The challenges of conducting clinical development in rare / orphan diseases: The Industry Perspective

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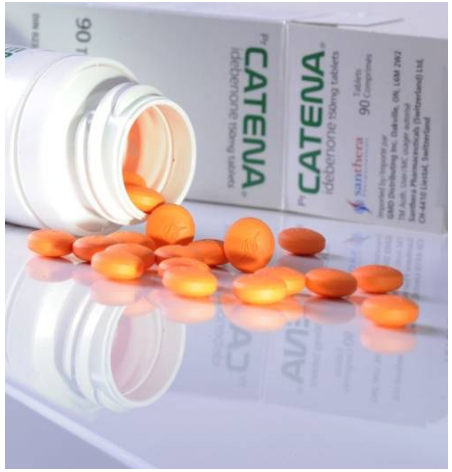
Muscle Study Group, September 22, 2009

Agenda

- Santhera - business focus on orphan neuromuscular diseases
- Business opportunities and regulatory framework for orphan drugs
- Challenges & solutions for drug development in orphan diseases
- Development program for idebenone (CATENA®) in DMD

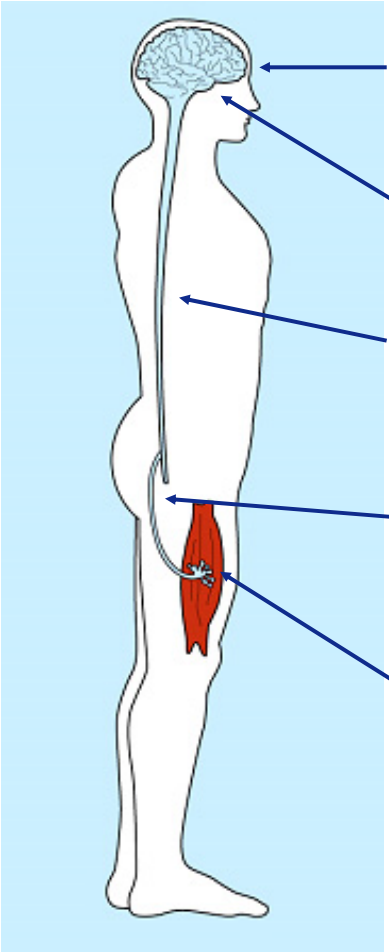
Santhera at a glance

- Focus on small molecules for orphan neuromuscular and mitochondrial diseases (high unmet medical need)
- Headquartered in Liestal/Basel (Switzerland) with North American office in Boston
- Robust pipeline of 3 compounds in 7 indications
- CATENA® for Friedreich's Ataxia successfully launched in Canada



- Partnerships established in commercialization (Takeda), clinical development (Biovail) and in-licensing (Novartis)
- Listed on SIX Swiss Exchange

Santhera's business focus



Movement disorders
- **Dyskinesia in Parkinson's Disease**
- **Primary Progressive Multiple Sclerosis**
- **Huntington's disease**

Mitochondrial diseases
- **Leber's Hereditary Optic Neuropathy**
- **MELAS Syndrome**

Sensory-motor deficits
- **Friedreich's Ataxia**
- **Spinal cord injury**
- **Charcot-Marie-Tooth neuropathies,...**

Motorneuron diseases
- **Amyotrophic lateral sclerosis**
- **Guillain-Barre syndrome**
- **Peripheral nerve injuries,...**

Muscle diseases & muscle wasting
- **Duchenne Muscular Dystrophy**
- **Cachexia (e.g. Cancer Cachexia)**
- **Congenital Muscular Dystrophy**
- **Myasthenia gravis**
- **Spinal muscular atrophies**

Selected examples, areas highlighted in **red** reflect Santhera's current areas of focus

Business opportunities and regulatory framework for orphan drugs

Favorable regulatory background

Country	Definition of OD	Market Exclusivity	Other Incentives
USA (1983) 	Less than 200,000 patients (~7.5 / 10k) - or any disease where drug development does not provide a positive ROI	7 years	Tax credit up to 50% of total costs (even for unsuccessful trials), study design assistance, eventually trial funding
EU (2000) 	Less than 5 / 10k - or any disease where drug development does not provide a positive ROI	10 years	Free pre-submission meetings with EMEA; 50% reduction in fees for all steps of obtaining MAA

