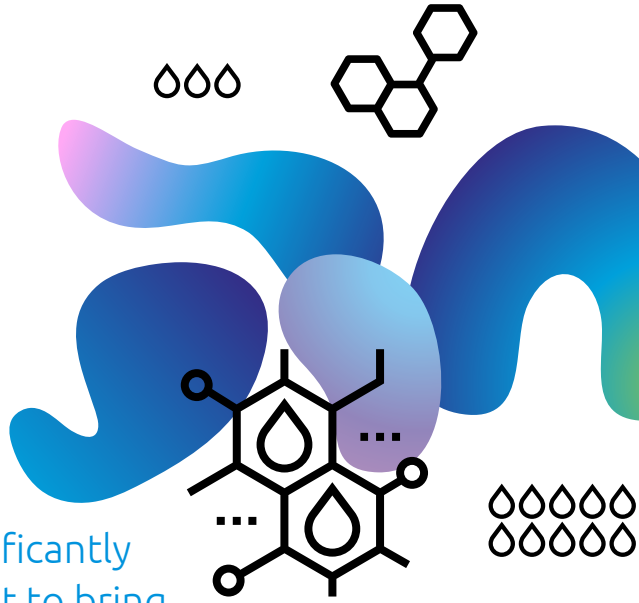
Our Innovation



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 discovery, development and commercialization of innovative treatments, challenging accepted paradigms to answer the questions that matter most.

We have a diversified and balanced innovation portfolio covering multiple therapeutic areas, including CNS, cardiovascular and immunological disorders, as well as orphan diseases.

Our Innovation

Innovation Portfolio

PIVLAZ™ / clazosentan

QUVIVIQ™ / daridorexant

Aprocitentan

Lucerastat

Selatogrel

Cenerimod

Other Compounds

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Product / Compound	Mechanism of Action	Disease Area	Status
PIVLAZ / clazosentan	Endothelin receptor antagonist	Cerebral vasospasm assoc. with aneurysmal subarachnoid hemorrhage	**Commercially available** in Japan since 20 April 2022 Global Phase 3 – recruitment complete
QUVIVIQ / daridorexant	Dual orexin receptor antagonist	Insomnia	**Commercially available** in the US since 2 May 2022 Approved in the EU Under review in Switzerland and Canada Phase 3 in Japan – recruitment complete Phase 2 in pediatric insomnia – recruiting
Aprocitentan*	Dual endothelin receptor antagonist	Resistant hypertension management	Phase 3 successful – filing by end 2022
Lucerastat	Glucosylceramide synthase inhibitor	Fabry disease	Phase 3 – primary endpoint not met Open Label Extension study ongoing
Selatogrel	$P2Y_{12}$ receptor antagonist	Suspected acute myocardial infarction	Phase 3 recruiting
Cenerimod	$S1P_1$ receptor modulator	Systemic lupus erythematosus	Phase 3 in preparation
ACT-539313	Selective orexin 1 receptor antagonist	Under evaluation	-
ACT-1004-1239	ACKR3 / CXCR7 antagonist	Multiple Sclerosis	Phase 2 in preparation
Sinbaglustat	GBA2/GCS inhibitor	Rare lysosomal storage disorders	Phase 1 complete
ACT-1014-6470	-	Immunology	Phase 1
ACT-777991	-	Immunology	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 ACT-709478 (NBI-827104), Idorsia's novel T-type calcium channel blocker. ACT-709478 is currently investigated in a Phase 2 study for the treatment of a rare form of pediatric epilepsy.

PIVLAZ / clazosentan

Clazosentan is a fast-acting, selective endothelin A (ET_A) receptor antagonist commercially available in Japan and being developed as an intravenous infusion for the prevention of vasospasm-related delayed cerebral ischemia in patients following an aneurysmal subarachnoid hemorrhage.

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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. An emergency procedure (endovascular coiling or microsurgical clipping) is required to stop the hemorrhage.

The worldwide incidence of aSAH is 7.9 per 100,000 patient years worldwide. Notably, aSAH is a significant problem in Japan, with an incidence three times higher than the rest of the world.

