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.

Idorsia aims to deliver new products with the potential to significantly change the treatment options in their target diseases. We want to bring new perspectives to the development of innovative compounds, challenging accepted paradigms to answer the questions that matter most. Our key assets have the potential to transform treatment in the target indications.
## Development Pipeline

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Target Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daridorexant</td>
<td>Dual orexin receptor antagonist</td>
<td>Insomnia</td>
<td>NDA submitted, MAA in preparation</td>
</tr>
<tr>
<td>Aprocitentan*</td>
<td>Dual endothelin receptor antagonist</td>
<td>Resistant hypertension management</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
| Clazosentan   | Endothelin receptor antagonist           | Vasospasm associated with aneurysmal subarachnoid hemorrhage | Japan: Filing in preparation  
Global: Phase 3 ongoing | |
| Lucerastat    | Glucosylceramide synthase inhibitor      | Fabry disease                                           | Phase 3                                                     |
| Selatogrel    | P2Y12 receptor antagonist                | Suspected acute myocardial infarction                  | Phase 3 in preparation                                     |
| Cenerimod     | S1P1 receptor modulator                  | Systemic lupus erythematosus                           | Phase 2                                                     |
| ACT-774312    | CRTH2 receptor antagonist                | Nasal polyposis                                        | Phase 2                                                     |
| ACT-539313    | Selective orexin 1 receptor antagonist    | Psychiatric disorders                                  | Phase 2 in preparation                                     |
| Sinbaglustat  | GBA2/GCS inhibitor                       | Rare lysosomal storage disorders                        | Phase 1 complete                                           |
| ACT-1004-1239 | CXCRI7 antagonist                        | Immunology / Cancer Immunotherapy                      | Phase 1                                                     |
| ACT-1014-6470 | -                                        | Immunology                                              | Phase 1                                                     |
| ACT-541478    | -                                        | CNS                                                    | Phase 1                                                     |

* In collaboration with Janssen Biotech to jointly develop aprocitentan, Janssen Biotech has sole commercialization rights worldwide.

Neurocrine Biosciences has a global license to develop and commercialize our ACT-709478, a novel T-type calcium channel blocker, for the treatment of a rare form of pediatric epilepsy. In November 2020, Neurocrine announced the initiation of a Phase 2 study for ACT-709478.
Daridorexant is a dual orexin receptor antagonist (DORA) developed for the treatment of insomnia. The Phase 3 registration program demonstrated the efficacy of daridorexant on objective and subjective sleep parameters, and showed positive effects on daytime functioning, while keeping a favorable safety profile.

Insomnia is a condition of overactive wake signaling that can have a profound effect on the lives of patients. Insomnia can be defined as difficulty falling asleep and/or staying asleep, occurring at least three times a week for a minimum of three months.

Insomnia is a common problem. Population-based epidemiological studies suggest that approximately 10% of the general population have complaints of sleep disruption with associated symptoms of distress or daytime functional impairment consistent with the diagnosis of insomnia disorder.

**Current status**

In June 2018, we initiated a Phase 3 registration program comprising two confirmatory studies of three-month duration, together with a long-term extension study. Both pivotal studies are complete, having enrolled around 1,850 patients with insomnia at over 160 sites across 18 countries. As insomnia often presents later in life, and elderly patients are more susceptible to experience fragmented sleep, early awakening and daytime sleepiness, around 40% of the recruited population was aged 65 years or older.

The confirmatory double-blind, randomized, placebo-controlled, polysomnography studies investigated three doses of daridorexant (10 mg, 25 mg, and 50 mg) on sleep and daytime functioning parameters, objectively in a sleep lab by polysomnography and subjectively with a daily patient diary at home. The impact of insomnia on patients’ daytime functioning was measured daily using the sleepiness domain score from the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), a Patient Reported Outcome (PRO) instrument validated according to the FDA Guidance for Industry. 804 patients continued treatment in the ongoing 40-week extension study which will measure the effect of all three doses vs. placebo, generating data for long-term treatment of insomnia.

Results of the first study, investigating daridorexant doses of 25 and 50 mg vs. placebo, were reported in April 2020. Compared to placebo, the study demonstrated efficacy of treatment with daridorexant on objective and subjective sleep parameters and daytime functioning, with patients reporting no morning sleepiness, no signals suggestive of rebound insomnia compared to baseline sleep parameters, and no withdrawal symptoms upon treatment discontinuation.

