Idorsia – Reaching out for more
The following information contains certain “forward-looking statements”, relating to the company’s business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “are expected to”, “will”, “will continue”, “should”, “would be”, “seeks”, “pending” or “anticipates” or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company’s investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company’s existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.
15 June 2017
The purpose of Idorsia is to discover, develop and commercialize innovative medicines to help more patients.

We have more ideas, we see more opportunities and we want to transform the horizon of therapeutic options.
Ponesimod approved in the US and EU.

Highlights:

- Phase 3 studies with lucerastat and aprocitentan fully recruited.

Daridorexant NDA / MAA submitted to US FDA, EMA, Swissmedic.

- Phase 2b study with cenerimod recruitment concluded.

Clazosentan NDA submitted to PMDA.

- Phase 3 study with selatogrel initiated.
Idorsia Today

>1,000
Highly qualified professionals

11
Compounds in the pipeline, with six in late-stage development

Commercial Presence
established in US and underway in markets around the world

> 550
State-of-the-art laboratory workspaces

Strong
balance sheet

> 550
State-of-the-art laboratory workspaces
Our Strategic Priorities

Our mid-term key priorities to achieve long-term success:

1. Deliver at least three products to market
2. Build a world-class commercial organization
3. Bring Idorsia to sustainable profitability
4. Fuel our pipeline with new discoveries
5. Utilize state-of-the-art technologies to drive innovation
**Clinical development pipeline**

**Systemic lupus erythematosus**
- Cenerimod
  - S1P1 receptor modulator
  - Status: Phase 2b recruitment complete

**Suspected acute myocardial infarction**
- Selatogrel
  - P2Y12 receptor antagonist
  - Status: Phase 3 recruitment complete

**Resistant hypertension management**
- Aprocitentan*
  - Dual endothelin receptor antagonist
  - Status: Phase 3 recruitment complete

**Fabry disease**
- Lucerastat
  - Glucosylceramide synthase inhibitor
  - Status: Phase 3 complete – 1st endpoint not met

**Rare lysosomal storage disorders**
- Sinbaglustat
  - GBA2/GCS inhibitor
  - Status: Phase 1 complete

**Binge eating disorder**
- ACT-539313
  - Selective orexin 1 receptor antagonist
  - Status: Phase 2

**Insomnia**
- Daridorexant
  - Dual orexin receptor antagonist
  - Status: Under review with health authorities

**Cerebral vasospasm associated with aSAH**
- Clazosentan
  - Selective endothelin (ETA) receptor antagonist
  - Status Global: Phase 3
  - Status Japan: NDA submitted

**Resistant hypertension management**
- Aprocitentan*
  - Dual endothelin receptor antagonist
  - Status: Phase 3 recruitment complete

**Immunoology**
- ACT-1004-1239
  - CXCR7 antagonist
  - Status: Phase 1

**Immunology**
- ACT-1014-6470
  - Status: Phase 1

**Rare pediatric epilepsy**
- ACT-709478
  - Novel T-type calcium channel blocker
  - Status: Phase 2

* In collaboration with Janssen Biotech, Inc.

Neurocrine Biosciences has a global license to develop and commercialize Idorsia’s ACT-709478.
Idorsia is at an inflection point with major catalysts expected in the near-term

- **Daridorexant**
  - **FILING:** US FDA followed by EMA
  - **INITIATION:** Phase 3 “SOS-AMI”
  - **RESULTS:** Phase 3 “MODIFY”

- **Clazosentan**
  - **FILING:** Japan
  - **RESULTS:** Phase 2b “CARE”

- **Cenerimod**
  - **RESULTS:** Phase 2b “CARE”

- **Lucerastat**
  - **RESULTS:** Phase 3 “MODIFY-OLE”

- **Selatogrel**
  - **INITIATION:** Phase 3 “SOS-AMI”

- **Daridorexant**
  - **APPROVAL & commercial LAUNCH**

- **Clazosentan**
  - **APPROVAL & commercial LAUNCH in JAPAN**

- **Aprocitentan**
  - **RESULTS:** Phase 3 “PRECISION”

- **Clazosentan**
  - **APPROVAL & commercial LAUNCH in JAPAN**
Idorsia revenues in the future

Net sales
- **Primary Care:** daridorexant
- **Orphan:** lucerastat, clazosentan
- **Specialty:** cenerimod, selatogrel

Milestones & Royalty streams
- ponesimod
- aprocitentan
- T-type calcium channel blocker

Rich pipeline allows substantial leverage of the commercial organization
Idorsia's first revenue stream

**Ponvory™** (ponesimod) to treat adults with **relapsing forms of multiple sclerosis (MS)**

- **US FDA approved Ponvory™ in March 2021**
- **European Commission (EC) approved Ponvory™ in May 2021**

**Phase 3 data presented by Janssen**
Ponesimod showed **superiority versus Aubagio** (teriflunomide) 14 mg in adults with relapsing multiple sclerosis

**Revenue sharing agreement**
Idorsia is entitled to receive **8% of the net sales** of ponesimod

- Ponesimod is an investigational highly-selective **phingosine-1-phosphate receptor 1 (S1P₁) modulator** that functionally inhibits S1P receptor activity
- Reduces the number of circulating lymphocytes that can cross the blood-brain barrier
- MS is a chronic autoimmune inflammatory disease of the CNS affecting **2.3 million** people worldwide\(^1\)

\(^1\) National Multiple Sclerosis Society

\(^\n\) This medicinal product is subject to additional monitoring.
Find a comprehensive description of our pipeline assets as follows:

1. Daridorexant  
2. Lucerastat  
3. Aprocitentan  
4. Clazosentan  
5. Selatogrel  
6. Cenerimod  
7. ACT-539313  
8. Other

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Slide 192
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Daridorexant in insomnia

Daridorexant is investigational, in development and not approved or marketed in any country.
High unmet need for effective, safe medications to treat insomnia

Insomnia: A disease of the night and the day

- Estimated approximately 20 million (10\%\textsuperscript{1}) adults in the US suffer from chronic insomnia
- Insomnia has a significant impact on patients’ productivity, quality of life and long-term health outcomes
- Existing therapies typically improve either sleep onset or maintenance, have not demonstrated benefit on daytime performance and can be associated with adverse events

\textsuperscript{1} Morin CM, et al. Insomnia disorder. Nat Rev Dis Primers 2015;1:15026
Who gets insomnia and what is the impact?

Insomnia is a common problem

Risk factors
• Age (more common with ageing)
• Gender (women > men)
• Lower socio-economic status
• Physical disorder
• Psychiatric disorder (depression, anxiety, alcohol and drug abuse)

Impact
• Physically and mentally fatigued, anxious and irritable
• Increased the risk of malaise, fall, accidents, and injury
• Impaired daytime functioning
• Decreased memory and concentration, cognitive decline
• Leading cause of absenteeism and reduced productivity, burden to society
• Higher rate of mortality
How is insomnia treated, what are the limitations?

Sleep hygiene
- Active patient participation required

Cognitive behavioral therapy
- Recommended first-line therapy but inconsistently practiced
  - Not easily accessible
  - Often not reimbursed
  - Active patient participation required

Pharmacological therapy
- Many have significant limitations
  - Insufficient acute effect: lack of sustained effect through the night
  - Insufficient long-term effect: lack of continued benefit over time
  - Next morning residual effect
  - Abuse potential, withdrawal effect, and rebound
  - May have significant adverse effects
The orexin system is crucial for the regulation of wakefulness

Orexin stimulates many wake-promoting pathways

- LHA / PH: Orexin
- LC: OX₁R
- TMN: OX₂R
- Raphe: OX₁R and OX₂R
- LTD / PPT: OX₁R and OX₂R
- VTA: OX₁R and OX₂R

LHA = lateral hypothalamic area; PH = posterior hypothalamus
LC = locus coeruleus; TMN = tuberomammillary nucleus; LDT = laterodorsal tegmental nucleus; VTA = ventral tegmental area; PPT = pedunculopontine nucleus

Sakurai, T. 2007
Daridorexant in insomnia

Rationale

• There remains a need for effective and safe treatments for insomnia

• Accumulating evidence for the role of the orexin (OX) system to regulate wake drive has led to the development of new treatments for insomnia disorder that inhibit OX signaling

Daridorexant

• a potent and selective dual orexin receptor antagonist (DORA)

• selected to promote sleep onset and sleep maintenance, without impairing the next day
Daridorexant optimization process

>25,000 compounds synthesized in the orexin program in 7 years

Targets  Hits

300,000 – 400,000 compounds

1361  263  83  12

Improved Leads

Drug Candidate

Daridorexant

Optimized duration of action (rapid onset, efficacy through the night, no next-day hangover)

Human pharmacokinetic and pharmacodynamic prediction

Potent dual OX1 and OX2 receptor blockade in vitro

No major drug-drug interaction

High brain penetration

High affinity in receptor binding and functional assays

In vitro cytochrome P450 profile

Physicochemical properties and confirmation in vivo

Optimal in vivo efficacy

In vivo efficacy tested in rats and dogs

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

Preclinical → healthy subjects → patients

Desired profile

High *in vitro* potency

→ *in vivo* efficacy

Quick absorption and short half-life

→ fast onset of action, “appropriate” duration of action to act throughout the night, and to avoid next morning residual effect

Safety is key

• No deterioration of next-day functioning
• No rebound, no withdrawal symptoms upon treatment cessation
• No safety concerns
Clinical development

- Single and multiple ascending dose
- Adults and elderly subjects
- Night time administration
- Pharmacokinetic and pharmacodynamic characterization

Phase 2 studies

- Two studies, in adults and elderly patients with insomnia
- All information required to design confirmatory pivotal studies

Entry into man studies

Today

Clinical pharmacology program

Phase 3 confirmatory studies
Different by design – next generation DORA

Optimized pharmacokinetic profile

Plasma concentrations (ng/ml)

- Fast absorption
- Optimal half-life (8 h)
- No accumulation over time
- No active metabolites

Daridorexant is investigational, in development and not approved or marketed in any country.
Fast and time limited pharmacodynamic effect

25 mg

Speed of eye movements (degree/sec)

0 2 4 6 8 10 12

Time (h)

Adult Healthy Volunteer – Daytime dosing

Elderly Healthy Volunteer – Daytime dosing

Person performing eye movement test

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

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No pharmacodynamic effect on next morning

Karolinska Sleepiness Scale Score

- 9: Very sleepy
- 8: Sleepy, but no effort keeping awake
- 7: Neither alert nor sleepy
- 6: Alert, normal level
- 5: Very alert

Time after first dose (h) – measures 8 hours after dosing

Placebo

25 mg

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

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Phase 2 studies – Purpose and objectives

**Purpose**
To provide necessary information to adequately design the confirmatory trials

**Objectives**
To characterize the dose response on objective and subjective sleep parameters
To document the safety profile including adverse events, residual effect, rebound and withdrawal

**Focus in particular**
- Dose definition
- Patient population characterization
- Endpoint definition
Two Phase 2 studies completed

