



Clinical development of Puldysa[®] (idebenone)

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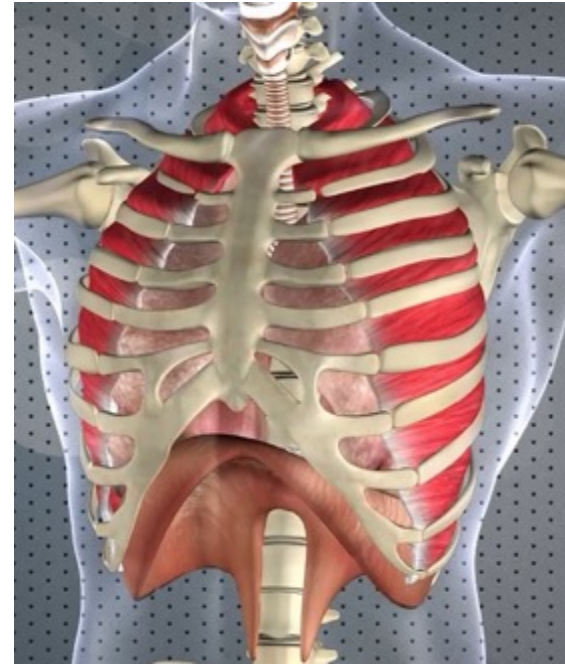
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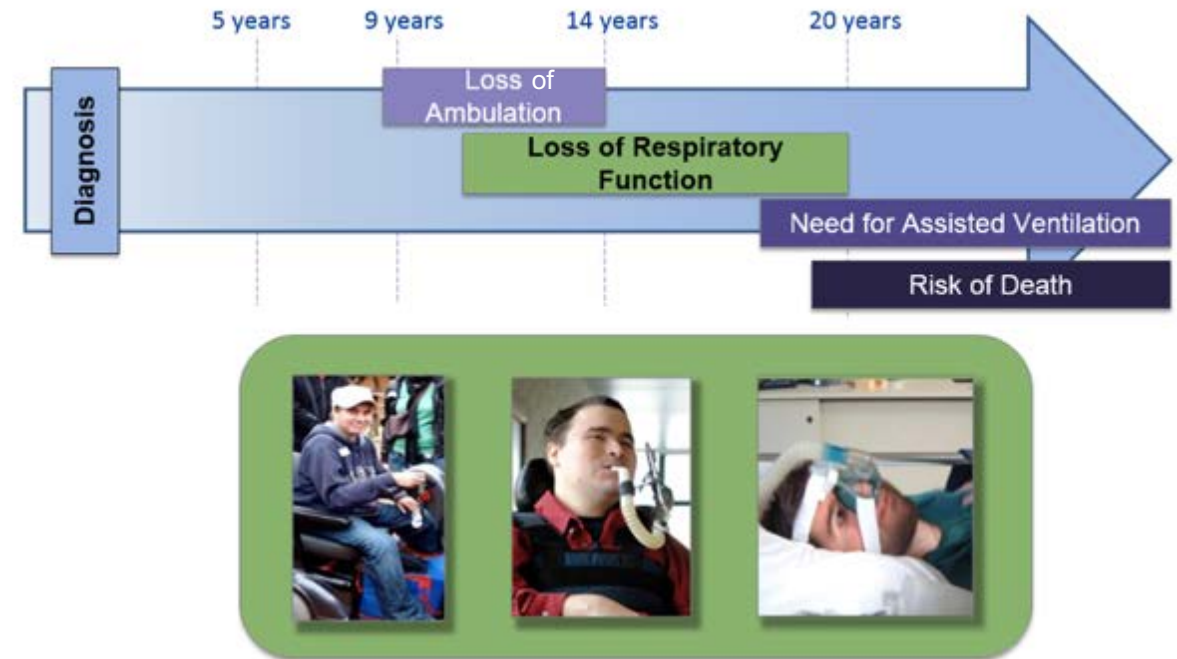
Understanding respiratory function in DMD



