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>
<tr>
<td>Clazosentan</td>
<td>Endothelin receptor antagonist</td>
<td>Cerebral vasospasm assoc. with aneurysmal subarachnoid hemorrhage</td>
<td>Japan: Filing in preparation Global: Phase 3 ongoing</td>
</tr>
<tr>
<td>Lucerastat</td>
<td>Glucosylceramide synthase inhibitor</td>
<td>Fabry disease</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Selatogrel</td>
<td>P2Y12 receptor antagonist</td>
<td>Suspected acute myocardial infarction</td>
<td>Phase 3 in preparation</td>
</tr>
<tr>
<td>Cenerimod</td>
<td>S1P1 receptor modulator</td>
<td>Systemic lupus erythematosus</td>
<td>Phase 2b</td>
</tr>
<tr>
<td>ACT-539313</td>
<td>Selective orexin 1 receptor antagonist</td>
<td>Binge eating disorder</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Sinbaglustat</td>
<td>GBA2/GCS inhibitor</td>
<td>Rare lysosomal storage disorders</td>
<td>Phase 1 complete</td>
</tr>
<tr>
<td>ACT-1004-1239</td>
<td>CXCR7 antagonist</td>
<td>Immunology</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ACT-1014-6470</td>
<td>-</td>
<td>Immunology</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ACT-541478</td>
<td>-</td>
<td>CNS</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ACT-777991</td>
<td>-</td>
<td>Immunology</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

* 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. In November 2020, Neurocrine announced it had initiated a Phase 2 study investigating ACT-709478 for the treatment of a rare form of pediatric epilepsy.
Daridorexant

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.

Current status
The new drug application (NDA) was submitted to the US FDA in January 2021. Should market authorization be received on schedule, this would allow for commercialization and launch in the US in the first half of 2022.

Available clinical data
The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind 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 placebo-controlled studies investigated the effects of 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.

More than 800 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.

The Phase 3 registration program demonstrated statistically significant and clinically meaningful improvements in sleep and daytime functioning which were sustained over time. The results showed efficacy during the night and the day, in respect of sleep maintenance, sleep onset, total sleep time and daytime functioning. The nighttime symptoms were improved while preserving the proportions of sleep stages. The Phase 3 program provided a deep understanding of the efficacy and tolerability profile of daridorexant.

The highest (50 mg) dose was the most effective, followed by 25 mg, while the 10 mg dose had only a marginal effect.

A key consideration in the treatment of insomnia is the reversal of daytime functioning impairment associated with sleep difficulties.
– altered mood, cognition, and tiredness. To date, no insomnia studies have reported on the effects of pharmacological intervention on daytime functioning using an adequately developed and validated PRO instrument. At 50 mg, daridorexant produced consistent and meaningful improvements in scores for daytime functioning across all IDS1Q domains. Patients on daridorexant felt more energetic and less sleepy, and reported better alertness, cognition and mood.

Daridorexant was well tolerated and had a favorable safety profile in adult and elderly patients. Adverse reactions reported with a frequency of ≥ 2% in daridorexant-treated patients and greater (≥ 1%) than in placebo-treated patients in 3-month efficacy trials were headache, somnolence, fatigue, dizziness, and nausea. There was no excess of morning sleepiness, as assessed by the morning visual analogue scale (VAS), even at 50 mg. The incidence of somnolence was low and did not increase with daridorexant 50 mg compared to placebo. The incidence of adverse events of special interest, considering the potential association of orexin deficiency with narcolepsy, was low, with isolated cases of sleep paralysis or hallucinations in the daridorexant treatment groups.

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 which have been included in the filing with health authorities.

**Milestones**
- 2021 NDA submitted to US FDA
- 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 is a once-daily, potent dual (ET\textsubscript{A} and ET\textsubscript{B}) 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 risk factors, 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 whose blood pressure remains high despite receiving at least three antihypertensive medications from different classes, including a diuretic, at optimal doses are categorized in hypertension guidelines and the medical community as having resistant hypertension.

Current status
In June 2018, Idorsia initiated PRECISION, a Phase 3 study to demonstrate the antihypertensive effect of aprocitentan when added to standard of care in patients with resistant hypertension. Idorsia, in consultation with regulatory agencies, designed a single placebo-controlled study which efficiently addresses both the short-term efficacy of aprocitentan and the durability of its effects in long-term treatment. The study aims to randomize 600 patients at approximately 180 sites in around 20 countries, and results are targeted for the first half of 2022.

