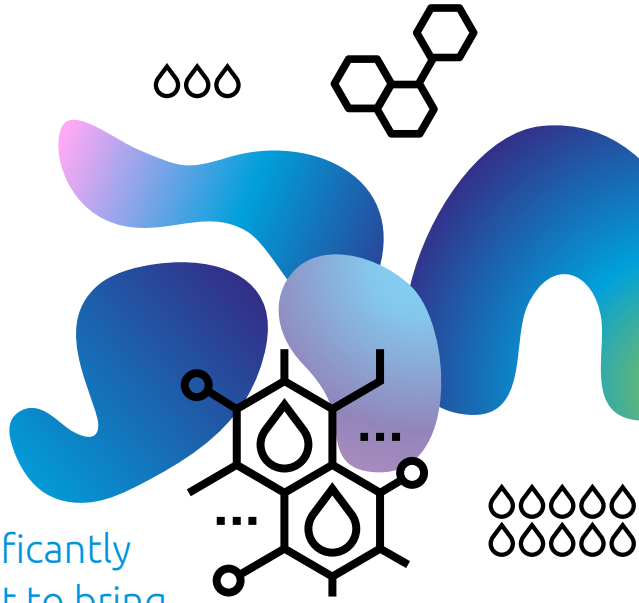
More innovation – from bench to bedside



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 portfolio, comprising assets developed and/or marketed by Idorsia and assets that are partner-led to maximize the value we have created. Our drug discovery engine has produced innovative drugs with the potential to transform the treatment paradigm in multiple therapeutic areas, including CNS, cardiovascular, and immunological disorders, as well as orphan diseases.

The company also has a vaccine platform for the discovery and development of glycoconjugate vaccines containing synthetic antigenic glycan molecules, with or without a carrier protein, to prevent infection.

Innovation Portfolio

Idorsia-led

Compound	Target indication	Mechanism of action	P1	P2	P3	R	C	Status
QUVIVIQ™ (daridorexant)	Insomnia	Dual orexin receptor antagonist	■	■	■	■	■	Commercially available in the US, Germany, Italy, Switzerland, Spain, the UK, Canada, Austria, France, and Sweden; approved throughout the EU
TRYVIO™ (aprocitentan)	Systemic hypertension in combination with other antihypertensives	Dual endothelin receptor antagonist	■	■	■	■	■	Commercially available in the US
JERAYGO™ (aprocitentan)	Resistant hypertension in combination with other antihypertensives	Dual endothelin receptor antagonist	■	■	■	■	□	Approved in the EU; Marketing authorization applications submitted in the UK, Canada, and Switzerland
Lucerastat	Fabry disease	Glucosylceramide synthase inhibitor	■	■	■	□	□	Phase 3 primary endpoint not met; open-label extension study ongoing Phase 3 focused on renal function in preparation
Daridorexant	Pediatric insomnia	Dual orexin receptor antagonist	■	■	□	□	□	Phase 2 in pediatric insomnia ongoing
ACT-1004-1239	Demyelinating diseases including MS	ACKR3/CXCR7 antagonist	■	■	□	□	□	Phase 2 in preparation
ACT-777991	Vitiligo	CXCR3 antagonist	■	■	□	□	□	Phase 2 in preparation
Sinbaglustat	Rare lysosomal storage disorders	GBA2/GCS inhibitor	■	□	□	□	□	Phase 1 complete
IDOR-1117-2520	Immune-mediated disorders	Undisclosed	■	□	□	□	□	Phase 1 ongoing
IDOR-1134-2831	*Clostridium difficile* infection	Synthetic glycan vaccine	■	□	□	□	□	Phase 1 ongoing

P1: Phase 1, P2: Phase 2, P3: Phase 3, R: Registration, C: Commercially available

