



# Clinical development of Catena<sup>®</sup> (idebenone) in DMD

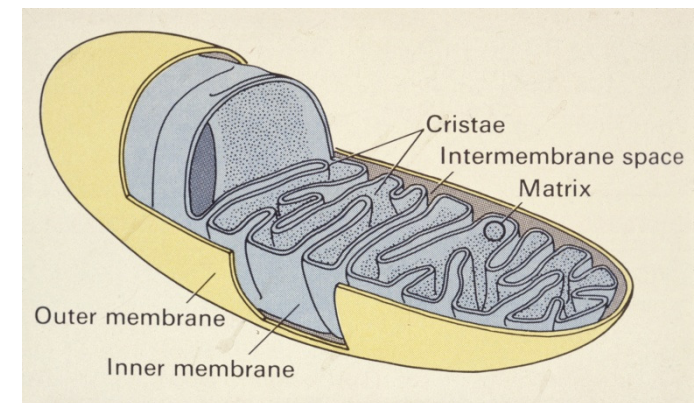
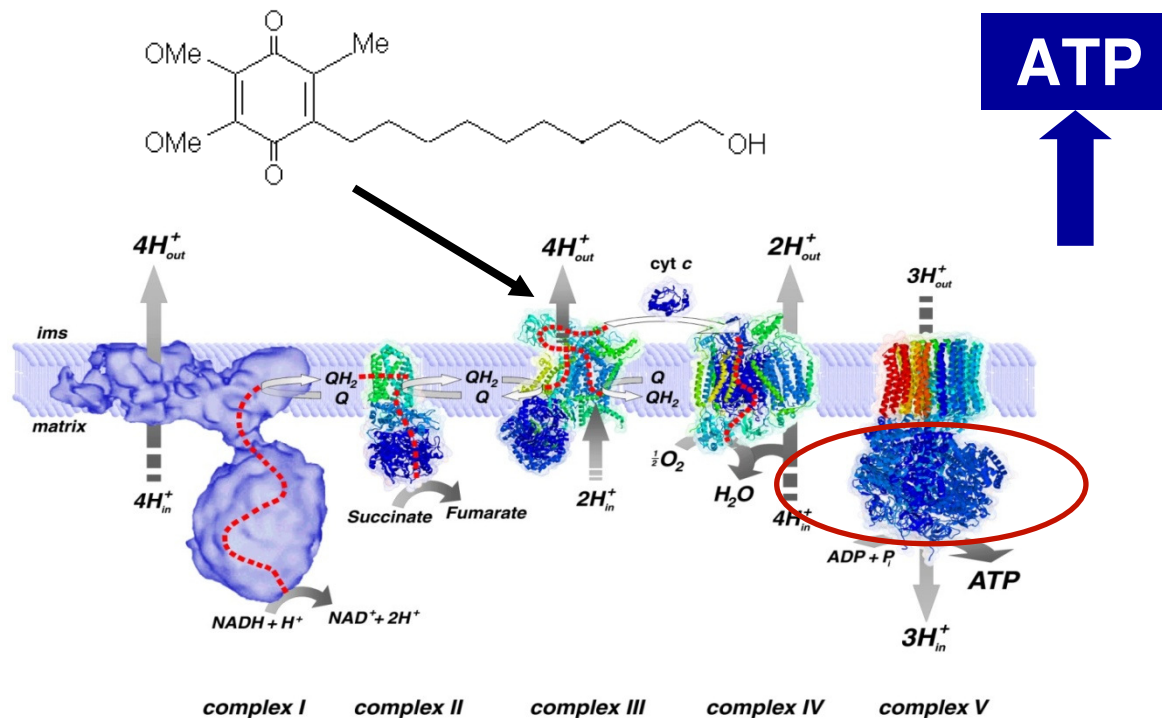
Action Duchenne Annual Conference November 2011