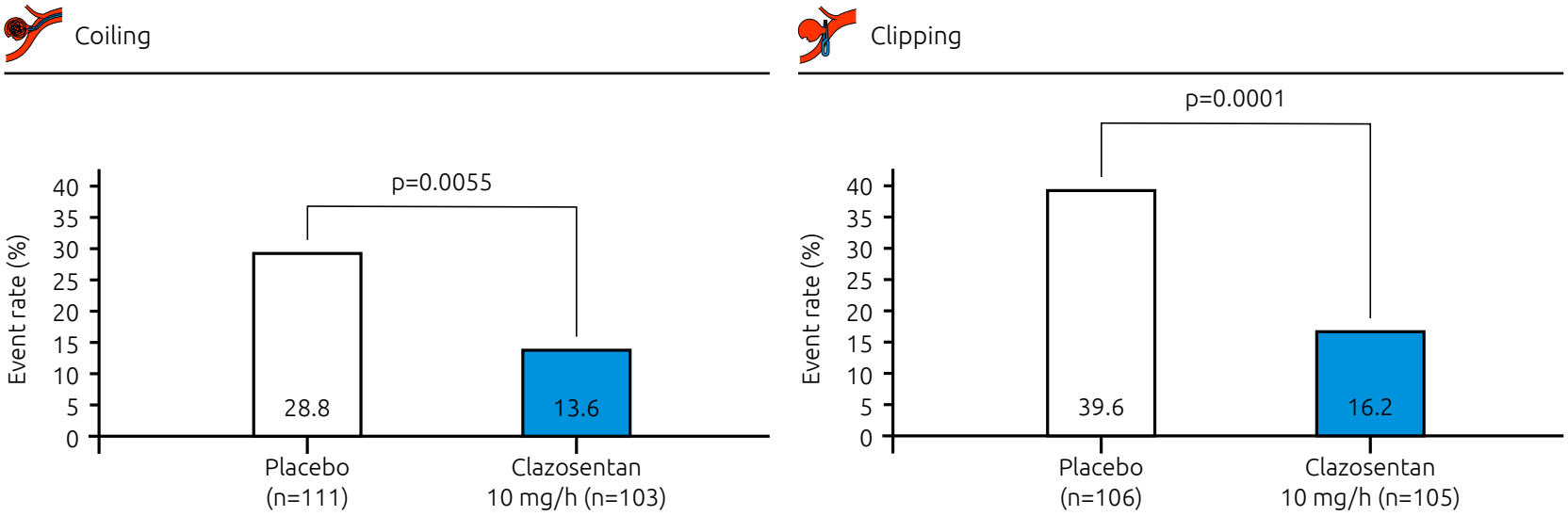
Bleeding and the release of endothelin – a potent vasoconstrictor produced by the neighboring vascular endothelium – can lead to cerebral vasospasm (constriction of arteries in the brain), which usually starts 3 days after aSAH onset and peaks in intensity between 8 and 11 days. This diminishes blood flow to the brain, and about one third of all aSAH patients consequently experience worsening of their neurological condition. Cerebral vasospasm is one of the leading secondary causes of disability in patients with aSAH.

The treatment landscape

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. Fasudil and ozagrel are used to improve cerebral vasospasm for patients in Japan and other Asian countries. Nimodipine is used for patients with aSAH in the US and EU, although an effect on cerebral vasospasm has not been shown. There has been no innovation for patients suffering from the events associated with cerebral vasospasm in more than 25 years.

Top-line results from the Japanese registration program

Incidence of vasospasm-related morbidity and all-cause mortality



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.

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Japanese registration program

A Phase 2 study in Japanese and Korean patients showed that 10 mg/h clazosentan administered by continuous intravenous infusion significantly reduced vasospasm and the overall incidence of vasospasm-related morbidity and all-cause mortality. On that basis, a registration program was initiated with clazosentan in Japan in May 2016.

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 and vasospasm-related morbidity and all-cause mortality. 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.

As shown in the charts above, both studies demonstrated a statistically significant ($p<0.01$) reduction in the combined incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH. Clazosentan showed a numerical reduction in the combined incidence of all-cause morbidity and mortality. The effect of clazosentan on this endpoint was significant ($p<0.05$) in the pre-planned pooled analysis.

There were no unexpected safety findings in these registration studies. Treatment-emergent adverse events occurring in >5% of 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).

Current status in Japan

In January 2022, PIVLAZ (clazosentan) 150 mg was approved in Japan for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction and cerebral ischemic symptoms after aSAH. PIVLAZ was launched in Japan in April 2022. In Japan, clazosentan has regulatory data protection after approval, leading to eight years' exclusivity.

PIVLAZ
clazosentan

Global registration program

Several studies have built our understanding of the role of clazosentan in preventing 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 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) 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 (DIND), 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.

The studies confirmed the well-documented safety profile of clazosentan, which has now been administered to more than 2000 patients around the world. The side effects of clazosentan can be managed according to 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 avoiding excessive fluid administration so as to maintain euvolemia.

All this evidence, together with the registration program in Japan, suggests that clazosentan has the potential to prevent vasospasm-related delayed cerebral ischemia and to reduce the need for invasive neurovascular intervention.

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Current status of the global registration study

REACT is a 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 has completed recruitment with 409 patients – treated either with microsurgical clipping or endovascular coiling – randomized 1:1 to placebo or clazosentan 15 mg/h. The study is expected to conclude by the end of 2022, reporting results in the first quarter of 2023.

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.

Milestones

2022 PIVLAZ (clazosentan) launched in Japan
2020 Japanese registration program reports positive results
2019 Global Phase 3 study initiated
2016 Japanese registration program initiated
2006 Orphan status granted in the US
2003 Orphan status granted in Europe

Key scientific literature

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- 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.
- Roux S. et al. J Pharmacol Exp Ther 1997; 283:1110-1118.

QUVIVIQ / daridorexant

Daridorexant is a dual orexin receptor antagonist (DORA) commercially available in the US, approved in the EU, under review with other health authorities, and in development in Japan as a treatment for insomnia. The global Phase 3 registration program evaluated the safety and efficacy of daridorexant on objective and subjective sleep parameters. The results have been reported in The Lancet Neurology.

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Insomnia is a condition of overactive wake signaling, which can have a profound effect on patients' lives. It can be defined as a combination of dissatisfaction with sleep quantity or quality and a significant negative impact on daytime functioning. It involves difficulty initiating and/or maintaining sleep at least three times a week for a minimum of three months.

