Phase 3 investigation of clazosentan for vasospasm post-aneurysmal subarachnoid hemorrhage
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More knowledge – Powered by science

Jean-Paul Clozel, MD
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 clazosentan for vasospasm post-aneurysmal subarachnoid hemorrhage

Guy Braunstein, MD
Head of Global Clinical Development
Aneurysmal subarachnoid hemorrhage (aSAH)

A sudden life-threatening bleeding occurring in the subarachnoid space

- aSAH is caused by the rupture of an aneurysm – a weak, bulging spot on the wall of a cerebral artery
- Prevalence: 9 in 100’000 worldwide – it is an orphan disease

- Emergency repair is required to stop the hemorrhage

**Pre-treatment**
Ruptured aneurysm

**Brain surgery:** Clipping of the aneurysm

**Catheter intervention:** Releasing of platinum coils

Subarachnoid space
Brain
Skull
Scalp

Phase 3 initiation in vasospasm post-aSAH | June 2018
Cerebral vasospasm post-aSAH

Can occur between 4 and 14 days after aSAH securing

• Cerebral vasospasm is a strong contraction of the arteries in the brain surrounding the hemorrhage

• Narrowing of the blood vessel limits blood flow decreasing the amount of blood supplied to the brain

Baseline aSAH: normal MCA

7 day after SAH: cerebral vasospasm
Clinical manifestations of vasospasm

From asymptomatic detected by systematic angiography to serious neurological symptoms

- Mood change, agitation
- Blurred or double vision
- Focal numbness, weakness, paralysis
- Worsening of headache
- Difficulty speaking or being unable to speak
- Loss of consciousness
- Dizziness
- Confusion
- Loss of consciousness

Long-term consequence of vasospasm

- Necrosis of an area of brain tissue
- Physical deficit
- Social and emotional impact, affecting all aspects of someone’s life

Brain infarct due to vasospasm
Available therapy for vasospasm

Hemodynamic therapy
- Inducing high blood pressure in an attempt to force a blood supply to the brain region affected by the vasospasm

Rescue therapy
- Invasive neurovascular intervention
  - balloon angioplasty
  - intra-arterial administration of vasodilators
- Often needs to be repeated multiple times over the course of several days
- Requires highly-trained specialists in an intensive care setting
- Clinical efficacy unproven in randomized controlled trials
- Is associated with medical risks

No pharmacological therapy for cerebral vasospasm
- Except for fasudil in Japan and Korea
- Nimodipine approved in most countries for preventing ischemic events secondary to aSAH (but whether it acts on cerebral vasospasm is unproven)

Phase 3 initiation in vasospasm post-aSAH | June 2018
Rationale for clazosentan for cerebral vasospasm

Role of endothelin in cerebral vasospasm

Cerebral vasospasm is caused by the release of vasoactive mediators after a bleed on the brain triggering vessels to contract.

Patients with cerebral vasospasm show high levels of endothelin in their cerebral spinal fluid.

Endothelin is one of the most powerful, long-acting vasoactive mediators that causes blood vessels to contract.

Clazosentan

- ETA selective ERA
- Highly soluble
- Ideal for intravenous administration
- Fast onset of action
Learning from clazosentan program

From this program, we know:

• Which patients would benefit most
• What dose should be given
• How to manage the treatment and in particular the safety of clazosentan
• How to measure treatment benefit short-term and long-term

This acquired knowledge is incorporated into the design of the REACT study

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

Phase 3 initiation in vasospasm post-aSAH | June 2018

More than 1’800 patients treated with clazosentan providing significant experience in vasospasm post-aSAH and a well documented safety profile.
What we have learned through our experience with clazosentan...