Thomas Meier, PhD; Nick Coppard, PhD

on behalf of the DELPHI and DELOS study investigators

## Idebenone enhances mitochondrial electron flux and increases ATP levels

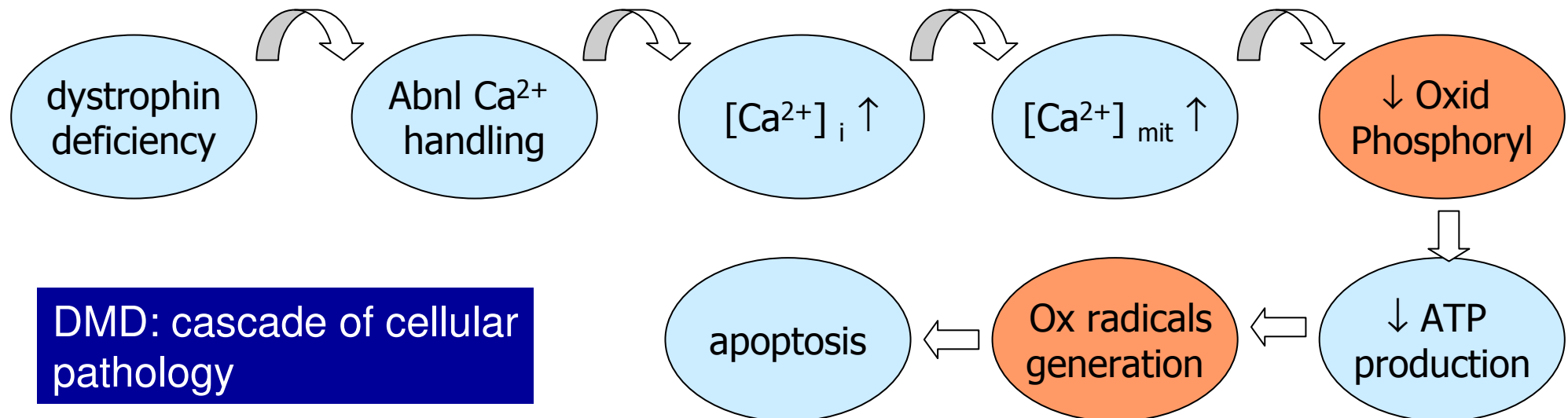
- During oxidative phosphorylation, electron transport through a chain of complexes generates a proton gradient which is used to generate ATP
- Idebenone<sub>(R)</sub> facilitates electron flux by an NQO1-dependent mechanism
- Idebenone<sub>(R)</sub> inhibits lipid peroxidation and membrane damage by ROS
- Orally bioavailable (can be taken as tablets)
- Catena<sup>®</sup> (idebenone) is approved in Canada for Friedreich's Ataxia



NQO1: NADH:quinone oxidoreductase 1

## Mitochondrial deficiency in DMD

- Calcium ( $\text{Ca}^{2+}$ ) is a key regulator of mitochondrial function
- $\text{Ca}^{2+}$  dysregulation plays a key role in several pathologies such as ROS generation and apoptosis
- Dystrophin-deficient muscle fibres are overloaded with  $\text{Ca}^{2+}$



Idebenone increases ATP production and decreases ROS  
There is a clear scientific rationale for idebenone in DMD

# Preclinical efficacy data with idebenone in animal model for DMD



European Heart Journal (2009) **30**, 116–124  
doi:10.1093/eurheartj/ehn406

**PRECLINICAL RESEARCH**

## Long-term blinded placebo-controlled study of SNT-MC17/idebenone in the dystrophin deficient *mdx* mouse: cardiac protection and improved exercise performance

Gunnar M. Buyse<sup>1\*</sup>, Gerry Van der Mieren<sup>2</sup>, Michael Erb<sup>3</sup>, Jan D'hooge<sup>4</sup>, Paul Herijgers<sup>2</sup>, Erik Verbeken<sup>5</sup>, Alejandro Jara<sup>6</sup>, An Van Den Bergh<sup>2</sup>, Luc Mertens<sup>7</sup>, Isabelle Courdier-Fruh<sup>3</sup>, Patrizia Barzaghi<sup>3</sup>, and Thomas Meier<sup>3</sup>