Insomnia as a persistent disorder is quite different from a brief period of poor sleep, and it can take its toll on both physical and mental health. Idorsia's research has shown that poor-quality sleep can affect many aspects of daily life, including the ability to concentrate, mood, and energy levels.

Insomnia is a common problem. The prevalence of insomnia disorder is approximately 10%. On this basis, and assuming a US adult population of around 250 million, there are approximately 25 million adults in the US who suffer from insomnia.

The treatment landscape

The goal of treatments for insomnia is to improve sleep quality and quantity, as well as daytime functioning, while avoiding adverse events and next-morning residual effects. Current recommended treatment of insomnia includes sleep hygiene recommendations, cognitive behavioral therapy and pharmacotherapy.

With regard to prescription medications, patients are treated with products indicated for insomnia, as well as off-label treatments. The on-label treatment category primarily comprises drugs that induce sleep by enhancing GABA, the primary inhibitory neurotransmitter in the brain, which works by slowing brain activity in a non-targeted manner. There are two main categories of GABA agonists – benzodiazepines and non-benzodiazepines. In addition, other approved insomnia medications include a melatonin receptor agonist and a low-dose tricyclic antidepressant. The first products in a new class of dual orexin receptor antagonists are available in North America and certain Asia-Pacific markets. The most widely used off-label treatment for insomnia in the US is trazodone, a selective serotonin reuptake inhibitor (SSRI) which has an off-target sedation effect.

Global registration program

The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind extension study. The program enrolled around 1,850 patients with insomnia. 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 40-week extension study, which measured the effect of all three doses vs. placebo, generating data for long-term treatment of insomnia.

Phase 3 data has been reported in The Lancet Neurology: The pivotal studies demonstrated that daridorexant 50 mg significantly improved sleep onset, sleep maintenance and self-reported total sleep time at months one and three compared to placebo. The largest effect was observed with the highest dose (50 mg), followed by 25 mg, while the 10 mg dose did not have a significant effect. In all treatment groups the proportions of sleep stages were preserved, in contrast to findings reported with benzodiazepine receptor agonists.

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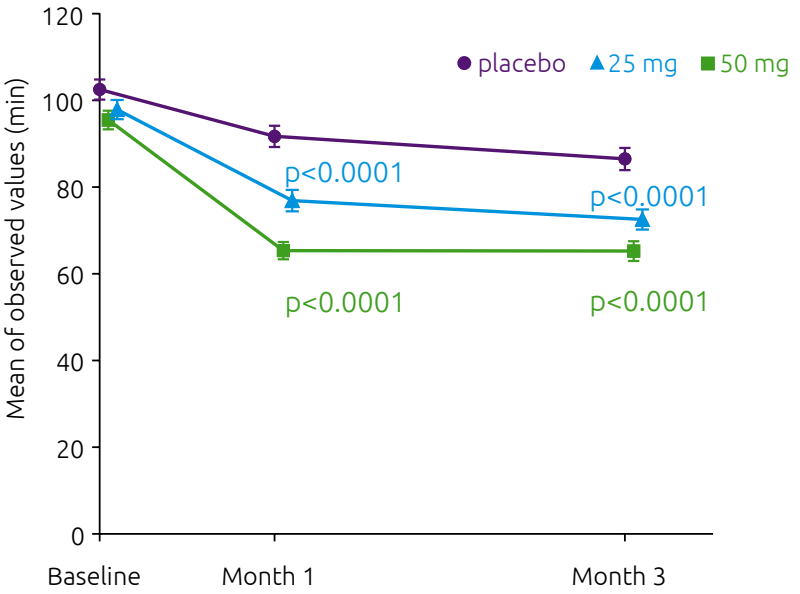
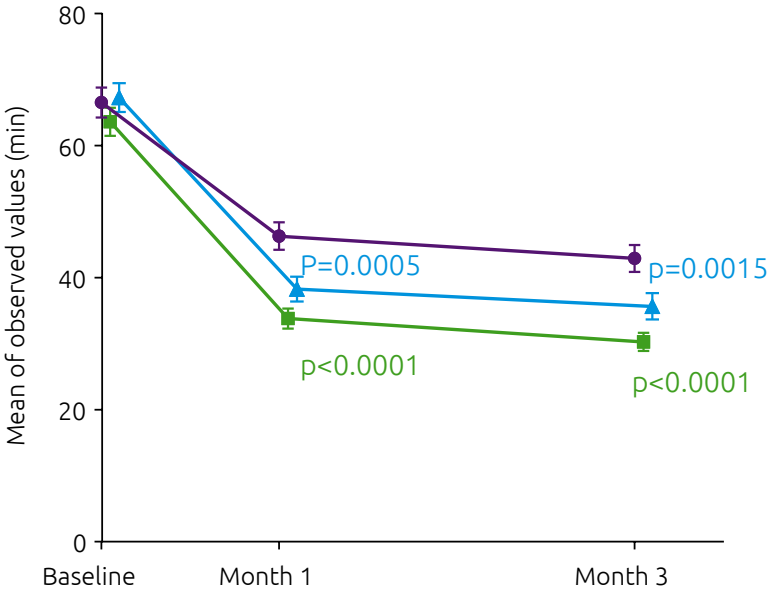
Wake time after sleep onset



Mean of observed wake time after sleep onset (WASO) values at study timepoints in study 1.