**Adult study: classical parallel group design**
- 4-week treatment to assess durability of effect
- Short treatment withdrawal at the end
- 4 dose levels (5 mg, 10 mg, 25 mg and 50 mg)
- Placebo and active arms (zolpidem)
- Objective and subjective sleep parameters

**Elderly study: cross over design**
- 2-night treatment
- 4 dose levels identical to adults
- Placebo-controlled
- Objective and subjective parameters

**In both studies, well-characterized insomnia patients**

<table>
<thead>
<tr>
<th></th>
<th>Self-reported insomnia at entry</th>
<th>Confirmed by polysomnography at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep induction</strong></td>
<td>≥ 30 minutes to fall asleep</td>
<td>Mean LPS ≥ 20 min</td>
</tr>
<tr>
<td><strong>Sleep maintenance</strong></td>
<td>Wake time during sleep ≥ 30 minutes</td>
<td>Mean WASO ≥ 30 min</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>Total sleep time ≤ 6.5 h</td>
<td>Mean TST &lt; 420 minutes</td>
</tr>
</tbody>
</table>
Adult study design

On treatment double blind (2 nights)

Randomization

Screening period

Run-in period

PSG measurements
Sleep diary

14–28 days

29 days

30 days

Screening
Double-blind treatment
Safety follow-up

Zolpidem 10 mg
Placebo
Daridorexant 5 mg
Daridorexant 10 mg
Daridorexant 25 mg
Daridorexant 50 mg

Daridorexant is investigational, in development and not approved or marketed in any country.
Adult study patient disposition

- **1005 screened**
- **360 randomized** (359 treated)
- **344 completed treatment**

**Entry**

- **664 enrolled in placebo PSG run-in**
  - 36%

**Sleep diary**
Subjective confirmation of chronic insomnia

**Polysomnography**
Objective confirmation of chronic insomnia

Daridorexant is investigational, in development and not approved or marketed in any country.
Demographics and baseline characteristics

**Adult study (N = 359)**

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>230 (64)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>321 (89)</td>
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</table>

<table>
<thead>
<tr>
<th>Baseline sleep parameters</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASO, min</td>
<td>97.5 (38.6)</td>
</tr>
<tr>
<td>LPS, min</td>
<td>71.8 (39.3)</td>
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<tr>
<td>TST, min</td>
<td>318.5 (56.6)</td>
</tr>
<tr>
<td>sWASO, min</td>
<td>80.4 (43.0)</td>
</tr>
<tr>
<td>sLSO, min</td>
<td>55.9 (27.1)</td>
</tr>
<tr>
<td>sTST, min</td>
<td>316.8 (52.6)</td>
</tr>
<tr>
<td>KSS</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>ISI©</td>
<td>21.2 (2.8)</td>
</tr>
</tbody>
</table>

This study was conducted at 38 sites in six countries (Germany, Hungary, Israel, Spain, Sweden, and the United States) at hospitals and sleep centers.

BMI, body mass index; ISI©, insomnia severity index©; KSS, Karolinska sleepiness scale; LPS, latency to persistent sleep; SD, standard deviation; sLSO, subjective latency to sleep onset; sTST, self-reported TST; sWASO, subjective WASO; WASO, wake after sleep onset.
Wake after sleep onset (WASO)

Adult study

Data shown as mean (SE)

Phase 2 studies

Daridorexant dose (mg)

Placebo 5 10 25 50 Zolpidem 10 mg

P<0.001

P=0.050

Change from baseline in WASO (min)

Days 1 & 2

Days 28 & 29

Daridorexant is investigational, in development and not approved or marketed in any country.
Latency to persistent sleep (LPS)

Adult study

Data shown as mean (SE)

Phase 2 studies

Change from baseline in LPS (min)

P<0.001

P=0.042

Days 1 & 2

Days 28 & 29

Data shown as mean (SE)
Subjective WASO & LSO
Adult study

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

Data shown as mean (SE)
Total sleep time (TST) & subjective TST

Adult study

Data shown as mean (SE)

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

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Normal sleep architecture preserved

Adult study

<table>
<thead>
<tr>
<th>Dose</th>
<th>S1</th>
<th>S2</th>
<th>SWS</th>
<th>REM</th>
<th>Total Sleep Time (min)</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10.7</td>
<td>57.4</td>
<td>12.6</td>
<td>19.3</td>
<td>357</td>
</tr>
<tr>
<td>5 mg daridorexant</td>
<td>10</td>
<td>55.1</td>
<td>15</td>
<td>19.9</td>
<td>371</td>
</tr>
<tr>
<td>10 mg daridorexant</td>
<td>10.7</td>
<td>56.8</td>
<td>12.5</td>
<td>20</td>
<td>384</td>
</tr>
<tr>
<td>25 mg daridorexant</td>
<td>9.8</td>
<td>55.4</td>
<td>12.5</td>
<td>22.3</td>
<td>387</td>
</tr>
<tr>
<td>50 mg daridorexant</td>
<td>10</td>
<td>56.2</td>
<td>13</td>
<td>20.8</td>
<td>403</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>9.8</td>
<td>57.9</td>
<td>15.4</td>
<td>16.9</td>
<td>388</td>
</tr>
</tbody>
</table>

Duration as % of Total Sleep Time (TST)

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

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Adult study

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=60)</th>
<th>5 mg (n=60)</th>
<th>10 mg (n=58)</th>
<th>25 mg (n=60)</th>
<th>50 mg (n=61)</th>
<th>Zolpidem 10 mg (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with ≥1 TEAE</td>
<td>18</td>
<td>21</td>
<td>22</td>
<td>23</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Anxiety</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal pain</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tooth infection</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Participants with ≥1 serious AE</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Participants with ≥1 AE of special interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Treatment with daridorexant was well tolerated
- There was no evidence of rebound insomnia or withdrawal syndrome

Daridorexant is investigational, in development and not approved or marketed in any country.
Karolinska sleepiness scale (morning assessment)

Adult study

*9-point scale; 5 = Neither alert nor sleepy
Lower scores indicate less sleepiness

Mean KSS score (±SD)*

Extremely sleepy, fighting sleep

Extremely alert

Daridorexant dose (mg)

Baseline
Days 1 & 2
Days 15 & 16
Days 28 & 29

Placebo 5 10 25 50 zolpidem

*9-point scale; 5 = Neither alert nor sleepy
Lower scores indicate less sleepiness

Daridorexant is investigational, in development and not approved or marketed in any country.
Elderly study design

Screening period

Placebo nights

Randomization

Treating periods

1 2 3 4 5

Washout

Washout

Washout

Washout

Screening

Double-blind treatment

Safety follow-up

Daridorexant is investigational, in development and not approved or marketed in any country.
Elderly study patient disposition

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

Entry

149 screened

39%

101 enrolled in placebo PSG run-in

Sleep diary
Subjective confirmation of chronic insomnia

58 randomized

Polysomnography
Objective confirmation of chronic insomnia

54 completed treatment
Demographics and baseline characteristics

Elderly study (N = 58)

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>69</td>
<td>(65-85)</td>
</tr>
<tr>
<td>Sex, n (%) – Male</td>
<td>19</td>
<td>(33)</td>
</tr>
<tr>
<td>– Female</td>
<td>39</td>
<td>(67)</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>25.8</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Race, n(%) – White</td>
<td>54</td>
<td>(93)</td>
</tr>
<tr>
<td>– Black or African American</td>
<td>3</td>
<td>(5)</td>
</tr>
<tr>
<td>– American Indian or Alaska Native</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Baseline sleep parameters Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WASO, min</td>
<td>116.9</td>
<td>(40.2)</td>
</tr>
<tr>
<td>LPS, min</td>
<td>75.1</td>
<td>(50.0)</td>
</tr>
<tr>
<td>TST, min</td>
<td>295.8</td>
<td>(57.6)</td>
</tr>
<tr>
<td>sWASO, min</td>
<td>99.6</td>
<td>(65.7)</td>
</tr>
<tr>
<td>sLSO, min</td>
<td>65.7</td>
<td>(43.2)</td>
</tr>
<tr>
<td>sTST, min</td>
<td>301.7</td>
<td>(64.5)</td>
</tr>
<tr>
<td>KSS</td>
<td>5.1</td>
<td>(1.8)</td>
</tr>
<tr>
<td>ISI©</td>
<td>20.5</td>
<td>(3.0)</td>
</tr>
</tbody>
</table>

BMI, body mass index; ISI©, insomnia severity index©; KSS, Karolinska sleepiness scale; LPS, latency to persistent sleep; SD, standard deviation; sLSO, subjective latency to sleep onset; sTST, self-reported TST; sWASO, subjective WASO; WASO, wake after sleep onset.

Daridorexant is investigational, in development and not approved or marketed in any country.
Wake after sleep onset (WASO)

Elderly study

Change from baseline in WASO (min)

Dots: LS Mean changes from baseline; bars: 95% CIs; dotted line = 95% CI of curve

Daridorexant dose (mg)

Placebo 5 10 25 50

0 10 20 30 40 50 60 70

p < 0.001

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

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WASO by quarter of the night

Elderly study

Dose-dependent effects were observed for WASO throughout the night.

Change from baseline in WASO (min)

Data shown as mean (SE)

Phase 2 studies

1st Quarter
2nd Quarter
3rd Quarter
4th Quarter

Placebo
Daridorexant 5 mg
Daridorexant 10 mg
Daridorexant 25 mg
Daridorexant 50 mg

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Latency to persistent sleep (LPS)

Elderly study

Dots: LSMean changes from baseline; bars: 95% CIs; dotted line = 95% CI of curve

Change from baseline in LPS (min)

p = 0.004

Placebo 5 10 25 50

Daridorexant dose (mg)
Subjective WASO & LSO

Elderly study

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Phase 2 studies

Mean change from baseline (min, 95% CI)

-20
-30
-40
0
20

sWASO
Baseline mean (overall) = 99.6 min

Placebo 5 10 25 50

Daridorexant dose (mg)

-60
-40
-20
0
20

sLSO
Baseline mean (overall) = 65.7 min

Placebo 5 10 25 50

Daridorexant dose (mg)
Total sleep time (TST) & subjective TST

Elderly study

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

Phase 2 studies

Mean change from baseline (min, 95% CI)

**TST**
Baseline mean (overall) = 295.8 min

**sTST**
Baseline mean (overall) = 301.7 min
Safety results

Elderly study

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

<table>
<thead>
<tr>
<th>n, (%)</th>
<th>SB-Placebo (N=58)</th>
<th>Placebo (N=54)</th>
<th>5 mg (N=56)</th>
<th>10 mg (N=54)</th>
<th>25 mg (N=55)</th>
<th>50 mg (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with ≥1 adverse event</td>
<td>6</td>
<td>8</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Adverse event for ≥2 participants in any dose group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

- No SAE, no deaths
- No narcolepsy-like events
- No suicidal ideation
- No complex sleep behaviors
- Four participants discontinued due to adverse events
Karolinska sleepiness score (morning assessment)

Elderly study

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

9-point scale:
5 = Neither alert nor sleepy. Lower score indicates improvement.

