Idorsia’s clinical development comprises a broad spectrum of expertise clustered within multiple departments: therapy area units, strategic development, clinical pharmacology, biostatistics and data management, drug safety, drug regulatory affairs, clinical operations and life cycle management. Life cycle cross-functional teams – under the leadership of a life cycle leader – bring expertise from preclinical development, clinical development and technical operations to the efficient development of new medicines. They steer the compounds from entry-into-human studies through to submission of the dossier to health authorities, approval and maintenance of the licence during the commercialization phase until loss of exclusivity of the medicine in the major markets and beyond. Idorsia’s clinical development manages clinical programs to the appropriate scientific, medical and operational standards to generate the information required by health authorities worldwide.

Idorsia’s drug discovery focuses on novel molecular target families, implementing appropriate state-of-the-art technologies. In particular, the target families include G-protein coupled receptors (“GPCRs”), ion channels and certain enzymes. The drug discovery team facilitate the combination of drug discovery technology with human expertise and teamwork, in a single research center based in Allschwil, Switzerland.
### Development Pipeline

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* In collaboration with Janssen Biotech to jointly develop and solely commercialize aprocitentan worldwide.

** In Japan, market registration trials are being conducted, with results expected in the second half of 2018.

*** Idorsia has exclusive option to worldwide rights to ReveraGen’s Vamorolone.
Lucerastat

Lucerastat is an oral monotherapy offering a new treatment approach with the potential to alleviate the symptoms of Fabry disease.

Fabry disease is a rare genetic disorder involving a deficiency or dysfunction of α galactosidase A – an enzyme that normally breaks down a fatty waste product known as Gb3 in the cells of the body. Over time, this may result in a build-up of Gb3 deposits throughout the body, particularly in the kidneys, heart and nervous system. The symptoms range from pain in the hands and feet, eye and stomach problems, to stroke and kidney failure, depending on which organs are affected. Because the symptoms are non specific, Fabry disease is often undetected or misdiagnosed.

Lucerastat is a small-molecule iminosugar which inhibits glucosylceramide synthase and has the potential to provide substrate reduction therapy for oral treatment of Fabry disease. In an exploratory study in patients with Fabry disease, treatment with lucerastat in addition to ERT demonstrated a marked decrease in plasma levels of metabolic substrates associated with the development of the disease. The study also demonstrated that lucerastat is well tolerated in patients with Fabry disease.

**Current status**

In the first half of 2018, Idorsia expects to initiate a pivotal Phase 3 study designed to assess the effects of lucerastat on neuropathic pain and gastrointestinal symptoms, as well as safety and tolerability, in patients with Fabry disease. The study is expected to enroll around 100 patients and to last approximately 20 months.

Lucerastat for Fabry disease has received Orphan Drug designation in the US and in the EU and at the beginning of 2018, the European Medicines Agency (EMA) agreed with Idorsia’s paediatric investigation plan for lucerastat for the treatment of pediatric patients with Fabry disease. Idorsia has already initiated activities according to the agreed plan.

**Available clinical data**

The findings of the Phase 1 program have demonstrated that lucerastat was safe and well tolerated in patients with Fabry disease. In a Phase 1b study in patients with Fabry disease, treatment with lucerastat on top of enzyme replacement therapy demonstrated a marked decrease in the plasma levels of metabolic substrates related to the development of the disease.

**Milestones**

2016  Phase 1b study completed

**Key scientific literature**

Aprocitentan (ACT-132577)

Aprocitentan is an orally active dual endothelin receptor antagonist which is being investigated for patients whose hypertension is uncontrolled despite the use of at least three anti-hypertensive drugs.

Resistant hypertension is defined as persisting high systemic blood pressure (i.e., failure to lower blood pressure to a pre-defined threshold) despite concurrent administration of three antihypertensive therapies of different pharmacological classes at maximal or optimal doses, including a diuretic. Resistant hypertension is associated with a higher risk of cardiovascular disease. In addition, patients with resistant hypertension often have a medical history of diabetes mellitus and may develop chronic kidney disease as a complication of the hypertension, increasing their vulnerability and the complexity of treatment.

Current status
In a Phase 2 study, the efficacy, safety and tolerability of aprocitentan was evaluated in patients with essential hypertension so as to identify the optimal dose for further studies. Based on the positive results from the dose-finding study and following feedback from health authorities, Idorsia is currently finalizing the design of a Phase 3 study. This will be specifically designed to evaluate the initial and long-term effects of aprocitentan on systolic and diastolic blood pressure in patients requiring resistant hypertension management (RHM). The study is expected to start in the first half of 2018. If successful, it will provide the basis for registration of the product.

