Phase 3 investigation of lucerastat for patients with Fabry disease

Investor Webcast – May 2018
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More knowledge – Powered by science

Jean-Paul Clozel
CEO
Our Strategic Priorities

5 key priorities to ensure the company’s success over the next 5 years

1. Deliver at least three products to market
2. Build a commercial organization
3. Bring Idorsia to profitability in a sustainable manner
4. Create a pipeline with a sales potential of CHF 5 billion
5. Utilize state-of-the-art technologies

Phase 3 initiation in Fabry disease | May 2018
Phase 3 investigation of lucerastat for patients with Fabry disease

Guy Braunstein
Head of Global Clinical Development
Fabry disease

Mechanism: Reduced/absent α-galactosidase A – over years or decades – results in accumulation of Gb3 in lysosomes of many tissues.

A genetic X-linked disorder

Accumulation of Gb3 in cells

Inflammation and fibrosis

Signs and symptoms of Fabry disease

Ceramide

GlcCer synthase

Gb1

Gb2

Gb3

α-galactosidase A (α-GalA)
Fabry disease

Mechanism: Reduced/absent α-galactosidase A – over years or decades – results in accumulation of Gb3 in lysosomes of many tissues.
Inheritance pattern in Fabry disease

X-linked recessive genetic disease

• GLA gene mutation results in defective lysosomal enzyme α-GalA
• In turn, this results in Gb3 accumulation
• Random X-inactivation in Fabry female ‘carriers’: both genders affected
• Male have generally classical phenotype
• Females have higher residual level enzyme and
  – are affected later
  – progress slower
  – have more variable phenotype
Clinical manifestations of Fabry disease
Large spectrum of clinical, heterogeneous manifestations

- Gradually progressing in severity from childhood to adulthood
- Major impact on quality of life
- Slow progressive damage to vital organs over decades
- Earlier death

**Clinical manifestations of Fabry disease**

- **Brain**
  - Strokes (in severe cases), and dizziness
- **Skin**
  - Dark red spots or rashes, burning / tingling sensations, sensitivity to temperature and profuse sweating
- **Kidneys**
  - Cysts, reduced kidney function, progressive kidney failure
- **Digestive Tract**
  - Abdominal pain, constipation, diarrhea, and nausea
- **Eyes**
  - The appearance of the eyes changes
- **Ears**
  - Tinnitus, hearing loss, and vertigo
- **Heart**
  - Cardiomyopathy with rhythmia, valvular dysfunction, ischemia, left heart failure
- **Neuropathic pain**
  - Pain resulting from damage to or dysfunction of the nervous system
Diagnosis of Fabry disease

**Clinical symptoms**
- Neuropathic pain
- GI
- Hearing loss
- Hypohydrosis

**Clinical events**
- Stroke
- Cardiac events
- Renal events

**Pedigree analysis**
- Family members
- Children ➔ Parents

**Enzyme assay**
- Leukocyte
- α-GalA

**Genotyping**
- >830 mutations

**Biomarkers**
- Gb3 in plasma and urine

Phase 3 initiation in Fabry disease | May 2018
Epidemiology of Fabry disease

- Estimated prevalence of diagnosed Fabry disease in general population (2001): 1.4 per 100’000 (1.0 in males and 1.9 in females)
- Incidence (males): 0.01 to 0.03 per 100’000 per year; incidence (females): up to 0.05 per 100’000
- Patients diagnosed with Fabry disease in EU28 and US in 2014:

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU-28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>7,324</td>
<td>2,509</td>
<td>4,815</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>659</td>
<td>279</td>
<td>380</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>268</td>
<td>75</td>
<td>193</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>4,607</td>
<td>1,578</td>
<td>3,029</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>414</td>
<td>175</td>
<td>239</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>168</td>
<td>47</td>
<td>121</td>
</tr>
</tbody>
</table>
Current therapies in Fabry disease

• No curative therapy
• Symptomatic treatments not satisfactory
• Etiological therapies limited
  – Enzyme replacement therapy:
    – Fabrazyme (agalsidase beta) (US and EU)
    – Replagal (agalsidase alfa) (EU only)
  – Chaperone therapy
    – Galafold (migalastat) (EU only)

- Enzyme replacement therapy:
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  - Replagal (agalsidase alfa) (EU only)

- Chaperone therapy
  - Galafold (migalastat) (EU only)

i.v. infusion, bi-weekly
Immunogenicity
Partial efficacy

Galafold for patients with amenable mutation
1 capsule orally, fasted, every other day
Lucerastat key attributes