Mean KSS score (SD)

- Extremely sleepy, fighting sleep
- Extremely alert

Baseline
Next morning after treatment

Phase 2 studies

Daridorexant dose (mg)

Placebo 5 10 25 50
Phase 2 conclusion

Efficacy ✅
• Daridorexant dose-dependently improved sleep onset, sleep maintenance, and total sleep time in adult and elderly chronic insomnia patients

Safety ✅
(in the limit of the study design)
• No sign of rebound or withdrawal symptoms
• No clinically relevant next morning hang-over effect
• Good safety and tolerability in both age groups at all dose levels

Three doses selected for Phase 3 in both age groups ✅
• 10 mg, 25 mg and 50 mg

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Daridorexant registration program

Robust program in adult and elderly insomnia patients

Following completion of Phase 2 studies, two similar pivotal studies of 3-month duration in moderate and severe insomnia

Efficacy

- Objective and subject sleep parameters (onset and maintenance) by polysomnography (PSG) and sleep diary questionnaire (SDQ)
- Daytime functioning assessed by insomnia daytime symptoms and impact questionnaire (IDSIQ)
- Replicated in two confirmatory studies

Safety

- Adverse events, vital signs, biochemistry and hematology
- Next morning residual “hang-over” effect
- Withdrawal/physical dependence, and rebound insomnia

Comprehensive clinical pharmacology program including:

- Driving performance, interaction (medicines, alcohol), Safety in specific population (COPD, obstructive sleep apnea, liver and renal impairment), drug abuse potential

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Phase 3 program overview

- **Design**
  - 3 double-blind, randomized, placebo-controlled, multicenter international studies

- **Doses**
  - **301**: placebo, 25 mg & 50 mg
  - **302**: placebo, 10 mg & 25 mg
  - **303**: placebo, 10 mg, 25 mg, and 50 mg

- **Duration**
  - 3-month treatment in main studies, 301 & 302, and 9-month in extension study, 303

- **Sample size** (combined adult and elderly)
  - 900 patients/study
  - Extension study: All subjects who complete either 301 or 302
Study design

**Screening 20-31 days**
- Single-blind placebo run-in

**Treatment Period 84 days**
- Placebo or 25 mg or 10 mg daridorexant
- Double-blind

**Safety Follow-up 30 days**
- Single-blind placebo run-out

**V** = site visit
- **V1** = 1 polysomnography night
- **V2** = 2 consecutive polysomnography nights
- **V3** = 1 polysomnography night
- **V4** = 2 consecutive polysomnography nights
- **V5** = 1 polysomnography night
- **V6** = 2 consecutive polysomnography nights
- **V7** = 1 polysomnography night
- **V8** = 2 consecutive polysomnography nights
- **V9** = 1 polysomnography night
- **V10** = 2 consecutive polysomnography nights
- **V11** = 1 polysomnography night

**Daily assessment of sleep and daytime functioning**

**EODBT** = End of double-blind treatment
- **EOT** = End-of-Treatment
- **EOS** = End-of-Study
- **HD** = High dose
- **LD** = Low dose

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Phase 3 extension – Study Design

Screening

- Randomization
  - V1

Treatment Period 40 weeks

- Week 2
  - V2
- Week 13
  - V3
- Week 26
  - V4

Run out period

Safety Follow up 30 days

- Week 40
  - EODBT, V5
- Week 41
  - EOT, V6
- Week 44
  - EOS, V7

Placebo

10 mg daridorexant
25 mg daridorexant
50 mg daridorexant

Patients assigned to any daridorexant arms in the confirmatory studies will receive the same dose.
Patients assigned to placebo in the confirmatory studies will be randomized to receive either placebo or 25 mg daridorexant in a 1:1 ratio.

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Key assessments

Objective measures of night parameters by polysomnography (PSG) in the sleep lab

Subjective measures of night parameters by the sleep diary questionnaire (SDQ)

Assessment of impact of insomnia during the day by the insomnia daytime symptoms and impact questionnaire (IDSIQ)

Objective sleep assessment

Patient’s oriented outcome daily recorded

Phase 3 program

Daridorexant is investigational, in development and not approved or marketed in any country.
Objective sleep assessments
Repeated polysomnography recordings in a sleep lab in all patients

- Assess insomnia objectively
- Ensure well-characterized insomnia patients are randomized
- Establish solid baseline during placebo run-in
- Measure primary endpoint at Month 1 and Month 3
  - Latency to persistent sleep
  - Wakening after sleep onset
- Assess the potential for rebound
- Collect comprehensive information on total sleep time and sleep architecture

Sensors measure brain activity, eye movements, muscle tone, respiratory, and heart parameters.

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Sleep diary questionnaire (SDQ)

Daily recording

**Morning questionnaire**
- 10 questions related to medication, quantification of sleep, awakenings
- 3 visual analog scales related to quality and deepness of sleep and feeling in the morning

**Evening questionnaire**
- 2 questions related to napping
- 2 visual analog scales related to alertness and ability to perform

**Total sleep time**
Secondary endpoint

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Subjective assessment of daytime functioning

Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) validated according to FDA guidelines

**Measures**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clear-Headed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Concentrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Forgetful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Worried</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Frustrated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Irritable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Stressed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Energetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Effort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Refreshed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Mentally Tired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Physically Tired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Sleepy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Awake</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Alert/cognition” domain score (0-60)

“Mood” domain score (0-40)

“Sleepiness” domain score (0-40)

Daytime functioning measured by sleepiness domain score

Secondary endpoint

Items are ranked on a numeric rating scale from 0-10

11. How **mentally tired** did you feel today?

Not at all mentally tired

Very mentally tired

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Primary objective
• To evaluate the efficacy of daridorexant on objective sleep parameters in patients with insomnia.

Secondary objective
• To evaluate the efficacy of daridorexant on subjective sleep parameters and daytime functioning in patients with insomnia.

Safety objective
• To assess the safety and tolerability of daridorexant in patients with insomnia during treatment and upon treatment discontinuation.
Primary and secondary endpoints
Study-wise type 1 error controlled at 0.05 (across 16 comparisons to placebo)

Primary endpoints (night)
- Wakening after sleep onset by PSG
- Latency to persistent sleep by PSG

Secondary endpoints (night and day patients’ feeling)
- Subjective total sleep time by SDQ
- Sleepiness score during the day by IDSIQ

Two dose levels
- High dose vs. placebo
- Low dose vs. placebo

Two assessment time points
- Month 1
- Month 3

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Statistical design and hypothesis testing

\[ \alpha \div 2 \quad \alpha = 0.05 \quad \alpha \div 2 \]

- **H1** WASO
- **H2** LPS
- **H3** sTST
- **H4** IDSIQ
- **H5** WASO
- **H6** LPS
- **H7** sTST
- **H8** IDSIQ
- **H9** WASO
- **H10** LPS
- **H11** sTST
- **H12** IDSIQ
- **H13** WASO
- **H14** LPS
- **H15** sTST
- **H16** IDSIQ

**High dose vs placebo**
- Month 1: **H1** WASO, **H3** sTST, **H5** WASO, **H7** sTST, **H9** WASO, **H13** WASO
- Month 3: **H7** sTST, **H8** IDSIQ, **H11** sTST, **H15** sTST

**Low dose vs placebo**
- Month 1: **H2** LPS, **H4** IDSIQ, **H6** LPS, **H12** IDSIQ, **H10** LPS
- Month 3: **H14** LPS, **H15** sTST, **H16** IDSIQ

Carried forward to **H9 / H10**: **H3** sTST, **H4** IDSIQ, **H7** sTST, **H8** IDSIQ

---

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Baseline characteristics

<table>
<thead>
<tr>
<th>Well-characterized moderate and severe insomnia patients</th>
<th>Self-reported insomnia at entry</th>
<th>Confirmed by polysomnography at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep induction</strong></td>
<td>≥ 30 minutes to fall asleep</td>
<td>Mean LPS ≥ 20 min</td>
</tr>
<tr>
<td><strong>Sleep maintenance</strong></td>
<td>Wake time during sleep ≥ 30 minutes</td>
<td>Mean WASO ≥ 30 min</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>Total sleep time ≤ 6.5 h</td>
<td>Mean TST &lt; 420 minutes</td>
</tr>
</tbody>
</table>
Study patient disposition

1st study entry

3326 screened

placebo run-in

930 randomized

853 completed treatment

847 completed placebo run-out

2nd study entry

3683 screened

placebo run-in

924 randomized

856 completed treatment

837 completed placebo run-out

Sleep diary & polysomnography
Subjective & objective confirmation of chronic insomnia

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### Demographic characteristics

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>1st pivotal study</th>
<th>2nd pivotal study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>930</td>
<td>924</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>624 (67.1)</td>
<td>638 (69.0)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>55.4 (15.3)</td>
<td>56.7 (14.2)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>39.5%</td>
<td>45.0%</td>
</tr>
<tr>
<td>25 – ≤ 30</td>
<td>41.7%</td>
<td>38.2%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>18.8%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Median time from diagnosis, years</td>
<td>7.1</td>
<td>8.1</td>
</tr>
</tbody>
</table>

The first study was conducted at 75 hospitals and sleep centers in 10 countries (Germany, Australia, Canada, Denmark, Italy, Poland, Serbia, Spain, Switzerland and the United States).

The second study was conducted at 61 hospitals and sleep centers in 11 countries (Germany, United States, Belgium, Bulgaria, Canada, Czech Republic, Finland, France, Hungary, South Korea, Sweden).