Innovation Portfolio

Partner-led

Compound	Target indication	Mechanism of action	Partner Terms	Status P1	P2	P3	R	C	
QUVIVIQ™ (daridorexant)	Insomnia	Dual orexin receptor antagonist	**Simcere:** license to develop and commercialize for Greater China region	■	■	■	■	□	Approved for the treatment of insomnia in Hong-Kong
QUVIVIQ™ (daridorexant)	Insomnia	Dual orexin receptor antagonist	**Nxera Pharma:** license to develop and commercialize for Asia-Pacific region (exluding China)	■	■	■	■	□	Approved for the treatment of insomnia in Japan
Daridorexant	Insomnia	Dual orexin receptor antagonist	**Simcere:** (see above)	■	■	■	□	□	NDA submitted in Greater China
Selatogrel	Acute myocardial infarction	$P2Y_{12}$ inhibitor	**Viatris:** worldwide development and commercialization rights	■	■	■	□	□	Phase 3 “SOS-AMI” program ongoing
Cenerimod	Systemic lupus erythematosus	$S1P_1$ receptor modulator	**Viatris:** worldwide development and commercialization rights (excluding Japan, South Korea and certain countries in the Asia-Pacific region)	■	■	■	□	□	Phase 3 “OPUS” program ongoing
Daridorexant	Posttraumatic stress disorder (PTSD)	Dual orexin receptor antagonist	**US Department of Defense (DOD):** Idorsia is supporting a clinical study sponsored by the US DOD to develop new therapies to treat PTSD	■	■	□	□	□	Phase 2 ongoing
ACT-1002-4391	Immuno-oncology	EP_2 / EP_4 receptor antagonist	**Owkin:** global license to develop and commercialize	■	□	□	□	□	Phase 1 in preparation

P1: Phase 1, P2: Phase 2, P3: Phase 3, R: Registration, C: Commercially available

Daridorexant

Daridorexant is a dual orexin receptor antagonist (DORA) which blocks the binding of the wake-promoting orexin neuropeptides. Rather than inducing sleep through broad inhibition of brain activity, daridorexant selectively blocks the activation of orexin receptors. Consequently, daridorexant decreases the wake drive, allowing sleep to occur, without altering the proportion of sleep stages.

Chronic insomnia disorder 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.

Chronic insomnia disorder 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.

Chronic insomnia disorder is a common problem, with the prevalence being 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 chronic insomnia disorder.

The treatment landscape

The goal of treatments for insomnia is to improve sleep quality and quantity, as well as daytime functioning, while avoiding 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. These have now been joined by daridorexant, which is available in the US and the first countries in Europe. The most widely used off-label treatment for insomnia in the US is 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 is now complete, having enrolled around 1,850 patients with insomnia. As insomnia often presents later in life, and elderly patients are more likely 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 (Study 1: 50 mg and 25 mg; Study 2: 25 mg and 10 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, including patient input.

More than 800 patients continued treatment in the 40-week extension study, which measured the effect of all three doses versus placebo, generating data for long-term treatment of insomnia.

As reported by Mignot E, et al. in the February 2022 issue of *The Lancet Neurology*, the pivotal studies demonstrated that daridorexant significantly improved sleep onset, sleep maintenance and self-reported total sleep time at months 1 and 3 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.

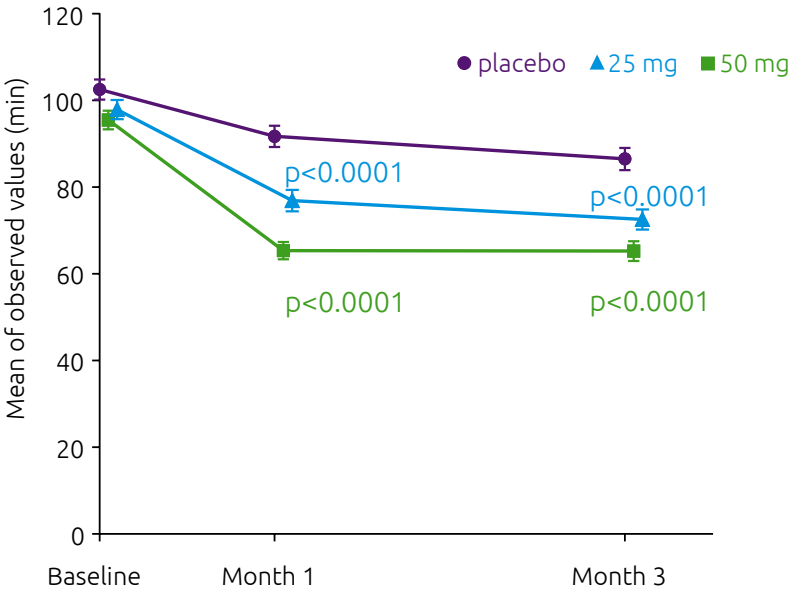
A major focus of the trials was to evaluate the impact of daridorexant on daytime functioning in patients with insomnia, as assessed by the IDSIQ. The sleepiness domain score of the IDSIQ was evaluated as a key secondary endpoint in both pivotal studies, and comparisons to placebo included control for multiplicity. Daridorexant 50 mg demonstrated a highly significant improvement in daytime sleepiness at month 1 and month 3, while 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, mood) and total score (p values <0.0005 versus placebo not adjusted for multiplicity). Improvements in daytime functioning with 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 (including somnolence and falls) across the dosing range. 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 with daridorexant.

