Clinical Development

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.

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
Aprocitentan*	Dual endothelin receptor antagonist	Resistant hypertension management	Phase 3
Clazosentan	Endothelin receptor antagonist	Vasospasm associated with aneurysmal subarachnoid hemorrhage	Phase 3
Daridorexant	Dual orexin receptor antagonist	Insomnia	Phase 3
Lucerastat	Glucosylceramide synthase inhibitor	Fabry disease	Phase 3
Cenerimod	$S1P_1$ receptor modulator	Systemic lupus erythematosus	Phase 2
Selatogrel	$P2Y_{12}$ receptor antagonist	Suspected acute myocardial infarction	Phase 2
ACT-774312	CRTH2 receptor antagonist	Nasal polyposis	Phase 2
ACT-519276	GBA2/GCS inhibitor	Rare CNS diseases	Phase 1
ACT-539313	Selective orexin 1 receptor antagonist	Psychiatric disorders	Phase 1
ACT-709478**	T-type calcium channel blocker	Epilepsy	Phase 1
ACT-1004-1239	-	Immunology / Cancer Immunotherapy	Phase 1
ACT-1014-6470	-	Immunology	Initiating Phase 1

* In collaboration with Janssen Biotech to jointly develop and solely commercialize aprocitentan worldwide.
** Idorsia has granted to a third party an option to license ACT-709478, this option will expire 60 days after the IND submission to the FDA, which is planned for late 2019

Idorsia has the option to license vamorolone from ReveraGen Inc. and has granted to Santhera Holding Ltd. the option to sub-license vamorolone worldwide (except Japan and South-Korea) for all indications.

Aprocitentan

Aprocitentan is an orally active dual endothelin receptor antagonist (ERA), which is being investigated for the treatment of patients whose blood pressure is uncontrolled despite receiving triple antihypertensive medications.

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 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.

Current status

In June 2018, Idorsia initiated PRECISION, a multi-center, double-blinded, placebo-controlled, randomized, parallel-group, 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, has designed a single study which will efficiently address both the short-term efficacy of aprocitentan and the durability of its effects in long-term treatment.

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.

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.

Idorsia is also initiating an additional blinded, randomized, placebo-controlled, Phase 3 study with aprocitentan in patients with chronic kidney disease (CKD) stage 3 or 4 whose blood pressure remains uncontrolled despite the use of at least two antihypertensive medications. The primary objective of this study is to demonstrate the safety and blood pressure lowering effect of 4-weeks' treatment with aprocitentan when added to background antihypertensive therapy. The study is expected to commence

enrolment in the first quarter of 2020, will enroll about 200 patients in approximately 100 sites from around 15 countries, and will last for about two years.

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 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 dose-response study, eligible patients with hypertension (mean sitting systolic/diastolic blood pressure 149.7/97.6 mmHg) received aprocitentan 5, 10, 25 or 50 mg, matching placebo or lisinopril 20 mg as a positive control, once daily for 8 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/diastolic AOBP, from baseline to week 8 were 10.3/6.3, 15.0/9.9, 18.5/12.0 and 15.1/10.0 mmHg for aprocitentan 5, 10, 25, and 50 mg, respectively vs. 7.7/4.9 mmHg for placebo and 12.8/8.4 mmHg for lisinopril. No changes in heart rate or body weight were observed for any dose of aprocitentan.

Estimated increases in plasma volume were 3.0%, 5.1%, 6.9%, and 9.5% for aprocitentan 5, 10, 25, and 50 mg, respectively, vs. 1.6% for lisinopril and a decrease of 0.3% for placebo. All these values are within the physiological variation range, i.e. below 10%. There was an expected dose-related decrease from baseline in the hemoglobin concentration in the aprocitentan groups (ranging from 1.3 to 6.7 g/L), versus increases of 2.2 and 0.1 g/L in the placebo and lisinopril groups, respectively.

The 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

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

Clazosentan

Clazosentan is a selective endothelin (ETA) 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, contributes to many patients experiencing cerebral vasospasm (constriction of arteries in the brain) between 4 and 14 days after aSAH securing. This diminishes blood flow to the brain, and about one third of patients consequently experience worsening of their neurological condition.

Today, patients with vasospasm are typically treated with hemodynamic therapy (the administration of fluids and agents to increase blood pressure) or a more invasive neurovascular intervention, such as balloon angioplasty or intra-arterial administration of vasodilators.