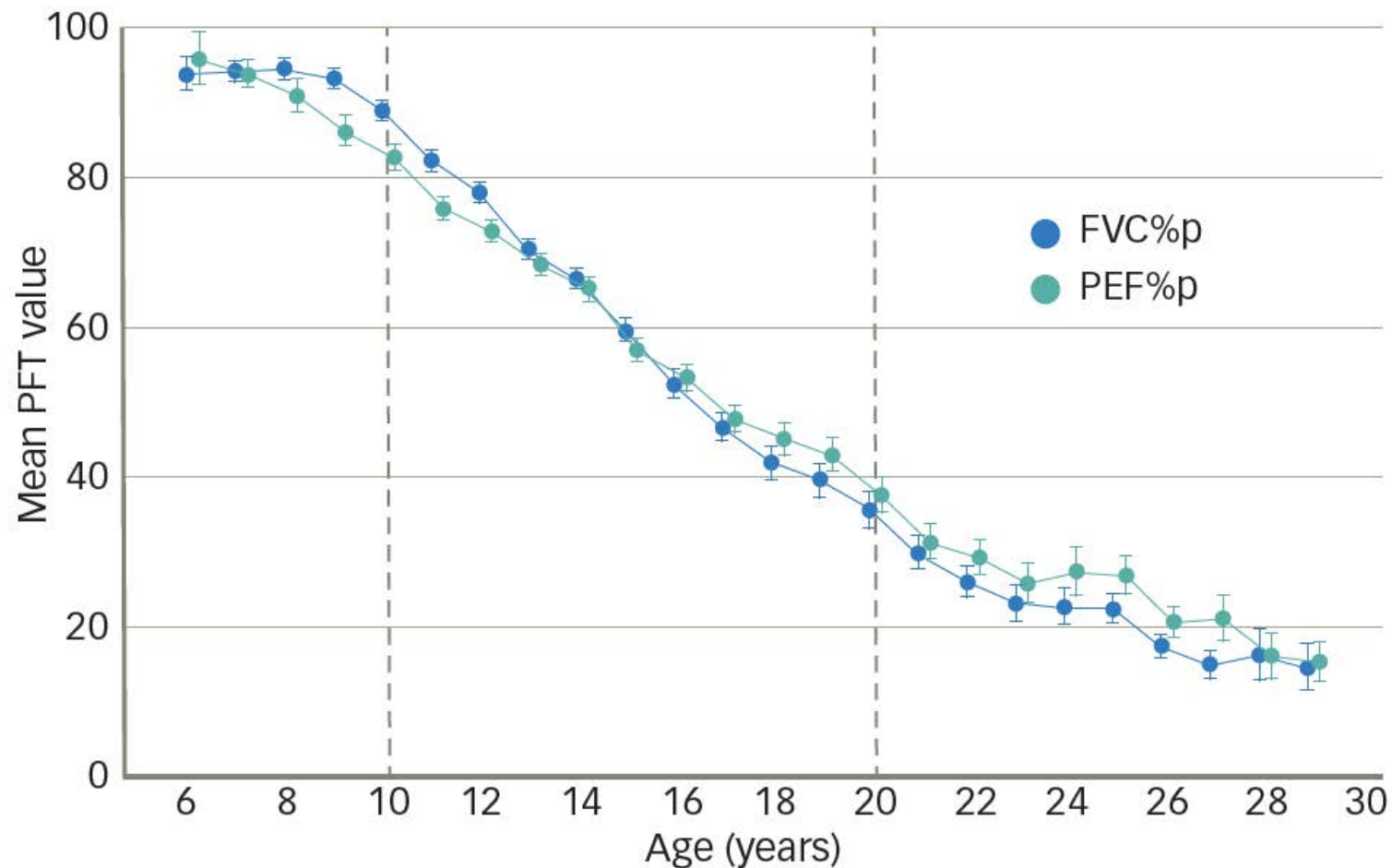
Medical need for effective treatment of respiratory illness in non-ambulatory patients with DMD

- Increasing respiratory muscle weakness in DMD leads to:
 - Decreased lung volumes and air flow
 - Decreased ability to cough effectively and clear airways of mucus
 - Increased risk of airway infections/pneumonias
- There are no approved pharmacological therapies for treating respiratory decline