Sebastien Roux, MD
Medical lead for clazosentan
**Clazosentan**

*Dose-dependent prevention of vasospasm*

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**Phase 2 study – angiographic endpoint**

- Clazosentan 1 to 15 mg/h versus placebo post-clipping and coiling

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Stroke 2008 39:3015-21
Clazosentan

5mg/hr dose is not high enough

Overall incidence of death and vasospasm-related morbidity

Phase 3 study – clinical morbidity / mortality endpoint

- Patients who received surgical clipping treated with 5mg/hr clazosentan

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

15mg/hr showed significant effect on morbidity / mortality

Overall incidence of death and vasospasm-related morbidity

<table>
<thead>
<tr>
<th>Event rate (%)</th>
<th>Placebo (n=189)</th>
<th>Clazosentan 5 mg/h (n=194)</th>
<th>Clazosentan 15 mg/h (n=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>24</td>
<td>15</td>
<td></td>
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<tr>
<td>0.3395</td>
<td>0.0073</td>
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</table>

Phase 3 study – clinical morbidity / mortality endpoint

- Patients who received endovascular coiling treated with 5 or 15mg/hr clazosentan

Randomized Trial of Clazosentan in Patients With Aneurysmal Subarachnoid Hemorrhage Undergoing Endovascular Coiling

R. Loeb Macdonald, MD, PhD; Randall T. Higashida, MD; Emmamela Keller, MD; Stephan A. Mayer, MD; Andy Molyneux, MD; Andreas Raabe, MD; Peter Vajkoczy, MD; Isabel Wanke, MD; Doris Bach, MSc; Aline Frey, PharmD; Pegov Neuwelt, PhD; Sébastien Roex, MD; Neal Kassell, MD

Stroke. 2012; 43(6):1463-9
**Clazosentan**

15mg/hr showed significant effect on primary endpoint

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Death (within 6 weeks)</th>
<th>New cerebral infarct</th>
<th>Delayed ischemic neurological deficits</th>
<th>Rescue therapy</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>13</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Clazosentan 5 mg/h</td>
<td>3</td>
<td>16</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Clazosentan 15 mg/h</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

**Phase 3 study – clinical morbidity / mortality endpoint**

- Consistent effect at 15 mg/hr on all morbidity events

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Clazosentan

10mg/hr dose showed similar results to CONSCIOUS-3 in Japanese patients

Phase 2 study – exploratory endpoint

• Clazosentan significantly reduced vasospasm-related morbidity and mortality events
In patients with established vasospasm

Pilot study – angiographic endpoint

Key findings:
- Clazosentan acts on some large brain arteries but the real benefit is in the effect on smaller arteries not accessible to endo-arterial therapy
- Clazosentan has a considerable impact on vasospasm when caught early enough

Admission Baseline (prior to clazosentan) 3h post clazosentan

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

Well documented safety profile

Side effects of clazosentan

Hypotension
Lung complications (pulmonary edema)
Peripheral edema

Main side effects are manageable

Risk mitigation

Blood pressure control with vasopressors in ICU
Euvolemia, iv fluid restriction
Euvolemia, iv fluid restriction

> 1'800 patients treated

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Phase 3 initiation in vasospasm post-aSAH | June 2018
Which patients are at highest risk of vasospasm?

Patients with “thick and diffuse” clot

- Characterized by large amount of subarachnoid blood on hospital admission cerebral CT scan
- Represents approximately 50% of overall aSAH population
Which patients are at highest risk of vasospasm?

<table>
<thead>
<tr>
<th>Event</th>
<th>Thick and diffuse</th>
<th>Other</th>
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<tr>
<td>Rescue Therapy</td>
<td></td>
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<td>DIND</td>
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<tr>
<td>New Cerebral Infarcts</td>
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<td></td>
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<tr>
<td>Death</td>
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</table>

- Data from previous CONSCIOUS program demonstrates the high event rates for vasospasm and related ischemic complications.
Clazosentan

In high-risk patient population

Clot size impacts the absolute treatment effect (individual morbidity / mortality components)

Thick and Diffuse Clots

Phase 3 studies – clinical morbidity / mortality endpoint

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Phase 3 initiation in vasospasm post-aSAH | June 2018
REACT study design incorporates these learnings

- Selection of the a **high-risk** patient population
- Selection of the **dose**
- Selection of the **best measure** to demonstrate efficacy
- Optimized patient management **guidelines** to ensure patient safety
Primary objective
• To determine the efficacy of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia, in patients with aSAH

