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 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
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

**Brain**
- Strokes (in severe cases), and dizziness

**Eyes**
- Neuropathic pain: Pain resulting from damage to or dysfunction of the nervous system
- The appearance of the eyes changes

**Ears**
- Tinnitus, hearing loss, and vertigo

**Heart**
- Cardiomyopathy with arrhythmia, valvular dysfunction, ischemia, left heart failure

**Kidneys**
- Cysts, reduced kidney function, progressive kidney failure

**Skin**
- Dark red spots or rashes, burning / tingling sensations, sensitivity to temperature and profuse sweating

**Digestive Tract**
- Abdominal pain, constipation, diarrhea, and nausea

**Phase 3 initiation in Fabry disease | May 2018**
Diagnosis of Fabry disease

**Clinical symptoms**
Neuropathic pain, GI, hearing loss, hypohydrosis

**Clinical events**
Stroke, cardiac and renal events

**Pedigree analysis**
Family members
Children ➔ Parents

**Enzyme assay**
Leukocyte α-GalA

**Genotyping**
>830 mutations

**Biomarkers**
Gb3 in plasma and urine
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>
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<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>

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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)

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

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

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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 is investigational, in development and not approved or marketed in any country.
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Lucerastat is a substrate reduction therapy that targets the metabolism of sphingolipids, particularly GlcCer (glycosylceramide) and LacCer (lactosylceramide). It works by inhibiting the enzyme UGCG, which is involved in the de novo synthesis of ceramide and gangliosides. By inhibiting UGCG, Lucerastat prevents the synthesis of these lipids, thereby reducing their accumulation.

In the context of Fabry disease, which is characterized by the accumulation of GlcCer and LacCer, Lucerastat helps to lower the levels of these lipids, thereby alleviating the symptoms associated with the disease.

Key points:
- **Mode of action**: Substrate reduction therapy
- **Lucerastat** inhibits UGCG, reducing the synthesis of ceramide and gangliosides.
- **GlcCer** and **LacCer** are metabolites targeted for reduction.
- **Fabry disease** is characterized by the accumulation of GlcCer and LacCer.
- **Lucerastat** is investigational 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

Confirmatory study
• MODIFY

Patient survey

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
10 patients with Fabry disease received lucerastat on top of ERT

4 patients with Fabry disease on ERT

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

Exploratory study design

Lucerastat is investigational, in development and not approved or marketed in any country.
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

Lucerastat is investigational, in development and not approved or marketed in any country.
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

Lucerastat is investigational, in development and not approved or marketed in any country.
## Exploratory study biomarker results

### Biomarker reduction

<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>

Lucerastat is investigational, in development and not approved or marketed in any country.
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
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**

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**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
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

Lucerastat is investigational, in development and not approved or marketed in any country.
MODIFY: Design

**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/previously treated)

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

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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)
- Pseudo-naïve patients: ERT bi-weekly
- Naïve patients: Never treated with ERT

Randomization

Screening period (diary card)

Week 1

Placebo

Lucerastat

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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).
• 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
“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