Current status: Global registration study

In February 2019, Idorsia initiated REACT, a prospective multicenter, double-blind, randomized, placebo-controlled, parallel-group, 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.

Approximately 400 patients – treated either with microsurgical clipping or endovascular coiling – are expected to be enrolled at 100 sites across 15 countries. Patients will be randomized to receive either clazosentan (15 mg/hr) or placebo for a treatment period of up to 14 days. The study is expected to run for over two years.

REACT will enroll aSAH patients identified as being at high risk of developing delayed ischemic neurological deficit because of high-volume hemorrhage, as assessed by CT scan on hospital admission. Patients experiencing asymptomatic moderate to severe cerebral vasospasm within 14 days of aSAH 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% 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: Japanese registration program

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. aSAH 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 aSAH. 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 treated for aSAH by endovascular coiling. The recruitment is ongoing, and results are expected around mid-2020, with a rapid turnaround for filing of the dossier with the Japanese health authority.

Milestones

2019 Global Phase 3 study initiated
2016 Japanese Phase 3 program initiated
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.
- Macdonald R L, et al. Stroke 2008; 39:3015–3021.
- Vajkoczy P, et al. Journal of Neurosurgery 2005; 103:9-17.
- Roux S. et al. J Pharmacol Exp Ther 1997; 283:1110-1118.

Daridorexant

Daridorexant (ACT-541468) is a dual orexin receptor antagonist (DORA) for the treatment of insomnia. It has potential to deliver fast onset of sleep and a duration of action not exceeding a normal night, while preserving 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.

Insomnia is now recognized as a condition that requires clinical attention, regardless of any other medical problems the patient might have. Insomnia is often underdiagnosed and undertreated. It is estimated that around 70% of people with persistent insomnia never seek medical help.

Current status

In June 2018, Idorsia initiated a Phase 3 registration program with daridorexant for the treatment of adult and elderly patients with insomnia. The registration program comprises two confirmatory studies together with a long-term extension study, which will recruit a total of 1,800 patients with insomnia at over 160 sites across 18 countries. As insomnia often presents later in life, around 40% of the recruited population will be aged 65 years or older. The confirmatory studies will investigate three doses (10 mg, 25 mg, and 50 mg), on objective and subjective sleep and daytime functioning parameters. Patients will be treated for three months in the two trials, with the opportunity to continue treatment in a 40-week extension study.

The Phase 3 program aims to confirm the positive results observed in the Phase 2 clinical program. The first study is finishing recruitment, so we are confident that the results will be available in the first half of next year and the second study will follow shortly thereafter. In addition, a comprehensive clinical pharmacology program is to be conducted in parallel.

Available clinical data

The safety and efficacy of daridorexant 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. In both studies, treatment with daridorexant dose-dependently improved sleep onset and sleep maintenance, with significant reductions in LPS (latency to persistent sleep) and WASO (wake after sleep onset), at the time points measured. Treatment was generally well tolerated across all doses, with no narcolepsy-like symptoms, no evidence of suicidal ideation, no complex sleep behaviors, and no dose-limiting safety events. There was no residual next-morning effect at any dose (as measured by e.g. the Karolinska Sleepiness Scale). In addition, self-reported next-day functioning (daytime alertness, morning sleepiness, daytime ability to function) assessed by a Visual Analog Scale was improved across all dose groups in elderly patients.

The first multi-center, double-blind, randomized, placebo-controlled, active-reference, parallel-group, polysomnography dose-response Phase 2 study to assess the efficacy and safety of daridorexant (5, 10, 25, 50 mg) in 360 adult patients (64% female; ranging from 18 to 64 years) with insomnia disorder showed a significant

(p<0.001) dose-dependent decrease in WASO at Days 1 & 2 (average decrease of wake time after sleep onset from baseline on the first 2 nights of treatment, measured by polysomnography). Observed mean reductions from baseline to Days 1 & 2 for WASO were −28.99, −33.75, −39.64, and −45.49 min for ascending daridorexant doses (placebo, −20.98 min; zolpidem, −31.23 min), and were sustained at Days 28 & 29 (−37.76, −43.74, −39.84, −46.97 min for ascending daridorexant doses; placebo, −33.80 min; zolpidem, −37.08 min).

Daridorexant also significantly (p<0.05) decreased LPS (latency to persistent sleep) at doses 10 mg and higher in a dose-dependent manner. Observed changes in mean LPS from baseline to Days 1 & 2 were −26.88, −29.31, −36.14, and −36.41 min for ascending daridorexant doses (placebo, −22.02 min; zolpidem, −45.12 min). Reductions in LPS were sustained at Days 28 & 29.