Daridorexant at both 25 and 50 mg significantly improved sleep onset and sleep maintenance. Daridorexant also significantly improved subjective total sleep time. The results were consistently statistically significant at month 1 and at month 3, indicating sustained benefit. Furthermore, treatment with daridorexant improved patients’ daytime functioning from baseline at month 1 and month 3.

The most frequent treatment-emergent adverse events reported over 3% incidence and higher than placebo were nasopharyngitis and headache. Somnolence was reported in 6 (1.9%) patients on placebo, 11 (3.5%) patients on daridorexant 25 mg, and 5 (1.6%) patients on daridorexant 50 mg.

Results of the second study investigating...
daridorexant doses 10 and 25 mg, were reported in July 2020. The study confirmed the findings of the first pivotal study, demonstrating efficacy of treatment with daridorexant on objective and subjective sleep parameters and showed positive effects on daytime functioning, with patients reporting no morning sleepiness compared to placebo, no signals suggestive of rebound insomnia compared to baseline sleep parameters, and no withdrawal symptoms upon treatment discontinuation.

The safety profile was consistent with the results of the first study. The most frequent treatment-emergent adverse events reported over 3% incidence and higher on 25 mg of daridorexant than placebo were nasopharyngitis, headache, somnolence and fatigue.

Furthermore, the similar design of the two Phase 3 studies allowed for the two groups of 25 mg and placebo to be pooled and a pre-planned analysis to be made. The pooled analysis supports the safety and efficacy of the 25 mg dose of daridorexant.

In addition, an interim analysis of the ongoing 40-week extension study, once all patients had received six months of treatment (during the core and the extension study together), has been conducted. The study, which primarily measures the safety of long-term treatment with daridorexant and allows an exploratory analysis of the maintenance of efficacy, did not uncover new emerging safety findings, neither qualitatively nor quantitatively, while the efficacy on sleep and daytime functioning was maintained over the longer duration treatment.

Idorsia has now collected the required data and submitted the new drug application (NDA) to the US FDA on January 8, 2021. This in turn allows for commercialization and launch – subject to approval – in the first half of 2022.

Available clinical data
Prior to the Phase 3 program, the safety and efficacy of daridorexant in adult and elderly patients with insomnia was evaluated in a comprehensive Phase 2 program, comprising two studies, one of which included zolpidem 10 mg 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.

In addition, a comprehensive clinical pharmacology program has been conducted totaling 18 studies and including, amongst others, studies assessing abuse liability, drug-drug interactions, next-morning driving in healthy participants, the effect of daridorexant on respiratory function in patients with chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA), and the pharmacokinetics of daridorexant in patients with liver and renal impairment. The program showed robust results to be included in the filing with health authorities.

Milestones
2021 NDA submitted to US FDA on Jan 8
2020 Both pivotal studies report positive results
2018 Initiation of Phase 3 registration program
2017 Completion of Phase 2 clinical program
2015 Initiation of Phase 1 clinical program

Key scientific literature
Aprocitentan: An Oral Drug for Resistant Hypertension

Aprocitentan is an orally active, potent, dual endothelin receptor antagonist (ERA), which is being investigated for the treatment of patients whose blood pressure is uncontrolled despite receiving triple antihypertensive therapy, so-called resistant hypertension. Hypertension (high blood pressure) is one of the most common cardiovascular risks, and its prevalence continues to rise. According to a recent study, there are more than 1 billion people living with hypertension worldwide. Left uncontrolled, hypertension can lead to life-threatening conditions such as stroke, ischemic heart disease, or kidney disease.

Patients with a 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, the patient's background antihypertensive therapies will be transitioned to a standardized triple 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-bind treatment period designed to demonstrate the effect of aprocitentan on blood pressure after 4 weeks, compared to placebo. Patients then enter a treatment period where they receive aprocitentan 25 mg for 32 weeks. This is followed by a randomized double-blind 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.

Collaboration Agreement with Janssen Biotech
In December 2017, Janssen Biotech, Inc. 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 is overseeing the Phase 3 development and regulatory submission for difficult-to-control hypertension. The costs will be shared equally between both partners. Janssen will oversee the Phase 3 development and submission for any additional indications and will have the sole worldwide commercialization rights.