Latency to persistent sleep



Mean of observed latency to persistent sleep (LPS) values at study timepoints in study 1.

WASO and LPS values are the mean of polysomnography recordings obtained over two consecutive nights during the 3-month double-blind treatment period. Error bars show standard error of the mean. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures.

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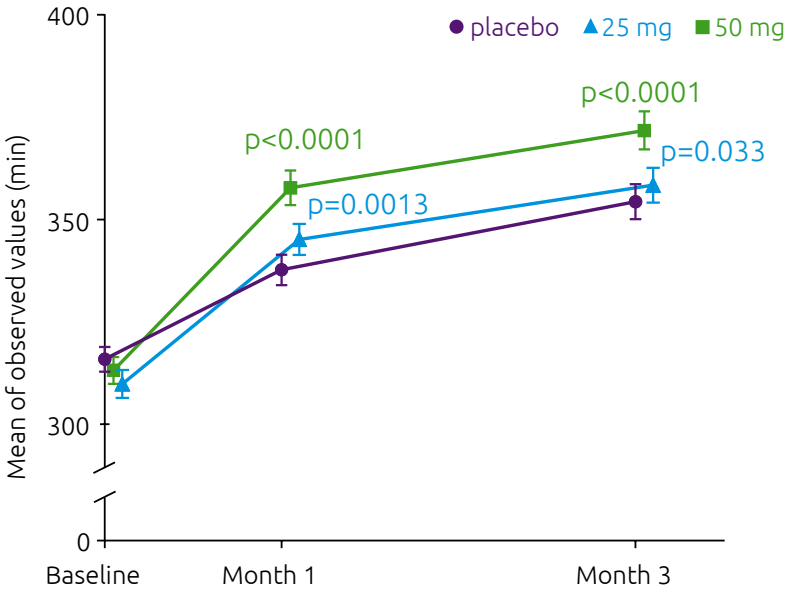
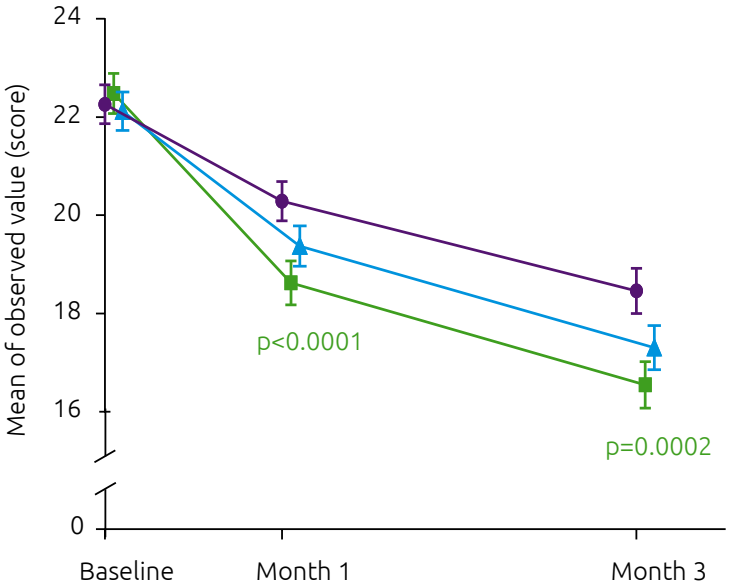
Subjective total sleep time



Mean of observed self-reported total sleep time (sTST) values at study timepoints in study 1.

IDSIQ sleepiness domain



Mean of observed IDSIQ sleepiness domain scores at study timepoints in study 1.

Data for sTST and IDSIQ scores are based on the mean of daily entries in the 7 days before polysomnography nights. Error bars show standard error of the mean. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures.

Mignot E, et al. *Lancet Neurol.* 2022; 21: 125–39

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A major focus of the trials was to evaluate the impact of daridorexant on daytime functioning in patients with insomnia, as assessed by the IDSIQ. IDSIQ is a validated patient-reported outcomes instrument specifically developed according to FDA guidelines, including patient input, to measure daytime functioning in patients with insomnia. The sleepiness domain score of the IDSIQ was evaluated as a key secondary endpoint in both pivotal studies and comparisons to placebo included control for multiplicity. Daridorexant 50 mg demonstrated highly statistically significant improvement in daytime sleepiness at month one and month 3. The sleepiness domain score was not significantly improved on 25 mg in either study at either timepoint. Daridorexant 50 mg also improved the additional IDSIQ domain scores (alert/ cognition domain, mood domain) and total score (p-values < 0.0005 versus placebo not adjusted for multiplicity). Improvements in daytime functioning by daridorexant 50 mg progressively increased over the three months of the study.

The overall incidence of adverse events was comparable between treatment groups. Adverse events occurring in more than 5% of participants were nasopharyngitis and headache. There were no dose-dependent increases in adverse events across the dosing range, including somnolence and falls. Further, no dependence, rebound insomnia or withdrawal effects were observed upon abrupt discontinuation of treatment. Across treatment groups, adverse events leading to treatment discontinuation were numerically more frequent with placebo than daridorexant.

