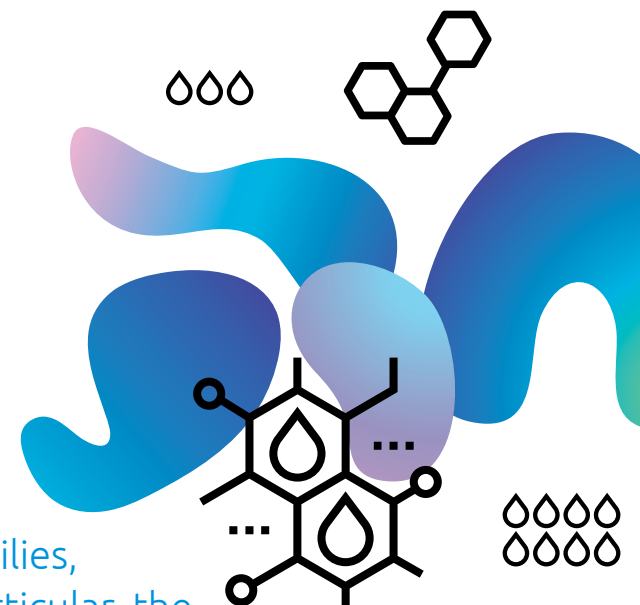




# Drug Discovery & Clinical Development

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 facilitates the combination of drug discovery technology with human expertise and teamwork, in a single research center based in Allschwil, Switzerland.



## Drug Discovery and Clinical Development

Development Pipeline

Aprocitentan

Clazosentan

Lucerastat

Nemorexant

Cenerimod

Other Compounds

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 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.

# Development Pipeline



Compound	Mechanism of Action	Target Indication	Status
<a href="#">Aprocitentan*</a>	Dual Endothelin receptor antagonist	Resistant hypertension management	Phase 3
<a href="#">Clazosentan**</a>	Endothelin receptor antagonist	Vasospasm associated with aneurysmal subarachnoid hemorrhage (aSAH)	Advancing to Phase 3
<a href="#">Lucerastat</a>	Glucosylceramide synthase (GCS) inhibitor	Fabry disease	Phase 3
<a href="#">Nemorexant</a>	Dual orexin receptor antagonist	Insomnia	Phase 3
<a href="#">Cenerimod</a>	S1P <sub>1</sub> receptor modulator	Systemic lupus erythematosus	Phase 2
<a href="#">ACT-246475</a>	P2Y <sub>12</sub> receptor antagonist	Acute coronary syndrome (ACS)	Phase 2
<a href="#">ACT-774312</a>	CRTH2 receptor antagonist	Nasal polyposis	Advancing to Phase 2
<a href="#">ACT-519276</a>	GBA2/GCS inhibitor	Orphan CNS disease	Phase 1
<a href="#">ACT-539313</a>	Selective orexin 1 receptor antagonist	Anxiety	Phase 1
<a href="#">ACT-709478</a>	T-type calcium channel blocker	Epilepsy	Phase 1

## Drug Discovery and Clinical Development

### > Development Pipeline

Aprocitentan

Clazosentan

Lucerastat

Nemorexant

Cenerimod

Other Compounds

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

\*\* Market registration trials are being conducted in Japan.

# Aprocitentan



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.

Hypertension, or high blood pressure, remains the most frequent addressable risk factor of cardiovascular morbidity/mortality outcomes, ahead of smoking and obesity, as reported by the 2015 Global Burden of Disease, Injuries, and Risk Factor Project collaborating with WHO.

Patients whose blood pressure remains high despite receiving at least three antihypertensive medications from different classes, including a diuretic, at maximal tolerated dose are categorized as having resistant hypertension. Patients with resistant hypertension are typically older and often suffer from obesity, sleep apnea, and/or diabetes mellitus. Uncontrolled hypertension can lead to multiple cardiovascular and renal adverse outcomes, including stroke, heart disease, and kidney failure. These co-morbidities increase a patient's vulnerability and the complexity of their treatment.

## Drug Discovery and Clinical Development

Development Pipeline

### > Aprocitentan

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Lucerastat

Nemorexant

Cenerimod

Other Compounds

### Current status

In June 2018, Idorsia initiated PRECISION, a multi-center, double-blinded, placebo-controlled, randomized, parallel-group, Phase 3 study to demonstrate the blood pressure lowering effect of aprocitentan when added to standard-of-care in resistant hypertension patients. Idorsia, following consultation with regulatory agencies, has designed an efficient, single Phase 3 study. The study will address both the short-term efficacy of aprocitentan and the durability of its effect on long-term treatment in a placebo-controlled manner.