Drug Discovery and Clinical Development

Development Pipeline
Daridorexant
Aprocitentan
Clazosentan
Lucerastat
Selatogrel
Cenerimod
Other Compounds
Aprocitentan has demonstrated a synergistic effect with other antihypertensive drugs (RAAS blockers) in animal models, and the clinical pharmacology profile suggests that there is a low propensity for drug-drug interaction. In animal models of salt-dependent hypertension, aprocitentan demonstrated efficacy on blood pressure and renal and cardiac protection.

The overall incidence of adverse events observed in the aprocitentan groups (ranging from 22.0% to 40.2%) was similar to that seen in the placebo group (36.6%). Overall, the most common events were hypertension, headache, and nasopharyngitis.

**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**

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**Available clinical data**

In a Phase 2 dose-response study, patients with hypertension (mean sitting systolic/diastolic blood pressure of 149.7/97.6 mmHg) received monotherapy with aprocitentan 5, 10, 25 or 50 mg, matching placebo or lisinopril 20 mg as a positive control, once daily for eight weeks using a randomized, double-blind, parallel-group study design. Blood pressure was measured at baseline and weeks 2, 4, 8, and 10 (withdrawal) with an automated office blood pressure (AOBP) device, which recorded and averaged multiple blood pressure readings while the patient was unattended and resting quietly.

A total of 490 eligible patients were randomized, with 430 patients successfully completing the double-blind treatment period. Decreases in sitting systolic and diastolic AOBP, from baseline to week 8 were 10.3 and 6.3, 15.0 and 9.9, 18.5 and 12.0 and 15.1 and 10.0 mmHg for aprocitentan 5, 10, 25, and 50 mg, respectively vs. 7.7 and 4.9 mmHg for placebo and 12.8 and 8.4 mmHg for lisinopril. No changes in heart rate were observed for any dose of aprocitentan. The dose response was therefore consistent across parameters, with efficacy observed at 10 and 25 mg, with no additional effect at 50 mg. The effect of aprocitentan was demonstrated to cover a 24-hour period.
Clazosentan

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

Aneurysmal subarachnoid hemorrhage (aSAH) is a rare condition involving 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 can lead to cerebral vasospasm (constriction of arteries in the brain) usually occurring between four and fourteen days after aSAH. This diminishes blood flow to the brain and about one third of patients consequently experience worsening of their neurological condition. Cerebral vasospasm is one of the leading secondary causes of disability and death in those that experience aSAH.

The prevalence of aSAH is estimated to be between 6 and 9 per 100,000 worldwide and is a significant problem in Japan with an incidence around twice as high as in many other countries of the world.

Current status: Global registration study
In February 2019, Idorsia initiated REACT, a double-blind, randomized, placebo-controlled, Phase 3 study to investigate the efficacy and safety of clazosentan for the prevention of clinical deterioration due to vasospasm-related delayed cerebral ischemia in adult patients following aSAH. The Phase 3 study builds upon the learnings from the previous clazosentan studies to identify patients at high risk of vasospasm and delayed cerebral ischemia, the optimal dose, the best measure to demonstrate efficacy and an optimized patient management guideline to ensure patient safety.

Approximately 400 patients—treated either with microsurgical clipping or endovascular coiling—are being enrolled at approximately 95 sites across 15 countries. Patients are randomized to receive continuous infusion of either clazosentan (15 mg/hr) or placebo prophylactically, on top of local standard of care, for a period of up to 14 days. REACT is enrolling aSAH patients identified as being at high risk of developing vasospasm and subsequent delayed cerebral ischemia because of high-volume hemorrhage, as assessed by CT scan on hospital admission. Patients experiencing asymptomatic cerebral vasospasm, as measured by angiography, within 14 days of aSAH may also be included. Completion of the study is targeted for the second half of 2022.

Available clinical data
Previously, clazosentan was investigated for the prevention of angiographic vasospasm in patients with aSAH in a Phase 2 study, CONSCIOUS-1 which demonstrated dose-dependent prevention of vasospasm. 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, an 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% relative risk reduction (p=0.0074).

The 15 mg/h 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 show any effect of clazosentan on long-term clinical outcome.

