Phase 3 investigation of aprocitentan for resistant hypertension management

Investor Webcast – June 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
Aprocitentan
Collaboration with Janssen Biotech, Inc.

• Janssen Biotech, Inc. and Idorsia are collaborating in respect of the development and commercialization of aprocitentan and any of its derivative compounds or products

• Idorsia has received a one-time milestone payment of USD 230 million

• Both parties will have joint development rights over aprocitentan, while Janssen Biotech, Inc will have the sole manufacturing and commercialization rights

• The development costs will be shared equally between both partners

• Idorsia will oversee Phase 3 development and regulatory submission for the first indication

• Janssen will oversee the Phase 3 development and submission for any additional indications

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Phase 3 investigation of aprocitentan for resistant hypertension management

Guy Braunstein
Head of Global Clinical Development
Hypertension as a cardiovascular risk factor

30% of adult population is hypertensive

20% of them are unaware of hypertension

Hypertension, or high blood pressure, remains the most frequent addressable risk factor of cardiovascular morbidity/mortality outcomes, ahead of smoking and obesity

Reported by the 2015 Global Burden of Disease, Injuries, and Risk Factor Project collaborating with WHO

The definition of hypertension was recently updated to be a persistently elevated blood pressure above 130/80 mm Hg

ACA/AHA Task Force on Clinical Practice Guidelines 2017
What is resistant hypertension?

**Definition**

**Resistant hypertension**
Patients whose blood pressure remains high, despite receiving at least three antihypertensive medications from different classes, including a diuretic, at maximal tolerated dose.

**Not resistant hypertension**
Pseudo-resistant hypertension due to:
- White coat effect
- Medical inertia
- Poor adherence to treatment
- Inappropriate blood pressure measurement
Treatable secondary hypertension.
Resistant hypertension
Clinical phenotypes

Typical characteristics of patients with resistant hypertension

High baseline blood pressure and chronicity of uncontrolled hypertension
Older age; especially > 75 years
Excessive dietary sodium
Target organ damage (left ventricular hypertrophy, chronic kidney disease)
Ethnicity (black)
Sex (women)
Aortic stiffening
Diabetes
Obesity
Atherosclerotic vascular disease

Poorer prognosis: higher incidence of major cardiovascular events

REACH Registry n = 53,530

Cumulative incidence (%)

Medication usage:
- Less than 3 Medications
- 3 Medications
- 4 Medications
- 5 or More Medications

Time Until CVD/MI/Stroke (Months)
Resistant hypertension
Therapeutic options

Current (2018) Medical Treatment Principles

Pharmacological therapy
• Check that each drug is used at the maximum tolerated level
• Optimize diuretic treatment
• Add antihypertensive drugs with different mechanism of action
  • Aldosterone receptor antagonist (PATHWAY 2) or B1-blockers if not contraindicated

Device-based therapy (need confirmation of their benefit)
• Renal denervation
• Baroreflex activation therapy

“There is an urgent public health need for additional therapies acting on pathways different from those currently used, in line with the underlying disease mechanism.”
Prof. John Chalmers, MD
Aprocitentan in resistant hypertension

Rationale

Endothelin (ET) System is involved in resistant hypertension

ET system is activated in hypertension and especially in salt-and volume-dependent hypertension.

Resistant hypertension is often a salt- and volume-dependent hypertension.

ET-1 increase is associated with most risk factors linked to resistant hypertension.

ET system may play a role in vascular remodeling, cardiac hypertrophy and the complications of resistant hypertension.
Aprocitentan in resistant hypertension

Rationale

- Potent dual ETA and ETB receptor antagonist
- Synergistic effect with other antihypertensive drugs (RAAS blockers) in animal models
- Demonstrated efficacy of aprocitentan on blood pressure, renal and cardiac protection in animal models of salt-dependent hypertension
- Low potential for drug-drug interaction
- Evidence of blockade of both receptors in vivo in humans
- Demonstrated blood pressure decrease in patients with essential hypertension

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Orally active
Aprocitentan in resistant hypertension

Clinical development

- Confirmation of dual ETA and ETB receptor blockade
- No dose adjustment in patients with any degree of renal impairment
- Low potential for drug-drug interaction