Collaboration Agreement with Janssen Biotech
On December 1, 2017, Janssen Biotech, Inc. (Janssen), one of the Janssen Pharmaceutical Companies of Johnson & Johnson, entered into a collaboration agreement with Idorsia to jointly develop and commercialize aprocitentan and any of its derivative compounds or products. Both parties have joint development rights over aprocitentan. Idorsia will oversee the Phase 3 development and regulatory submission. The costs will be shared equally between both partners. Janssen will oversee the Phase 3 development and submission for any additional indications.
Available clinical data
In a Phase 2 study that evaluated the efficacy, safety and tolerability of a once-a-day oral regimen of four dose levels of aprocitentan in patients with essential hypertension, 490 patients were randomized to receive either aprocitentan 5, 10, 25, 50 mg, placebo, or lisinopril 20 mg once daily. The results were announced in May 2017 and showed a mean reduction from baseline in diastolic blood pressure between 6.3 and 12.0 mmHg in a statistically significant dose-dependent manner for the aprocitentan groups versus a decrease of 4.9 mmHg in the placebo group and a decrease of 8.4 mmHg in the lisinopril group (in the per-protocol population comprised of 410 patients).

Systolic blood pressure reductions ranged from 10.3 to 18.5 mmHg in a statistically significant dose-dependent manner in the aprocitentan groups and were 7.7 and 12.8 mmHg in the placebo and lisinopril groups, respectively. These findings were confirmed in all randomized patients (Intent-to-Treat principle) and by 24 hours Ambulatory Blood Pressure Monitoring.

The safety population included 327 patients in the aprocitentan groups, 82 patients in the placebo group and 81 in the lisinopril group. Aprocitentan was well tolerated across all four doses in this patient population. Discontinuation from study treatment due to an adverse event ranged between 1.2% and 3.7% for the aprocitentan groups versus 6.1% in the placebo group and 3.7% in the lisinopril group. The overall frequency of adverse events was similar to those observed in the placebo group. In this study, there were two cases of increased liver enzymes above three times the upper limit of the normal range, one in the placebo and one in the aprocitentan 5 mg group. Four cases of peripheral edema were observed, two in the aprocitentan 25 mg group and two in the aprocitentan 50 mg group. Mean body weight remained unchanged from baseline in the aprocitentan 5, and 10 mg groups, increased by 0.4 kg in the aprocitentan 25 and 50 mg groups, and by 0.3 kg in the placebo group and decreased by 0.3 kg on lisinopril. There was an expected dose-related decrease from baseline in the hemoglobin concentration in the aprocitentan groups (ranging from 1.3 to 6.7 g/L) versus increases of 2.2 and 0.1 g/L in the placebo and lisinopril groups, respectively.

Milestones
2017  Collaboration agreement with Janssen Biotech
2017  Positive results for the dose-response study
2015  Initiation of Phase 2 dose-response study
2014  Initiation of Phase 1 clinical program

Key scientific literature
ACT-541468 is a dual orexin receptor antagonist (DORA) for the treatment of insomnia. It has potential for fast onset of sleep and a duration of action not exceeding a normal night, while maintaining natural sleep architecture.

Insomnia – the most commonly reported sleep disorder worldwide – is defined as a combination of dissatisfaction with sleep and a significant negative impact on daytime functioning. Dissatisfaction with sleep refers to difficulty in initiating and/or maintaining sleep on at least three nights per week for at least three months, despite adequate opportunity to sleep.

Based on preclinical data, dual orexin receptor antagonism maintains natural sleep architecture. Preclinical data suggests that ACT-541468 will have a low potential for abuse. Data from a comprehensive Phase 1 program indicates that ACT-541468 has a suitable pharmacokinetic and pharmacodynamic profile to deliver fast onset of sleep, a duration of action which is well suited for appropriate sleep maintenance, and low potential for next day residual effect. These properties are being explored clinically and, if confirmed, will give ACT-541468 the potential to be differentiated from current sleep medications.

Current status
The safety and efficacy of ACT-541468 in adult and elderly patients with insomnia was evaluated in a comprehensive Phase 2 program, comprising two studies. Both studies showed the desired effect on sleep maintenance and onset, with a significant dose-response relationship; treatment was generally well tolerated.

In the first half of 2018, following feedback from health authorities, Idorsia expects to initiate a pivotal Phase 3 registration program. The program consists of three studies designed to evaluate time to sleep onset and duration of action in patients with insomnia, as well as providing long-term safety information.