Industry in neuromuscular research

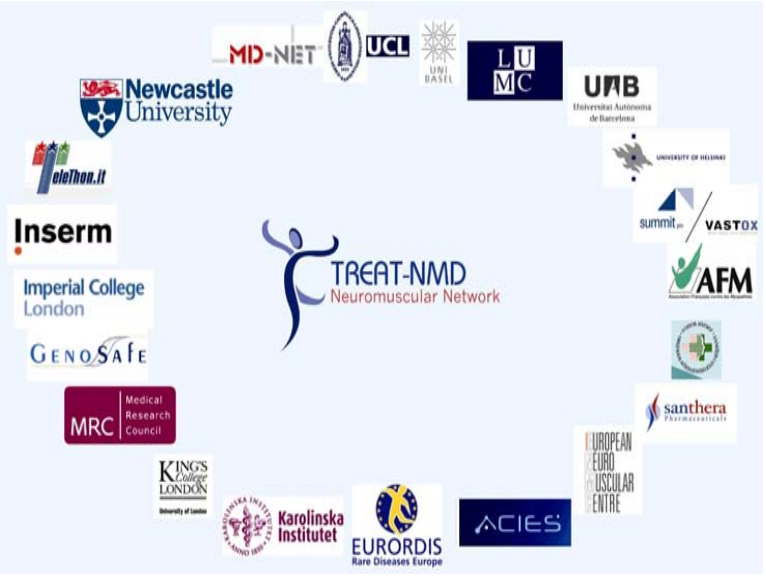
Challenges in clinical development of orphan drugs

Phase I	Phase II	Phase III	Regulatory filing
• Epidemiology not well described • Advertising has low chance of reaching patients • No regular patient flow to “average” hospital • Few specialist centers see most of the patients (long travel distances!) • Natural history data on disease progression are sparse			• Regulators lack expert knowledge in the area • Endpoints are not always established or agreed upon •EU: Centralized procedure

Patient organizations & networks can link to patients and provide advocacy

Friedreich's Ataxia Research Alliance

- Create disease awareness
- Lobby government organizations (NIH, FDA)
- Patient registries
- Support research in the field of FRDA
- Support recruitment into US clinical trials



TREAT-NMD (EU funded Network of Excellence)

- Create awareness about DMD & SMA
- Coordinate activities within EU & worldwide
- Support research in the field of NMDs
- Provide clinical trial infrastructure in NMDs
- EU-wide patient registries

Orphan Drugs:
Implications for sales and marketing strategies

➢ **Key differences in access to patients**

Conventional	Orphan
▪ Push-market - competitive marketing environment	▪ Pull-market - high medical need
▪ Large sales forces required	▪ Specialized sales approach with targeting
▪ Extensive PR campaigns (direct to patient in some countries) are the norm	▪ Targeted PR strategy (opinion leader management)
▪ Distribution via whole sellers and pharmacies	▪ Opportunity for closed distribution network and added value programs

CATENA
idebenone 150mg tablets

santhera Pharmaceuticals

Approved in Canada for the treatment for Friedreich's Ataxia

CATENA® Patient Support Program

Coordination	Reimbursement	Medical	Field Services
▪ New patient starts ▪ Coordination of care ▪ Integrated with reimbursement & patient pharmacy services	▪ Insurance coordination ▪ Integration with Specialty Pharmacy to maximize patient starts, data tracking & compliance	▪ Medical Inquiries ▪ Adverse Event Reporting	▪ Dispense across Specialty Pharmacies ▪ Compliance to unique product parameters

1-866-270-1733
One phone call for patients and physician for CATENA in Canada

Multiple product opportunities for orphan neuromuscular & mitochondrial diseases

	Preclinical	Phase I	Phase II	Phase III	Filing	Market
Catena® in Canada Friedreich's Ataxia						
Catena® / Sovrima® Friedreich's Ataxia						
Catena® / Sovrima® Duchenne Muscular Dystrophy						
Catena® Leber's Hereditary Optic Neuropathy						
Catena® MELAS Syndrome						
Catena® Primary Progressive Multiple Sclerosis						
JP-1730/fipamezole Dyskinesia in Parkinson's Disease						
SNT-317/omigapil Congenital Muscular Dystrophy						

Development program with idebenone (CATENA®) for Duchenne Muscular Dystrophy

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[1]*, Gerry Van der Mieren[2], Michael Erb[3], Jan D'hooge[4], Paul Herijgers[2], Erik Verbeken[5], Alejandro Jara[6], An Van Den Bergh[2], Luc Mertens[7], Isabelle Courdier-Fruh[3], Patrizia Barzaghi[3], and Thomas Meier[3]