A pilot study evaluating the early effect of clazosentan on reversing established cerebral vasospasm in large proximal cerebral artery segments at three hours post-initiation suggests that clazosentan has the potential to improve large vessel vasospasm upon early administration. In 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, a clearly visible improvement in vessel diameter at three and 24 hours could be observed.

Those studies have also established an extensive safety profile with over 2,000 patients treated.

Clazosentan has been granted orphan drug designation in Europe (2003) and the US (2006), leading to regulatory exclusivity protection of ten and seven years, respectively.

**Current status: Japanese registration program**

A Phase 2 study in Japanese and Korean patients showed that 10 mg/hr of clazosentan administered by continuous intravenous infusion 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.

The program consisted of two double-blind, randomized, placebo-controlled studies assessing the efficacy and safety of clazosentan in reducing vasospasm-related morbidity and all-cause mortality events in adult Japanese patients following aSAH. Patients were randomized to receive continuous infusion of either 10 mg/hr clazosentan or placebo for up to 15 days following the onset of aSAH. The two studies followed the same study design, with one enrolling 221 patients whose aneurysm was secured by surgical clipping and the other enrolling 221 patients whose aneurysm was secured by endovascular coiling.

Both studies demonstrated that clazosentan reduced the occurrence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH with statistical significance (p<0.01 for both studies). 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 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. Further analysis is ongoing including additional pooled analysis of data from both studies.

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).

Idorsia Japan plans to file the New Drug Application with the Japanese Pharmaceuticals and Medical Devices
Agency in the first half of 2021. This would in turn allow for commercialization and launch in Japan in the first half of 2022, should market authorization be received.

**Milestones**

2020  Japanese registration program reports positive results  
2019  Global Phase 3 study initiated  
2016  Japanese registration program initiated  
2006  Orphan status granted in US  
2003  Orphan status granted in Europe

**Key scientific literature**

Lucerastat is an oral inhibitor of glucosylceramide synthase which offers a potential new treatment approach for patients living with Fabry disease, irrespective of mutation type. Preclinical studies have shown that lucerastat is rapidly absorbed and is widely distributed to most tissues, including the central nervous system, kidney and heart.

Fabry disease is a rare, life-threatening, X-linked lysosomal storage disorder caused by mutations in the GLA gene leading to a deficiency or dysfunction of alpha-galactosidase A (alpha-Gal A), an enzyme that normally breaks down a fatty substance known as globotriaosylceramide (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 diagnosed prevalence of Fabry disease in 2018 was approximately 7,500 patients in the United States and the EU-5 (i.e., France, Germany, Italy, Spain and the United Kingdom), according to Delveinsight.

The symptoms range from neuropathic pain (primarily in the hands and feet) and gastro-intestinal, skin and eye problems, to hypertension, progressive kidney damage, cardiomyopathy and stroke.

Since most symptoms are non-specific, 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.

Lucerastat, an oral inhibitor of glucosylceramide synthase (GCS), acts by reducing the synthesis of the lipid Gb3 as oppose to supporting the breakdown of Gb3, thus reducing damaging build-up. This is known as Substrate Reduction Therapy (SRT). Since this mechanism is independent of the deficiency or dysfunction of alpha-galactosidase A, it should not be limited to specific mutations in the GLA gene.

**Current status**
In May 2018, Idorsia initiated MODIFY, a double-blind, randomized, placebo-controlled, Phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. The primary objective of the study is to determine the effects of treatment on neuropathic pain over a six-month period, as measured by our Fabry disease neuropathic pain instrument. Neuropathic pain is one of the main clinical symptoms in Fabry disease, affecting quality of life and which can present from childhood in many patients. Other manifestations of the disease with slower progression (renal impairment and cardiac disease) appear at later stages of the disease. Therefore, neuropathic pain is an accessible, clinically relevant and measurable disease outcome representing a high medical need and suited for assessment in a six-month treatment period.

As key secondary objectives, the study will also determine the effect of lucerastat on gastro-intestinal symptoms (abdominal pain and diarrhea) and confirm the effect of lucerastat on Fabry-specific biomarkers. At the end of the double-blind period, patients will have the option of entering an open-label extension study to determine long-term safety and to explore long-term efficacy and its disease-modifying potential as measured by eGFT, LVMI and biomarkers of Fabry disease.