Daridorexant treatment was well tolerated at all doses, with no evidence of dose-dependent adverse effects. Treatment-emergent adverse events (TEAEs) were reported in 35%, 38%, 38%, and 34% of the patients treated with 5, 10, 25, and 50 mg daridorexant, respectively (30% for placebo; 40% for zolpidem). The main TEAEs across all groups were headache, somnolence, and nasopharyngitis. No signs of next-morning residual effects or rebound insomnia were observed, and there were no reports of serious adverse events related to daridorexant.

In the second multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response Phase 2 study to assess the efficacy and safety of daridorexant (5, 10, 25, 50 mg) in elderly patients with insomnia disorder, 58 patients (67% female; ranging from 65-85 years) were randomized.

A dose-response relationship was demonstrated for WASO (p<0.001) and LPS (p=0.004). Observed mean reductions from baseline to Days 1 & 2 for ascending doses for WASO were; (placebo, −14.13), −18.43, −32.37, −44.20, and −61.11 min, and for LPS were; (placebo, −33.88), −37.92, −44.61, −44.81, and −44.88 min.

Self-reported next-day functioning was improved across all groups. The most frequent treatment-emergent adverse events were fatigue, nasopharyngitis, gait disturbance, and headache (all ≤7%), with no apparent relationship to dose (except fatigue [50 mg], 7%).

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

2019 License agreement with Mochida in Japan
2018 Initiation of Phase 3 registration program
2017 Completion of Phase 2 clinical program
2014 Initiation of Phase 1 clinical program

Key scientific literature

– Brisbare-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.

Lucerastat

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

Fabry disease is a rare, life-threatening, genetic disorder involving 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 buildup of Gb3 deposits throughout the body, particularly in the kidneys, heart and nervous system.

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

New therapeutic options are needed to treat the underlying mechanism of the disease and provide symptomatic relief.

Current status

In May 2018, Idorsia initiated MODIFY, a multicenter, double-blind, randomized, placebo-controlled, parallelgroup 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 (validated by health authorities). At the end of the double-blind period, patients will have the option of entering in an open-label extension study. Approximately 108 patients are expected to be enrolled and randomized to lucerastat or placebo in a 2:1 ratio. The study is expected to last into 2021.

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

Available clinical data

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.

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

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.

Cenerimod

Cenerimod is a selective sphingosine-1-phosphate 1 ($S1P_1$) receptor 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 malfunctions and attacks the body's own tissues, which can affect the skin, joints, gut, blood cells, lungs, and other organs. 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.

Cenerimod blocks the egress of lymphocytes from lymphoid organs, thereby reducing circulating autoreactive T and B cells that can invade target organs. This pharmacodynamic effect is sustained with continued daily oral dosing and is reversible upon drug discontinuation.

Current status

In December 2018, Idorsia initiated a multiple-dose, efficacy and safety study with cenerimod for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE. The multicenter, randomized, double-blind, placebo-controlled, parallel-group study will enroll around 500 patients, who will be randomized into four cenerimod treatment arms: 0.5, 1, 2, and 4 mg once-daily orally or placebo for up to 12 months. Patients will 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.

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

In a Phase 1 study, cenerimod showed marked and sustained circulating lymphocyte lowering effects.

A Phase 2 safety study with cenerimod, which investigated the effect of cenerimod on circulating lymphocytes, disease activity, safety and pharmacokinetics in SLE patients, has been conducted.

The study was conducted in two parts, A and B, which were separated by an independent safety review. Patients with SLEDAI-2K score ≥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. Predefined Day 1 safety assessments included heart rate (HR) monitoring and hourly 12-lead ECG monitoring (pre-dose, to 6 hours post-dose). Endpoints included treatment-emergent adverse events (TEAEs), changes in total lymphocyte count, SLEDAI-2K score (modified [mSLEDAI] to exclude leucopoenia), anti-dsDNA antibody, a disease relevant biomarker, and pharmacokinetic assessments.

Part A included 49 patients (12:12:13:12 receiving cenerimod 0.5, 1, 2 mg or placebo, respectively); Part B included 18 patients (13 cenerimod 4 mg; 5 placebo). 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 score of −2.420 ($p=0.0306$), and a decrease in anti-dsDNA of −28.80 U/mL ($p=0.0146$) compared with placebo. All treatment groups reported 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%). After the first dose, cenerimod induced minimal, transient and dose-dependent decreases in HR; 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. Trough plasma concentrations revealed that steady-state conditions were reached after 4–8 weeks of once-daily dosing and dose-proportionality was observed.