Low molecular weight iminosugar

- Inhibitor of glucosylceramide synthase
- Oral administration
- Highly soluble with complete absorption
- Access to most tissues, including peripheral & central nervous system
- Renal excretion of unchanged drug
- Orphan drug status granted in the US and EU
Lucerastat

Mode of action: substrate reduction therapy

Lucerastat is investigational, in development and not approved or marketed in any country.
Lucerastat in Fabry disease
Clinical development plan

Clinical pharmacology studies
- SAD and MAD studies
- Renal impairment study
- tQT study

Exploratory study
- Safety and proof of mechanism study

Patient survey

Confirmatory study
- MODIFY

Pediatric study
- Plan agreed with EMA
- Study to run in parallel to MODIFY

Potential beyond initial plan

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Lucerastat clinical pharmacology

- Half-life: approximately 6 hours – twice daily dosing
- Dose-proportional exposure
- >85% of the dose excreted unchanged in urine
- Negligible food effect
- Low potential for drug-drug interaction
- Dose adjustment required in subjects with renal function impairment

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>1000 mg b.i.d.</td>
</tr>
<tr>
<td>≥ 45 and &lt; 60</td>
<td>750 mg b.i.d.</td>
</tr>
<tr>
<td>≥ 30 and &lt; 45</td>
<td>500 mg b.i.d.</td>
</tr>
<tr>
<td>≥ 15 and &lt; 30</td>
<td>250 mg b.i.d.</td>
</tr>
</tbody>
</table>

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Guérard et al. (2017) Orphanet J Rare Dis
Guérard et al. (2017) J Clin Pharmacol
Exploratory study design

Prospective, single-center, open-label, randomized, study in 14 male/female adult patients with Fabry disease receiving enzyme replacement therapy (ERT)

- 10 patients with Fabry disease received lucerastat on top of ERT
- 4 patients with Fabry disease on ERT

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Exploratory study objectives

Primary objective:
• To assess the safety and tolerability of lucerastat 1000 mg b.i.d. for 12 weeks

Secondary objectives:
• To investigate the effect of lucerastat on plasma biomarker levels following a 12-week treatment
• To assess the effect of lucerastat on renal and cardiac function
• To determine the 12-hour pharmacokinetic profile of lucerastat at steady state
• To identify metabolites in plasma
Exploratory study patient demographics

**Lucerastat group:**
- 6 females, 4 males
- Mean age (SD): 47.7 (15.0), range from 18 to 67
- Mean ERT duration in years (SD): 4.5 (2.6)

**Control group:**
- 4 males
- Mean age (SD): 39.8 (19.1), range from 21 to 62
- Mean ERT duration in years (SD): 6.3 (4.2)

**Medical history:**
- All patients had comorbidities, most of them manifestations of Fabry disease
- None of these affected eligibility for the study
- Overall balanced between groups
Exploratory study safety results

- Lucerastat was safe and well tolerated in patients with Fabry disease over 12 weeks on top of ERT
  - One Serious Adverse Event, unrelated to lucerastat:
    - Re-occurrence of atrial fibrillation in a patient with underlying hypertrophic cardiomyopathy
  - No specific pattern in the nature and distribution of Treatment-Emergent Adverse Events
  - No trends for changes from baseline in:
    - Vital signs, body weight, ECG recordings, clinical laboratory parameters

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Exploratory study biomarker results
Biomarker reduction

Mean % (SD) biomarker reduction from baseline at week 12

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Lucerastat group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Gb3</td>
<td>-55.0% (10.5)</td>
<td>-6.9% (12.6)</td>
</tr>
<tr>
<td>Urine Gb3</td>
<td>-52.5% (21.2)</td>
<td>-8.6% (54.4)</td>
</tr>
<tr>
<td>GlcCer</td>
<td>-49.0% (16.5)</td>
<td>-6.5% (9.7)</td>
</tr>
<tr>
<td>LacCer</td>
<td>-32.7% (13.0)</td>
<td>-3.9% (2.8)</td>
</tr>
</tbody>
</table>

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Exploratory study conclusions

- Lucerastat was safe and well tolerated in patients with Fabry disease over 12 weeks on top of ERT
- Pharmacokinetic findings consistent with previous studies in healthy subjects
- Proof of mechanism achieved with lucerastat:
  - Lucerastat significantly reduced Fabry disease-elevated Gb3 and other relevant biomarkers

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Fabry patients survey – Goals

1) Better understand patients’ disease and needs from the patient perspective
2) Investigate key aspects of the Phase 3 study MODIFY with respect to symptoms: neuropathic pain and gastrointestinal symptoms
3) Complement existing information/data from the literature

In addition, collect information on:
• Use of enzyme replacement therapy (ERT)
• Impact on daily life
• Participation in clinical trials
Fabry patients experience significant Neuropathic Pain—combining intensity, frequency & location.