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BMI, body mass index; LPS, latency to persistent sleep; SD, standard deviation; TST, Total Sleep Time; WASO, wake after sleep onset

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Objective sleep parameters
At 25 mg vs. placebo: highly consistent effect with that of the first pivotal study

The studies demonstrated the efficacy of daridorexant in **objective sleep parameters**

<table>
<thead>
<tr>
<th>1st pivotal study</th>
<th>50 mg vs placebo</th>
<th>25 mg vs placebo</th>
<th>2nd pivotal study</th>
<th>25 mg vs placebo</th>
<th>10 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 1 month</strong></td>
<td>LPS</td>
<td>significant improvement</td>
<td>significant improvement</td>
<td>LPS</td>
<td>numerical improvement*</td>
</tr>
<tr>
<td>WASO</td>
<td>significant improvement</td>
<td>significant improvement</td>
<td>WASO</td>
<td>significant improvement</td>
<td>numerical improvement</td>
</tr>
<tr>
<td><strong>At 3 months</strong></td>
<td>LPS</td>
<td>significant improvement</td>
<td>significant improvement</td>
<td>LPS</td>
<td>numerical improvement*</td>
</tr>
<tr>
<td>WASO</td>
<td>significant improvement</td>
<td>significant improvement</td>
<td>WASO</td>
<td>significant improvement</td>
<td>numerical improvement</td>
</tr>
</tbody>
</table>

* almost reaching significant improvement

The effect observed at 1 month was **sustained** at 3 months

Daridorexant is investigational, in development and not approved or marketed in any country.
Subjective sleep parameters
SDQ

The studies demonstrated the efficacy of daridorexant in increasing patient’s assessed total sleep time

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Month</th>
<th>sTST</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st pivotal</td>
<td>50 mg vs</td>
<td>1</td>
<td>significant</td>
<td>improvement</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg vs</td>
<td>1</td>
<td>significant</td>
<td>improvement</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>significant</td>
<td>improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd pivotal</td>
<td>25 mg vs</td>
<td>1</td>
<td>significant</td>
<td>improvement</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg vs</td>
<td>1</td>
<td>numerical</td>
<td>improvement</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>significant</td>
<td>improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The effect observed at 1 month was sustained at 3 months.
Daytime functioning
IDSIQ sleepiness domain

Daridorexant 50 mg showed statistical improvement of patient’s daytime functioning

<table>
<thead>
<tr>
<th></th>
<th>50 mg vs placebo</th>
<th>25 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st pivotal study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>IDSIQ</td>
<td>numerical</td>
</tr>
<tr>
<td></td>
<td><strong>significant</strong></td>
<td><strong>improvement</strong></td>
</tr>
<tr>
<td>At 3 months</td>
<td>IDSIQ</td>
<td>numerical</td>
</tr>
<tr>
<td></td>
<td><strong>significant</strong></td>
<td><strong>improvement</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>25 mg vs placebo</th>
<th>10 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2nd pivotal study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>IDSIQ</td>
<td>numerical</td>
</tr>
<tr>
<td></td>
<td>numerical</td>
<td></td>
</tr>
<tr>
<td>At 3 months</td>
<td>IDSIQ</td>
<td>numerical</td>
</tr>
<tr>
<td></td>
<td>numerical</td>
<td></td>
</tr>
</tbody>
</table>

The effect observed at 1 month was **sustained** at 3 months

Daridorexant is investigational, in development and not approved or marketed in any country.
# Overview of treatment emergent adverse events

<table>
<thead>
<tr>
<th>Subjects with at least one event</th>
<th>1st pivotal study</th>
<th>2nd pivotal study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daridorexant</td>
<td>Placebo</td>
</tr>
<tr>
<td>AE during the double-blind study period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>50 mg n = 308</td>
<td>25 mg n = 310</td>
</tr>
<tr>
<td></td>
<td>116 (37.7)</td>
<td>117 (37.7)</td>
</tr>
<tr>
<td>AEs leading to premature discontinuation of double-blind study treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>50 mg n = 308</td>
<td>25 mg n = 308</td>
</tr>
<tr>
<td></td>
<td>3 (1.0)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>3 (1.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>AE of special interest (after blinded, independent adjudication)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>50 mg n = 308</td>
<td>25 mg n = 308</td>
</tr>
<tr>
<td></td>
<td>2 (0.6)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>AE with fatal outcome*</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

* A 78-year male patient died due to cardiac arrest in the ER after presenting with chest pain. The patient had a history of stroke, hypertension and systolic murmur and the investigator assessed the case as not related to the study drug.

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# Most frequent adverse events*

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>1st pivotal study</th>
<th>2nd pivotal study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daridorexant</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>n = 308</td>
<td>n = 310</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Subjects with at least one event</td>
<td>117 (37.7)</td>
<td>116 (37.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (6.8)</td>
<td>20 (6.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (5.2)</td>
<td>19 (6.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (2.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (1.9)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (1.6)</td>
<td>11 (3.5)</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>4 (1.3)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.3)</td>
<td>7 (2.3)</td>
</tr>
</tbody>
</table>

* Ordered by 50 mg daridorexant

Daridorexant is investigational, in development and not approved or marketed in any country.
### Clinically relevant adverse events*

<table>
<thead>
<tr>
<th>Adjudicated by Independent Safety Board</th>
<th>1st pivotal study</th>
<th>2nd pivotal study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects with at least one event</strong></td>
<td>Daridorexant</td>
<td>Placebo</td>
</tr>
<tr>
<td>Narcolepsy-like symptoms related to excessive daytime sleepiness</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Narcolepsy-like symptoms related to complex sleep behavior including hallucinations/sleep paralysis**</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Narcolepsy-like symptoms related to cataplexy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other Adverse Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (1.6)</td>
<td>11 (3.5)</td>
</tr>
<tr>
<td>REM sleep abnormal</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Overdose</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

pivotal study

1st pivotal study

2nd pivotal study

- **treatment arm not disclosed to maintain the blinded nature of the extension study**

* Ordered by 50 mg daridorexant

** treatment arm not disclosed to maintain the blinded nature of the extension study

Daridorexant is investigational, in development and not approved or marketed in any country.
Two positive pivotal studies enable filing

Remarkable consistency between studies

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>WASO</th>
<th>LPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st pivotal study</strong></td>
<td>Daridorexant 50 mg</td>
<td>Daridorexant 25 mg</td>
</tr>
<tr>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>sTST</th>
<th>IDsIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st pivotal study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2nd pivotal study</strong></th>
<th>Daridorexant 25 mg</th>
<th>Daridorexant 10 mg</th>
<th>1 month</th>
<th>3 months</th>
<th>1 month</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>√</td>
<td>√</td>
<td>NS*</td>
<td>NS*</td>
<td>NS*</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>NS*</td>
<td>NS*</td>
<td>NS*</td>
<td>NS*</td>
<td>NS*</td>
<td>NS*</td>
</tr>
</tbody>
</table>

* Numerical trend

Safety and tolerability profile consistent between both pivotal studies

- No dose-dependent treatment emergent adverse events
- Low rate of clinically relevant adverse events
- No next morning hang-over effect
- No sign of rebound insomnia
- No withdrawal symptoms

Daridorexant is investigational, in development and not approved or marketed in any country.
Program conclusion

The program with daridorexant demonstrated statistically significant and clinically meaningful improvements at month 1 and at month 3.

**Efficacy during the night and the day**
- Sleep onset
- Sleep maintenance
- Total sleep time
- Daytime functioning

**Safety and tolerability profile consistent between both pivotal studies**
- No dose-dependent treatment emergent adverse events
- Low rate of clinically relevant adverse events
- No next morning hang-over effect
- No sign of rebound insomnia
- No withdrawal symptoms

Daridorexant is investigational, in development and not approved or marketed in any country.
Preparing for a successful launch
Targeted for 2022

Differentiated profile
Potential to improve sleep and daytime functioning without compromising safety

Disruptive impact
Opportunity to transform and modernize insomnia market

Smart partnering
Strong regional partners to reach broad primary care audience
- Syneos Health in the US
- Mochida in Japan

Daridorexant is investigational, in development and not approved or marketed in any country.
Collaboration with Syneos Health
Selected as commercialization partner to launch daridorexant in the US

• Idorsia will build the core capabilities needed to successfully launch daridorexant

• Syneos Health selected as commercialization partner in order to effectively reach the primary care market, which accounts for a large volume of insomnia prescriptions

• Syneos Health brings a robust customer-facing sales expertise and proven track record in launching new products in the US

• An innovative, revenue-driven agreement to accelerate and maximize reach to patients

• Together we will lead the transformation and modernization of the insomnia market in the US

Daridorexant is investigational, in development and not approved or marketed in any country.
License agreement with Mochida
Supply, co-development and co-marketing of daridorexant in Japan

• Idorsia entitled to:
  – initial payment of 1 billion JPY (approx. CHF 9 million)
  – three additional development and regulatory milestones
  – sales milestones and tiered royalty payments based on net sales
• Costs associated with the co-development of daridorexant will be shared
• Idorsia – with oversight from a Joint Development Committee – will be responsible for:
  – design and conduct of additional preclinical and clinical studies
  – health authority registration

Daridorexant is investigational, in development and not approved or marketed in any country.
Daridorexant for insomnia
Dual orexin receptor antagonist

First sleeping pill to show a consistent benefit in daytime functioning, using a validated instrument

- Daridorexant Phase 3 program has concluded – supporting the chronic use of daridorexant in insomnia
- New drug application (NDA) submitted to the US FDA in January 2021
- Marketing authorisation application (MAA) submitted to the EU EMA in March 2021
- MAA submitted to Switzerland’s Swissmedic in April 2021
- Commercial launch targeted for Q2 2022 as we begin the transformation and modernization of the insomnia market

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

Fabry disease is a **rare inherited lysosomal storage disorder** in which a particular **lipid** (a fat-like substance) can’t be broken down by the body, leading to its build-up in the cells of the body organs which results in cell and organ damage.

Fabry disease is often undetected or misdiagnosed.

As the disease is progressive, **early diagnosis is essential** to manage the symptoms as soon as possible and reduce the risk of developing serious complications.
What is the role of lipids in the body?

- Lipids are fat-like substances such as fatty acids, oils, waxes and steroids. A well-known example is cholesterol.
- Lipids are stored naturally in the body’s cells and organs and are vital to their healthy functioning.
- Normally, the body is able to process lipids effectively, which keeps them within healthy levels.

What happens in patients with lysosomal storage disorders?

**Normal breakdown of lipids**

<table>
<thead>
<tr>
<th>What happens in patients with lysosomal storage disorders?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal breakdown of lipids</strong></td>
</tr>
<tr>
<td>Lipid (fatty molecules)</td>
</tr>
<tr>
<td>Broken-down lipids exit cell to be processed further</td>
</tr>
</tbody>
</table>

**When enzyme to break down lipid is deficient**

<table>
<thead>
<tr>
<th>What happens in patients with lysosomal storage disorders?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When enzyme to break down lipid is deficient</strong></td>
</tr>
<tr>
<td>Lipids can’t be processed and build up in cell</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What happens in patients with lysosomal storage disorders?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unbroken-down waste</strong></td>
</tr>
<tr>
<td>Products collect in cell</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What happens in patients with lysosomal storage disorders?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipids can’t be processed and build up in cell</strong></td>
</tr>
</tbody>
</table>
Fabry disease
Biochemical mechanism

Dysfunctional or absent \( \alpha \)-galactosidase A results in accumulation of \( \text{Gb3} \) in various organs

- **Cer**: ceramide
- **GCS**: glucosylceramide synthase
- **GlcCer**: glucosylceramide
- **Gb3**: globotriaosylceramide
- **lysoGb3**: globotriaosylsphingosine
- **\( \alpha \)-GalA**: \( \alpha \)-galactosidase A
- **SM**: sphingomyelin
- **Sph**: sphingosine

---

**Legend**

- **SM**: sphingomyelin
- **Cer**: ceramide
- **GCS**: glucosylceramide synthase
- **GlcCer**: glucosylceramide
- **Gb3**: globotriaosylceramide
- **lysoGb3**: globotriaosylsphingosine
- **\( \alpha \)-GalA**: \( \alpha \)-galactosidase A
- **SM**: sphingomyelin
- **Sph**: sphingosine
Inheritence 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