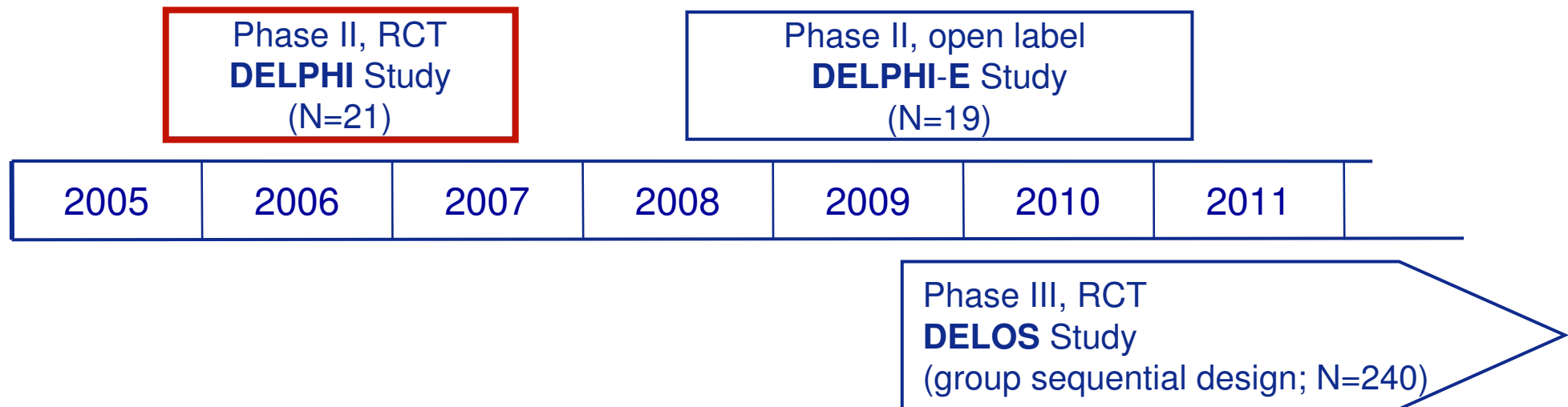
### Results:

- Treatment with idebenone normalized diastolic cardiac function abnormalities
- Idebenone prevented mortality from cardiac pump failure during dobutamine stress
- Idebenone reduced inflammation in cardiac tissue
- Idebenone improved exercise performance
- Results provided justification to start clinical development in human patients



## Santhera's development program with idebenone (CATENA®) in DMD

- 12-month treatment
- Catena®: 450 mg/day
- 21 boys, aged 8 to 16 years
- Ambulatory & non-ambulatory patients
- Endpoints: cardiac and respiratory function
- 24-month treatment
- Catena®: 450/900 mg/day by body weight
- 19 boys, aged 11 to 19 years
- Endpoints: respiratory & cardiac function



- 12-month treatment
- Catena®: 900 mg/day
- Group-sequential design (steroid non-users / users)
- Endpoints: respiratory function
- **Study open for enrolment in EU and USA**

# Results from DELPHI Study



ELSEVIER

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



Neuromuscular Disorders 21 (2011) 396–405



[www.elsevier.com/locate/nmd](http://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

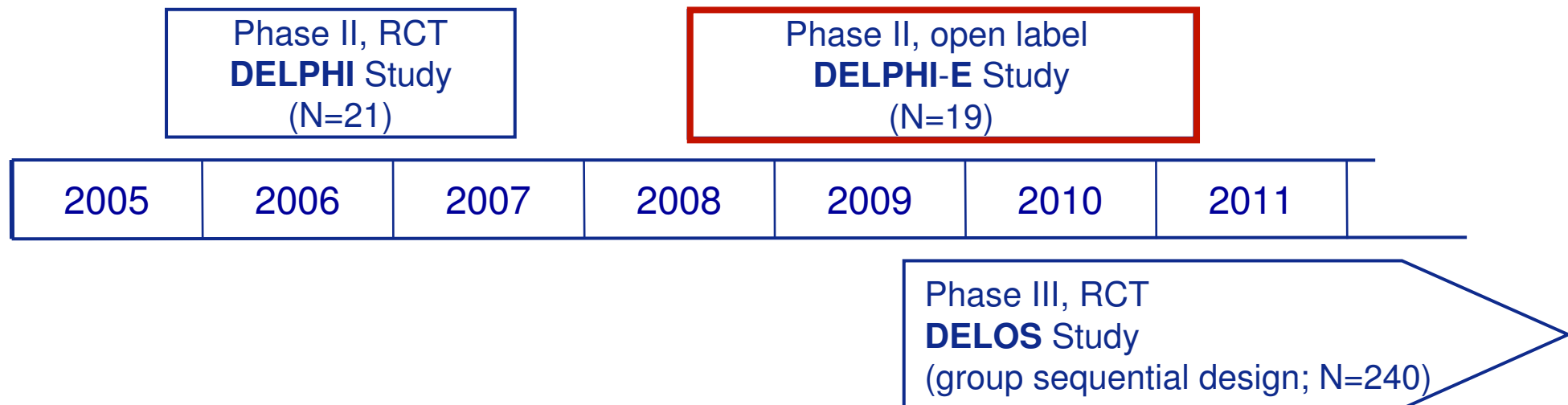
Gunnar M. Buyse<sup>a,\*</sup>, Nathalie Goemans<sup>a</sup>, Marleen van den Hauwe<sup>a</sup>, Daisy Thijs<sup>b</sup>, Imelda J.M. de Groot<sup>c</sup>, Ulrike Schara<sup>d</sup>, Berten Ceulemans<sup>e</sup>, Thomas Meier<sup>f</sup>, Luc Mertens<sup>b</sup>