Progressive respiratory function loss results in need of assisted ventilation

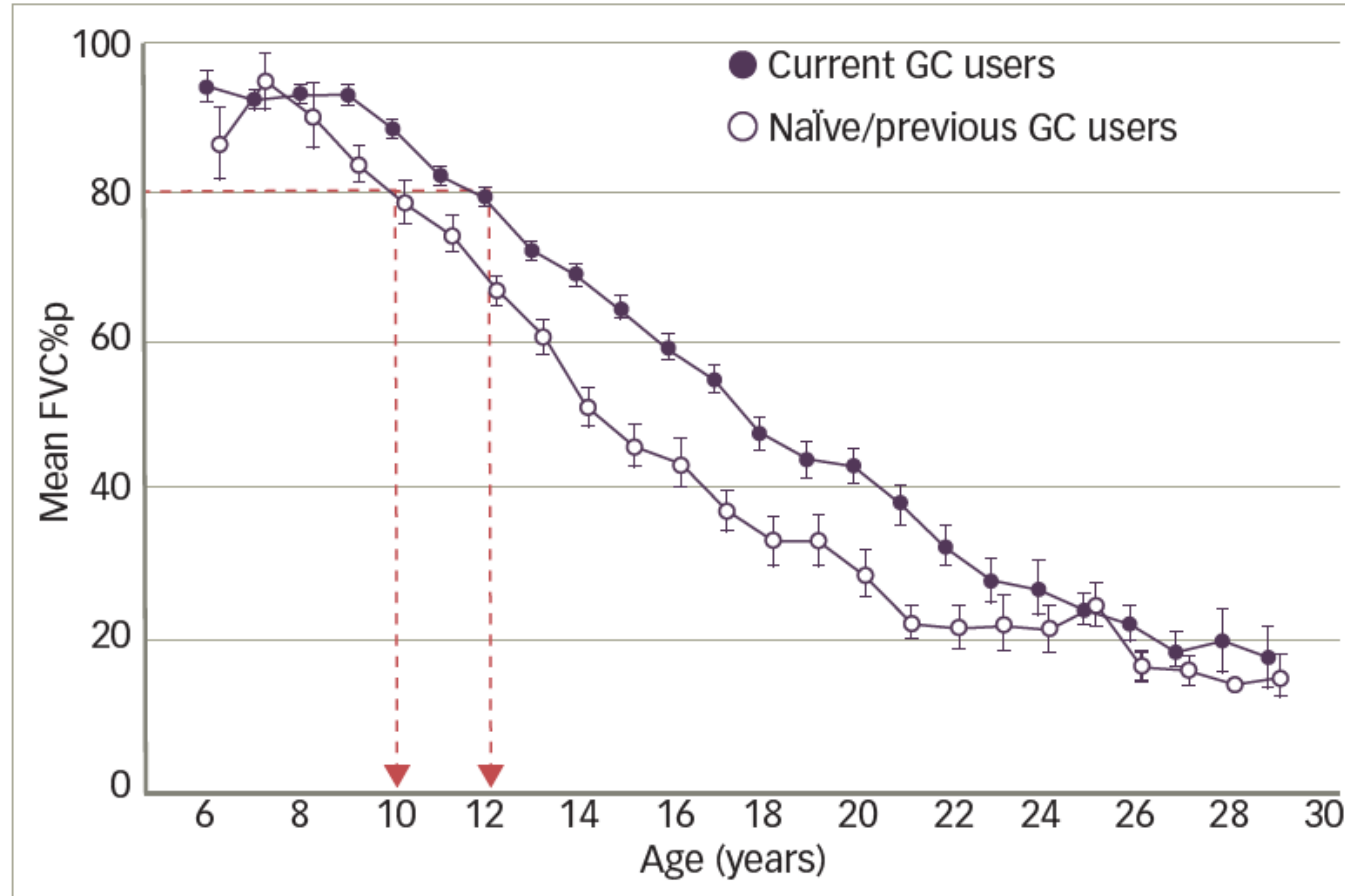


Respiratory function follows a linear decline over time



Data are mean \pm SEM of pulmonary function tests (PFT) from 334 patients of the CINRG-DNHS;
Dotted lines at ages 10 and 20 years: period of approximately linear decline in PEF%p and FVC%p.
Mayer OH, et al. US Neurology 2017;13:35–41. McDonald et al. Neuromuscular Disorders 2018; 28: 897-909

Glucocorticoids delay the onset of respiratory function decline by 2-3 years but not the annual rate of decline



Data is mean \pm SEM (n=334); GC= glucocorticoid

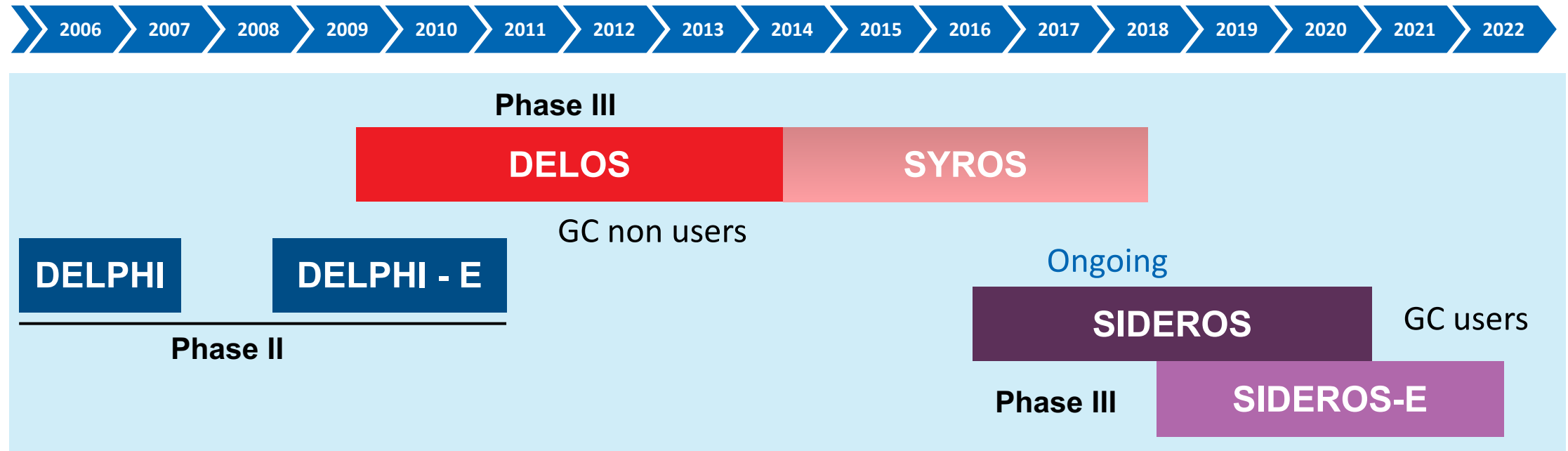
Red arrows indicate shift in start of pulmonary function decline by GC use of about 2-3 years.

Mayer OH, *et al. US Neurology* 2017;13:35-41. McDonald et al. *Neuromuscular Disorders* 2018; 28: 897-909



Clinical development of Puldysa[®] (idebenone) as treatment of respiratory dysfunction

Overview of clinical development of idebenone in DMD



Idebenone is an investigational compound in the US and is not approved by the FDA

DELOS: Completed Phase 3 study

Objective: To study how effective idebenone is compared to placebo on treating respiratory dysfunction in patients with DMD not on glucocorticoid steroids

DELOS: Placebo-controlled study in patients with DMD age 10 and older

Study details

64

males with
DMD

92%

of patients
were no longer
walking

17

centers in
Europe and
USA

52

weeks
▲
Idebenone
or placebo

Data from placebo-controlled DELOS study showed that idebenone slowed loss of respiratory function over 12 months

- *Idebenone* slowed loss of expiratory respiratory function (peak expiratory flow, PEF%p) and met the study primary endpoint ^{1,2}
- Consistent treatment effects were seen for inspiratory function (inspiratory flow reserve, IFR) and global respiratory function (forced vital capacity, FVC%p) ^{1,3, 4,*}
- *Idebenone* also reduced the risk of bronchopulmonary adverse events (such as airway infections), the need of systemic antibiotic treatment and risk of hospitalization due to respiratory complications ^{5,*}

1) Buyse et al. 2015; Lancet 385:1748-57;

2) Buyse et al. 2018; J Neuromuscular Diseases 5: 419–430.;

3) Mayer et al. 2017; J Neuromuscular Diseases. 4:189-98.;