Patients with a history of resistant hypertension undergo a thorough screening and run-in period. This confirms the diagnosis of resistant hypertension by excluding pseudo or apparent resistant hypertension. During the screening period, the patient’s background antihypertensive therapies are 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 are then 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, Idorsia entered into a collaboration agreement with Janssen Biotech, Inc., to jointly develop 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 are 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.

Available clinical data
In a Phase 2 dose-response study, patients with hypertension received monotherapy with four doses of aprocitentan or placebo (lisinopril was used as a positive control) for eight weeks, using a randomized, double-blind study design. A total of 490 eligible patients were randomized, with 430 patients successfully completing the double-blind treatment period. Blood pressure was measured carefully with an unattended automated office blood pressure device. The results are shown in the charts below. No changes in heart rate were observed for any dose of aprocitentan. There was a clear dose response on both diastolic and systolic blood pressure, with clinically relevant effects observed at 10 mg, 25 mg, and 50 mg, with no additional effect at 50 mg. The effect of aprocitentan was shown to cover a 24-hour period.

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
Clazosentan is a fast-acting, selective endothelin A (ET\textsubscript{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 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 4 and 14 days after aneurysm securing. 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 at least twice as high as in many other countries of the world.

Current status: Global registration study
In February 2019, Idorsia initiated REACT, a 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 incorporates the learnings from the clazosentan program 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. The study aims to randomize approximately 400 patients – treated either with microsurgical clipping or endovascular coiling – at around 95 sites across 15 countries, and results are targeted for the second half of 2022.

Available clinical data
Several studies have built our understanding of the role of clazosentan in preventing or reversing cerebral vasospasm. In 2006, results were reported for clazosentan in the prevention of angiographic vasospasm in patients with aSAH. The Phase 2 dose-finding study, CONSCIOUS-1, demonstrated dose-dependent prevention of vasospasm.

This 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. In 2010, CONSCIOUS-2 showed that the 5 mg/h dose of clazosentan, administered by continuous intravenous infusion, 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 (15 mg/h), administered by continuous intravenous infusion, significantly reduced cerebral
The studies confirmed the well-documented safety profile of clazosentan, which has now been administered to approx. 2000 patients around the world. The side effects of clazosentan are managed based on clear protocol guidelines: hypotension can be mitigated using blood pressure control with vasopressors in the ICU, while lung complications (such as pulmonary edema) can be managed by aiming to maintain euvolemia by avoiding excessive fluid administration.

Clazosentan has been granted orphan drug designation in Europe (2003) and the US (2006), leading to regulatory exclusivity protection of 10 and 7 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.

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 suggests that, with early administration, clazosentan has the potential to improve large-vessel vasospasm. 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 was observed in vessel diameter at 3 and 24 hours.

In November 2020, Idorsia announced positive top-line results from the Japanese registration program investigating clazosentan in adult Japanese patients post-aSAH. The program consisted of two studies assessing the efficacy and safety of clazosentan in reducing vasospasm-related morbidity and all-cause mortality events. 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.

In Japan, clazosentan has regulatory data protection after approval, leading to eight years’ exclusivity.

Both studies demonstrated a statistically significant (p<0.01) reduction in the occurrence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH. 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 in these registration studies. 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

Lucerastat is an oral inhibitor of glucosylceramide synthase, offering a potential new treatment approach for patients living with Fabry disease, irrespective of mutation type.

Fabry disease is a rare, life-threatening, 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 US and the EU-5 (i.e., France, Germany, Italy, Spain and the UK).

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. Preclinical studies have shown that lucerastat is rapidly absorbed and is widely distributed to most tissues, including the central nervous system, kidney and heart.

Current status
In May 2018, Idorsia initiated MODIFY, a Phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. The study aims to determine the effects of treatment on neuropathic pain over a 6-month period, as measured by Idorsia’s Fabry disease neuropathic pain instrument (developed in accordance with health authority guidance). 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 disease-modifying potential, as measured by estimated glomerular filtration rate (eGFR), left ventricular mass index and biomarkers of Fabry disease. Enrollment in the study concluded at the end of 2020, with more than 100 patients being randomized to lucerastat or placebo in a 2:1 ratio. Results of this study are therefore expected in 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 enzyme replacement therapy induced a marked decrease in plasma levels of metabolic substrates associated with the development of the disease.

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

In an animal model of Fabry disease, treatment with lucerastat reduced Gb3 levels and related biomarkers in dorsal root ganglia, the kidneys and the heart.

