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

Thomas Meier, PhD (Chief Scientific Officer)
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

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

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Regulatory filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Epidemiology not well described</td>
<td>• Advertising has low chance of reaching patients</td>
<td>• No regular patient flow to “average” hospital</td>
<td>• Regulators lack expert knowledge in the area</td>
</tr>
<tr>
<td>• No regular patient flow to “average” hospital</td>
<td>• Few specialist centers see most of the patients (long travel distances!)</td>
<td>• Natural history data on disease progression are sparse</td>
<td>• Endpoints are not always established or agreed upon</td>
</tr>
<tr>
<td>• Natural history data on disease progression are sparse</td>
<td></td>
<td></td>
<td>• EU: Centralized procedure</td>
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</table>
Patient organizations & networks can link to patients and provide advocacy

- 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

<table>
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<tr>
<th>Conventional</th>
<th>Orphan</th>
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<tr>
<td>Push-market - competitive marketing environment</td>
<td>Pull-market - high medical need</td>
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<tr>
<td>Large sales forces required</td>
<td>Specialized sales approach with targeting</td>
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<td>Extensive PR campaigns (direct to patient in some countries) are the norm</td>
<td>Targeted PR strategy (opinion leader management)</td>
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<tr>
<td>Distribution via whole sellers and pharmacies</td>
<td>Opportunity for closed distribution network and added value programs</td>
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Approved in Canada for the treatment for Friedreich’s Ataxia
CATENA® Patient Support Program

Coordination
- New patient starts
- Coordination of care
- Integrated with reimbursement & patient pharmacy services

Reimbursement
- Insurance coordination
- Integration with Specialty Pharmacy to maximize patient starts, data tracking & compliance

Medical
- Medical Inquiries
- Adverse Event Reporting

Field Services
- Dispense across Specialty Pharmacies
- Compliance to unique product parameters

1-866-270-1733
One phone call for patients and physician for CATENA in Canada
<table>
<thead>
<tr>
<th>Product</th>
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<th>Phase III</th>
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<th>Market</th>
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<tr>
<td>Catena® in Canada</td>
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<td>Primary Progressive Multiple Sclerosis</td>
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<tr>
<td>JP-1730/fipamezole</td>
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<td></td>
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<td></td>
<td>Dyskinesia in Parkinson’s Disease</td>
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<tr>
<td>SNT-317/omigapil</td>
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<td></td>
<td>Congenital Muscular Dystrophy</td>
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Development program with idebenone (CATENA®) for Duchenne Muscular Dystrophy
Preclinical efficacy data with idebenone in animal model for DMD

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: Duchenne Efficacy study in Long-term Protocol of High dose Idebenone
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
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
**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.

when it comes to science
we know how to move people
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