In addition to the results published in *The Lancet Neurology*, the final results of the 40-week extension study with daridorexant became available in April 2021. This 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, efficacy for sleep and daytime functioning appeared to be maintained over the longer treatment duration.

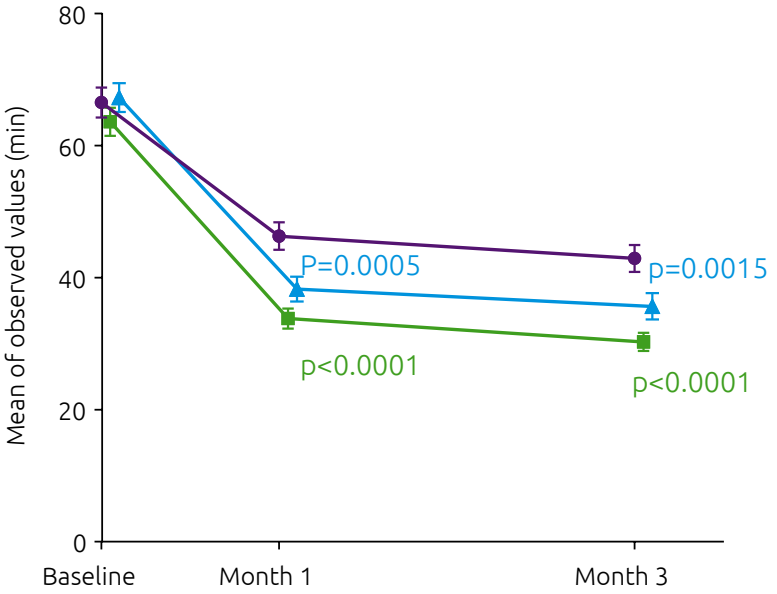
Furthermore, a comprehensive clinical pharmacology program has been conducted, with a total of 18 studies assessing, for example, abuse liability, drug-drug interactions, next-morning driving in healthy participants, the effects of daridorexant on respiratory function in patients with chronic obstructive pulmonary disease or obstructive sleep apnea, and the pharmacokinetics of daridorexant in patients with liver and renal impairment.

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

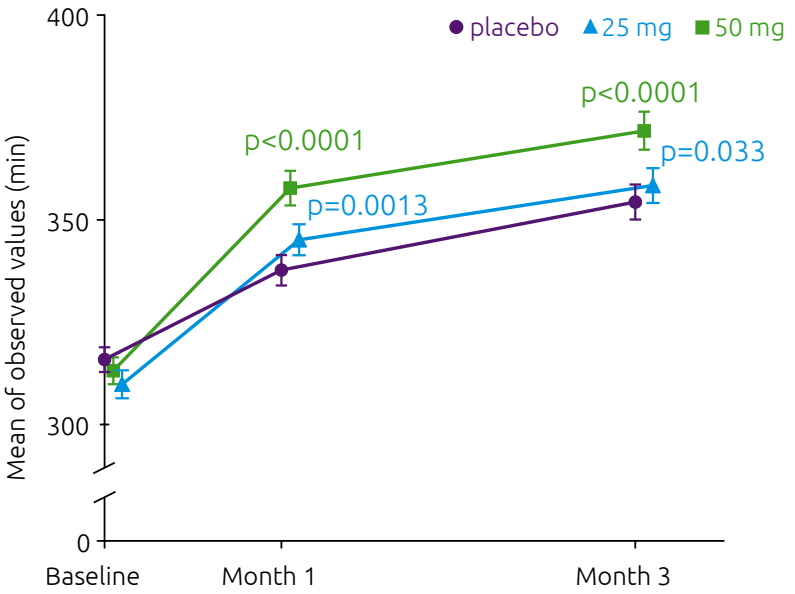


Mean of observed latency to persistent sleep (LPS) values at study timepoints in study 1.

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.