The results of the 40-week extension study with daridorexant became available in April 2021. The study collected information on the safety of long-term treatment as well as allowing an exploratory analysis of the maintenance of efficacy. There were no new emerging safety findings. Moreover, the efficacy on sleep and daytime functioning appeared to be maintained over the longer treatment duration.

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.

Current status in the US

In January 2022, QUVIVIQ (daridorexant) 25 mg and 50 mg was approved by the US FDA for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. QUVIVIQ was launched in the US on May 2, 2022. For more information about QUVIVIQ in the US, see the **Full Prescribing Information.**

Current status in the EU

In April 2022, the European Commission granted marketing authorization for QUVIVIQ (daridorexant) for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning, making it Europe's first approved dual orexin receptor antagonist. QUVIVIQ is expected to be available in the first European country before the end of the year. For more information about QUVIVIQ in the EU, see the **Summary of Product Characteristics.** In the UK, the formal approval by the Medicines and Healthcare products Regulatory Agency (MHRA) is expected soon.

Current status in the rest of the world

Daridorexant is currently under review with Swissmedic and Health Canada.

In Japan, a Phase 3 study with daridorexant has completed recruitment.

Current status in pediatric insomnia

Idorsia has initiated a Phase 2, double-blind, randomized, placebo-controlled, dose-finding study to assess the efficacy, safety, and pharmacokinetics of multiple-dose oral administration of daridorexant in pediatric patients aged between 10 and < 18 years with insomnia disorder. The primary objective of the study is to characterize the dose-response relationship of daridorexant on objective total sleep time (TST) using polysomnography. The study is expected to enroll around 150 patients, who will be randomized in a 1:1:1:1 ratio to 10, 25, 50 mg daridorexant, or placebo. The development program has been designed based on advice and agreement with the US FDA and the EU PDCO via a Pediatric Study Plan and Pediatric Investigational Plan.

Milestones

2022 European Commission approves QUVIVIQ
2022 QUVIVIQ launched in the US
2022 Phase 3 data reported in The Lancet Neurology
2021 MAA submitted to EMA (March), Swissmedic (April), and Health Canada (August)
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

- Mignot E, et al. Lancet Neurol. 2022; 21: 125–39
- Dauvilliers, Y., et al. (2020). Ann Neurol 87(3): 347-356.
- Zammit, G., et al. (2020). Neurology 94(21): 1-11.
- Muehlan, C., et al. (2020). J Clin Psychopharmacol 40(2): 157-166.
- Muehlan, C., et al. (2020). J Psychopharmacol 34(3): 326-335.
- Boof, M. L., et al. (2019). Eur J Clin Pharmacol 75(2): 195-205.
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- Muehlan, C., et al. (2018). Clin Pharmacol Ther 104(5): 1022-1029.
- Treiber, A., et al. (2017). J Pharmacol Exp Ther 362(3): 489-503.
- Brisbare-Roch, C., et al. (2007). Nat Med 13(2): 150-5.

Aprocitentan

Aprocitentan is a novel, oral, potent, dual (ET_A and ET_B) endothelin receptor antagonist (ERA), which was developed for the treatment of patients whose blood pressure is not adequately controlled despite receiving triple antihypertensive therapy, known as 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.

Global registration study

In May 2022, Idorsia announced positive top-line results of PRECISION, the Phase 3 study investigating aprocitentan for the treatment of patients whose blood pressure is not adequately controlled despite receiving at least triple antihypertensive therapy. Aprocitentan significantly reduced blood pressure when added to standardized combination background antihypertensive therapy in patients with resistant hypertension over 48 weeks of treatment.

Idorsia, in consultation with regulatory agencies, designed PRECISION to be a single, international, multi-center, blinded randomized study with three sequential treatment parts. The study design addressed both the 4-week placebo-controlled efficacy of 12.5 and 25 mg aprocitentan (Part 1) and the durability of its effects in long-term active treatment with 25 mg aprocitentan for a further 32 weeks (Part 2) followed by a 12-week placebo-controlled withdrawal period with patients re-randomized to 25 mg or placebo (Part 3).

In Part 1, the first double-blind treatment period of 4 weeks, a total of 730 patients were randomized to receive a tablet of aprocitentan 12.5 mg (N=243), 25 mg (N=243), or placebo (N=244) once daily. After 4 weeks of treatment, a statistically significant and clinically meaningful reduction in the primary endpoint measure of systolic blood pressure – assessed by measurement at trough of unattended automated office blood pressure (AOBP) – was observed in both the 12.5 mg ($p<0.005$) and 25 mg ($p<0.005$) aprocitentan groups compared to placebo.

Following the 4-week double-blind, placebo-controlled treatment period, patients entered Part 2, a single-blind treatment period, where all patients were treated with 25 mg aprocitentan for a further 32 weeks. The mean reduction from baseline in systolic blood pressure was maintained during this treatment period, for those patients who were on aprocitentan during Part 1. Patients switching from placebo to aprocitentan rapidly achieved the same blood pressure reduction as seen in Part 1.