- GI symptoms are heterogeneous in nature and frequency.
- Large impact of neuropathic pain on quality of life.
- Large majority of patients are willing to participate in a clinical trial.

Fabry patients survey – Key results:

- 51.5% (189/367) of the patients report frequent pain AND moderate/severe pain.
- 74.7% (274/367) of the patients report pain in hands & feet AND moderate/severe pain.
- 50% of the patients report all three.
- 52.0% (191/367) of the patients report frequent pain AND pain in hands & feet.

N=367
Designing the confirmatory study

- Informed design based on patients survey
- Development of endpoint measurement – neuropathic pain, based on Brief Pain Inventory instrument, modified for Fabry’s neuropathic pain according to FDA guidelines for PRO
  - Concept elicitation
  - Cognitive debrief
  - Usability testing in different languages
- Development and validation of electronic tool to collect pain and gastro-intestinal daily data
- Input from patient organization and from specialists
- Input from regulatory agencies including FDA, and in Europe through scientific advice and the VHP procedure

Lucerastat is investigational, in development and not approved or marketed in any country.
MODIFY: A multicenter, double-blind, randomized, placebo controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease.

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MODIFY: Objectives

• **Primary objective**
  – To determine the effect of lucerastat on neuropathic pain in patients with Fabry disease

• **Secondary objectives**
  – To determine the effect of lucerastat on gastro-intestinal symptoms (abdominal pain and diarrhea) in patients with Fabry disease and GI symptom(s) at baseline
  – To confirm the effect of lucerastat on biomarkers of Fabry disease
  – To determine the safety and tolerability of lucerastat in patients with Fabry disease

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MODIFY: Design

Randomization 2:1 (N=108)

Lucerastat (n=72)

Placebo (n=36)

Screening

6-7 weeks

6 months

Primary/secondary efficacy endpoints

Open, uncontrolled, Extension

**Site visits:** Screening, Randomization, Months 1, 2 (phone), 3, 4 (phone), 5, 6 + 2 FU visits (phone)

**Stratification by:**
- Sex
- ERT use (on ERT at screening vs never treated/previous treated)

**Lucerastat dose:**
- 1000 mg b.i.d.
- Adjusted in subjects with moderate renal failure

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MODIFY: Patient population

• Confirmed Fabry disease – presence of at least 1 mutation in GLA (the gene coding for α-galactosidase A) as measured with genetic test
• Neuropathic pain in the last 3 months preceding the screening period
• Three options for ERT status at baseline

Switched patients

ERT bi-weekly for at least 12 months
(stable dose regimen during the last 3 months)

Last ERT

Pseudo-naïve patients

ERT bi-weekly

Last ERT

No ERT in at least the last 6 months

Naïve patients

Never treated with ERT

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MODIFY: Endpoints

• **Primary efficacy endpoint:**
  – The primary efficacy endpoint is a response to study treatment on neuropathic pain, defined as a reduction from baseline to Month 6 of at least 30% in the “modified” BPI-SF3 score of “neuropathic pain at its worst in the last 24 hours”.

• **Secondary efficacy endpoints:**
  – Change from baseline to Month 6 in the average daily 11-point Numerical Rating Scale (NRS-11) score of “abdominal pain at its worst in the last 24 hours” in subjects with GI symptoms at baseline.
  – Change from baseline to Month 6 in the number of days with at least one stool of a Bristol Stool Scale (BSS) consistency Type 6 or 7 in subjects with GI symptoms at baseline;
  – Change from baseline to Month 6 in plasma globotriaosylceramide (Gb3).
Summary

- Fabry disease is a rare genetic disorder with limited therapeutic options and a high medical need
- Lucerastat is a small molecule, oral monotherapy with the potential as a new treatment approach for patients with Fabry disease, irrespective of their genetic mutation type
- Proof of mechanism achieved in exploratory study where lucerastat was well-tolerated
- Lucerastat has orphan drug status in US and EU
- Phase 3 study to assess effects of lucerastat on neuropathic pain and safety and tolerability – ongoing
- Pediatric study planned to run in parallel

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“The sensations that I get – it feels like my hands are on fire. It feels like there’s a thousand needles poking at my hands and feet... If I was to get out of bed and I was to walk, it would feel like I’m walking on hot coals with needles jabbing into my feet.”

- Patient