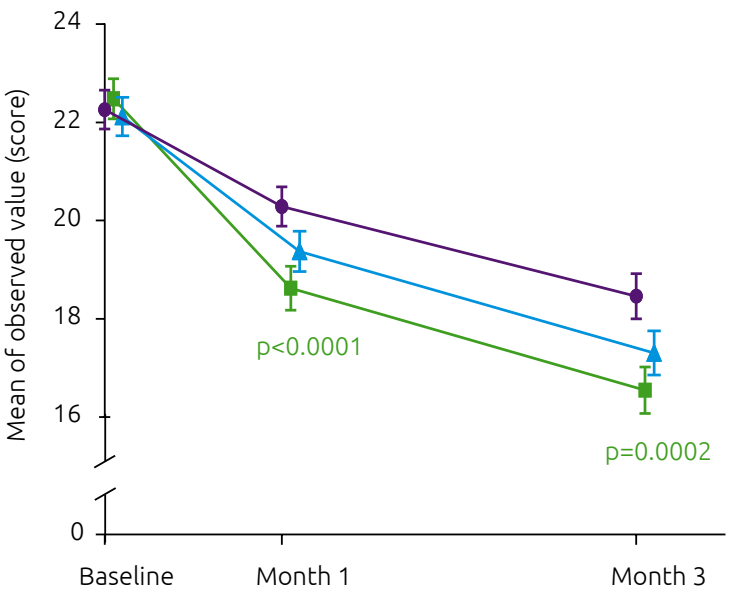
Mignot E, et al. *Lancet Neurol.* 2022; 21: 125–39

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

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 in May 2022. For more information about QUVIVIQ in the US, see the **Full Prescribing Information**.

Current status in the EUCAN region

In April 2022, marketing authorization for QUVIVIQ was granted by the European Commission and subsequently by the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain 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. In November 2022, QUVIVIQ was launched in Italy and Germany, followed by Spain in September, UK in October 2023, and Austria in February 2024 , France in March 2024, and Sweden in September 2024. For more information about QUVIVIQ in the EU, see the Summary of Product Characteristics. Marketing authorization for QUVIVIQ was also granted by Swissmedic in December 2022, and the company made QUVIVIQ available to patients in Switzerland in June 2023. For more information about QUVIVIQ in Switzerland, see the Patient Information and Information for Healthcare Professionals. Market authorization for QUVIVIQ was also granted by Health Canada in April 2023, and the company made it available to patients in Canada in November 2023. For more information about QUVIVIQ in Canada, see the Product Monograph.

Current status in global clinical development

A Phase 4 study to investigate the efficacy of daridorexant in patients with insomnia and comorbid nocturia (NCT05597020) has finished with daridorexant at a daily dose of 50 mg delivering positive topline results. The study results will be made available in peer-reviewed publications.

Idorsia is conducting a Phase 2, dose-finding study to assess the efficacy, safety, and pharmacokinetics of multiple-dose oral administration of daridorexant in pediatric patients aged 10 to <18 years with insomnia disorder (NCT05423717). 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 mg, 25 mg, or 50 mg daridorexant, or placebo. The study is part of a US FDA-approved Pediatric Study Plan and an EU PDCO-approved Paediatric Investigational Plan.

Milestones

2024 QUVIVIQ launched in Sweden
2024 Positive results in patients with insomnia and comorbid nocturia
2024 QUVIVIQ launched in Austria
2023 QUVIVIQ launched in Switzerland, Spain, UK, and Canada
2022 QUVIVIQ launched in Italy and Germany
2022 European Commission approves QUVIVIQ
2022 QUVIVIQ launched in the US
2022 Phase 3 data reported in The Lancet Neurology
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

- Fietze I., et al. 2022 Oct;39(10):795-810.
- Kunz, D. et al. CNS Drugs (2022).
- 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.
- Muehlan, C., et al. (2019). Curr Drug Metab 20(4): 254-265.
- Muehlan, C., et al. (2019). Eur Neuropsychopharmacol 29(7): 847-857.
- 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 once-daily, orally active, dual endothelin receptor antagonist, which inhibits the binding of ET-1 to ET_A and ET_B receptors. Aprocitentan has a low potential for drug-drug interaction and a mechanism of action that is ideally suited for lowering blood pressure in adult patients whose hypertension is not adequately controlled by other drugs.

Hypertension is one of the leading causes of cardiovascular disease worldwide, impacting an estimated 1.3 billion people globally. Approximately 10% of these people have uncontrolled blood pressure (BP), despite receiving at least three antihypertensive medications from different classes, at optimal doses and they are categorized in hypertension guidelines as having resistant hypertension. Compared with adults whose hypertension is well controlled, adults with uncontrolled hypertension have greater risk of heart attack, heart failure, stroke, end-stage renal disease and death.