Secondary objectives
• To evaluate the effect of clazosentan on the incidence of all-cause new or worsened cerebral infarction $\geq 5 \text{ cm}^3$ in volume at Day 16 post-study drug initiation
• To evaluate the effect of clazosentan on long-term clinical outcome, cognition, and health-related Quality of Life at Week 12 post-aSAH
• To evaluate the safety and tolerability of clazosentan in the selected population up to 24 hours post-study drug discontinuation
REACT: Design

400 patients (200 placebo/200 clazosentan) from 100 trial sites across 15 countries

Observation: 14 days post-study drug initiation

Placebo Treatment & Observation

Clazosentan 15mg/h Treatment & Observation

Screening

Randomization

Aneurysm rupture (aSAH)

Hospital admission

Aneurysm securing within 72h post-aSAH

End of study drug

End of 24h Follow-up

Week 12 post-aSAH

EOS

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Phases and Dates:

- Phase 3 initiation in vasospasm post-aSAH: June 2018
Target population: elevated risk of developing delayed cerebral ischemia (DCI)

High-risk for developing cerebral vasospasm
- “thick and diffuse” clot on hospital admission CT scan
- clazosentan administered in prevention of vasospasm

Objective to prevent DCI, subsequent clinical deterioration, and related ischemic complications

Early vasospasm without neurological deterioration
- clazosentan administered in treatment of vasospasm

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Phase 3 initiation in vasospasm post-aSAH | June 2018
The occurrence of clinical deterioration due to DCI, from study drug initiation up to 14 days post-study drug initiation

- Worsening of 2 points on neurological scales, lasting for at least 2 hours
- Entirely or partially due to cerebral vasospasm
- Centrally adjudicated

Episodes of neurological worsening must be avoided because they may:

- lead to brain infarcts, if left untreated
- aggravate or degrade into further ICU complications (e.g., coma with pulmonary complications)
- increase the length of stay in ICU
- trigger the performance or administration of invasive endovascular therapies (angioplasty or multiple sessions of intra-arterial vasodilators)
Secondary endpoints

• Occurrence of all-cause new or worsened cerebral infarction ≥ 5 cm³ at Day 16 post-study drug initiation

• Long-term clinical outcome assessed by the GOSE at Week 12 post-aSAH, dichotomized into poor (score ≤ 4) and good outcome (score > 4)

• Instruments used to assess long-term effect:
  – Glasgow Outcome Scale (extended)
  – Montreal Cognitive Assessment
  – Modified Rankin Scale
  – Quality of life instruments (Stroke Specific QOL, the EQ-5D, and the Oxford Participation and Activities Questionnaire)
Japanese registration program

- Two identically designed studies (one in clipped patients, one in coiled patients) evaluating the effect of **clazosentan 10 mg/h** versus placebo on vasospasm-related morbidity and mortality and all-cause morbidity and mortality
  - Death, new cerebral infarcts, delayed ischemic neurological deficits
- Study design and main endpoints similar to CONSCIOUS-2 and -3 studies
- **160 patients (80 per treatment arm) in each study**
- Study expected to report results before year-end

Clazosentan is investigational, in development and not approved or marketed in any country.
• Developed as intravenous infusion for prevention and treatment of cerebral vasospasm in patients who have suffered an aSAH

• Has potential to prevent ischemic complications of cerebral vasoconstriction and to decrease the need for invasive intervention

• Registration studies in Japan expected to complete in second half of 2018

• REACT – Phase 3 study evaluating the safety and efficacy of clazosentan in an enriched aSAH population to start later in 2018

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Idorsia Pharmaceuticals Japan

Jean-Paul Clozel, MD
CEO
Why launch our first affiliate in Japan

• Many drugs discovered and developed by Idorsia address important clinical needs in Japan, such as:
  – Fabry Disease
  – Resistant hypertension
  – Systematic Lupus Erythematosus

• Dr. Satoshi Tanaka Leadership: Built Actelion Japan and developed and launched 5 drugs on the Japanese market
“It is very frustrating to see our patients survive the initial trauma of the brain hemorrhage and seemingly make a recovery, only for the vasospasm to take hold and cause significant long-term damage.”

— Physician