Patients with history of resistant hypertension will undergo a thorough screening and run-in period. This will confirm the diagnosis of resistant hypertension by excluding pseudo or apparent resistant hypertension. During the screening period, patient's background anti-hypertensive therapies will be transitioned to a standardized fixed combination of a calcium channel blocker (amlodipine), an angiotensin receptor blocker (valsartan), and a diuretic (hydrochlorothiazide).

Patients with true resistant hypertension will then be randomized to receive aprocitentan 12.5 mg, 25 mg, or placebo once-daily. The study consists of 3 sequential treatment periods. The first is a double-blind treatment period designed to demonstrate the effect of aprocitentan on blood pressure at Week 4, compared to placebo. Patients then enter a treatment period where they are treated with 25 mg aprocitentan for 32 weeks. This is followed by a double-blind, randomized withdrawal treatment period where patients will remain either on aprocitentan 25 mg or switch to placebo for 12 weeks. The latter treatment period is designed to demonstrate the durability of the blood pressure lowering effect of aprocitentan. Patients will then enter a 30-day safety follow-up period.

From the initial screened patient population, at least 600 patients will be randomized and at least 300 patients are expected to complete the study. The study will be conducted in approximately 100 sites in around 20 countries.



## Drug Discovery and Clinical Development

Development Pipeline

### > Aprocitentan

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### 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 25mg 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

- 2018** Phase 3 study initiated
- 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

– Iglarz M, et al. Clin Sci 2010; 119:453-63

# Clazosentan



Clazosentan is an endothelin receptor antagonist being developed as an intravenous infusion for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia in patients following an aneurysmal subarachnoid hemorrhage.

Aneurysmal subarachnoid hemorrhage (aSAH) is a sudden life-threatening bleeding occurring in the subarachnoid space. It is caused by the rupture of an aneurysm – a weak, bulging spot on the wall of a cerebral artery. Emergency surgical repair (endovascular coiling or microsurgical clipping) is required to stop the hemorrhage.

The bleeding and the release of a vasoconstrictor, endothelin, by the neighboring vascular endothelium, causes many patients to experience vasospasm (constriction of arteries in the brain). This diminishes blood flow to the brain and as a consequence, about one third of patients experience worsening of their neurological condition. Patients with thick and diffuse blot clots are at a significantly higher risk of experiencing cerebral vasospasm. Today, patients with vasospasm are typically treated with hemodynamic therapy, or more invasive neurovascular intervention such as balloon angioplasty or intra-arterial administration of vasodilators

## Current status of the global registration study

In June 2018, Idorsia announced that it is initiating a Phase 3 study, REACT, to investigate the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia in patients following an aneurysmal subarachnoid hemorrhage.

**REACT is a prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study in adult patients with aSAH. Approximately 400 patients, regardless of whether their hemorrhage has been treated with surgical clipping or endovascular coiling are expected to be enrolled. Patients will be enrolled from 100 trial sites across 15 countries who will be randomized to either 15 mg/hr clazosentan or placebo for a treatment period of up to 14 days. The study is expected to begin later in 2018 and run for around 27 months.**

**REACT will enroll aSAH patients identified as being at high-risk of developing delayed**

**ischemic neurological deficit because of high volume of their hemorrhage, as assessed by CT scan on hospital admission. Patients experiencing asymptomatic moderate to severe cerebral vasospasm within 14 days of securing the aneurysm may also be included.**

## 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 dose of clazosentan (5 mg/h) used in CONSCIOUS-2 did not allow a statistically significant treatment effect to be observed, resulting in the premature termination of CONSCIOUS-3. However, exploratory analysis of the data collected in CONSCIOUS-3 showed that a higher dose of clazosentan, i.e. 15 mg/h, significantly reduced cerebral vasospasm-related morbidity and all-cause mortality, with a 44%

## Drug Discovery and Clinical Development

Development Pipeline

Aprocitentan

> Clazosentan

Lucerastat

Nemorexant

Cenerimod

Other Compounds

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Cenerimod

Other Compounds

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.