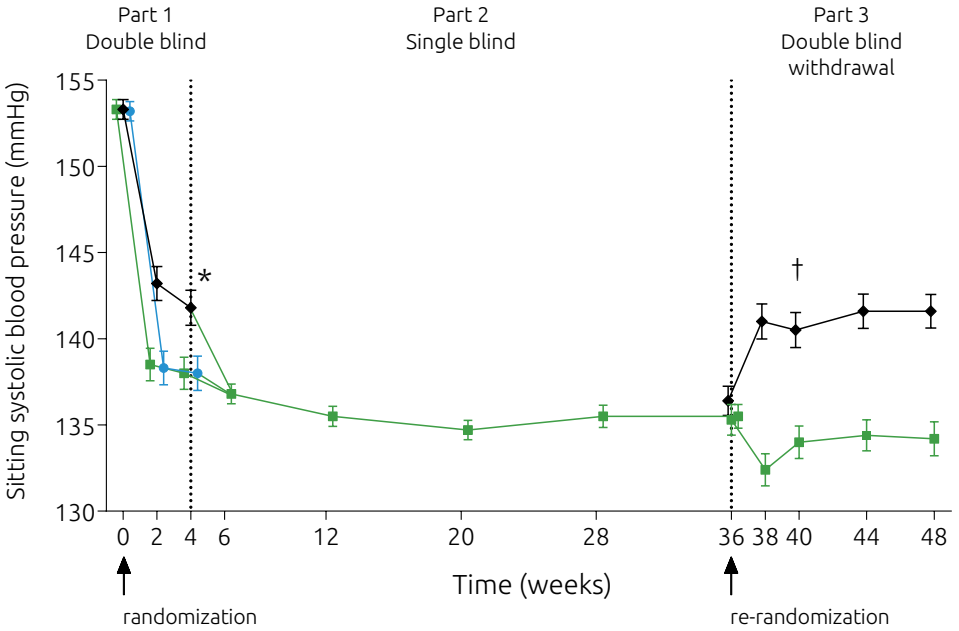
Endothelin (ET)-1, via its receptors (ET_A and ET_B), mediates a variety of effects such as vasoconstriction, fibrosis, cell proliferation, inflammation, aldosterone production and is upregulated in hypertension. Aprocitentan is a dual ERA that inhibits the binding of ET-1 to ET_A and ET_B receptors and hence the effects mediated by these receptors. The effects of ET-1 bear many similarities with the pathophysiology of hypertension and the resistance to other antihypertensive drugs in some patients (often with risk factors such as obesity, sleep apnea, older age, kidney failure, type 2 diabetes, and African Americans), can be explained by an endothelin-dependent hypertension. This is now confirmed by the efficacy of aprocitentan in the PRECISION study.

Aprocitentan was evaluated as a monotherapy in a Phase 2 study in patients with hypertension, and as an add-on therapy in a Phase 3 study called PRECISION in patients with confirmed resistant hypertension. In the Phase 3 registration study, PRECISION, aprocitentan showed statistically significant and clinically meaningful reduction in BP which was maintained for up to 48 weeks when added to a combination of background antihypertensive therapies in patients with resistant hypertension. In PRECISION, aprocitentan was generally well tolerated with no major safety concerns. The most frequent adverse event with aprocitentan was mild-to-moderate edema/fluid retention.

Global registration study

PRECISION was a multicenter, blinded, randomized, parallel-group, Phase 3 study, which was performed in hospitals or research centers in Europe, North America, Asia, and Australia. Patients were eligible for randomization if their sitting systolic blood pressure (SBP) was 140 mm Hg or higher despite taking standardized background therapy consisting of three antihypertensive drugs, including a diuretic. The study consisted of three sequential parts: Part 1 was the 4-week double-blind, randomized, and placebo-controlled part, in which 730 patients were randomized to aprocitentan 12.5 mg (n=243), aprocitentan 25 mg (n=243), or placebo (n=244) in a 1:1:1 ratio; Part 2 was a 32-week single (patient)-blind part, in which all patients received aprocitentan 25 mg (n=704); and Part 3 was a 12-week double-blind, randomized, and placebo-controlled withdrawal part, in which patients were re-randomized to aprocitentan 25 mg (n=307) or placebo (n=307) in a 1:1 ratio. The primary and key secondary endpoints were changes in