**Milestones**

- **2018** Phase 3 study initiated
- **2016** Phase 1b study completed

**Key scientific literature**

Selatogrel

Selatogrel is a potent, fast-acting, reversible, and highly selective P2Y\textsubscript{12} receptor antagonist, being developed for the treatment of acute myocardial infarction (AMI) in patients with a history of AMI. It is intended to be self-administered subcutaneously via a drug delivery system (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 800,000 people living in the US will suffer a 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 late 2019, Idorsia entered into a global agreement with Antares Pharma, Inc., to develop a novel drug-device product combining selatogrel with the Antares QuickShot\textsuperscript{®} auto-injector for subcutaneous delivery. The drug-device product is being tested in usability and reliability studies tailored for emergency use, to ensure safe and effective use can be demonstrated in preparation for a Phase 3 study.

In consultation with health authorities, Idorsia is preparing a large, international Phase 3 study, involving approximately 14,000 patients, to evaluate the efficacy and safety of self-administered subcutaneous injection of selatogrel for the treatment of 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 has been agreed with the FDA. This indicates the FDA’s approval of the adequacy and acceptability of specific critical elements of overall protocol design (e.g., entry criteria, dose selection, endpoints and planned analyses) for a study intended to support a future marketing application.

In December 2020, the FDA designated the investigation of selatogrel for the treatment of suspected AMI as a “fast-track” development program. This designation is intended to promote communication and collaboration between the FDA and pharmaceutical companies for drugs that treat serious conditions and fill an unmet medical need.
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.

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

Key scientific literature
Cenerimod is a highly selective sphingosine-1-phosphate 1 (S1P<sub>1</sub>) receptor modulator, given as an oral once-daily tablet, 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. There is a higher prevalence of lupus among people of Asian and Afro-Caribbean origin than in Caucasians.

While the cause of SLE is not fully known, T and B lymphocytes are considered the key immune system cells playing a key role in the development of SLE. T and B lymphocytes have S1P<sub>1</sub> receptors on the surface which enable the lymphocytes to detect the signaling molecule sphingosine-1-phosphate or S1P, which is responsible for lymphocyte trafficking from the lymph nodes to the blood. Cenerimod binds to the S1P<sub>1</sub> 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 CARE, a multiple-dose, efficacy and safety study with cenerimod, for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE. The aims of the study are to assess the safety and efficacy of cenerimod treatment at four different dose levels; to determine the appropriate dose, patient population and endpoints for further development in SLE; and to evaluate the effects on quality of life and fatigue, using patient-reported outcome instruments, as well as the effects on SLE biomarkers. Randomization will be completed by the end of February 2021, with at least 350 patients enrolled. The results are targeted for the second half of 2021.

In December 2017, the FDA designated the investigation of cenerimod for the treatment of SLE as a “fast-track” development program. This designation is intended to promote communication and collaboration between the FDA and pharmaceutical companies for drugs that treat serious conditions and fill an unmet medical need.
Available clinical data
In a Phase 2 proof-of-concept study investigating the effect of cenerimod on circulating lymphocytes, disease activity, safety and pharmacokinetics in SLE patients, cenerimod dose-dependently reduced total lymphocyte count from baseline to end of treatment (p< 0.001). In addition, the antibody-producing B cells, which are elevated in patients with SLE and critical to the disease process, were markedly reduced by cenerimod. The study provided promising data, with an early indication of efficacy being numerical reductions in mSLEDAI-2K (one of the measures of disease activity) and in anti-double-stranded DNA antibodies. This is very encouraging, especially considering that the result was seen after only 12 weeks of treatment.

Cenerimod was well tolerated at all dose levels. The occurrence of adverse events was similar in all five treatment groups.

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

Key scientific literature
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-539313**
ACT-539313 is a selective orexin 1 receptor antagonist being investigated in a Phase 2 proof-of-concept study for binge eating disorder. 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. Preclinical studies have shown that orexins play an important role in compulsive, binge-like feeding behaviors. Furthermore, orexin receptor antagonists have reduced binge-like eating behavior in animal models. Our study will be the first to study orexin 1 receptor antagonism as a new mechanism of action for patients with eating disorders.

**Sinbaglustat**
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**
ACT-1004-1239 is a CXCR7 antagonist intended for immunology disorders 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.

**ACT-777991**
ACT-777991, an immunology 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.

Idorsia Pharmaceuticals Ltd
Hegenheimermattweg 91
CH-4123 Allschwil
Switzerland

Investor.relations@idorsia.com
Phone +41 58 844 10 10
www.idorsia.com