More recently, a pilot study evaluating the early effect of clazosentan on reversing established cerebral vasospasm in large proximal cerebral artery segments at 3 hours post-initiation, showed that clazosentan acts on some large brain arteries but the real benefit is in the effect on smaller arteries not accessible to endo-arterial therapy. A post-hoc analysis of the effect of clazosentan on reversing established cerebral vasospasm in the entire cerebral vasculature, including smaller distal vessel segments and the cerebellar arteries, showed a clearly visible improvement in vessel diameter at 3 hours, in a significant proportion of patients. Detailed results will be provided in scientific communication.

Those studies have also established an extensive safety profile with over 1'800 patients treated.

### Current status of the registration program in Japan

A Phase 2 study in Japanese and Korean patients showed that 10 mg/hr clazosentan significantly reduced vasospasm, and vasospasm-related morbidity and mortality events. On that basis, a registration program was initiated with clazosentan in Japan in May 2016. Aneurysmal subarachnoid hemorrhage is a significant problem in Japan with a prevalence around twice as high as in the rest of the world.

The program consists of two prospective, multicenter, double-blind, randomized, placebo-controlled studies to assess the efficacy and safety of clazosentan in reducing vasospasm, and vasospasm-related morbidity and mortality events in adult patients with aneurysmal subarachnoid hemorrhage. Patients are randomized to either 10 mg/hr clazosentan or placebo for up to a cumulative maximum of 15 days following the onset of aSAH. The two studies follow the same study design, with one enrolling patients whose aSAH was

treated by surgical clipping and the other enrolling patients who were treated for aSAH by endovascular coiling. Each of the two Japanese studies have enrolled 160 patients. Based on a lower than anticipated number of events, Idorsia has decided to increase the number of patients recruited into each study. Recruitment is now expected to last into 2019. The company will provide further information with the Full Year financial reporting in February 2019.



### Milestones

- 2006 Orphan status granted in US
- 2003 Orphan status granted in Europe

### Key scientific literature

- Fujimura, et al. Cerebrovasc Dis 2017;44:59–67.
- Macdonald R L, et al. Stroke. 2012; 43(6):1463-9.
- Macdonald R L, et al. The Lancet. Neurology, 2011; 10(7):618-625.
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- Vajkoczy P, et al. Journal of Neurosurgery 2005; 103:9-17.
- Roux S. et al. J Pharmacol Exp Ther 1997; 283:1110-1118.

# Lucerastat



Lucerastat is an oral monotherapy offering a new treatment approach for a very broad spectrum of patients living with Fabry disease.

Fabry disease is a rare, life threatening, inherited lysosomal storage disorder in which a particular lipid, called globotriaosylceramide (Gb3), accumulates in cells of many organs of the body. This build-up results in cellular dysfunction leading to a range of signs and symptoms from neuropathic pain (pain primarily in the hands and feet), stomach, skin and eye problems, to hypertension, progressive kidney damage, cardiomyopathy, and stroke. New treatment options are needed to treat the underlying mechanism of the disease and provide symptomatic relief.

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.

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## Current status

**In May 2018, Idorsia initiated MODIFY, a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. The study aims to determine the effect of study treatment on neuropathic pain during 6 months of treatment, measured with Idorsia's validated Fabry disease pain**

**instrument. At the end of the double-blind period, patients will be given the possibility to enter in an open label extension study. Approximately 108 patients are expected to be enrolled, randomized in a 2:1 ratio to either lucerastat or placebo. The study is expected to run for around 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.

## Drug Discovery and Clinical Development

Development Pipeline

Aprocitentan

Clazosentan

> **Lucerastat**

Nemorexant

Cenerimod

Other Compounds



## Drug Discovery and Clinical Development

Development Pipeline

Aprocitentan

Clazosentan

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Nemorexant

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Other Compounds

### Available clinical data

Idorsia preclinical research with a mouse model of Fabry disease has shown that glucosylceramide synthase inhibition with lucerastat reduces the accumulation of Gb3 in kidney and certain nerve endings. Furthermore, Idorsia has shown that lucerastat lowers Gb3 in cultured cells from patients with Fabry disease of both sexes harboring different GLA genetic mutation types.

The safety, tolerability, pharmacodynamics, and pharmacokinetics of oral lucerastat were evaluated in an exploratory study in adult patients with Fabry disease. In this single-center, open-label, randomized study, 10 patients received lucerastat 1000 mg b.i.d. for 12 weeks on top of enzyme replacement therapy and four patients with Fabry disease received ERT only. A rapid decrease in

plasma Gb3, a marker of Fabry disease, and its precursors was observed, demonstrating that lucerastat 1000 mg b.i.d. inhibits GCS and provides alpha-GalA substrate reduction with a fast onset in adult patients with Fabry disease on ERT.