Aprocitentan has significant and sustained efficacy



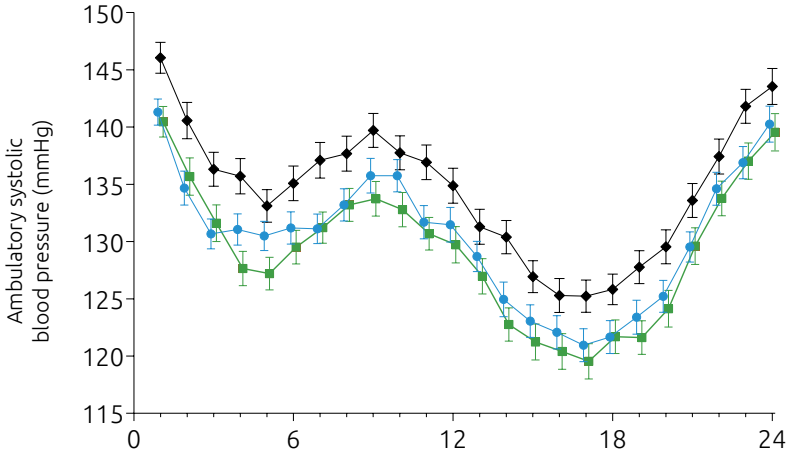
***Primary endpoint**
P=0.0042 for aprocitentan 12.5 mg vs placebo
P=0.0046 for aprocitentan 25 mg vs placebo

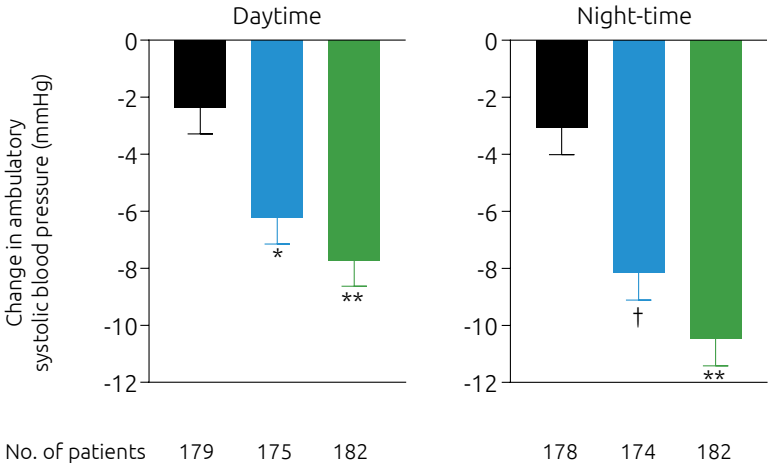
†Key secondary endpoint
P<0.0001 for aprocitentan 25 mg vs placebo

Bars are standard error of the mean
Values are offset from each other for readability

Schlaich MP, et al. *Lancet*. 2022; 400(10367):1927-1937.

Efficacy confirmed by Ambulatory BP monitoring at Week 4





Placebo
Aprocitentan 12.5 mg
Aprocitentan 25 mg

Bars are standard error of the mean
Values are offset from each other for readability

Placebo
Aprocitentan 12.5 mg
Aprocitentan 25 mg

*P=0.003, †P=0.0002, **P<0.0001 vs placebo, not corrected for multiplicity

Our Innovation

Innovation Portfolio

Daridorexant

> **Aprocitentan**

Lucerastat

Early-stage pipeline

Partner-led portfolio

Schlaich MP, et al. *Lancet.* 2022; 400(10367):1927-1937.

unattended office SBP from baseline to week 4 and from withdrawal baseline to week 40, respectively. Secondary endpoints included 24-h ambulatory blood pressure changes.

At baseline, 69.2% of patients were obese or severely obese, 54.1% had diabetes, 22.2% had stage 3-4 chronic kidney disease and 19.6% had congestive heart failure. At screening, 63% of all patients who were randomly assigned were prescribed four or more antihypertensive drugs.
As reported by Schlaich MP, et al. in the November 2022 issue of The Lancet, the least square mean change in office SBP at 4 weeks was –15.3 mmHg for aprocitentan 12.5 mg, –15.2 mmHg for 25 mg, and –11.5 mmHg for placebo, for a difference versus placebo of –3.8 mmHg (p=0.0042) and –3.7 mmHg (p=0.0046), respectively (the primary endpoint). Office diastolic blood pressure (DBP) also decreased with both aprocitentan doses compared to placebo (–3.9 mmHg for the 12.5 mg dose and –4.5 mmHg for the 25 mg dose). Office SBP and DBP were maintained during Part 2 in patients previously receiving aprocitentan and decreased within the first 2 weeks of Part 2 before stabilizing in those previously receiving placebo. In Part 3, office SBP after 4 weeks of withdrawal (week 40) (the key secondary endpoint) increased significantly with placebo compared to aprocitentan (5.8 mmHg; p<0.0001). Office DBP also increased with placebo compared to aprocitentan (5.2 mmHg; p<0.001). The difference between the two groups remained up to week 48.

