Idorsia’s clinical development comprises a broad spectrum of expertise clustered within multiple units: 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 leaders – 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 license 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”), anti-infective targets, ion channels and certain enzymes. The drug discovery team comprises approximately 380 professionals, facilitating 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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* Johnson and Johnson has option to jointly develop and solely commercialize worldwide

** In Japan a Phase 2 study was completed in 2017 and market registration trials have started

*** Idorsia has exclusive option to worldwide rights to ReveraGen’s Vamorolone
Aprocitentan (ACT-132577)

Aprocitentan is an orally active dual endothelin receptor antagonist that is being investigated for patients whose hypertension is uncontrolled despite the use of multiple anti-hypertensive drugs, so-called resistant hypertension.

Current status
Aprocitentan completed a Phase 2 study, in May 2017, 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 (i.e., the most common type of hypertension that by definition has no identifiable cause) to identify the optimal doses for further studies. Based on the positive results, Idorsia is now discussing with health authorities the design of a Phase 3 program which will consist of two studies evaluating the effect of aprocitentan on systolic and diastolic blood pressure in patients with resistant hypertension. The program will also provide long-term safety information. If successful, the program will provide the basis for registration and differentiation of the product.

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.

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. Patients with resistant hypertension are also more likely to have a medical history of chronic kidney disease and diabetes mellitus, amplifying their vulnerability and the complexity of treatment.

Preclinical research has shown that aprocitentan is effective in hypertensive animal models. Aprocitentan has potential as an oral, potent, once-a-day drug with a long-lasting effect on reducing blood pressure.

Drug Discovery and Clinical Development
Development Pipeline
> Aprocitentan
ACT-541468 (DORA)
Clazosentan
Cenerimod
Lucerastat
Phase 1 Compounds
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.

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.

Milestones

2015  Initiation of Phase 2 dose-response study
2014  Initiation of Phase 1 clinical program

Key scientific literature

ACT-541468 (DORA) is a dual orexin receptor antagonist which targets the orexin system and is intended to treat insomnia.

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, for the benefit of patients.

**Current status**

In July 2017, Idorsia announced positive results for a comprehensive Phase 2 program with ACT-541468 in insomnia. The program comprised two placebo-controlled dose-response studies evaluating the safety and efficacy of ACT-541468 in both adult and elderly patients with insomnia, with a total of 418 patients participating in the trials. Both studies met their primary endpoint. The results showed the desired effect on sleep maintenance and onset, with a significant dose-response relationship. The positive results of the Phase 2 program support the decision to initiate a pivotal registration program with ACT-541468 in insomnia.

**Available clinical data**

The first 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 study, conducted in 58 elderly patients (ranging from 65 to 85 years), confirmed the efficacy and safety profile of ACT-541468 in this 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 is an endothelin receptor antagonist in development as an intravenous infusion for cerebral vasospasm secondary to aSAH.

Aneurysmal subarachnoid hemorrhage (aSAH) is a sudden life-threatening bleeding occurring in the subarachnoid space. It is caused by the rupture of an aneurysm that causes blood to escape and accumulate in the space around the brain. To stop the bleeding, endovascular coiling or microsurgical clipping is required.

In about half of aSAH patients, after a few days of improvement, a worsening of their condition may occur due to a cerebral vasospasm (constriction of intracerebral arteries), which is at least in part explained by a release of endothelin subsequently to the bleeding event. Cerebral vasospasm diminishes blood flow to the brain and contributes to the severity of brain damage and the poor long-term outcomes associated with aSAH.

There is no effective pharmacotherapy available for the prevention or the treatment of cerebral vasospasm and its severe complications. Idorsia believes clazosentan can decrease the need for rescue invasive intervention, which is currently used to alleviate vasospasm associated with aSAH at high cost and with high medical risk.

**Current status**

Currently, clazosentan is being investigated in a Phase 2 study, REVERSE, which evaluates whether clazosentan has a rapid effect in reversing angiographically confirmed cerebral vasospasm in patients with aSAH treated by endovascular coiling or surgical clipping. Results are expected to be discussed with health authorities by the end of 2017.

**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**

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
Cenerimod completed a Phase 2 safety study that investigated the pharmacodynamics, safety and tolerability of cenerimod in adult patients with SLE in May 2017. Based on the positive results of the study, cenerimod will move into an exploratory Phase 2 dose-finding study to deliver all the information required to design the Phase 3 program.

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
Lucerastat

Lucerastat is an iminosugar that inhibits glucosylceramide synthase and has the potential to provide substrate reduction therapy. It is being evaluated for the treatment of Fabry disease.

Fabry disease is a rare inherited genetic disorder in which patients have a deficiency or dysfunction of the enzyme α-galactosidase A (α-GalA). This enzyme is essential for breaking down a fatty waste product called globotriaosylceramide (Gb3) in the cells of the body. The genetic defect, which is on the X-chromosome, leads to accumulation of Gb3 within the cells of the body. This build-up results in a cytotoxic reaction causing malfunction of many cell types and organs, including blood vessels, skin, eyes, gastrointestinal system, kidney, heart, and the central nervous system.

Lucerastat is an oral monotherapy that has potential for patients with Fabry disease regardless of their mutation. In an exploratory clinical study in patients with Fabry disease receiving enzyme replacement therapy, treatment with oral lucerastat demonstrated a marked decrease in the plasma levels of metabolic substrates thought to be related to the development of the disease.

Lucerastat for Fabry disease has received Orphan Drug designation in the US and in the EU.

Current status

The design of a pivotal Phase 3 study, expected to start in 2018, is currently under discussions with health authorities.

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

Phase 1 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. Idorsia currently has four compounds in Phase 1 clinical development.

ACT-246475, a P2Y12 receptor antagonist in 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, and the study design for Phase 2 is currently being developed.

ACT-774312, a CRTH2 receptor antagonist in 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. ACT-774312 has entered Phase 1, and a decision to move into Phase 2 is expected in the second half of 2017.

ACT-539313, a selective orexin 1 receptor antagonist (SORA) in 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. Phase 1 trials are ongoing, with a decision to move into Phase 2 expected in the second half of 2017.

ACT-709478, a T-type calcium channel blocker in 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 study has been initiated to evaluate the effect in photosensitive epilepsy patients following single dose administration.