Available clinical data
The first Phase 2 study in 360 adults (ranging from 18 to 64 years), with a treatment duration of 4 weeks, showed a significant dose dependent decrease in WASO at Day 1 & 2 (average decrease of wake-time after sleep onset from baseline on the first 2 nights of treatment, measured by polysomnography). In addition, ACT-541468 significantly decreased LPS (latency to persistent sleep) in a dose-dependent manner. Treatment with ACT-541468 was generally well tolerated. There were no reports of serious adverse events related to ACT-541468.

The positive readouts of the second Phase 2 study, conducted in 58 elderly patients (ranging from 65 to 85 years), confirmed the efficacy and safety profile of ACT-541468 in this patient population. The results of this study also showed a significant decrease in WASO and LPS at Day 1 & 2 in a dose-dependent manner.
Data from an extensive Phase 1 program showed an optimal pharmacokinetic and pharmacodynamic profile for a sleep medication, together with excellent safety and tolerability.

**Milestones**
- **2017** Completion of Phase 2 clinical program
- **2014** Initiation of Phase 1 clinical program

**Key scientific literature**
- Roth T. 2007;3 Suppl 5:S7-10.
Clazosentan

Clazosentan is an endothelin receptor antagonist being developed as an intravenous infusion for the prevention and treatment of cerebral vasospasm in patients who have suffered an aneurysmal subarachnoid hemorrhage (aSAH).

Aneurysmal subarachnoid hemorrhage (aSAH) is a sudden life-threatening bleeding occurring in the subarachnoid space (i.e., between two layers of the protective membranes surrounding the brain). It is caused by the rupture of an aneurysm – a weak, bulging spot on the wall of a brain artery – which allows blood to escape and accumulate in the space around the brain. Surgical repair (endovascular coiling or microsurgical clipping) is required to prevent fatal rebleeding.

In about one third of patients with aSAH, worsening of the neurological condition may occur due to delayed cerebral vasospasm (constriction of arteries in the brain). Cerebral vasospasm diminishes blood flow to the brain and may lead to cerebral infarction and poor long-term outcomes. Currently, invasive endoarterial intervention is used to treat cerebral vasospasm. This therapy is associated with medical risks and often requires repeated procedures. No effective medication is available for the prevention or treatment of cerebral vasospasm.

**Current status**

Several studies have built our understanding of the effects of clazosentan on cerebral vasospasm, suggesting that it has the potential to prevent ischemic complications of cerebral vasoconstriction and to decrease the need for invasive intervention.

In Japan, two registration studies evaluating the safety and efficacy of clazosentan in reducing vasospasm-related morbidity and mortality events after aneurysm-securing procedures are being conducted. Results are expected in the second half of 2018.

Later in 2018, Idorsia expects to initiate a Phase 3 study evaluating the safety and efficacy of clazosentan in an aSAH population enriched for the risk of cerebral vasospasm.

**Available clinical data**

Previously, clazosentan was investigated for the prevention of angiographic vasospasm in patients with aSAH in a Phase 2 study, CONSCIOUS-1. This study was followed by two Phase 3 studies, CONSCIOUS-2 and CONSCIOUS-3, to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality. The treatment effect of clazosentan 5 mg/h in CONSCIOUS-2 did not reach statistical significance, resulting in the premature termination of recruitment into CONSCIOUS-3. However, analysis of the data collected in CONSCIOUS-3 showed that clazosentan 15 mg/h significantly reduced cerebral vasospasm-related morbidity and all-cause mortality, with a 44% relative risk reduction (p=0.0074). This dose also significantly reduced the incidence of delayed ischemic neurological deficit with a 54% relative risk reduction (p=0.0038). In addition, clazosentan reduced the need for rescue therapy for vasospasm. Clazosentan did not improve long-term clinical outcome.
Milestones
2015  Initiation of Phase 2 proof of concept to treat vasospasm in patients with aSAH
2011  Phase 3 CONSCIOUS-3 study discontinued
2010  Phase 3 CONSCIOUS-2 study concluded - primary endpoint not met
2006  Orphan status granted in US
2003  Orphan status granted in Europe

Key scientific literature
Cenerimod is a selective sphingosine-1-phosphate receptor 1 (S1P1) modulator, which potentially offers a novel approach for systemic lupus erythematosus (SLE) – a disease with limited treatment options.

SLE, the most common form of Lupus, is an autoimmune disease. In SLE, the body’s immune system, which normally protects us from infections, mistakenly attacks healthy tissue, which can affect the skin, joints, kidneys, brain, and other organs. While the cause of SLE is not fully known, T and B lymphocytes are considered to play a major role in the disease.