### Milestones

**2018** Phase 3 study initiated

**2016** Phase 1b study completed

### Key scientific literature

- Guérard N, et al. Clin Pharmacol Ther. 2017;103:703-11.
- Guérard N, et al. J Clin Pharmacol. 2017;57:1425-31.
- Guérard N, et al. Orphanet J Rare Dis. 2017; 12(1):9
- Welford R, et al. Molecular Genetics and Metabolism. 2017;120 (Abstract 360): S139.



# Nemorexant



Nemorexant (proposed INN for 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 nemorexant will have a low potential for abuse. Data from a comprehensive Phase 1 and Phase 2 program indicates that nemorexant 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 nemorexant the potential to be differentiated from current sleep medications.

## Current status

**In June 2018, Idorsia initiated a Phase 3 registration program with nemorexant for the treatment of adult and elderly patients with insomnia. The Phase 3 program aims to confirm the positive results observed in the comprehensive Phase 2 clinical program in both adult and elderly patients with insomnia and is based on interaction with Health Authorities.**

**The program comprises two confirmatory studies together with a 40-week extension study which will recruit a total of 1,800 patients with insomnia from over 160 sites across 18 countries and is anticipated to run for around 2 years.**

**The confirmatory polysomnography studies will assess the efficacy and safety of nemorexant on objective and subjective sleep and daytime functioning parameters in adult and elderly patients with insomnia disorder. The first study will evaluate treatment with 25 mg and 50 mg doses**

**over 3 months, while the second study will measure treatment with 10 mg and 25 mg doses over 3 months. The 40-week extension study will measure all three doses, generating data for long-term treatment of insomnia.**

## Available clinical data

The safety and efficacy of nemorexant in adult and elderly patients with insomnia was evaluated in a comprehensive Phase 2 program, comprising two studies and included zolpidem as an active reference. Both studies showed the desired effect on sleep maintenance and onset, with a significant dose-response relationship; treatment was generally well tolerated.

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

## Drug Discovery and Clinical Development

Development Pipeline

Apricitentan

Clazosentan

Lucerastat

> **Nemorexant**

Cenerimod

Other Compounds

first 2 nights of treatment, measured by polysomnography). In addition, nemorexant significantly decreased LPS (latency to persistent sleep) in a dose-dependent manner. Treatment with nemorexant was generally well tolerated. There were no reports of serious adverse events related to nemorexant.

The positive readouts of the second Phase 2 study, conducted in 58 elderly patients (ranging from 65 to 85 years), were consistent with the efficacy and safety

profile of nemorexant for 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

- 2018** Initiation of Phase 3 registration program
- 2017** Completion of Phase 2 clinical program
- 2014** Initiation of Phase 1 clinical program

### Key scientific literature

- Brisbane-Roch C. et al. Nat Med. 13(2):150-5; 2007.
- Hoever P et al. Clin Pharmacol Ther Clin Pharmacol Ther. 2012; 91(6); 975-985.
- Roth T. 2007;3 Suppl 5:S7-10.

## Drug Discovery and Clinical Development

Development Pipeline

Aprocitentan

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Lucerastat

### > Nemorexant

Cenerimod

Other Compounds

# Cenerimod



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

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- Borchers AT, et al. Autoimmun Rev. 2010; 9(5):A277-87.
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- Rahman A, Isenberg DA. N Engl J Med. 2008; 358:929-39.
- Abu-Shakra M, et al. J Rheumatol 1995; 22(7):1259-64.

## Drug Discovery and Clinical Development

Development Pipeline

Aprocintentan

Clazosentan

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Nemorexant

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Other Compounds

# 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 antagonist for the treatment of nasal polyposis**

ACT-774312 is an oral CRTH2 antagonist being developed for the treatment of nasal polyposis. Idorsia believes that there is a significant need for new oral therapies to treat nasal polyposis in patients whose disease is not fully controlled with current therapies. Current evidence suggests that disease pathogenesis in nasal polyposis involves type-2 inflammatory processes and that a CRTH2 antagonist can be effective in reducing ongoing inflammation and nasal polyp burden. A proof-of-concept Phase 2 study has been initiated.

## **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.

### **Drug Discovery and Clinical Development**

Development Pipeline

Aprocitentan

Clazosentan

Lucerastat

Nemorexant

Cenerimod

[» Other Compounds](#)

**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.

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**Drug Discovery  
and Clinical  
Development**

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