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This was followed by Part 3, a double-blind, placebo-controlled, randomized withdrawal treatment period where 614 patients were re-randomized to aprocitentan 25 mg or placebo for 12 weeks. After 4 weeks in the withdrawal period, systolic blood pressure increased significantly on placebo compared to aprocitentan 25 mg ($p<0.0001$), the key secondary endpoint. This provided replication of the treatment effect of aprocitentan and confirmed its durable antihypertensive effect.

The reduction in systolic and diastolic blood pressure assessed by measurement of unattended automated office blood pressure during the study, was confirmed by the 24-hour ambulatory blood pressure monitoring (ABPM), demonstrating BP reduction across the entire 24 h period (notably during the night).

The topline results show that aprocitentan was generally well tolerated with no major safety concerns in this patient population at both doses and with a low discontinuation from study treatment due to an adverse event in the first 4 weeks double-blind study period: 2.5% and 2.0% for aprocitentan 12.5 mg and 25 mg groups respectively versus 0.8% in the placebo group. Treatment-emergent adverse events (TEAEs) during the 4-week double-blind study period were reported in 27.6% and 36.7% of the patients treated with 12.5 and 25 mg aprocitentan, respectively, versus 19.4% in the placebo group. The most frequent TEAEs reported over 3% incidence and higher than placebo was edema / fluid retention.

There were no additional emerging safety findings in the subsequent treatment period taking the total to 48 weeks. Importantly, the overall incidence of Major Adverse Cardiac Events (MACE) reflected the expected occurrence in this patient population. Approximately 30% of patients developed edema / fluid retention, at one time point during the entire study duration, with >95% being mild to moderate in intensity. Two (<1%) of these adverse events were serious (both on aprocitentan 25mg). Only seven (<1%) of patients discontinued treatment due to edema / fluid retention. Edema / fluid retention was mostly reported by patients within the first 4-week double-blind study period (9.1% and 18.4% for aprocitentan 12.5 mg and 25 mg groups respectively, versus 2.1% in the placebo group).

The conclusion of the clinical development program as that aprocitentan is an investigational treatment with a new mode of action for patients with difficult-to-control hypertension. Aprocitentan reduces blood pressure compared to placebo by week 4 of treatment and the effect is maintained over a period of 48 weeks. The safety profile, together with the long half-life, and low potential for drug-drug interactions observed in the clinical pharmacology program, is conducive for a chronic treatment to be used for patients who often have several comorbidities and are treated with multiple pharmacological therapies. The effect demonstrated in the Phase 3 study was consistent across multiple methodologies of blood pressure monitoring and in key sub-populations.

Current status

In May 2022, Idorsia announced positive top-line results of PRECISION, the company will now discuss the results with health authorities with the aim to file the new drug application for aprocitentan with the US FDA by the end of the year, closely followed by other health authorities. Idorsia will also make the detailed results of the Phase 3 study available through scientific presentation and peer-reviewed publications.

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 has conducted the Phase 3 development and will be responsible for the regulatory submission for the treatment of patients whose hypertension is not adequately controlled. 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.

Milestones

2022 Phase 3 study successful
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
- Clozel M. Can J Physiol Pharmacol 2022, Mar 4 online.
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Lucerastat

Lucerastat is an oral substrate reduction therapy investigated for the treatment of adult patients with Fabry disease.

Our Innovation

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Aprocitentan

> **Lucerastat**

Selatogrel

Cenerimod

Other Compounds

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 symptoms range from neuropathic pain 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 opposed to supporting the breakdown of Gb3, thus reducing damaging build-up. This is known as Substrate Reduction Therapy (SRT).

Global registration study

MODIFY was a double-blind, randomized, placebo-controlled study to determine the efficacy and safety of lucerastat as an oral monotherapy in adult patients with Fabry disease. 118 patients were randomized in a 2:1 ratio to either lucerastat or placebo. At the end of the double-blind period, 107 patients entered in an ongoing open label extension study, which aims to determine the long-term safety and tolerability of lucerastat oral therapy and to further evaluate its clinical efficacy on renal and cardiac function, in adult patients with Fabry disease over a period of up to a further 48 months.

While lucerastat (1000 mg b.i.d) did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo, the company has made observations on renal function and cardiac echocardiography which, if confirmed with longer-term data, would indicate a treatment effect on the main organs affected by the disease.

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Lucerastat demonstrated a substantial reduction in levels of the Fabry-disease biomarker plasma Gb3 after 6 months of treatment. A nominally significant ($p<0.0001$) difference in the change from baseline to month 6 in plasma Gb3 between lucerastat and placebo was observed, with a decrease of approximately 50% observed in plasma Gb3 in the lucerastat treatment group compared to an increase of 12% in the placebo group. Interestingly, a decrease in plasma Gb3 was observed in virtually every patient on treatment with lucerastat. Likewise, a nominally significant ($p=0.02$) difference in the percent change from baseline to month 6 in plasma lysoGb3 between lucerastat and placebo was also observed. The change in these Fabry-disease biomarkers was maintained or further improved with continued lucerastat treatment in the OLE.