Recruitment was completed at the end of 2020 with more than 100 patients ultimately being randomized to lucerastat.
or placebo in a 2:1 ratio. Results of this study are targeted for the second half of 2021.

Lucerastat for Fabry disease has received orphan drug designation in the US and the EU and is under review in Japan. In 2018 and further in 2020, the EMA agreed with the company'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
In an exploratory study in patients with Fabry disease, treatment with lucerastat in addition to ERT induced a marked decrease in plasma levels of metabolic substrates associated with the development of the 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, 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.

The study also indicated that lucerastat is well tolerated in patients with Fabry disease.

In a previous non-clinical study on male and female Fabry mice treated for 20 weeks with lucerastat at 1200 mg per kilogram per day as a food admixture, lucerastat demonstrated the potential to reduce Gb3 levels in target organs compared to non-treated controls.

Milestones
2018 Phase 3 study completed
2016 Phase 1b study completed

Key scientific literature
Selatogrel

Selatogrel is a potent, fast-acting, reversible, and highly-selective P2Y_{12} receptor antagonist being developed for the treatment of a suspected acute myocardial infarction (AMI) in patients with a history of AMI. It is intended to be self-administered subcutaneously via an auto-injector.

An AMI, or heart attack, is a life-threatening condition that occurs when blood flow to the heart muscle is suddenly decreased or completely cut off. It is usually caused by a blood clot or blockage in one or more of the coronary vessels supplying blood to the heart muscle. An AMI requires immediate treatment and medical attention as any delay in intervention can result in irreversible damage to the heart muscle. According to the Centers for Disease Control and Prevention, each year more than 600,000 persons living in the US will suffer their first heart attack and around 200,000 will suffer a recurring heart attack.

Although the management of AMI has improved in recent decades, morbidity and mortality associated with AMI remain high, with the majority of early deaths occurring prior to hospital admission. As a result, early action is crucial for survival, however there are no treatment options available for the critical time from onset of AMI symptoms to first medical contact.

Current status
In consultation with health authorities, Idorsia is preparing a large (approximately 14,000 patients), Phase 3 study to evaluate the efficacy and safety of self-administered subcutaneous injection of selatogrel for the treatment of a suspected AMI in patients with a history of AMI. Participating patients will be trained on when and how to self-inject treatment. Initiation of the registration study is targeted for the first half of 2021. A special protocol assessment (SPA) has been agreed with the FDA and "fast-track" designation was granted.

In late 2019, Idorsia entered into a global agreement with Antares Pharma, Inc. to develop a novel drug-device product combining selatogrel with the Antares subcutaneous QuickShot® auto-injector. The product is going to be tested through usability and reliability studies tailored for emergency use to ensure safe and effective use can be demonstrated ahead of the Phase 3 study.

Available clinical data
Two Phase 2 studies in patients with chronic coronary syndromes and AMI, respectively, have 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 four to eight hours, depending on the dose. Selatogrel was safe and well tolerated in both studies and there were no treatment-emergent serious bleeds.

The first study was a multicenter, double-blind, randomized, placebo-controlled study assessing the pharmacodynamics, pharmacokinetics, tolerability and safety of a single subcutaneous injection of selatogrel either in the thigh or in the abdomen at two different doses in adults with chronic coronary syndromes. In the study, 345 patients received selatogrel 8 mg (n=114), selatogrel 16 mg (n=115) or placebo (n=116). 97% were on background therapy with aspirin (or its derivative carbasalate) and 35% on oral P2Y12 receptor antagonist (clopidogrel 23%, prasugrel 4%, ticagrelor 8%). The primary objective of the study was to characterize inhibition of platelet aggregation relative to placebo. Platelet reactivity was assessed by VerifyNow PRU (P2Y12 reaction units) test before injection and 15 minutes, 30 minutes and 1, 2, 4, 8...
and 24 hours after injection. The primary endpoint, patients (responders) having PRU < 100 starting at 30 minutes and lasting ≥3 hours after a single study treatment injection, was achieved in 89% of patients receiving selatogrel 8 mg, and 90% of patients receiving selatogrel 16 mg compared with 16% in the placebo group (P<0.0001). Inhibition of platelet aggregation was observed as early as 15 minutes post-dose. PRU levels were maintained at 2 and 4 hours for both doses and gradually returned to pre-dose levels by 24 hours post-dose. Selatogrel was well tolerated: mild dyspnea (or moderate dyspnea, n=1, with 16 mg) occurred in 5% and 9% of patients with selatogrel 8 mg and 16 mg, respectively, vs 0% with placebo; dizziness occurred in 4% and 4% vs 1%, respectively, without significant hemodynamic or ECG changes. Bleeding events occurred in 9.6% and 4.3% of patients with selatogrel 8 mg and 16 mg, respectively, vs 6.9% with placebo. All bleeding events were of mild intensity except one of moderate intensity, which was reported in the placebo group. No major bleeding event was reported during the study.