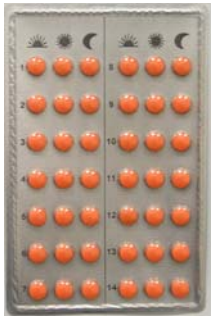
Results:

- **Treatment with idebenone normalized diastolic cardiac function abnormalities (i.e. end diastolic pressure and time constant of isovolumetric relaxation phase)**
- **Idebenone prevents mortality from cardiac pump failure during dobutamine stress**
- **Idebenone reduces inflammation in cardiac tissue**
- **Idebenone improves exercise performance**
- **Justification to start Phase II study in human patients**

Phase II proof-of-concept clinical trial (DELPHI trial)

DESIGN :

- **12 months, double-blind, randomized, placebo-controlled, single center study at University of Leuven (Belgium); PI: Gunnar Buyse**
- **Number of DMD patients: 21 boys, 8 to 16 years old**
- **Primary endpoint: change from baseline to week 52 in peak systolic radial strain of left ventricle (LV) inferolateral wall, assessed by CDMI (Color Doppler Myocardial Imaging)**
- **Additional endpoints included:**
  - **Cardiac functional parameters (other myocardial deformation parameters, global systolic and diastolic function parameters, cardiac geometry, heart rate,...)**
  - **Respiratory function**
  - **Timed walking test and skeletal muscle strength**
- **Dose levels: 450 mg/d; 13 active, 8 placebo**



DELPHI: **D**uchenne **E**fficacy study in **L**ong-term **P**rotocol of **H**igh dose **I**debenone

Summary of clinical data obtained in Phase II DELPHI trial with idebenone (Catena®)

- Idebenone was safe and well tolerated in patients with DMD
- Idebenone improved myocardial function properties
- Idebenone also improved respiratory strength measures (peak expiratory flow, maximum mouth pressures)
- Potential protective approach for ALL dystrophin-deficient patients

Basis for planning of Phase III study

DELOS - Phase III Study with idebenone (Catena®) in DMD

Study Title: **A Phase III Double-Blind, Randomised, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Idebenone in 10 – 18 Year Old Patients with DMD**

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

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

Study sites: **~25 in Europe, USA and Canada**

Patients: **240**

Efficacy variables and study endpoints

Primary endpoint:

The change from Baseline to Week 52 in percent predicted Peak Expiratory Flow (PEF % predicted)

Secondary efficacy variables:

- **Pulmonary function (FVC, MIP, MEP, PCF)**
- **Muscle strength (hand-held myometry)**
- **Motor function (Brooke and Vignos scales)**
- **Quality of Life (PedsQL®)**
- **Safety & Tolerability (labs, physical exam, ECG and echocardiogram)**

Endpoints discussed with FDA and EMEA

Summary

- Orphan drug legislation set the regulatory framework for drug development for rare diseases
- Challenges during development due to low patient numbers and lack of knowledge (of all parties)
- Requirement for special efforts during patient recruitment
- Efforts needed to share state of the art knowledge with regulators
- Orphan drugs allow for focused marketing strategies
- Partnerships with patient organizations during all stages of product development
- Idebenone (CATENA®) as example for successful drug development in multiple orphan neuromuscular / mitochondrial diseases

Hopefully she'll never
hear the name Santhera
as she grows up...

...but if she needs us,
we'll be with her
every step of the way.

As an emerging speciality pharmaceutical company, Santhera believes that the development of small molecules has a big future.

Unmet medical need is what drives our work. Particularly rare diseases and the development of orphan drugs where there are no current alternatives.

That's why we are busy developing novel solutions to improve the lives of patients with severe neuromuscular diseases.

At Santhera we care about people – every step of the way.

Date of preparation: August 2008

when it comes to science

we know how to move people

santhera
Pharmaceuticals

DELOS study started patient enrolment

santhera Pharmaceuticals

santhera Pharmaceuticals

Takeda

Takeda Pharmaceutical Company Limited

Initiation of Pivotal Phase III Study with Catena®/Sovrima® (Idebenone) in Duchenne Muscular Dystrophy

Liestal, Switzerland and Osaka, Japan, September 2, 2009 – Santhera Pharmaceuticals (SIX: SANN, "Santhera"), a Swiss specialty pharmaceutical company focused on orphan neuromuscular diseases, and Takeda Pharmaceutical Company Limited (TSE: 4502, "Takeda") announced today that Santhera has initiated the pivotal Phase III study with Catena®/Sovrima® (INN: idebenone) for the treatment of Duchenne Muscular Dystrophy, one