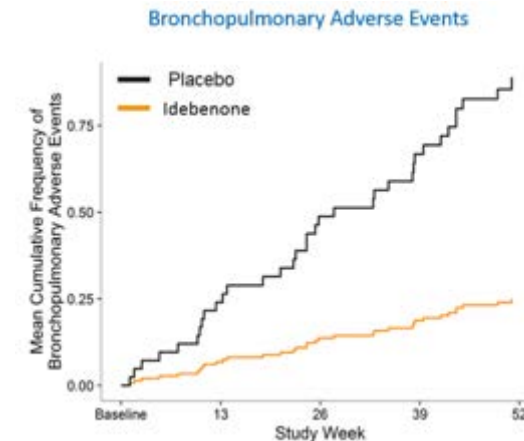
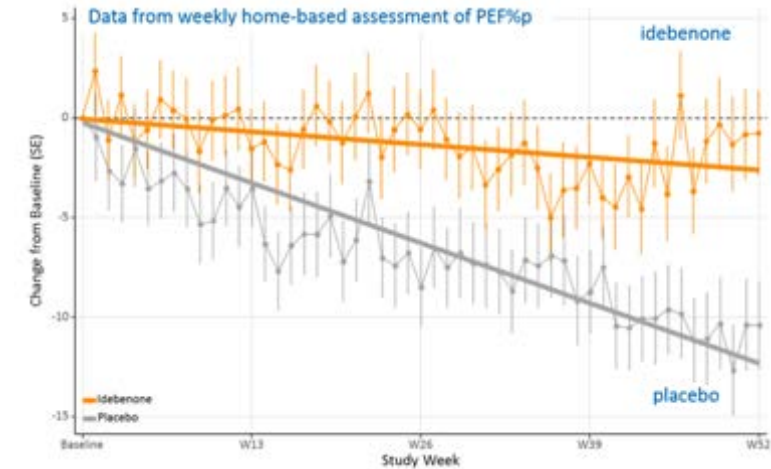
4) Buyse et al., 2017; Pediatric Pulmonology 52:508-515;

5) McDonald et al., 2016; Neuromuscular Disorders 26: 473–480

* These statements have not been evaluated by any health regulatory agency including the FDA

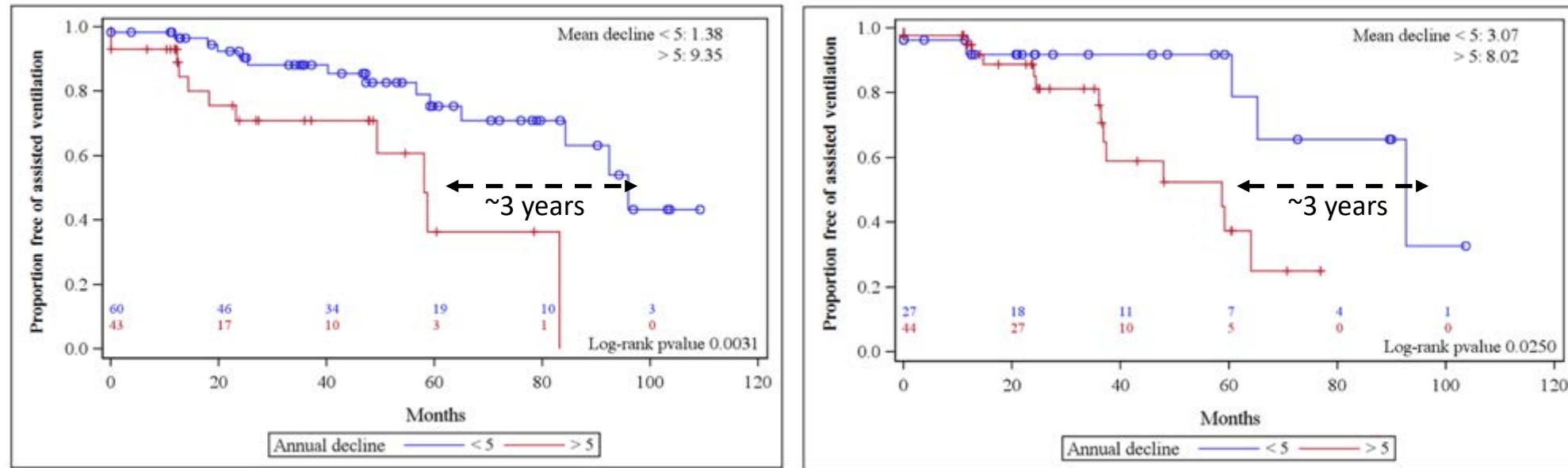
PEF%p: peak expiratory flow percent predicted

FVC%p: forced vital capacity percent predicted



Rate of change of PEF%p and FVC%p predicts time to clinically relevant milestone

Time from crossing 50% of PEF%p (left) and FVC%p (right) to **initiation of assisted ventilation** (CINRG study)