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Strokes (in severe cases), and dizziness</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Cysts, reduced kidney function, progressive kidney failure</td>
</tr>
<tr>
<td>Skin</td>
<td>Dark red spots or rashes, burning / tingling sensations, sensitivity to temperature and profuse sweating</td>
</tr>
<tr>
<td>Ears</td>
<td>Tinnitus, hearing loss, and vertigo</td>
</tr>
<tr>
<td>Eyes</td>
<td>The appearance of the eyes changes</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiomyopathy with arrhythmia, valvular dysfunction, ischemia, left heart failure</td>
</tr>
<tr>
<td>Digestive Tract</td>
<td>Abdominal pain, constipation, diarrhea, and nausea</td>
</tr>
</tbody>
</table>

Neuropathic pain
Pain resulting from damage to or dysfunction of the nervous system
## Diagnosis of Fabry disease

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Clinical events</th>
<th>Pedigree analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain, GI,</td>
<td>Stroke, cardiac</td>
<td>Family members (between children and</td>
</tr>
<tr>
<td>hearing loss, hypohydrosis</td>
<td>and renal events</td>
<td>parents)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enzyme assay</th>
<th>Genotyping</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte α-GalA</td>
<td>&gt;830 mutations</td>
<td>Gb3 in plasma and urine</td>
</tr>
</tbody>
</table>
## Epidemiology of Fabry disease

Patients diagnosed with Fabry disease in EU-5 and US in 2018

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU-5</td>
<td>3,507</td>
</tr>
<tr>
<td>UK</td>
<td>890</td>
</tr>
<tr>
<td>Italy</td>
<td>828</td>
</tr>
<tr>
<td>Germany</td>
<td>692</td>
</tr>
<tr>
<td>France</td>
<td>562</td>
</tr>
<tr>
<td>Spain</td>
<td>535</td>
</tr>
<tr>
<td>US</td>
<td>3,875</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7,382</strong></td>
</tr>
</tbody>
</table>

Delveinsight, Fabry Disease – Market Insight, Epidemiology and Market Forecast – 2028
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)
- i.v. infusion, bi-weekly
- Immunogenicity
- Partial efficacy

Chaperone therapy
- Galafold (migalastat) for patients with amenable mutation
- 1 capsule orally, fasted, every other day
Lucerastat in Fabry disease

Bioavailability
Orally available, highly soluble small molecule with rapid and complete absorption

Tissue penetration
Access to most tissues, including peripheral and central nervous system

For all mutations
Potential to treat all Fabry patients irrespective of the underlying enzyme mutation

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

Mode of action

By inhibiting GCS, lucerastat reduces the precursor of Gb3 (GlcCer) and Gb3 itself

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

Cer ceramide
GCS glucosylceramide synthase
GlcCer glucosylceramide
Gb3 globotriaosylceramide
lysoGb3 globotriaosylsphingosine
α-GalA α-galactosidase A
SM sphingomyelin
Sph sphingosine
Lucerastat has the potential to reduce Gb3 levels in target organs

Male and female Fabry mice treated for 20 weeks with lucerastat at 1200 mg/kg/day as food admix and compared to non-treated controls.

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

Idorsia data on file. Data collected in animal models does not necessarily predict human clinical effect.
Effect of different concentrations of lucerastat on GlcCer, Gb3, lysoGb3 lipid levels, and LysoTracker staining in cultured Fabry patients’ fibroblasts after 9 days of treatment.

Each point is the mean of duplicates (±SD)

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

Clinical development plan

- Better understand medical need from patient perspective

Patient survey

- Exploratory study
  - Safety and proof of mechanism study

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

Confirmatory study
  - MODIFY

Pediatric study
  - Plan agreed with EMA

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

Clinical pharmacology

Half-life: approximately 6 hours – twice daily dosing

Dose-proportional exposure

Negligible food effect

Low potential for drug-drug interaction

>85% of the dose excreted unchanged in urine

Dose adjustment required in subjects with renal function impairment

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

Guérard et al. (2017) Orphanet J Rare Dis
Guérard et al. (2017) J Clin Pharmacol
Lucerastat in Fabry disease

Exploratory study design

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

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

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

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

**Exploratory study patient demographics**

**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 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)

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

Idorsia - Reaching out for more | October 2021
Lucerastat in Fabry disease

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

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

Exploratory study results: rapid and additional reduction in Gb3 when added to enzyme replacement therapy

- 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

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

<table>
<thead>
<tr>
<th></th>
<th>Plasma GB3</th>
<th>Urinary Gb3</th>
<th>GlcCer</th>
<th>LacCer</th>
<th>Plasma LysoGB3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=10)</td>
<td>(n=10)</td>
<td>(n=10)</td>
<td>(n=10)</td>
<td>(n=10)</td>
<td></td>
</tr>
</tbody>
</table>

-55.0%* -52.5%** -49.0%* -32.7%* -5.4%^  

Control (n=4)

-6.9% -8.6% -6.5% -3.9% 2.7%

*P<0.0001,**statistical significance not calculated, ^non-significant

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

Goals

1. **Better understand** patients’ disease and needs from the patient perspective

2. **Investigate key aspects** of 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 survey

Key results

- 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

51.5% (189/367) of patients report frequent pain AND moderate/severe pain

74.7% (274/367) of patients report pain in hands & feet AND moderate/severe pain

50% of the patients report all three

52.0% (191/367) of patients report frequent pain AND pain in hands & feet

N=367
Lucerastat in Fabry disease
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.
Lucerastat in Fabry disease

Confirmatory study 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.
Lucerastat in Fabry disease
Confirmatory study design

Screening 6-7 weeks
- Randomization 2:1

Treatment 6 months
- Lucerastat
- Placebo

Open, uncontrolled, Extension
- Primary/secondary efficacy endpoints

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/previoulsy treated)

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

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

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

Confirmatory study 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).
Lucerastat for Fabry disease
Glucosylceramide synthase inhibitor

An oral substrate reduction therapy investigated for the treatment of adult patients with Fabry disease.

- In October 2021, Idorsia reported that MODIFY did not meet the primary endpoint
- Lucerastat was well tolerated and a substantial and consistent reduction of plasma Gb3 was observed, confirming the pharmacological activity of lucerastat
- Definitive decisions on the future of lucerastat will be made:
  - Once full analysis of the data is complete
  - When forthcoming interim analysis of the open label extension study is available – expected by the end of 2021

Lucerastat is investigational, in development and not approved or marketed in any country.
Aprocitentan in resistant hypertension management
What is resistant hypertension?

Definition

**True resistant hypertension**
Patients whose blood pressure remains high, despite receiving at least three antihypertensives of different pharmacological classes, including a diuretic, at optimal dose. It is estimated that 10% of patients treated for hypertension can be classified as having true resistant hypertension.

**Not resistant hypertension**
Pseudo-resistant hypertension due to:
- White-coat effect (in the presence of medical staff)
- Non-optimal treatment
- Poor adherence to treatment
- Inappropriate measurement

Treatable hypertension
Resistant hypertension
Medical need

• Hypertension is one of the most common cardiovascular risk factors, and its prevalence continues to rise

• There are more than 1 billion people living with hypertension worldwide\(^1\)

• Left uncontrolled, hypertension can lead to life-threatening conditions such as stroke, ischemic heart disease, or kidney disease.

• It is estimated that 10-12% of the hypertensive population can be classified as having true resistant hypertension\(^2\)

\(^1\) NCD Risk Factor Collaboration, 2017
\(^2\) Carey, 2019; Noubiap, 2019
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
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.

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

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

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

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Aprocitentan is investigational, in development and not approved or marketed in any country.
**Aprocitentan in resistant hypertension**

**Rationale**

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

Aprocitentan is investigational, in development and not approved or marketed in any country.
Idorsia received **up-front payment of USD 230 million**

Idorsia to receive **tiered royalties** on annual net sales (20% up to $500 million, 30% from $500 million up to $2,000 million, and 35% above $2,000 million)

Both parties have **joint development rights** over aprocitentan, while Janssen has the sole manufacturing and commercialization rights

- Idorsia is leading ongoing Phase 3 development and regulatory submission for resistant hypertension – costs **shared equally**
- Janssen would lead the Phase 3 development and submission for any additional indications – Janssen would fund any costs for development with Idorsia reimbursing 50% by off-setting royalty (if any)

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

Phase 2 study

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

Today

SPIRIT survey

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

Phase 3 confirmatory study

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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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Aprocitentan in resistant hypertension

Aprocitentan dose-dependently decreases blood pressure

Aprocitentan is investigational, in development and not approved or marketed in any country.
### Aprocitentan in resistant hypertension

### Phase 2 safety results

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Aprocitentan group</th>
<th>Lisinopril group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety population / in patients</td>
<td>82</td>
<td>327</td>
<td>81</td>
</tr>
<tr>
<td>Discontinuation from study treatment due to an adverse event</td>
<td>6.1%</td>
<td>1.2% – 3.7%</td>
<td>3.7%</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>–</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Cases of increased liver enzymes above three times the upper limit of the normal range</td>
<td>1</td>
<td>1 – – – – – –</td>
<td>2</td>
</tr>
<tr>
<td>Cases of peripheral edema</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Change of mean body weight / in kg</td>
<td>+ 0.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose related change from baseline in the hemoglobin concentration</td>
<td>Increase</td>
<td>Expected decrease</td>
<td>Increase</td>
</tr>
</tbody>
</table>

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

Aprocitentan is investigational, in development and not approved or marketed in any country.
# Aprocitentan in resistant hypertension

## Confirmatory study design

<table>
<thead>
<tr>
<th>RHT confirmation</th>
<th>Efficacy and safety of aprocitentan</th>
<th>Safety Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td><strong>Part I</strong></td>
<td><strong>Part III</strong></td>
</tr>
<tr>
<td>Screening</td>
<td>Part II</td>
<td>Safety Follow-up</td>
</tr>
<tr>
<td>1 to 8 weeks</td>
<td>4 weeks</td>
<td>30 days</td>
</tr>
<tr>
<td>4 weeks</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>32 weeks</td>
<td></td>
</tr>
<tr>
<td>32 weeks</td>
<td>Withdrawal 12 weeks</td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Screening
- Individual background antihypertensive medication
- Standard background antihypertensive therapy
- Stabilization on standardized medication

### Part I
- **25 mg Aprocitentan**
- **12.5 mg Aprocitentan**
- Placebo

### Part II
- **25 mg Aprocitentan**
- **25 mg Aprocitentan**
- Placebo

### Part III
- **25 mg Aprocitentan**

### Randomization
- Continue standard background therapy

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Aprocitentan in resistant hypertension

Confirmatory study objectives

**Part I**
- Double-blind treatment
- 12.5 mg aprocitentan or 25 mg aprocitentan or placebo
- Period of 4 weeks
- To demonstrate the blood pressure lowering effect of aprocitentan when added to standard-of-care in true resistant hypertension patients

**Part II**
- Single-blind treatment
- 25 mg aprocitentan
- Period of 32 weeks
- To evaluate long-term safety and tolerability of aprocitentan when added to standard-of-care in true resistant hypertension patients