The results from ambulatory BP monitoring confirmed those derived from office measurements. At the end of Part 1, aprocitentan, after placebo correction, decreased both the 24-hour ambulatory SBP (–4.2 mmHg for the 12.5 mg dose and –5.9 mmHg for the 25 mg dose) and DBP (–4.3 mmHg for the 12.5 mg dose and –5.8 mmHg for the 25 mg dose). The placebo-corrected SBP lowering effect was –5.1 mmHg and –7.4 mmHg during the night time and –3.8 mmHg and –5.3 mmHg during the daytime, for the 12.5 mg and 25 mg doses, respectively. In Part 3, after 4 weeks of withdrawal (week 40), both the 24-hour ambulatory SBP and DBP increased with placebo compared with aprocitentan (6.5 mm Hg and 6.8 mm Hg respectively).

The effect of aprocitentan was consistent across subgroups of age (including patients ≥ 75 years), sex, race (including patients with Black or African American origin), BMI, baseline urine albumin-to-creatinine ratio (UACR) and medical history of diabetes, and was consistent with the effect in the overall population.

Treatment-emergent adverse events (TEAEs) during the 4-week double-blind study period (Part 1) 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 adverse event with aprocitentan was mild-to-moderate edema/fluid retention leading to discontinuation in seven patients during the study. Edema/fluid retention was reported more frequently with aprocitentan than with placebo in a dose-dependent fashion (9.1%, 18.4%, and 2.1% for patients receiving aprocitentan 12.5 mg, 25 mg and placebo, during Part 1, respectively; 18.2% for patients receiving aprocitentan 25 mg during Part 2; and 2.6% and 1.3% for patients on aprocitentan 25 mg and placebo, during Part 3, respectively).

Current status

TRYVIO™ (aprocitentan) 12.5mg tablets

In March 2024, TRYVIO™ (aprocitentan) 12.5 mg was approved by the US FDA for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. TRYVIO is commercially available in the US. For more information see the Full Prescribing Information including BOXED Warning (PI and Medication Guide).

Current status in the EUCAN region

JERAYGO™ aprocitentan

On June 27, 2024, the European Commission granted market authorization for JERAYGO™ (aprocitentan) for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products. The recommended dose is 12.5 mg orally once daily. The dose can be increased to 25 mg once daily for patients tolerating the 12.5 mg dose and in need of tighter blood pressure (BP) control.

For more information on the marketing authorization of JERAYGO in the European Union, please review the Summary of Product Characteristics (SmPC).

European Commission marketing authorization through the centralized procedure is valid in all European Union Member States, as well as the European Economic Area countries Iceland, Liechtenstein and Norway, and Northern Ireland under the Northern Ireland Protocol. Marketing authorization applications for the use of JERAYGO in the UK, Canada, and Switzerland have been submitted.

Milestones

2024 TRYVIO (aprocitentan) commercially available in the US

2024 Approved as JERAYGO (aprocitentan) by the EMA

2024 Approved as TRYVIO (aprocitentan) by the US FDA

2022 Phase 3 data simultaneously presented as late-breaker at AHA and published in The Lancet

2022 Phase 3 study successful

2018 Phase 3 study initiated

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

- Schlaich M, et al. The Lancet 2022; Dec 3;400(10367):1927-1937.
- Iglarz M, et al. Clin Sci 2010; 119:453-63
- Clozel M. Can J Physiol Pharmacol 2022, 100:573-83.
- Verweij P., et al. Hypertension. 2020; 75:956–965
- Danaietash P et al. J Clin Hypertension 2022; 24(7):804-813

Lucerastat

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

Fabry disease is a rare genetic, lysosomal storage disorder. It is 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 results in an accumulation of Gb3 deposits throughout the body, leading to progressive pathophysiology in the cardiovascular system, the nervous system, and organs including the kidneys, heart, skin, ears, and eyes.