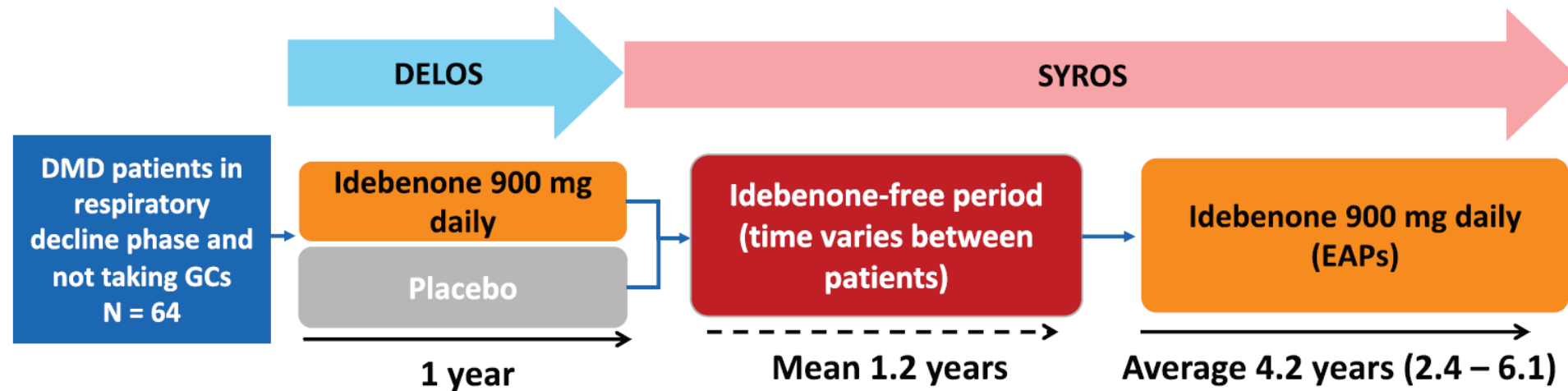


Source: McDonald et al (Poster presentation at MDA Conference 2019)

Annual decline slower than average (blue line) prolongs the time from crossing 50% to assisted ventilation by ~3 years compared with progression more rapid than average (red line)

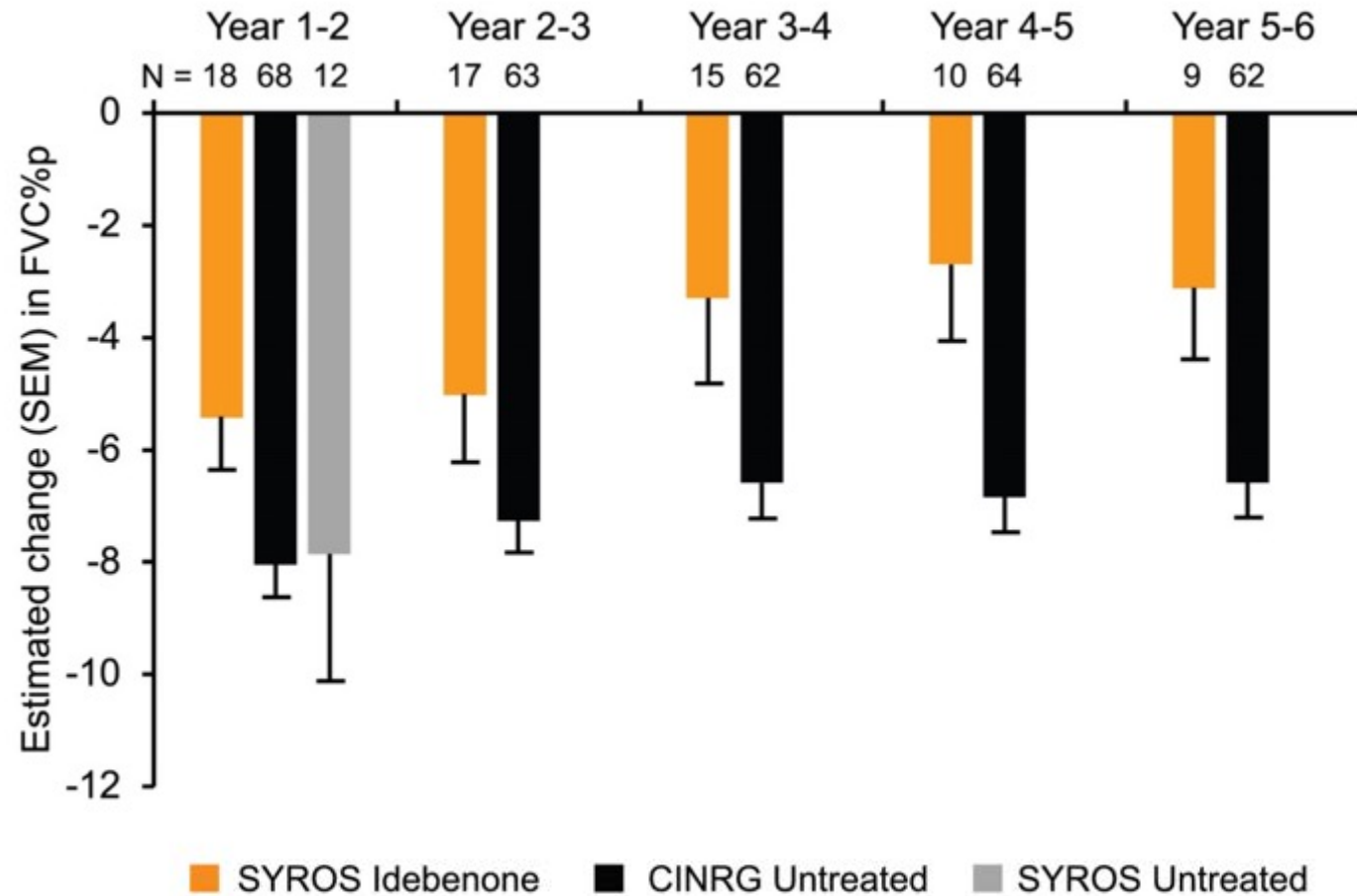
SYROS: New long-term efficacy data with idebenone on respiratory function outcomes – the real world approach

- Long-term efficacy data are desirable to inform about potential patient benefit in this chronic disease
- **SYROS** : prospectively planned collection of long-term respiratory function data from patients previously enrolled in the DELOS trial
- Long-term respiratory function data were collected from 18 patients treated with idebenone in Expanded Access Programs (EAPs) in Europe



Mayer et al. 2019; Poster presented at MDA Clinical and Scientific Conference; April 2019

SYROS: Idebenone treatment showed persistent effect on respiratory function for up to 6 years

