- There is a sizeable proportion of patients who cannot tolerate steroids at the time when respiratory function loss becomes evident
- There is an urgent unmet medical need to slow down the decline of respiratory function in these patients
- “Slowing down the accumulation and the progression of disability” recognized as clinically relevant (EMA guideline on DMD)
- Available data demonstrate that the investigational drug Raxone® slows down loss of respiratory function in patients not using steroids
- Raxone® was tested in patients without restriction to specific mutational or disease status (no competition to alternative treatment approaches)

SIDEROS - a new Phase 3 trial in patients using steroids

- **Objective:** To assess the efficacy of idebenone (Raxone®) compared to placebo, in slowing the loss of respiratory function in patients with DMD receiving glucocorticoids (GCs)
- **Endpoints:** Change in FVC%p (primary), change in other respiratory function outcomes (PEF%p, FEV1 etc.)
- **Patients:** ~260 DMD patients using stable GCs who have started to decline on respiratory function (at baseline 30% ≤ FVC%p ≤ 80%)
- **Randomization:** 1:1 to receive idebenone (900 mg/d) or placebo
- **Stratification for steroid regimen**
- **Treatment duration:** 78 weeks
- **Study conduct:** approx. 50 centers in Europe and US
- **Status:** Protocol completed, feasibility study completed
- **Study start:** 2Q2016; Study end: 3Q2019
- **Extension study**: Open label extension phase offered to trial participants

Advancing mitochondrial medicine towards treatments for

LHON

DMD

ppMS

Thank you for your attention