SPIRIT survey

- To characterize the RHT patient population
- To identify sites where these patients are managed

Clinical pharmacology

Phase 2 study

- Clinically relevant, dose-dependent lowering of blood pressure in essential hypertension patients
- Doses selected for further development

Phase 3 confirmatory study

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Phase 3 initiation for resistant hypertension management | June 2018
**Aprocitentan in resistant hypertension**

**Design**
Prospective, multi-center, double-blind, double-dummy, randomized, monotherapy, placebo- and active-reference, parallel group, Phase 2 dose-finding study in mild to moderate hypertension

**Patient population**
- Mild-to-moderate essential hypertension (Systolic BP/Diastolic BP ≥ 140/90 to < 180/110)
- Background medication stopped at screening
- Mean diastolic BP ≥ 90 to < 110 mmHg at randomization

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Phase 3 initiation for resistant hypertension management | June 2018
Aprocitentan in resistant hypertension

Aprocitentan dose-dependently decreases blood pressure

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Phase 2 study

Aprocitentan dose (mg)  
Lisinopril (mg)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Aprocitentan dose (mg)</th>
<th>Lisinopril (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10</td>
<td>25</td>
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<tr>
<td>20</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Mean change from baseline in SBP (mmHg)

Mean change from baseline in DBP (mmHg)

Diastolic Blood Pressure

Systolic Blood Pressure

Phase 3 initiation for resistant hypertension management | June 2018
### Safety results

#### Placebo

<table>
<thead>
<tr>
<th>N</th>
<th>Placebo</th>
<th>Aprocitentan</th>
<th>Lisinopril</th>
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<tbody>
<tr>
<td>82</td>
<td>82</td>
<td>82</td>
<td>80</td>
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</table>

#### Patients with at least one AE

<table>
<thead>
<tr>
<th>N</th>
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<th>Aprocitentan</th>
<th>Lisinopril</th>
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<tbody>
<tr>
<td>82</td>
<td>30 (37%)</td>
<td>18 (22%)</td>
<td>24 (29%)</td>
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</table>

#### Headache (12)

<table>
<thead>
<tr>
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<th>Aprocitentan</th>
<th>Lisinopril</th>
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<tbody>
<tr>
<td>82</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
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</table>

#### Nasopharyngitis (10)

<table>
<thead>
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<th>Aprocitentan</th>
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<tbody>
<tr>
<td>82</td>
<td>1</td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

#### Upper respiratory tract infection (9)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>82</td>
<td>1</td>
<td>0</td>
<td>4</td>
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#### Arthralgia (7)

<table>
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<tbody>
<tr>
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<td>2</td>
<td>0</td>
<td>1</td>
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#### Pain in extremity (5)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>82</td>
<td>1</td>
<td>1</td>
<td>0</td>
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</table>

#### Constipation (4)

<table>
<thead>
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<tbody>
<tr>
<td>82</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</table>

#### Hemoglobin decreased (4)

<table>
<thead>
<tr>
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<th>Lisinopril</th>
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<tbody>
<tr>
<td>82</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</table>

#### Edema peripheral (4)

<table>
<thead>
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<tbody>
<tr>
<td>82</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

#### Orthostatic hypotension (4)

<table>
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<tbody>
<tr>
<td>82</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</table>

#### AE leading to study treatment discontinuation

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<th>Lisinopril</th>
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<tbody>
<tr>
<td>82</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
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</table>

#### Patients with at least one SAE

<table>
<thead>
<tr>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>82</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

*AE = Averse Event; SAE = Serious Adverse Event*
Aprocitentan in resistant hypertension

Phase 2 conclusion

Efficacy ✓
- Dose response was consistent across all parameters measured
- Efficacy observed at 10 and 25 mg, with no additional effect at 50 mg
- The effect of aprocitentan covers the 24 h period

Safety ✓
(in the limit of the study design)
- well tolerated across all doses
- overall frequency of adverse events on aprocitentan was similar to placebo

Two doses selected for Phase 3
- 12.5 mg and 25 mg

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Phase 3 confirmatory study
Benefitting from consultation with regulatory agencies

PRECISION will assess the short-term efficacy of aprocitentan as well as the durability of the effect. It will provide replication of clinical evidence in a single study.