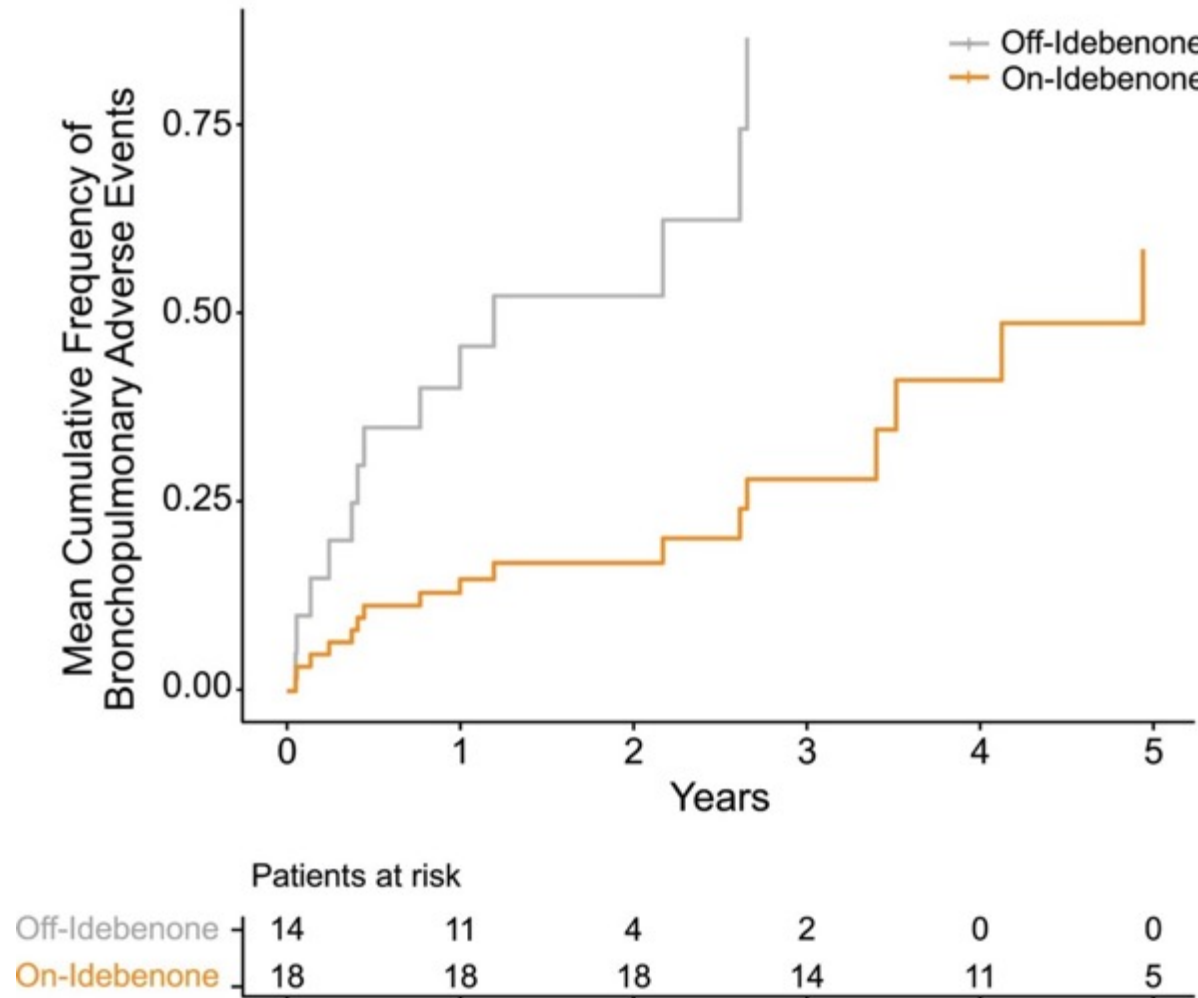


- *Idebenone* treatment showed a persistent effect in slowing decline in FVC%p for up to 6 years*
- Annual decline in FVC%p in patients on *idebenone* was consistently smaller than in untreated patients from a matched external control group (from CINRG Duchenne natural history study)

Mayer et al. 2019; Poster presented at MDA Clinical and Scientific Conference; April 2019

* These statements have not been evaluated by any health regulatory agency including the FDA

SYROS: Frequency of Bronchopulmonary Adverse Events (BAEs)



- Data show a reduced risk for BAEs during *idebenone* treatment periods
- Similar results as in DELOS study (McDonald et al., 2016)

Kaplan-Meier analysis (proportional means regression model) for cumulative frequency of BAEs by treatment. N=14 patients for Off-Idebenone periods; N=18 patients for On-Idebenone periods.