The second study was a multi-center, open-label, exploratory study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of selatogrel in adults with AMI. In this study, 47 patients received 8 mg (n=24) or 16 mg (n=23) selatogrel. Study-treatment concomitant medications included acetylsalicylic acid (98%), P2Y12 receptor antagonists (96%), heparins (94%), statins (94%), nitrates (68%) and morphine (38%). Blood samples were collected at baseline and at 15, 30, and 60 minutes post-dose and platelet reactivity (expressed as PRU) was evaluated using VerifyNow. The primary objective of the study was to assess the inhibition of platelet aggregation 30 minutes after a single subcutaneous injection of selatogrel.

The response to treatment, defined as PRU < 100 at 30 minutes post-dose, was achieved in 91% and 95% of patients with selatogrel 8 and 16 mg, respectively. Response rates were independent from STEMI/NSTEMI diagnosis, age and sex. PRU below 100 was observed as early as 15 minutes (8 mg: 75% of patients; 16 mg: 96% of patients) and sustained for up to 60 minutes post-dose (8 mg: 75% of patients; 16 mg: 96% of patients). Overall, 43% of patients had ≥1 TEAE, which were mainly of mild/moderate intensity. Ventricular tachycardia ([VT] 8 mg: 4/24; 16 mg: 3/23) which is a common outcome of AMI, was the most frequent TEAE and was reported as serious AE in two patients: one patient receiving 8 mg and one patient receiving 16 mg selatogrel. Neither of these events was considered to be related to selatogrel. Post-procedural hemorrhage (of mild intensity) occurred in one patient after percutaneous coronary intervention with radial access.

**Milestones**
- 2019 Drug-device development agreement with Antares Pharma Inc.
- 2018 Positive results for the Phase 2 studies

**Key scientific literature**
Cenerimod

Cenerimod is a selective sphingosine-1-phosphate 1 (S1P₁) receptor modulator, which potentially offers a novel approach for the treatment of systemic lupus erythematosus (SLE) – a disease with a significant impact on patients and limited treatment options.

SLE, the most common form of lupus, is an autoimmune disease. In SLE, the body’s immune system malfunctions and attacks the body’s own tissues, which can affect the skin, joints, gut, blood cells, lungs, and other organs. It is estimated that 1.5 million Americans, and at least five million people worldwide, have a form of lupus, and that 90% of people living with lupus are women, with most developing the disease between the ages of 15-44 and there is a higher prevalence of lupus among people of Asian and Afro-Caribbean origin compared to Caucasians.

While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune system cells that play a key role in the development of SLE. T and B lymphocytes have S1P₁ receptors on the surface which senses a gradient of sphingosine-1-phosphate or S1P, which is high in blood, guiding the lymphocytes out of lymph nodes towards the circulation. Cenerimod binds to the S1P₁ receptor which leads to internalization of the receptor, so that the lymphocyte can no longer sense S1P. As a result, the lymphocytes are held in the lymph nodes, reducing the availability of these key players in inflammation to the affected organs and tissues. The effect of cenerimod on lymphocyte trafficking is reflected by the dose-dependent, sustained and reversible reduction in circulating lymphocyte counts observed upon administration of cenerimod.