- Idebenone was safe and well tolerated in patients with DMD
- Idebenone improved myocardial function properties
- Idebenone improved respiratory strength measures (peak expiratory flow, maximum mouth pressures)
- For respiratory tests, patients not using glucocorticoids benefitted to a greater extent versus placebo than patients on concomitant glucocorticoids

## DELPHI-E study supports efficacy of idebenone on respiratory function



- 24-month treatment
- Catena<sup>®</sup>: 450/900 mg/day by body weight
- 19 boys, aged 11 to 19 years
- Endpoints: respiratory & cardiac function



## Data from 2-year open label study (DELPHI-E) Patient demographics



- Patients completing DELPHI were allowed to enrol in the DELPHI-E
- Time between DELPHI and DELPHI-E (off medication):  $1.7 \pm 0.3$  years (range: 1.2-2.1 y)
- Treatment with 450/900 mg/day Catena<sup>®</sup> (by body weight: below/above 45 kg)
- Age:  $15 \pm 2.6$  years (range: 11.6-19.3 years)
- 19 patients completed the study
- 11 of 19 patients were on glucocorticoid steroids
- 13 of 19 patients were in wheelchair

Data are mean  $\pm$  SD

## Data from the DELPHI-E study support idebenone efficacy in pulmonary function



Annual rates of change of pulmonary function parameters

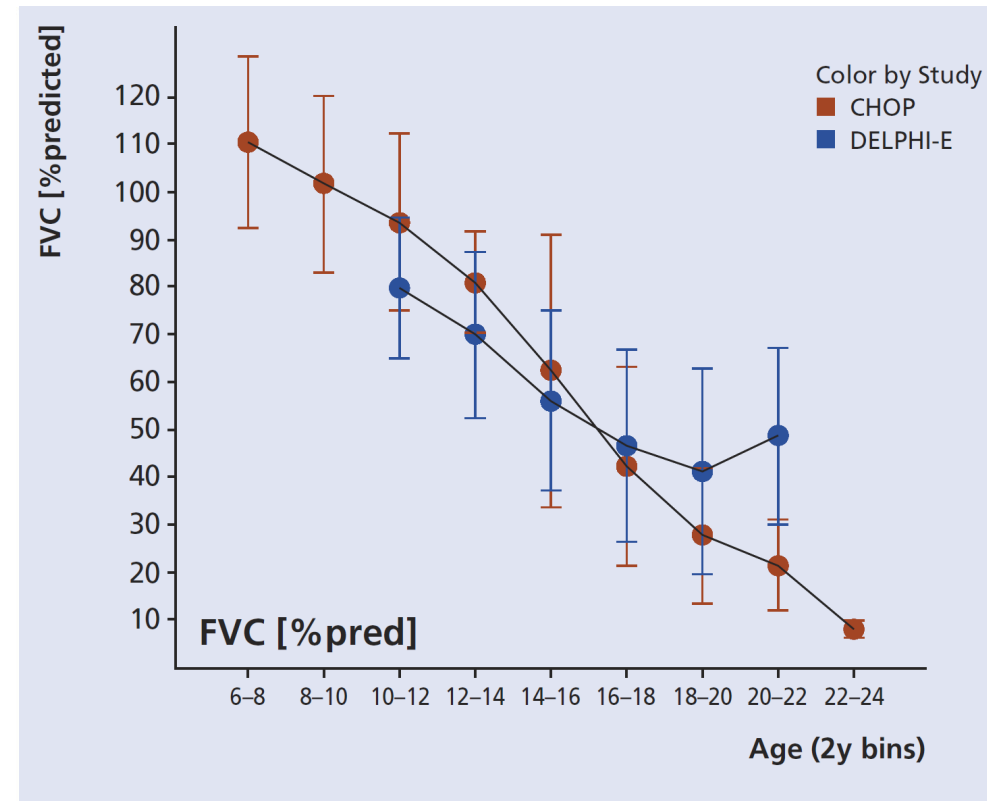
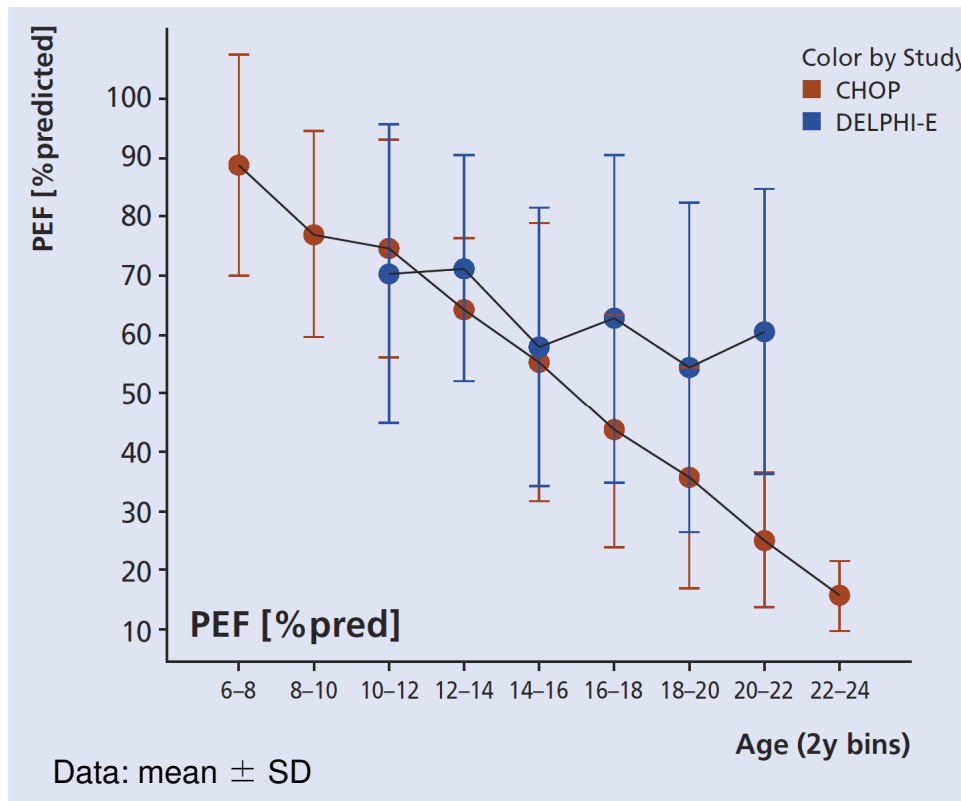
Parameter	DELPHI (Active)	DELPHI (Placebo)	off medication	DELPHI-E
PEF [%pred]	3.07 ± 15.14 (-24.30, 23.52)	-7.30 ± 14.47 (-30.53, 9.40)	-3.82 ± 8.49 (-18.07, 11.59)	-1.48 ± 7.21 (-12.95, 10.61)
FVC [%pred]	-0.81 ± 5.87 (-8.86, 8.37)	-0.61 ± 10.24 (-11.24, 19.11)	-6.88 ± 5.61 (-20.98, 3.38)	-6.26 ± 4.47 (-16.00, -0.53)
MIP [%pred]	3.08 ± 13.49 (-18.24, 27.54)	-0.04 ± 7.78 (-14.28, 8.73)	-9.03 ± 8.22 (-28.64, -0.05)	0.65 ± 5.80 (-8.45, 13.56)
Age*	13.40 ± 2.30 (9.38, 16.34)	10.70 ± 1.99 (9.40, 15.10)	13.35 ± 2.51 (10.38, 17.34)	15.05 ± 2.62 (11.64, 19.27)

Data are mean ± SD (min, max)

- During the time when patients were off medication there was a noticeable decline in all pulmonary function parameters
- Despite the increasing age, the rate of decline was numerically lower for PEF and MIP % predicted during DELPHI-E treatment period
- Preservation of respiratory strength measures is clinically meaningful