**Part III**
- Double-blind, randomized, withdrawal treatment
- 25 mg aprocitentan or placebo
- Period of 12 weeks
- To demonstrate that the effect of aprocitentan on blood pressure is durable when added to standard-of-care in true resistant hypertension patients

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Aprocitentan in resistant hypertension

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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Aprocitentan in resistant hypertension

Confirmatory 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 for difficult-to-control hypertension

Dual endothelin receptor antagonist

Targeting the endothelin pathway for the first time in systemic hypertension has great potential for the treatment of difficult-to-control or “resistant” hypertension

- PRECISION: recruitment complete
- Results expected mid-2022

Aprocitentan is investigational, in development and not approved or marketed in any country.
Clazosentan in cerebral vasospasm post-aneurysmal subarachnoid hemorrhage

Clazosentan is investigational, in development and not approved or marketed in any country.
Aneurysmal subarachnoid hemorrhage (aSAH)
A sudden life-threatening bleeding occurring in the subarachnoid space

- **Caused by the rupture of an aneurysm** — a weak, bulging spot on the wall of a cerebral artery
- **Prevalence**: between 6 and 9 in 100,000 worldwide\(^1,2\)
- **Emergency repair** (endovascular coiling or microsurgical clipping) is required to stop the hemorrhage


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Two options for the treatment of aSAH

**Pre-treatment**
- Ruptured aneurysm
- Brain artery

**Brain surgery:**
- Clipping of the aneurysm

**Catheter intervention:**
- Releasing of platinum coils

Coil

Catheter
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

- Cerebral vasospasm is one of the leading secondary causes of disability and death in those that experience aSAH
Symptoms of vasospasm

From asymptomatic detected by systematic angiography to serious neurological symptoms

- Numbness or weakness of the face, arm or leg, especially on one side of the body, or in more severe cases, paralysis
- Dizziness
- Blurred or double vision
- Loss of consciousness
- Mood change, agitation
- Confusion
- Worsening of headache
- Dizziness
- Difficulty speaking or being unable to speak
- From asymptomatic detected by systematic angiography to serious neurological symptoms
- Symptoms of vasospasm
- Cerebral vasospasm
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
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)
Endothelin release

Role 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 in cerebral vasospasm

>2'000 patients treated with clazosentan providing significant experience in vasospasm post-aSAH and a well documented safety profile

- ETA selective ERA
- Highly soluble
- Suited for intravenous administration
- Fast onset of action

Clazosentan is investigational, in development and not approved or marketed in any country.
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
What we have learned through our experience with clazosentan...
Phase 2 study – angiographic endpoint

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

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

Overall incidence of death and vasospasm-related morbidity

Relative risk reduction 17%, 95% CI -4 to 33

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

Clazosentan in cerebral vasospasm
15mg/hr showed significant effect on morbidity / mortality

Phase 3 study – clinical morbidity / mortality endpoint
• Patients who received endovascular coiling treated with 5 or 15mg/hr clazosentan

Overall incidence of death and vasospasm-related morbidity

<table>
<thead>
<tr>
<th></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>Event rate (%)</td>
<td>0.0073</td>
<td>0.3395</td>
<td>0.3395</td>
</tr>
</tbody>
</table>

Stroke. 2012; 43(6):1463-9
Clazosentan in cerebral vasospasm

15mg/hr showed significant effect on primary endpoint

Incidence of death and each component of vasospasm-related morbidity

Phase 3 study – clinical morbidity / mortality endpoint

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

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

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

Overall incidence of death and vasospasm-related morbidity

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=55)</th>
<th>Clazosentan 5 mg/h (n=52)</th>
<th>Clazosentan 10 mg/h (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event rate (%)</td>
<td>26</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>p</td>
<td>0.003*</td>
<td>0.0729</td>
<td></td>
</tr>
</tbody>
</table>

Phase 2 study – exploratory endpoint
• Clazosentan significantly reduced vasospasm-related morbidity and mortality events

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

Japanese study

Preventive Effect of Clazosentan against Cerebral Vasospasm after Clipping Surgery for Aneurysmal Subarachnoid Hemorrhage in Japanese and Korean Patients

Miki Fujimura, Jin-Yang Joo, Jong-Soo Kim, Motonori Hatta, Yoshinari Yokoyama, Teiji Tominaga

Cerebrovasc Dis 2017;44:59–67
Clazosentan in cerebral vasospasm

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

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Clazosentan in cerebral vasospasm

Well documented safety profile

Side effects of clazosentan

- Hypotension
- Lung complications (pulmonary edema)
- Peripheral edema

Risk mitigation

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

> 1’800 patients treated

Main side effects are manageable

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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?

Patients with “thick and diffuse” clot

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

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Clazosentan in cerebral vasospasm

In high-risk patient population

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

Thick and Diffuse Clots

Proportion of patients with an event

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Clazosentan 5 mg/h</th>
<th>Clazosentan 15 mg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7.5%</td>
<td>5.8%</td>
<td>8.1%</td>
</tr>
<tr>
<td>New Cerebral Infarcts</td>
<td>19.4%</td>
<td>18.1%</td>
<td>8.1%</td>
</tr>
<tr>
<td>DIND</td>
<td>21.6%</td>
<td>11.7%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Rescue Therapy</td>
<td>28.2%</td>
<td>15.2%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

DIND = Delayed ischemic neurological deficits

Phase 3 studies – clinical morbidity / mortality endpoint

Clazosentan is investigational, in development and not approved or marketed in any country.
REACT study design incorporates these learnings

- Selection of the high-risk patient population
- Selection of the dose
- Selection of the best measure to demonstrate efficacy
- Optimized patient management guidelines to ensure patient safety

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

**Study design**

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

**Observation:** 14 days post-study drug initiation

---

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

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

Primary endpoint – highly relevant

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)

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Clazosentan in cerebral vasospasm

Secondary endpoints

- Occurrence of all-cause new or worsened cerebral infarction $\geq 5$ cm$^3$ at Day 16 post-study drug initiation
- Long-term clinical outcome assessed by the GOSE at Week 12 post-aSAH, dichotomized into poor (score $\leq 4$) 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)

Clazosentan is investigational, in development and not approved or marketed in any country.
Cerebral vasospasm-related morbidity and all-cause mortality was blindly adjudicated by an independent committee and defined by at least one of the following:

- All Death / New cerebral infarction due to cerebral vasospasm / Delayed Ischemic Neurologic Deficit (DIND) due to cerebral vasospasm

Two identically designed studies (one in clipped patients, one in coiled patients)

220 Japanese patients (110 placebo/110 clazosentan) in each study

**Observation:** 14 days post-aSAH

- Aneurysm rupture (aSAH)
- Hospital admission
- Screening & Aneurysm securing by clipping or coiling
- Placebo Treatment & Observation
- Clazosentan 10mg/h Treatment & Observation
- Follow-up

- within 48h Randomization 1:1
- 14 days post-aSAH End of study treatment
- Week 6 Morbidity / Mortality
- Week 12 GOSE mRS MMSE

- Cerebral vasospasm-related morbidity and all-cause mortality was blindly adjudicated by an independent committee and defined by at least one of the following:
  - All Death / New cerebral infarction due to cerebral vasospasm / Delayed Ischemic Neurologic Deficit (DIND) due to cerebral vasospasm

Clazosentan is investigational, in development and not approved or marketed in any country.
Clazosentan demonstrated significant reduction of vasospasm-related morbidity and all-cause mortality in patients following aSAH (primary endpoint).

Clazosentan showed a numerical reduction of all-cause morbidity and mortality in both studies. The effect of clazosentan on this endpoint was significant ($p<0.05$) in a pre-planned pooled analysis.

Encouraging positive trends were observed on long-term measures of clinical outcome (GOSE and mRS) at week 12.

Idorsia Japan submitted a New Drug Application (NDA) with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) on March 1, 2021.

There were no unexpected safety findings. Treatment emergent adverse events occurring >5% in the clazosentan group with a difference of >2% compared to placebo were vomiting and signs of hemodilution or fluid retention (i.e. hyponatremia, hypoalbuminemia, anemia, pleural effusion, brain and pulmonary edema).

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

A selective ETA receptor antagonist being developed as an intravenous infusion for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia following aSAH.

Registration studies in Japan
- Evaluated reduction of vasospasm-related morbidity and mortality following aSAH
- Positive top-line results
- NDA submitted to PMDA on March 1, 2021

Global Phase 3 “REACT” study ongoing
- REACT—investigating the efficacy and safety of clazosentan in an enriched aSAH population
- Results expected H2 2022

Clazosentan has orphan drug designation in US and EU leading to regulatory exclusivity protection of 7 and 10 years respectively. In Japan, clazosentan has data protection after approval leading to 8 years exclusivity.

Clazosentan is investigational, in development and not approved or marketed in any country.
Clazosentan for cerebral vasospasm
Selective endothelin receptor (ETA) antagonist

Novel pharmacological intervention to protect against cerebral ischemia post-subarachnoid hemorrhage

- Positive results in the Japanese registration program
- NDA submitted to the PMDA on March 1, 2021
- REACT: Recruitment EU/US steadily progressing, results expected in the second half of 2022

Clazosentan is investigational, in development and not approved or marketed in any country.
Selatogrel for suspected acute myocardial infarction (AMI)

Selatogrel is investigational, in development and not approved or marketed in any country.
Acute myocardial infarctions (AMI)

Heart attack can occur in:
All ages. All ethnicities. All genders.

1/3 of deaths in developed nations can be attributed to heart attack

80,000 people living in the US have a heart attack each year

Recurring heart attack

Average age at first heart attack – risk increases with age

66 72

80% of deaths caused by cardiovascular disease are due to heart attack and stroke

3.3m women die of heart attack worldwide every year

Women tend to underestimate the risk of heart attacks

Heart attack can occur in:
All ages. All ethnicities. All genders.

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80% of deaths caused by cardiovascular disease are due to heart attack and stroke

3.3m women die of heart attack worldwide every year

Women tend to underestimate the risk of heart attacks
What happens with AMI today?

- Onset of AMI symptoms
- Patient delay due to failure to recognize and react
- Patient calls for emergency service or travels to hospital
- Further delay while waiting for emergency services
- First medical contact
- Emergency medical care follow-up at hospital

Heart attack in progress

The longer the heart is deprived of oxygen the greater the loss of muscle and the worse the outcome for the patient

Selatogrel is investigational, in development and not approved or marketed in any country.
Unmet medical need in AMI

Onset of AMI symptoms

Likelihood of death from AMI (pre-hospital admission)

~20% prior to admission

~10% during admission

Heart attack in progress

Admission to hospital for treatment
Thrombus formation

Platelet rich

Fibrin rich

Mixed: Platelet & Fibrin

< 3 hours

3-6 hours

> 6 hours

P2Y$_{12}$ receptor antagonists may have a role at AMI symptom onset

Early intervention is key to improve outcome

Pre-requisites for this to happen

- Symptom recognition
- Fast-acting
- Safe product
- Short duration
- Easy-to-use treatment

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

‘Fast’ onset of action

‘Short’ duration of action

Potent and highly selective antagonist of the P2Y_{12} receptor

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

Pharmacokinetic data in humans. AUC increased essentially in a dose-proportional manner. T½ dose-dependently increased and ranged from approximately 1.3-9.2 h. This is likely associated with the lack of PK data at late time points in the low dose groups (i.e., plasma concentrations below the LLOQ) leading to shorter t½ estimates.