Based on patient historical data, mean estimated glomerular filtration rate (eGFR), a measure of kidney function, was decreasing prior to the study. During the 6 months of the MODIFY study, a slightly higher increase in eGFR was observed in the lucerastat group versus placebo, as measured by the eGFR slope. This potential effect of lucerastat on kidney function over 6 months of treatment was further evaluated at the interim analysis of the extension study. The average eGFR decline was -2.75 mL/min/1.73m2 per year on treatment overall, while in the two years preceding the study (historical values), the decline was -3.55 mL/min/1.73m2 per year. In a subgroup of patients with an eGFR value of less than or equal to 90 mL/min/1.73m2 at baseline, denoting kidney function impairment, a slower decline of eGFR of -3.41 mL/min/1.732 per year was observed on treatment versus an historical decrease of -6.29 mL/min/1.732 per year.

Also, in several patients treated with lucerastat, especially those with a high left ventricular mass index (LVMI) at baseline, a decrease of LVMI with lucerastat was seen. These data need to be further characterized.

In MODIFY, of the 118 patients enrolled, 80 patients were randomized to lucerastat. Lucerastat was well tolerated. No clinically meaningful change in vital signs, ECGs, or marked laboratory abnormalities was observed. Two patients in each group (lucerastat 2.5%; placebo 5.4%) discontinued due to adverse events. Serious adverse events (SAE) were reported in 5 patients (6.3%) and 1 patient (2.7%) in the lucerastat and placebo groups, respectively. No SAE was fatal, and all were considered as not related to study treatment. The interim analysis of the OLE study, which included 114 patients treated for an average duration of 15 months, provided a safety and tolerability profile consistent with that observed during 6-month randomized treatment period.

Current status

In December 2021, Idorsia reported that after the planned interim analysis of the open-label extension (OLE) of the Phase 3 MODIFY study with lucerastat for the treatment of adult patients with Fabry disease, the study will continue. The company will consult with health authorities in the first half of 2023 and discuss the additional data collected in the OLE study. The data includes the placebo-controlled 6-month treatment period with 118 patients in MODIFY, as well as the analysis of 107 patients who continued into the OLE, many of whom are treated with lucerastat for one year and some whom have received treatment for up to 2 years.

Milestones

2021 Phase 3 open label extension study continues
2021 Phase 3 study completed – primary endpoint not met
2018 Phase 3 study initiated
2016 Phase 1b study completed

Key scientific literature

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Our Innovation

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> **Lucerastat**

Selatogrel

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Other Compounds

Selatogrel

Selatogrel is a potent, highly selective, fast-acting and reversible $P2Y_{12}$ receptor antagonist, being developed for the treatment of acute myocardial infarction (AMI) in patients who are at high risk of recurrent AMI. It is self-administered subcutaneously via a drug delivery device (autoinjector) upon occurrence of symptoms suggestive of an AMI.

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Other Compounds

An AMI, or heart attack, is a life-threatening condition that occurs when blood flow to the heart muscle (myocardium) is suddenly decreased or completely cut off by a blood clot in one or more of the coronary vessels. An AMI requires immediate treatment, as any delay in intervention can result in irreversible damage to the heart muscle and adverse clinical outcomes. According to the US Centers for Disease Control and Prevention, each year more than 800,000 persons 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. The majority of deaths occur outside the hospital. Early action is crucial for survival and to preserve heart muscle.

Besides aspirin, there are no treatment options currently available for the critical time from onset of AMI symptoms to first medical contact. The development of selatogrel in an autoinjector aims to fulfill this medical gap: upon symptoms suggestive of a heart attack, patients would self-inject selatogrel as early as possible and immediately call for emergency medical help.

Global registration study

Idorsia is running an international, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to assess the clinical efficacy and safety of 16 mg selatogrel when self-administered (on top of standard-of-care) upon occurrence of symptoms suggestive of an acute myocardial infarction. The primary efficacy endpoint is the occurrence of death from any cause, or non-fatal AMI after any study treatment self-administration.

A Special Protocol Assessment has been agreed with the FDA. This indicates the FDA is in agreement with 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.

The FDA has also designated the investigation of selatogrel for the treatment of a suspected AMI in adult patients with a history of 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.

SOS-AMI has been designed as a patient-centric study in collaboration with patients. Patients participating in SOS-AMI will be trained by qualified professionals appointed at each study site, on how to recognize AMI symptoms, on how and where to self-inject treatment, and to call for emergency medical help immediately. Trainers will use standardized material mirrored across all countries, which has been developed with the support of education experts, feed-back from post-MI patients, and in alignment with current guidelines. The patient is empowered through focused education to take action. In addition, regular interaction is performed by telephone with the designated site trainer, minimizing the burden on the patient, particularly during times of a global pandemic.

Current status

The Phase 3 study with selatogrel is currently recruiting patients, with a target enrollment of approximately 14,000 patients who are at high risk of recurrent acute myocardial infarction. The recruitment of patients is ramping up as more sites are initiated, with a target of more than 500 sites in about 45 countries.

Collaboration Agreement with Halozyme

In 2019, Idorsia entered into a global development agreement with Halozyme (formerly Antares Pharma) to design and customize an autoinjector for selatogrel. Halozyme's autoinjector was selected for its robustness, reliability, ease-of-use and emergency-ready capabilities – key characteristics necessary due to the nature of AMI. Idorsia has confirmed the usability of Halozyme's autoinjector through human factor validation studies.