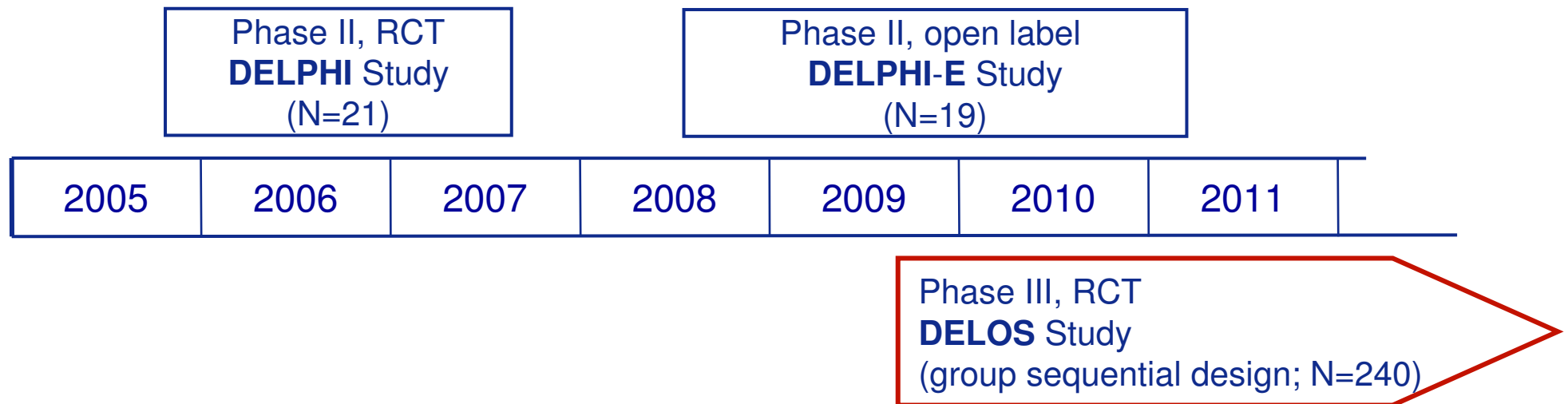
## Preservation of pulmonary function for patients in DELPHI-E compared to natural history data

Comparison in rate of change for PEF and FVC (% predicted) for patients in the DELPHI-E study on Catena<sup>®</sup> and patients in the natural history data set by CHOP



CHOP natural history data set courtesy of Finkel & Mayer:  
Data from 57 patients followed for up to 3 years (total of 123 visits)

## Phase III DELOS study open for enrolment



- 12-month treatment
- Catena®: 900 mg/day
- Group-sequential design (steroid non-users / users)
- Endpoints: respiratory function
- **Study open for enrolment in EU and USA**

# Objectives of the DELOS study

## Primary:

- To assess the efficacy of idebenone, compared to placebo, in improving or delaying the loss of respiratory function
- In clinical spirometric assessment at each study visit **and**
- Hand-held asthma device to be used on weekly basis



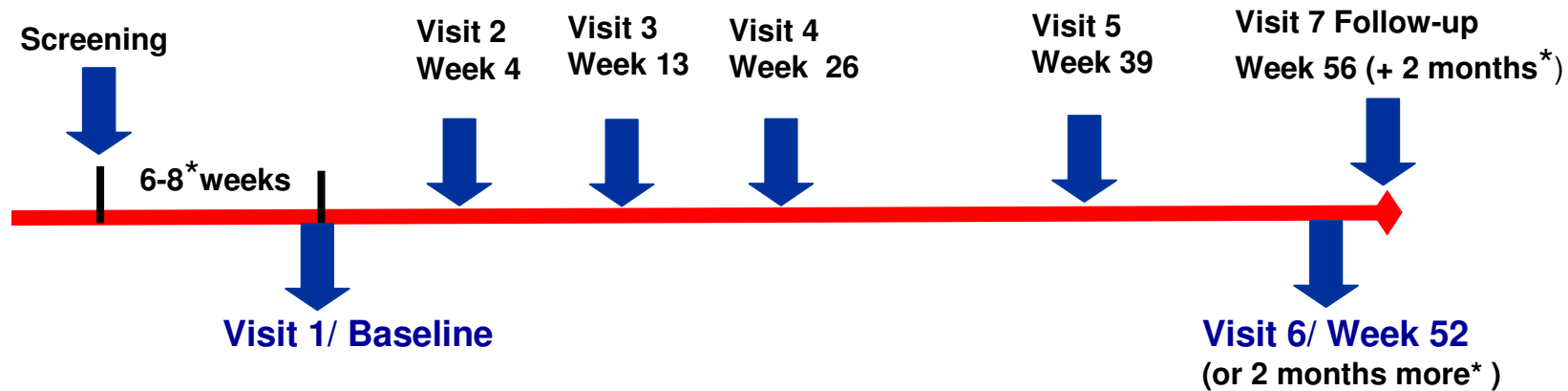
## Secondary:

To assess efficacy of idebenone in improving or delaying

- the loss of respiratory function using measures other than those used for the primary endpoint
- the loss of skeletal muscle strength/motor function
- the loss in quality of life

To assess the safety and tolerability of idebenone

## DELOS Study – Design & Dosing



- Study medication is Catena® or placebo
- 6 tablets daily (2 x 150 mg t.i.d.) with food
- Patients' participation: up to 15 (or 17\*) months



\* for non-steroid user patients who washed out from acute systemic steroid prior to Visit 1 and/or Visit 6/Week 52

## Who is eligible for this study? Inclusion/exclusion criteria

**Steroid use for the treatment of DMD will determine the time of enrolment (patient eligibility for Part I (steroid non-users) or Part II (steroid users))**

### INCLUSION CRITERIA:

- 10 – 18 years of age
- Documented diagnosis of DMD (or severe dystrophinopathy)
- Reproducible repeat PEF (<15% variation between screening and Baseline)
- **Patients ambulatory or in wheelchair eligible !**
- **No mutation type criteria**

### EXCLUSION CRITERIA:

- Patients require assisted ventilation
- Patients with DMD-related hypoventilation or non-DMD respiratory illness
- PEF normal (percent predicted > 80%)
- Symptomatic heart failure
- Taking medication with depressing or stimulating effect on respiration
- Planned or expected spinal fixation surgery

# DELOS study: Group Sequential Design



- Idebenone has a larger therapeutic effect on Peak expiratory flow (PEF) in patients not receiving concomitant glucocorticoids
- Phase III (DELOS) study powered to detect efficacy of idebenone in both subgroups

Total patients in DELOS study:  
240 patients (not including drop-outs)

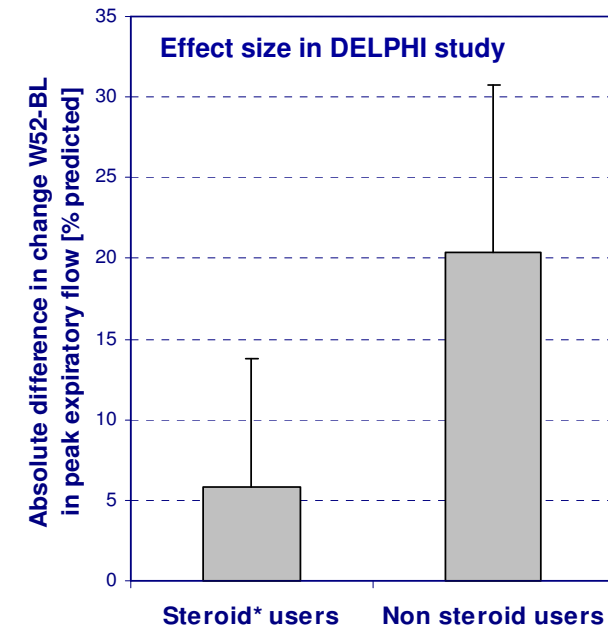
Patients **on** glucocorticoids:  
~200 patients

Patients **off** glucocorticoids:  
~40 patients

**not open for  
enrolment**

**open for enrolment**

- never used steroids
- did not use steroids chronically within last 12 months



## DELOS Study – Open for Enrolment



DELOS study currently open for enrolment in Europe (NL, BE, DE, AT, CH, S, F) and in the US at the Children's Hospital of Philadelphia

**Principal Investigator:** Gunnar Buyse, University Hospitals, Leuven, Belgium

**Lead Investigator North America:** Richard Finkel, Children's Hospital Philadelphia

The study protocol was endorsed by the FDA and the EMA during protocol assistance and pre-IND meetings and is approved by local IRBs in Europe and the USA.

The study is supported by PPMD, MDA, TREAT-NMD (patient calls).

### Further information can be obtained by:

- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- Nancy Videon, CHOP: [videon@email.chop.edu](mailto:videon@email.chop.edu), (267) 426.7163
- PPMD, Pat Furlong: [Pat@parentprojectmd.org](mailto:Pat@parentprojectmd.org), (513) 424.0696