Current status

Following a Phase 2 safety study in patients with SLE, in December 2018, Idorsia initiated a multiple-dose, efficacy and safety study with cenerimod (CARE) for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE to assess the efficacy of six months of cenerimod treatment at four different dose levels. The randomized, double-blind, placebo-controlled study is currently enrolling patients, who are randomized into four cenerimod treatment arms: 0.5, 1, 2, and 4 mg once-daily or placebo for up to 12 months. Patients receive study treatment in addition to background SLE therapy, which will be kept as stable as possible to avoid confounding the treatment effect. The study aims to validate the appropriate dose, patient population and endpoints for further development in SLE, as well as the effect on quality of life and fatigue using patient-reported outcome instruments and the effect on systemic lupus erythematosus biomarkers. Exploratory objectives over a 12 month treatment period are to assess the effect on disease activity, safety and tolerability, quality of life, fatigue and SLE biomarkers, as well as, from the sixth month of treatment onwards, the effects of dose reduction and withdrawal in subjects randomized to 4 mg who are re-randomized to either 2 mg or placebo. The results are targeted for the second half of 2021.

In December 2017, the US FDA designated the investigation of cenerimod for the treatment of SLE 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.
Available clinical data
A Phase 2 safety study investigating the effect of cenerimod on circulating lymphocytes, disease activity, safety and pharmacokinetics in SLE patients, has been conducted. This study was conducted in two parts, A and B, which were separated by an independent safety review. Patients with SLEDAI-2K score (modified [mSLEDAI] to exclude leucopenia) ≥2 points for mucocutaneous or musculoskeletal manifestations and positive serum test for ANA or anti-dsDNA antibodies were randomized evenly in Part A to cenerimod 0.5, 1, 2 mg or placebo once daily and 3:1 in Part B to cenerimod 4 mg or placebo once-daily and treated for 12 weeks. All 67 patients (A: 49; B: 18) met at least 4 ACR criteria in the past, 70% had 4 to 11 ACR criteria ongoing at screening. Mean (SD) mSLEDAI-2K was 7.7 (±3.1) at baseline. Endpoints included TEAEs, changes in total lymphocyte count; SLEDAI-2K score; anti-dsDNA antibody, a disease relevant biomarker; and pharmacokinetic assessments.

Cenerimod dose-dependently reduced total lymphocyte count from baseline to end of treatment (EOT; p< 0.001). In pairwise comparisons, cenerimod 1, 2, and 4 mg significantly decreased lymphocytes versus placebo (all p< 0.001). Exploratory analyses indicated clinical and biological improvement with cenerimod 4 mg with an estimated mean treatment effect on change from baseline to EOT in mSLEDAI-2K of −2.420 (p=0.0306), and a decrease in anti-dsDNA of −28.80 U/mL (p=0.0146) compared with placebo.

Cenerimod was well tolerated, with all treatment groups reporting similar and non-dose-related rates of TEAEs (cenerimod 0.5: 41.7%; 1: 41.7%; 2: 46.2%; 4 mg: 38.5%; and placebo: 58.8%). While S1P1 receptor modulators are known to transiently affect heart rate at initiation of therapy, cenerimod showed only a minimal, transient, dose dependent decrease in HR at first dose; no patient had an HR < 40 bpm at any time post baseline. Small decreases in pulmonary function, not dose-related, were observed in cenerimod-treated patients at EOT. Cenerimod did not increase blood pressure or show any effects on laboratory variables.

Milestones
2018 Initiation of a multiple-dose efficacy and safety study
2015 Initiation of a Phase 2 safety study

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-774312, a CRTH2 receptor 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 need for new oral therapies to treat allergic and type 2 inflammatory responses. 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 psychiatric disorders
ACT-539313 is a selective orexin 1 receptor antagonist being investigated for the potential treatment of psychiatric 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 2 program is in preparation.

Sinbaglustat, a GBA2/GCS inhibitor for rare lysosomal storage disorders
Based on a non-clinical program and completed Phase 1 studies, Idorsia considers developing sinbaglustat in rare lysosomal storage disorders (LSDs). To collect disease information from pediatric patients with early onset of LSDs, the company is conducting a natural history study called "RETRIEVE".

ACT-1004-1239, a CXCR7 antagonist for immunology / cancer immunotherapy
ACT-1004-1239 is a CXCR7 antagonist for immunology / cancer immunotherapy and currently investigated in a Phase 1 program.

ACT-1014-6470
ACT-1014-6470, an immunology compound, is currently investigated in a Phase 1 program.

ACT-541478
ACT-541478, a CNS compound, is currently investigated in a Phase 1 program.
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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