Milestones

2021 Initiation of Phase 3 registration study

2019 Drug-device development agreement with Halozyme

2018 Positive results for the Phase 2 studies

Key scientific literature

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- Adnet F, et al. Emerg Med J. 2011;28(10):884–6.
- Norris RM. BMJ 1998;316(7137):1065–70.
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- Neumann FJ, et al. 2018. Eur Heart J 2019;40(2):87–165
- Storey R. F, et al. Eur Heart J 2019;0, 1-9, doi:10.1093/eurheartj/ehz807
- Sinnaeve P, et al. J Am Coll Cardiol. 2020 May 26;75(20):2588-2597. doi: 10.1016/j.jacc.2020.03.059. PMID: 32439008.
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Cenerimod

Cenerimod is a highly selective sphingosine-1-phosphate 1 ($S1P_1$) 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 $S1P_1$ 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 $S1P_1$ 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.

Clinical development program

In November 2021, Idorsia completed the first treatment period of CARE, a multiple-dose, Phase 2b study with cenerimod, for the treatment of adult patients with moderately to severely active, autoantibody-positive SLE. The CARE study equally randomized 427 adult patients with SLE on background therapy, to cenerimod (0.5, 1, 2, 4 mg) or placebo. Patients randomized to cenerimod 4 mg showed an improvement in the modified-Systemic Lupus Erythematosus Disease Activity Index-2000 (mSLEDAI-2K) score compared to placebo from baseline to Month 6 (p=0.029). However, this result did not reach statistical significance in the formal testing strategy when adjusting for multiplicity of tests for the four doses against placebo.

The increasing improvement compared to placebo in mSLEDAI-2K with cenerimod 4 mg over time was further supported by a consistent improvement across several patient sub-populations, particularly in patients with more severe disease activity; on Systemic Lupus Erythematosus Responder Index 4 (SRI-4); and was associated with an effect on several biological markers of disease activity.

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> **Cenerimod**

Other Compounds

Cenerimod was well tolerated in all treatment groups such that similar rates of AEs were reported across all treatment groups, 0.5 mg: 49.4%; 1 mg: 64.7%; 2 mg: 59.3%; 4 mg: 58.3%; placebo: 54.7%, during six months of treatment. The most frequent treatment emergent adverse events reported over 5% incidence in any group and higher than placebo during six months of treatment were: abdominal pain, headache, and lymphopenia. A reversible decrease in lymphocyte count is linked to the mechanism of action of cenerimod and as expected lymphopenia was more often seen in patients treated with the higher 2 mg and 4 mg doses. Importantly, there was no increased rate of infections compared to placebo: 0.5 mg: 23.5%; 1 mg: 11.8%; 2 mg: 19.8%; 4 mg: 20.2%; placebo: 18.6%. While $S1P_1$ receptor modulators are known to transiently affect heart rate (HR) at initiation of therapy, to potentially decrease pulmonary function and increase blood pressure, cenerimod showed a transient, asymptomatic, dose-dependent decrease in HR at first dose; over the 6 months of treatment, effects on pulmonary function could not be discerned from placebo, and there was minimal to no effect on blood pressure.

After the initial 6 months of treatment, patients receiving cenerimod 4 mg were re-randomized in a 1:1 ratio to either cenerimod 2 mg or placebo, while the other treatment arms continued with the study treatment for a further treatment period of 6 months. The study has concluded the 12-month treatment period and is in the safety follow up period. The analysis of the 12-month treatment data has reinforced the decision to pursue cenerimod in a Phase 3 program.

The investigation of cenerimod for the treatment of SLE has been designated as a “fast-track” development program by the FDA. 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.

Current status

The Phase 2b study with cenerimod has concluded the 12-month treatment period and is in the safety follow up period. The analysis of the 12-month treatment data has reinforced the decision to pursue cenerimod for the treatment of systemic lupus erythematosus in a Phase 3 program. Following discussions with health authorities, the plans for the Phase 3 program are being finalized. Idorsia will make the detailed results of the Phase 2b study available through scientific presentations and peer-reviewed publications.

Milestones

2021 Phase 2b study provides clear pathway to Phase 3

2018 Initiation of a Phase 2b 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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- Rahman A, Isenberg DA. N Engl J Med. 2008; 358:929-39.
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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.

Our Innovation

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> **Other Compounds**

ACT-1004-1239

ACT-1004-1239 is a first-in-class, potent, selective ACKR3/CXCR7 antagonist. Preclinical data has shown both anti-inflammatory and promyelinating effects. The Phase 1 program is complete, and following feedback from the US FDA, we are finalizing the plan for a Phase 2 study with ACT-1004-1239 in multiple sclerosis.

ACT-539313

ACT-539313 is a potent, brain-penetrating, selective orexin 1 receptor antagonist. In the Phase 1 studies, ACT-539313 was well tolerated at single oral doses of up to and including 400 mg and at multiple oral doses of up to and including 200 mg twice daily for 10 days in healthy volunteers. Following an unsuccessful proof-of-concept study in binge eating disorder, the company is fully analyzing the data and expects to publish the results of the study in scientific literature.

Sinbaglustat

The company has closed a natural history study called “RETRIEVE” which collected disease information from pediatric patients with early onset of rare lysosomal storage disorders (LSDs). The company is now considering development options for sinbaglustat.

ACT-1014-6470

ACT-1014-6470, an immunology 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.

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