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

- **'Fast' onset of action**
- **'Short' duration of action**
- Potent and highly selective antagonist of the P2Y<sub>12</sub> receptor

Selatogrel 30 µg/kg s.c.

**Cyclic Flow Variations**

Preclinical data from a modified Folts model in guinea pigs

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

Effects of selatogrel and ticagrelor on blood loss in anesthetized Wistar rats

Rat thrombosis model. Dose dependent surgical blood loss after standardized punch biopsy of the spleen. Drugs administered by continuous infusion to achieve low-, intermediate-, and high-level inhibition of platelet aggregation. Selatogrel doses; 0.06, 0.2, 0.6 µg/kg/min. Ticagrelor doses; 2, 6, 20 µg/kg/min. After surgical wounding of the spleen, blood was collected for 30 min and the weight of lost blood determined. Data are means SEM, n = 9-35. *P < 0.05. **P < 0.01.

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

‘Fast’ onset of action

‘Short’ duration of action

Potent and highly selective antagonist of the P2Y₁₂ receptor
Key learnings from clinical pharmacology studies

Pharmacodynamics: Inhibition of platelet aggregation (IPA) with 16 mg selatogrel

- Modelling shows the rapid IPA onset within 15 minutes
- More than 90% of participants have more than 80% Inhibition 15 minutes after dosing
- Strong inhibition of platelet aggregation was modelled to last for 6-8h

Selatogrel is investigational, in development and not approved or marketed in any country.
Phase 2 clinical development

Selatogrel was tested in patients with chronic coronary syndrome and in patients experiencing an AMI to validate PK and PD profiles observed in clinical pharmacology studies.

- Subcutaneous administration by a healthcare professional (with syringe)
- 2 doses investigated: 8 and 16 mg

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

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Phase 2 clinical development

Selatogrel has a rapid PD effect following subcutaneous injection

- Both studies met their pharmacodynamic objectives of significantly inhibiting platelet aggregation.
  - Subcutaneous administration of selatogrel 8 mg and 16 mg has demonstrated a rapid onset of action, within 15 minutes, with the height of its effect extending over 4-8 hours, depending on the dose.

Data from chronic coronary syndrome study:
  - Consistent with results from AMI study.

Selatogrel is investigational, in development and not approved or marketed in any country.
Selatogrel was safe and well tolerated in both studies

<table>
<thead>
<tr>
<th>Treatment-emergent AEs*, n (%)</th>
<th>8 mg selatogrel (N=114)</th>
<th>16 mg selatogrel (N=115)</th>
<th>Placebo (N=116)</th>
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</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE</td>
<td>36 (32)</td>
<td>26 (23)</td>
<td>25 (22)</td>
</tr>
<tr>
<td>Patients with serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most frequent AEs (≥3 subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6 (5)</td>
<td>10 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Median duration, h</td>
<td>2.4</td>
<td>0.8</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (4)</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Vessel puncture site bruise</td>
<td>4 (4)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Contusion</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>3 (3)</td>
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<tr>
<td>Patients with ≥1 bleeding event</td>
<td>11 (10)</td>
<td>5 (4)</td>
<td>8 (7)</td>
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<tr>
<td>Major bleeding events</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data from chronic coronary syndrome study – Consistent with results from AMI study

*Treatment-emergent was defined as any AE occurring up to 48 h after treatment administration

Selatogrel is investigational, in development and not approved or marketed in any country.
The selatogrel-autoinjector combination product – a device designed for emergency use

• With 20 years of experience, Antares has a proven track record in developing drug-device combination products that are tailored to the therapeutic need and patient-friendly

• The companies have developed a novel drug-device product combining Idorsia’s selatogrel with the Antares subcutaneous QuickShot® auto-injector
The selatogrel-autoinjector combination product – a device designed for emergency use

- Robust
- Easy-to-use
- Reliable
- Emergency ready

The selatogrel-autoinjector has been found to be safe and to perform as intended for the intended users, uses, and use environments in the planned Phase 3 clinical study.
Patient training
Training-specific material mirrored across all regions

1. **When to inject?**
   Recognize the symptoms of AMI

2. **How to and where to inject?**
   Instruction on use of the autoinjector

Selatogrel is investigational, in development and not approved or marketed in any country.
Pre-requisites for early intervention in place

Time to prove the concept in a large registration study

- Symptom recognition
- Safe product
- Fast-acting
- Short duration
- Easy-to-use treatment

Selatogrel is investigational, in development and not approved or marketed in any country.
Selatogrel Outcome Study in suspected Acute Myocardial Infarction “SOS-AMI”

Putting selatogrel in the hands of patients

Selatogrel is investigational, in development and not approved or marketed in any country.
SOS-AMI Phase 3

A multi-center, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of self-administered subcutaneous selatogrel for prevention of all-cause death and treatment of acute myocardial infarction in subjects with a recent history of AMI.

Onset of symptoms → Patient recognizes symptoms → Patient first self-injects the study drug then calls emergency → Diagnosis

Think Heart First

Recognizing heart attack symptoms

1

SOS-AMI

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SOS-AMI: Operationalizing the study
14,000 patients planned to be randomized

Study design

Screening phase
Within 4 weeks from hospital discharge

Observation phase
Trainer follow-up, week 2, 1 month, then at 3 months intervals

Patient journey

High risk of repeat AMI
Training and placebo self-injection
Randomization 1:1 selatogrel vs placebo
Recognize symptoms and perform required actions
Treated at hospital

Selatogrel is investigational, in development and not approved or marketed in any country.
Data flow in SOS-AMI

**Primary efficacy endpoints:**
Death, AMI

**Primary safety endpoints:**
Severe Bleedings

**Clinical event committee**
(blinded independent adjudication)

**Ranking by severity**
using 6-point scale from “no event” up to “death”

**Ranking of bleeding by severity according to BARC definition**

BARC: Bleeding Academic Research Consortium

Selatogrel is investigational, in development and not approved or marketed in any country.
Selatogrel – Potential to change the way AMI is treated

- ‘Fast’ onset of action
- ‘Short’ duration of action
- Potent and highly selective antagonist of the P2Y$_{12}$ receptor
- Suitable for subcutaneous injection
How could AMI be managed in the future?

Onset of AMI symptoms  Self-administer selatogrel using autoinjector at symptom onset

Patient calls for emergency service or travels to hospital

First medical contact

Emergency medical care follow-up at hospital

Slowing or stopping of the heart attack

Early intervention leads to better short-term and long-term outcome

Selatogrel is investigational, in development and not approved or marketed in any country.
Cenerimod in systemic lupus erythematosus

Cenerimod is investigational, in development and not approved or marketed in any country.
Systemic lupus erythematosus (SLE)
Complex, systemic, autoimmune disease of unknown cause

Normal immune response
- Foreign threat invades
- Antibodies attack and remove invading threat
- Antibodies continue to protect body

Autoimmune response
- Immune system forms antibodies against its own body cells
- Antibodies attack the body’s own cells
- Antibodies remain in the body causing inflammation and tissue damage
Systemic lupus erythematosus (SLE)

Symptoms

- **Skin**: rashes, sensitivity to light
- **Fatigue**
- **Liver and spleen**: enlarged
- **Blood and circulation**: swollen glands, poor circulation in the fingers and toes, anemia
- **Joint and muscles**: aches and pains
- **Nervous system**: headaches, depression, and seizures
- **Fever and/or night sweats**
- **Weight**: changes
- **Kidney**: problems
- **Head**: hair loss, oral/nasal ulcers
- **Liver and spleen**: enlarged

• **Tissue damage across multiple organ systems**

• **Severe organ damage and significant mortality in subset of patients**
Systemic lupus erythematosus (SLE)

High medical need

- Lupus can range from mild to severe depending on how it affects the body
- **Limited treatment options** with a high need for new approaches

**Mild**
- joint and skin problems, tiredness

**Moderate**
- inflammation of other parts of the skin and body, including the lungs, heart, and kidneys

**Severe**
- inflammation causing severe damage to the heart, lungs, brain, or kidneys, which can be life threatening
Systemic lupus erythematous (SLE)

Epidemiology

- 5 million people worldwide have a form of lupus
- 90% female
- 10% male
- More common in people of Afro-Caribbean and Asian origin compared to Caucasians
- Peak incidence between 15 and 40 years
S1P₁ receptor modulation in SLE

Rationale

• **T and B lymphocytes** are considered the key immune cells that contribute to the symptoms of the disease

• T and B lymphocytes have receptors on the surface called “Sphingosine-1-phosphate receptor 1” (S1P₁)

• S1P₁ senses the gradient of sphingosine-1-phosphate or S1P, which is high in blood, guiding the lymphocytes out of lymph nodes towards the circulation

• S1P₁ receptor modulators bind to the S1P₁ receptor on the surface of T and B lymphocytes

• This interaction leads to internalization of the S1P₁ receptor

• Lymphocytes can no longer sense S1P and are held in the lymph nodes, reducing the availability of these key players in inflammation to the affected organs and tissues

• **S1P₁ receptor modulators have shown efficacy** in different preclinical models of systemic lupus erythematosus: MRL/lpr and BXSB mice
Cenerimod in SLE

**Oral drug**

**Novel approach to the treatment of SLE**

**S1P₁ Receptor Modulation**
S1P₁ is on the surface of T and B lymphocytes, and the modulation leads to internalization of the receptor.

Lymphocytes can no longer sense S1P and are held in the lymph nodes.