Cenerimod blocks the egress of lymphocytes from lymphoid organs, thereby reducing the availability of circulating effector T and B cells that can invade target organs. This pharmacodynamic effect is sustained with continued daily oral dosing, with no need for up-titration, and is slowly reversible upon drug discontinuation.

Current status
In a Phase 2 study in adult patients with SLE, cenerimod induced a dose-dependent reduction in lymphocyte count and was well tolerated at all dose levels. In December 2017, the US FDA designated the investigation of cenerimod for the treatment of systemic lupus erythematosus as a Fast Track development program. The Fast Track designation is intended to promote communication and collaboration between the FDA and the company for drugs that treat serious conditions and fill an unmet medical need.

Idorsia is currently discussing the development program with health authorities to advance cenerimod in this underserved disease as quickly as possible.

Available clinical data
In the Phase 1 program, cenerimod showed marked and sustained lymphocyte lowering effects, supporting further exploration in patients. Cenerimod completed a Phase 2 safety study that investigated the pharmacodynamics, safety and tolerability of cenerimod in adult patients with SLE. The study enrolled 67 patients to receive either 0.5, 1, 2 or 4 mg/day of cenerimod over a treatment period of 12 weeks. The investigated study population was representative for SLE and balanced across the four tested dose levels and placebo. The results of the study showed that cenerimod induces a dose-dependent reduction in lymphocyte count and was well tolerated at all dose levels. The occurrence of adverse events was similar in all five treatment groups.

Milestones
2015 Initiation of Phase 2 clinical development in systemic lupus erythematosus

Key scientific literature
Other Compounds

Idorsia has developed platforms of expertise in families of molecular targets which allow high productivity in the generation of innovative compounds potentially addressing a wide range of high unmet medical needs.

ACT-246475, a P2Y12 receptor antagonist for acute coronary syndrome
ACT-246475 is a P2Y12 receptor antagonist in development for the prevention of myocardial damage in acute coronary syndrome and is targeted for individuals at risk of a myocardial infarction. The compound meets a very specific pharmacokinetic profile, which requires the product to be well-absorbed subcutaneously after self-administration, with a rapid onset of action and 3 to 4 hours duration of action. ACT-246475 has completed Phase 1. A Phase 2 study was initiated in January 2018.

ACT-774312, a CRTH2 receptor antagonist for asthma and allergy disorders
ACT-774312 is an oral CRTH2 receptor antagonist being developed for the treatment of asthma and allergy disorders. Idorsia believes there is a significant need for new therapies to treat asthma and allergic patients whose disease is not fully controlled with conventional therapies. Current evidence suggests that treatment with a CRTH2 receptor antagonist can contribute to the better management of these conditions. A Phase 1 program is ongoing.

ACT-539313, a selective orexin 1 receptor antagonist (SORA) for anxiety disorders
SORA is a selective orexin 1 receptor antagonist being investigated for the potential treatment of anxiety disorders. It is a potent antagonist, brain-penetrating, and has shown anxiolytic (anxiety-inhibiting) effects after oral administration in four different preclinical models representing different sub-types of anxiety disorders. In these models, it did not induce sleep at anxiolytic doses. A Phase 1 program is ongoing.

ACT-709478, a T-type calcium channel blocker for epilepsy
ACT-709478 is a potent, brain-penetrating, selective triple calcium T-channel blocker for potential use in certain forms of generalized epilepsy. The compound has shown efficacy after oral administration in two animal models of generalized epilepsy. A Phase 2a study has been initiated to evaluate the effect in photosensitive epilepsy patients following single dose administration.

ACT-519276, a GBA2/GCS inhibitor for Orphan CNS diseases
While Idorsia advances its late-stage pipeline, it also replenishes the early-stage pipeline with new compounds. At the beginning of 2018, Idorsia began Phase 1 clinical development with ACT-519276 for orphan CNS diseases.
Idorsia is an independent biopharmaceutical company based on science and innovation. The company is specialized in the discovery and development of small molecules, to transform the horizon of therapeutic options. It is headquartered in Allschwil/Basel, Switzerland and is quoted on the SIX Swiss Exchange (tickersymbol: IDIA). All trademarks are legally protected by their respective owners.

Disclaimer This fact sheet has the sole purpose to provide members of the public with general information about the activities of Idorsia. The forward-looking statements in this fact sheet are based on current expectations and belief of company management, which are subject to numerous risks and uncertainties.

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