Milestones

2018 Initiation of a multiple-dose efficacy and safety study

2015 Initiation of a Phase 2 safety study

Key scientific literature

- Hermann V, et al. Lupus Science & Medicine 2019;6:e000354. doi:10.1136/lupus-2019-000354
- Juif P-E,et al. Int. J. Mol. Sci. 2017, 18, 2636; doi:10.3390/ijms18122636
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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.
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Selatogrel

Selatogrel is a potent, fast-acting, reversible, and highly-selective $P2Y_{12}$ receptor antagonist being developed for single subcutaneous self-administration for the treatment of a suspected acute myocardial infarction (AMI) in patients with a history of AMI.

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. The American Heart Association estimates that 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.

AMI is associated with a 30% mortality rate and about half of these deaths occur prior to arrival at the hospital. 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. The need for an early intervention has been highlighted by the guidelines of the European Society of Cardiology and the American College of Cardiology / American Heart Association, which identified the prehospital phase as the most critical and reiterated that efforts must be made to reduce the delay for treatment initiation to reduce death.

Current status

In consultation with health authorities, Idorsia is preparing a large, international, multi-center, Phase 3 study to investigate the efficacy and safety of subcutaneous self-administration of selatogrel for the treatment of a suspected AMI in patients with a history of AMI. Participating patients will be trained on when to inject and instructed on how to self-administer treatment.

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 stable coronary artery disease and acute myocardial infarction, 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 4-8 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 2 different doses in adults with stable coronary artery disease. In the study, 345 patients (mean age 65 y; 20% female; 31% diabetes) 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 $P2Y_{12}$ 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 ($P2Y_{12}$ reaction units) test before and 15 min, 30 min and 1, 2, 4, 8 and 24 h after injection.

Light-transmittance aggregometry (LTA; ADP 20 uM) was also performed.

The primary endpoint, patients (responders) having PRU < 100 starting at 30 min and lasting ≥3 h 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 min post-dose, PRU values (mean±SD) were 10±25 with selatogrel 8 mg, 5±10 with selatogrel 16 mg and 163±73 with placebo. PRU levels were maintained at 2 and 4 h for both doses and gradually returned to pre-dose levels by 24 h post-dose. Light-transmittance aggregometry (LTA) results were consistent with the VerifyNow results. Pharmacodynamic responses were similar for thigh and abdomen injection sites and were consistent across the different subgroups (age, sex, BMI, presence of chronic kidney disease or diabetes).

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, randomized, exploratory study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of selatogrel in adults with acute myocardial infarction. In this study, 47 patients (median age 69 y; 72% male; 62% STEMI; 94% Killip class 1) received 8 mg (n=24) or 16 mg (n=23) selatogrel. Study-treatment concomitant medications included acetylsalicylic acid (98%), $P2Y_{12}$ receptor antagonists (96%), heparins (94%), statins (94%), nitrates (68%) and morphine (38%). Blood samples were collected at baseline and at 15, 30, and 60 min 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 as defined by PRU < 100 at 30 min 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 min (8 mg: 75% of patients; 16 mg: 91% of patients) and sustained for up to 60 min post-dose (8 mg: 75% of patients; 16 mg: 96% of patients). Overall, 43% of patients had ≥1 treatment-emergent adverse event (TEAE), which were mainly of mild/moderate intensity. Ventricular tachycardia ([VT] 8 mg: 4/24; 16 mg: 3/23) 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. 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

– Storey R. F, et al. European Heart Journal 2019, 0, 1-9, doi:10.1093/eurheartj/ehz807

– Juif P, et al. The Journal of Clinical Pharmacology 2019, 59(1): 123-130. doi:10.1002/jcph.1296

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

SORA 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 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.

ACT-519276, a GBA2/GCS inhibitor for Rare CNS diseases

At the beginning of 2018, Idorsia began Phase 1 clinical development with ACT-519276 for rare CNS diseases.

ACT-1004-1239

At the beginning of 2019, Idorsia advanced ACT-1004-1239, a new immunology / cancer immunotherapy compound, into Phase 1.

ACT-1014-6470

Idorsia is initiating a Phase 1 program with ACT-1014-6470, intended to be developed in immunological disorders, towards the end of 2019.

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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Drug Discovery and Clinical Development

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