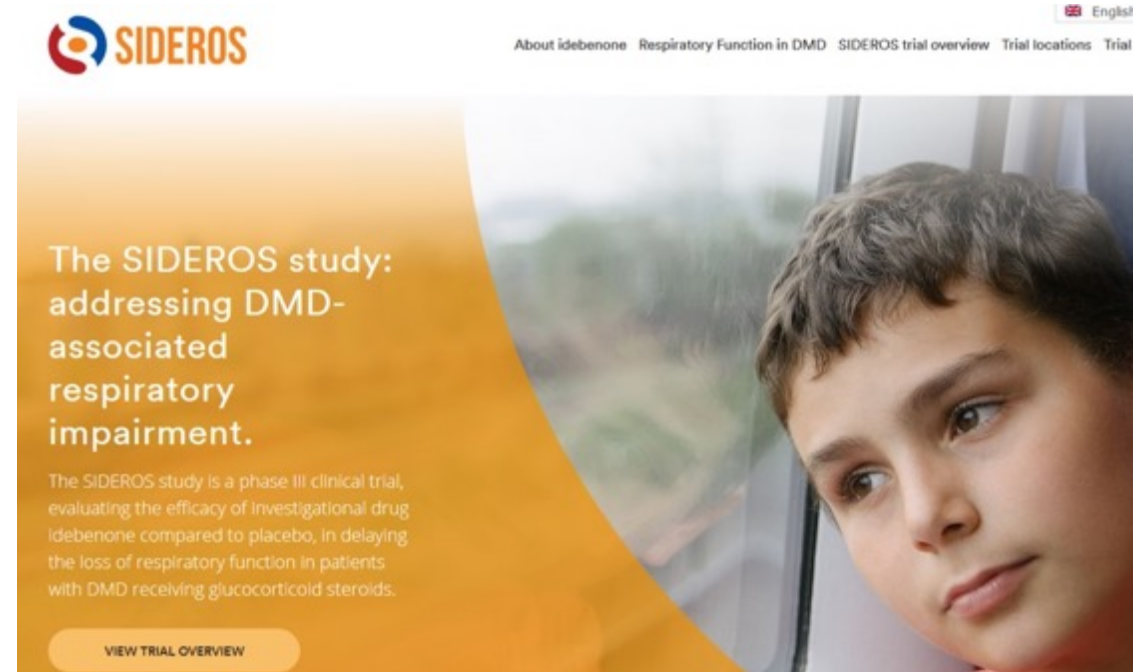
Recruiting now

**SIDEROS study: To test the efficacy of
idebenone in patients on glucocorticoid
treatment**

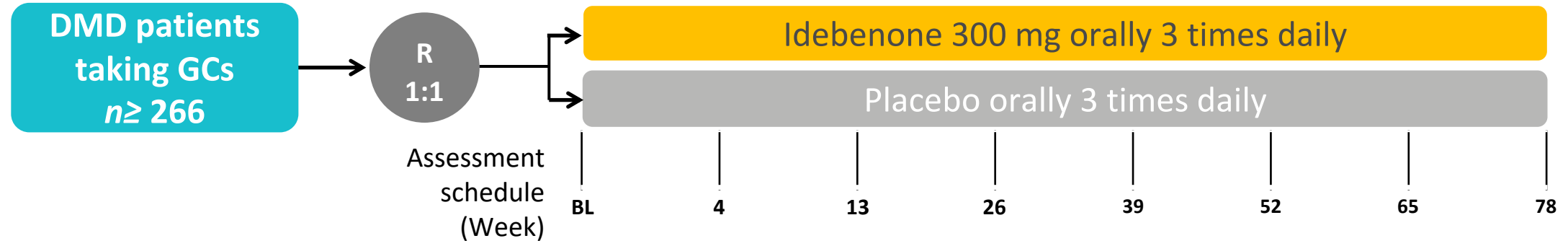
SIDEROS: Ongoing Phase 3 study

www.siderosdmd.com

- Currently the largest ongoing clinical trial in DMD (266 males)
- **Enrollment expected to complete in next few months**
- Ambulant and non-ambulant patients eligible for enrolment
- Patients of all mutation types eligible. Additional eligibility criteria apply
- Participants who complete SIDEROS and are considered eligible by their investigator are offered to participate in open-label SIDEROS Extension trial



SIDEROS Objective: To evaluate the efficacy of idebenone to slow respiratory function decline in patients using glucocorticoids (GCs)



Study type:	Randomized, placebo-controlled trial
Key eligibility criteria:	≥ 10 years, chronic use of systemic glucocorticoids and in respiratory function decline
Primary endpoint:	Change in FVC%p from baseline to week 78
Secondary endpoints:	Changes in PEF%p, time to loss of 10% in FVC, inspiratory flow reserve, others