**Tolerability Profile**
The evolving profile suggests that cenerimod is generally well tolerated.

**Promising Data**
Early indication of efficacy with numerical reduction in mSLEDAI-2K and anti-dsDNA antibodies.

---

**Dose dependent and reversible management of circulating lymphocyte counts**

Cenerimod is investigational, in development and not approved or marketed in any country.
Cenerimod in SLE
Study presented at ACR2019

Phase 2 safety study
Randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, and tolerability of cenerimod in adult patients with systemic lupus erythematosus

67 patients were enrolled to receive either placebo or 0.5, 1, 2 or 4 mg/day of cenerimod over a treatment period of 12 weeks.
Cenerimod in SLE

Study design

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

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Cenerimod in SLE
Dose-response for total lymphocyte count

Absolute change from baseline to EOT in total lymphocyte count (10^9/L)

- Placebo (n=16)
- 0.5 mg (n=12)
- 1 mg (n=10)
- 2 mg (n=13)
- 4 mg (n=9)

P<0.001 for dose-response

Dashed line represents the 95% CI

Analysis set: Modified Pharmacodynamic Set
EOT, end of treatment - Week 12

Cenerimod is investigational, in development and not approved or marketed in any country.
Cenerimod in SLE
Modified SLEDAI-2K over time

Mean mSLEDAI-2K score ± SE

Analysis Set: Modified Pharmacodynamic Set
modified SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000 modified to exclude leukopenia

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

Phase 2 conclusion

Dose-response ✔
- **Dose-dependent, sustained reduction** in circulating lymphocyte counts
- Reversible after treatment

Safety ✔
(in the limit of the study design)
- **Well tolerated at all dose levels**
- The occurrence of adverse events was similar in all five treatment groups

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

Multi-dose efficacy & safety study
Multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the **efficacy and safety** of cenerimod for the treatment of adult patients with moderately to severely active, autoantibody-positive systemic lupus erythematosus

**Patients** will be enrolled to receive either placebo or 0.5, 1, 2 or 4 mg/day of cenerimod for up to 12 months
Cenerimod in SLE

Study design

Randomization
5 groups (1:1:1:1:1)

Visit 1 2 8 15 18
Day -60 Day 1 6 months 12 months 16 months

Screening
up to 60 days

Treatment period 1
6 months

Echocardiography ancillary study
• 125 subjects echocardiography at screening and 6 months of treatment

Placebo 100 pts
Cenerimod 0.5 mg 100 pts
Cenerimod 1.0 mg 100 pts
Cenerimod 2.0 mg 100 pts
Cenerimod 4.0 mg 100 pts
Cenerimod 2.0 mg
Placebo

Follow-up
4 months

Treatment period 2
up to 6 months after treatment period 1

EOT
EOS

Re-randomization of 4 mg to placebo and 2 mg (1:1)
Cenerimod in SLE
Large efficacy & safety study in patients with SLE “CARE”

**Primary Objective**
- Assess the efficacy (disease activity) of 6 months cenerimod treatment given at 4 different dose levels in subjects with moderate to severe systemic lupus erythematosus

**Secondary Objectives (6 months)**
- Safety and tolerability of cenerimod doses
- Effect on quality of life and fatigue using patient reported outcome (PRO) instruments
- Effect on systemic lupus erythematosus biomarkers

**Exploratory objectives** (over a treatment period of up to 12 months)
- Effect on disease activity, safety and tolerability, quality of life, fatigue, and systemic lupus erythematosus biomarkers
- Starting from Month 6, the effects of dose reduction and withdrawal in subjects randomized to 4 mg who are re-randomized to either 2 mg or placebo

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

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Cenerimod for systemic lupus erythematosus

Selective sphingosine-1-phosphate 1 (S1P₁) receptor modulator

First oral immune-modulator active on both B and T cells could represent a novel approach to the treatment of SLE

- “Fast-track” designation received from FDA
- CARE: recruitment complete
- Results expected in Q2 2021
ACT-539313 is investigational, in development and not approved or marketed in any country.
Binge eating disorder (BED)
Repeated episodes of eating unusually large portions of food

- Associated with a sense of **lack of control over what is being eaten**
- **Significant psychological distress** (shame, guilt, embarrassment)
- **Absence of recurrent inappropriate compensatory behaviors** (purging, fasting, excessive exercise)
- Can range from **mild to severe** depending on the number of binge eating episodes per week
- Recognized as a distinct eating disorder in the Diagnostic and Statistical Manual of Mental Disorders (**DSM-5**), with specific criteria to aid diagnosis
What causes BED?

- Exact cause unknown, often multifactorial
- BED is thought to be linked to a combination of different factors including psychological, socio-cultural and genetic influences
- Can begin as occasional «comfort-eating»
- Nearly half of all people with BED have a history of depression
- Eating disorders tend to run in families (inherited factor and/or family dynamics)
- Regular dieting may be a risk factor in developing BED
Epidemiology

- **BED** is the most common eating disorder, more common than anorexia nervosa and bulimia nervosa combined.

- The overall lifetime incidence of **BED** in adults could be as high as **3.5% among women and 2% among men**.

- It is estimated that **40%** of those with **BED** are male.

- Usually first diagnosed in young adulthood (early to mid-20s) and symptoms may persist into middle age and even old age.

- Course may be remitting, recurrent, or chronic.
Orexins are neuropeptides produced by neurons in the hypothalamus. They bind to 2 receptors: OX1R and OX2R.

Orexin signaling is involved in emotional, physiological, and behavioral processes.

The OXR1 enhances the motivation to react to rewarding and/or fearful stimuli.

Preclinical studies have shown that orexins play an important role in driving compulsive binge-like consumption and that orexin receptor antagonists have reduced binge-like eating behavior in animal models.
ACT-539313 is a selective, potent, and brain-penetrating orexin 1 receptor antagonist, being developed for the treatment of adult patients with binge eating disorder.

In Phase 1 studies, ACT-539313 was well tolerated at single oral doses of up to and including 400 mg and at multiple oral doses of up to and including 200 mg twice daily for 10 days in healthy volunteers.
A multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 2 proof-of-concept study

Evaluation of the efficacy and safety of oral ACT-539313 in the treatment of adult patients with moderate to severe binge eating disorder

Designed following consultation with the US FDA

Study participants are randomized to receive either ACT-539313 at a dose of 100 mg twice daily, or placebo in a 1:1 ratio over a 12-week treatment period

The primary efficacy endpoint is the change from baseline to Week 12 in the number of binge eating days per week, defined as a day with at least one confirmed binge eating episode

Effect of ACT-539313 in modulating behavioral features that contribute to the psychopathology in BED, in addition to reducing the frequency of binge eating
Study design

**Screening** 2 - 4 weeks

**Double-blind treatment period** 12 weeks

**Follow-up** 10 ± 3 days

**Screening (V1)**

**Randomization (V2)**

**ACT-539313 100 mg b.i.d.**

**Placebo**

b.i.d. = twice daily
EOT = End-of-Treatment
EOS = End-of-Study
V = visit

ACT-539313 is investigational, in development and not approved or marketed in any country.

ACT-539313 is investigational, in development and not approved or marketed in any country.
ACT-539313 for binge eating disorder

Selective, potent, and brain-penetrating orexin 1 receptor antagonist

The first orexin 1 receptor antagonist to be studied as a new mechanism of action for adult patients with binge eating disorder

- Phase 2 proof-of-concept study initiated in March 2021
Idorsia’s other clinical development assets
The company has closed a natural history study called “RETRIEVE” which collected disease information from pediatric patients with early onset of rare lysosomal storage disorders (LSDs). The company is now considering development options for sinbaglustat.
Other early-stage pipeline assets

• **ACT-1004-1239** is a CXCR7 antagonist for immunology disorders in Phase 1 development

• **ACT-1014-6470** is a new immunological compound in Phase 1 development

• **ACT-777991** is a new immunological compound in Phase 1 development

These compounds are investigational, in development and not approved or marketed in any country.
Investigated by Neurocrine Biosciences in two Phase 2 studies for the treatment of a rare form of pediatric epilepsy known as epileptic encephalopathy with continuous spike and wave during sleep (EE-CSWS) and for essential tremor

- ~7,000 people have EE-CSWS and ~10 million have essential tremor in the US
- Neurocrine Biosciences has a global license to develop and commercialize Idorsia’s ACT-709478
- Rare Pediatric Disease Designation and Orphan Drug Designation from the US FDA for ACT-709478 in EE-CSWS
Idorsia’s drug discovery approach

- Single-center approach
- Fully integrated research informatics
- Focus on small molecules
- Few platforms of expertise
- Multiple therapeutic areas
- High medical input
More joy – Transforming the horizon

Our drug discovery process

Molecular-Biology (Target Finding)
Biochemistry (High Throughput Screening)
Structural Biology And Molecular Modeling
Medicinal Chemistry
Pharmacokinetics & Metabolism
Research Information Management
Pharmacology
Chemistry Process R&D
Lead Structure
Drug Candidate
Compound Library

Targets → Hits → Preclinical Development → Clinical Development → Registration → Launch
Financial information
US GAAP net results
in CHF millions, rounding differences may occur

Financial results as of June 30, 2021
Non-GAAP operating expenses
in CHF millions, rounding differences may occur

<table>
<thead>
<tr>
<th>Research</th>
<th>Development</th>
<th>Milestones</th>
<th>Inventory build</th>
<th>SG&amp;A</th>
<th>Non-GAAP operating expenses</th>
</tr>
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<tbody>
<tr>
<td>-54</td>
<td>-4</td>
<td>-6</td>
<td>-6</td>
<td>-34</td>
<td>-68</td>
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</tbody>
</table>

Financial results as of June 30, 2021
Cash flow

in CHF millions, rounding differences may occur

Liquidity @ Dec 31, 2020: 1,200
Non-GAAP Opex: -248
Milestones: 8
Capex: -17
Other: -16
Liquidity @ Jun 30, 2021: 927

Financial results as of June 30, 2021
Liquidity
in CHF millions, rounding differences may occur

<table>
<thead>
<tr>
<th>Description</th>
<th>Dec 31, 2020</th>
<th>Jun 30, 2021</th>
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<tbody>
<tr>
<td>Cash and Cash equivalents</td>
<td>141</td>
<td>164</td>
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<tr>
<td>Cash deposits &gt; 12 months</td>
<td>867</td>
<td>763</td>
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<tr>
<td>Cash deposits &lt; 12 months</td>
<td>192</td>
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<td>Other FX</td>
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<td>USD</td>
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<tr>
<td>CHF</td>
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</tr>
</tbody>
</table>

Financial results as of June 30, 2021
Non-GAAP OPEX
• Depreciation & Amortization
  ~ CHF 20 million
• Stock-Based Compensation
  ~ CHF 25 million

US GAAP operating expenses*
around CHF 665 million

Non-GAAP operating expenses*
around CHF 620 million

* Excluding unforeseen events

Functional R&D expenses
around CHF 360 million

Functional SG&A
around CHF 220 million

Inventory build
around CHF 35 million

Milestone payment
CHF 5 million

Financial Guidance for 2021

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Idorsia has a strong and visionary leadership team with the power and drive to create more remarkable innovations and more new medicines.
Idorsia Executive Committee

Jean-Paul Clozel
Chief Executive Officer

Martine Clozel
Chief Scientific Officer

Guy Braunstein
Head of Global Clinical Development

Simon Jose
Chief Commercial Officer

André C. Muller
Chief Financial Officer
Idorsia Leadership Team

Andrew C. Weiss  
Head of Investor Relations & Corporate Communications

Alex Khatuntsev  
Head of Global Human Resources

Oliver Peinelt  
Group General Counsel

Olivier Lambert  
Head of Global Pharmaceutical Development & Quality Assurance

Christoph Boss  
Head of Drug Discovery Chemistry

Ulrich Mentzel  
Head of Drug Discovery Pharmacology & Preclinical Development

Markus Riederer  
Head of Drug Discovery Biology

Stefan Abele  
Head of Chemical Development & Commercial Manufacturing
Be prepared for more