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Phase 3 confirmatory study

Study Design

RHT confirmation
Standardization
Stabilization

1 to 8 weeks
4 weeks
4 weeks

Screening
Screening
Run-in

Individual background antihypertensive medication
Standard background antihypertensive therapy
Stabilization on standardized medication

Part I
Part II
Part III

Efficacy and safety of aprocitentan

4 weeks
32 weeks
Withdrawal 12 weeks

Randomization
Re-Randomization
End of treatment
End of study

25 mg Aprocitentan
12.5 mg Aprocitentan
Placebo

25 mg Aprocitentan
25 mg Aprocitentan
Placebo

30 days

Safety Follow-up

Continue standard background therapy

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## Phase 3 confirmatory study

### Objectives

<table>
<thead>
<tr>
<th>Part I</th>
<th>Part II</th>
<th>Part III</th>
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<tbody>
<tr>
<td>• Double-blind treatment</td>
<td>• Single-blind treatment</td>
<td>• Double-blind, randomized, withdrawal treatment</td>
</tr>
<tr>
<td>• 12.5 mg aprocitentan or 25 mg aprocitentan or placebo</td>
<td>• 25 mg aprocitentan</td>
<td>• 25 mg aprocitentan or placebo</td>
</tr>
<tr>
<td>• Period of 4 weeks</td>
<td>• Period of 32 weeks</td>
<td>• Period of 12 weeks</td>
</tr>
<tr>
<td>• To demonstrate the blood pressure lowering effect of aprocitentan when added to standard-of-care in true resistant hypertension patients</td>
<td>• To evaluate long-term safety and tolerability of aprocitentan when added to standard-of-care in true resistant hypertension patients</td>
<td>• To demonstrate that the effect of aprocitentan on blood pressure is durable when added to standard-of-care in true resistant hypertension patients</td>
</tr>
</tbody>
</table>

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Phase 3 confirmatory study

Patient population: True resistant hypertension patients on standardized triple therapy

Mean systolic blood pressure ≥ 140 mmHg (measured by unattended automated office blood pressure measurement - AOBPM), despite a background antihypertensive medication of at least 3 different pharmacological classes (including a diuretic)

Confirmed diagnosis of resistant hypertension, mean blood pressure ≥ 140 mmHg by AOBPM, who are on standardized background medication therapy for at least 4 weeks

Standardized therapy
- Calcium channel blocker, amlodipine
- Angiotensin receptor blocker, valsartan
- Diuretic, hydrochlorothiazide

Mean systolic blood pressure ≥ 140 mmHg by AOBPM, despite stable standardized therapy

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Phase 3 confirmatory study

Study endpoints

Primary endpoint
• Change from baseline to week 4 of double-blind treatment in mean trough sitting systolic blood pressure by AOBPM

Key secondary endpoint
• Change from week 36 (start of withdrawal period) to week 40 in mean trough sitting systolic blood pressure by AOBPM

Other important endpoints
• Other clinically important blood pressure parameters at week 4 and week 40
  • Diastolic blood pressure by AOBPM
  • Systolic and diastolic blood pressure by 24-hr ambulatory blood pressure monitoring
• Safety assessments
• Pharmacokinetic assessment

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Aprocitentan has great potential in difficult to control hypertension – **resistant hypertension** – as an oral, once daily treatment based on:

- Pathophysiology of resistant hypertension
- Mode of action of aprocitentan
- Efficacy in essential hypertension (Phase 2)

We are collaborating with **Janssen Biotech** to jointly develop and commercialize aprocitentan

**Phase 3 study** ongoing to evaluate initial and long-term effects of aprocitentan on systolic and diastolic blood pressure in patients requiring resistant hypertension management

**This registration** program has benefitted from inputs from health authorities, in particular the US FDA
“Despite hypertension being a serious and growing problem around the world, there is surprisingly little research going on in the field.

It has been over 30 years since an anti-hypertensive drug working via a new pathway has been brought to the market.”

– Physician