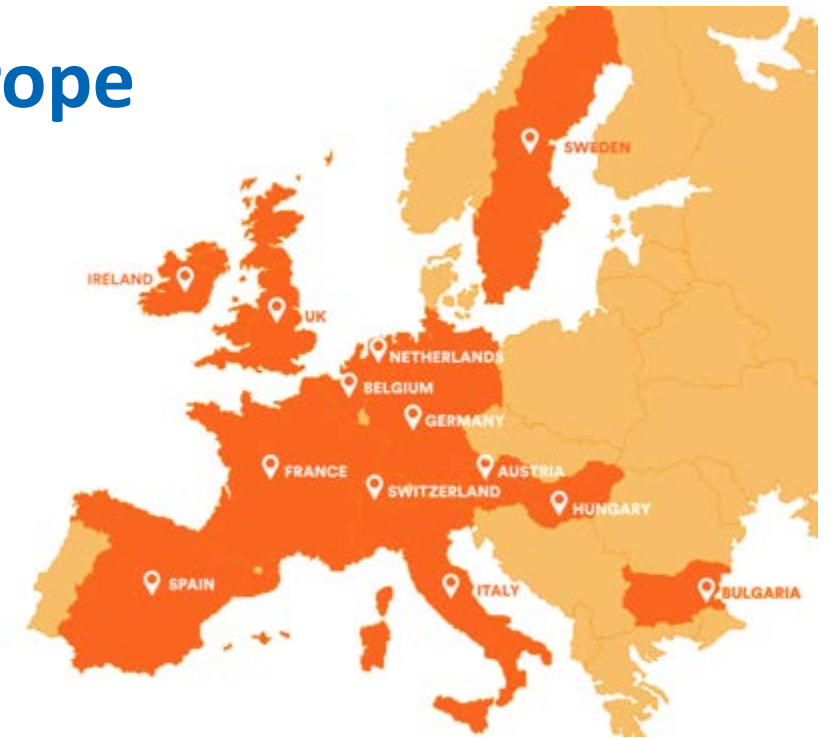
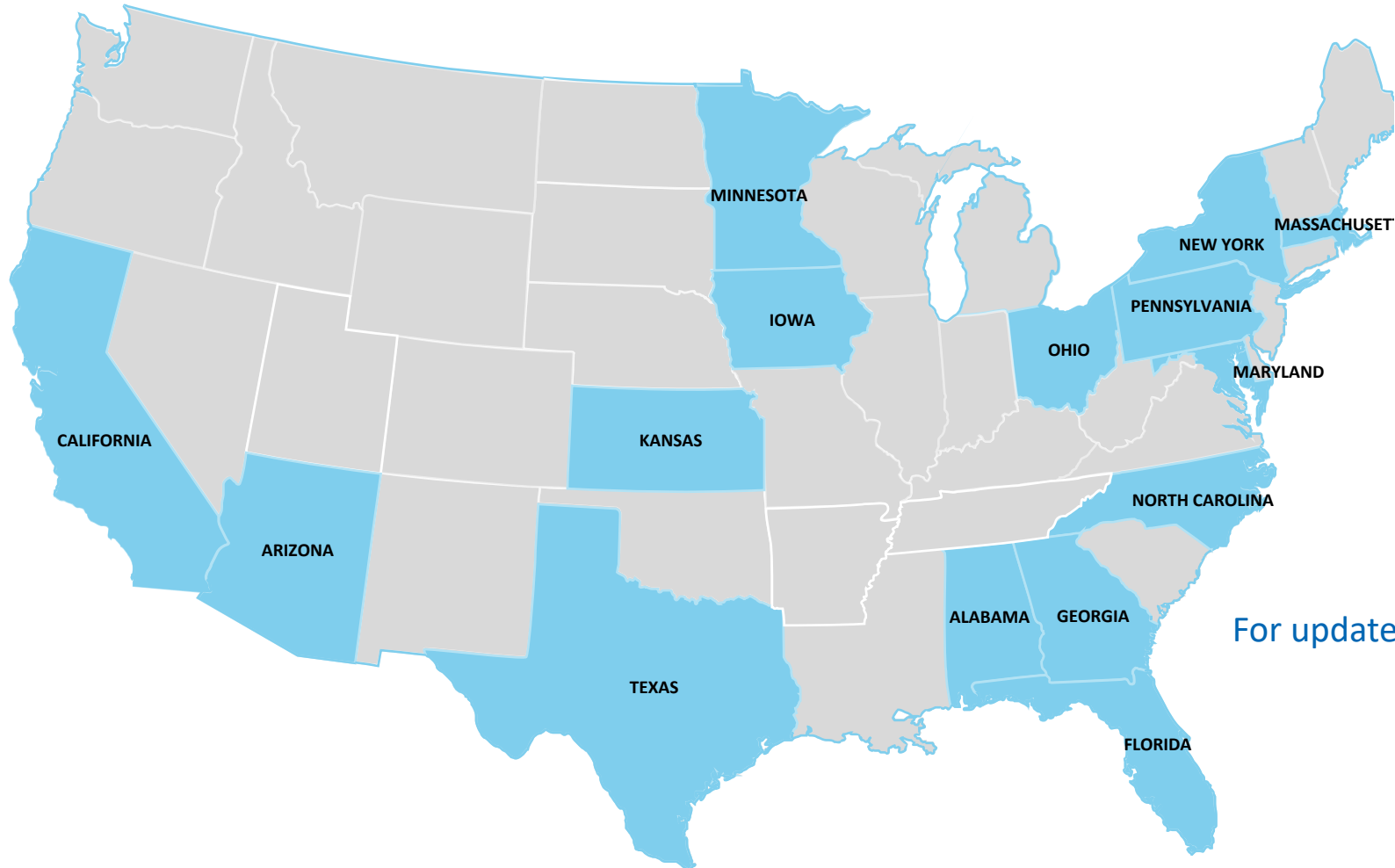
SIDEROS: key inclusion criteria

- Patients ≥ 10 years old at Screening (no upper age limit)
- Patients with all types of DMD mutations eligible
- Willing and able to provide consent
- **FVC between 80% and 35% at start of study**
- **Reliable FVC values at screening and baseline** (within defined margin)
- Chronic use of systemic glucocorticoid steroids for DMD for at least 12 months
- Immunization: pneumococcal vaccine, inactivated influenza vaccine



SIDEROS: clinical trial sites in the US and Europe

Approximately 60 study centers in USA, Europe and Israel



For updated information, please visit: www.siderosdmd.com

SIDEROS and regulatory plans for Puldysa® in DMD

United States

- Top-line SIDEROS data available 1H 2021
- Positive SIDEROS study allows for submission to FDA in US
- Plan to apply for full approval for all boys with DMD regardless of steroid use

Europe

- Successful Phase 3 DELOS study is basis for regulatory submission in Europe (May 2019)
 - Additional natural history data support clinical importance of treatment effect
 - Open-label real world SYROS-study support long-term effect
- Conditional Marketing Authorization for boys not using steroids
- SIDEROS-data: Plan to investigate expanded indication for boys using steroids

Summary

- Treating respiratory function decline is an urgent unmet medical need
- The DELOS-study reported statistically significant effect of Puldysa® (idebenone) on slowing the decline of respiratory function
- Real-world long-term data (SYROS) has reported effect on respiratory function up to 6 years of treatment
- Natural history data show clinical relevance of slowing decline of respiratory function in DMD
- Enrollment into Phase 3 SIDEROS trial expected to complete this fall
- SIDEROS outcome will be important for both US and EU regulatory submissions

Thank you

We would like to sincerely thank the patients and their carers for their trust and efforts to participate in clinical trials.

Your support enables us all to learn more about how therapies could be developed in the hope to benefit all patients.