Fabry disease affects a patient's life expectancy and quality of life. 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 Phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease. 118 patients were randomized in a 2:1 ratio to receive either lucerastat (80 patients) or placebo (38 patients). At the end of the 6-month double-blind period, 107 patients entered an ongoing open label extension (OLE) study, which aims to determine the long-term safety and tolerability of lucerastat oral therapy and to further evaluate its clinical effects on renal and cardiac function in adult patients with Fabry disease over an additional period of up to 48 months.

In October 2021, the company reported that lucerastat 1000 mg b.i.d. did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo. However, observations were made 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. After 6 months of treatment, lucerastat demonstrated a substantial reduction in levels of the Fabry disease biomarker plasma Gb3. A nominally significant ($p<0.0001$) difference was observed between lucerastat and placebo in the change in plasma Gb3 from baseline to month 6, with a decrease of approximately 50% in plasma Gb3 in the lucerastat treatment group, compared to an increase of 12% in the placebo group.

Based on historical patient 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, eGFR increased in both arms of the study (as measured by the eGFR slope), with a slightly higher increase observed in the lucerastat group than in the placebo group.

Lucerastat was well tolerated. No clinically meaningful changes in vital signs or ECGs or marked laboratory abnormalities were observed. Two patients in each group (lucerastat 2.5%; placebo 5.4%) discontinued treatment due to adverse events. Serious adverse events were reported in 5 patients (6.3%) in the lucerastat group and in 1 patient (2.7%) in the placebo group.

Lucerastat for Fabry disease has received orphan drug designation in the US and the EU and is under review in Japan.

Current status

In October 2021, the company reported that lucerastat 1000 mg b.i.d. did not meet the primary endpoint of reducing neuropathic pain during 6 months of treatment versus placebo. However, lucerastat demonstrated a substantial reduction in levels of the Fabry disease biomarker plasma Gb3 during the treatment period, 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. Furthermore, results suggested a treatment effect on kidney function. Lucerastat was well tolerated. Analysis of the ongoing open-label extension (OLE) of the Phase 3 study corroborated the long-term effect on plasma Gb3 levels and a potential positive long-term effect on kidney function. The analysis also showed a safety and tolerability profile consistent with that observed during the 6-month randomized treatment period. The company is conducting a kidney biopsy substudy within a subset of patients currently participating in the OLE study in order to steer further development in Fabry disease. In parallel, Idorsia is working with regulatory authorities to design the next Phase 3 study to evaluate the effect of lucerastat on renal function.

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

- Guérard N., et al. Clin Pharmacol Ther. 2018; 103(4):703-11.
- Welford RWD., et al. Hum Mol Genet 2018; 27(19): 3392-3403

Early-stage pipeline

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-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 SAD and MAD studies have been completed, and following feedback from the US FDA, plans for a Phase 2 study in multiple sclerosis are under preparation.

Sinbaglustat

Sinbaglustat, a non-lysosomal glucosylceramidase/glucosylceramide synthase (GBA2/GCS) inhibitor, has potential for the treatment of rare lysosomal storage disorders, following a Phase 1 clinical pharmacology program, the company ran a natural history study called “RETRIEVE” which collected disease information from pediatric patients with early onset of rare lysosomal storage disorders (LSDs). Based on this information, the company is now considering development options for sinbaglustat.

ACT-777991

ACT-777991, a CXCR3 antagonist, is currently investigated in a Phase 1 program with the target indication of vitiligo.

IDOR-1117-2520

IDOR-1117-2520 is currently investigated in a Phase 1 program with the target indication in immune-mediated disorders.

IDOR-1134-2831

IDOR-1134-2831 is a Idorsia’s synthetic glycan vaccine targeting *Clostridium difficile* infection (CDI). The first study in the Phase 1 clinical pharmacology program is enrolling healthy participants to assess the safety, tolerability, and immunogenicity of up to 3 ascending dose levels of the IDOR-1134-2831 vaccine.

Partner-led portfolio

For Idorsia, sophisticated partnerships are a way of gaining strategic access to technologies or products and fully exploiting our discovery engine and clinical pipeline. We seek suitable external project partners to maximize the value of internal innovation.

Daridorexant (Nxera Pharma)

Daridorexant is licensed to Nxera Pharma in the Asia-Pacific region (excluding China), and was approved for the treatment of insomnia in Japan in September 2024. Nxera Pharma plans to make QUVIVIQ available to insomnia patients in Japan as soon as possible.

Asia-Pacific region (excluding China): Australia, Brunei, Cambodia, Indonesia, Japan, Laos, Malaysia, Myanmar, New Zealand, Philippines, Singapore, South Korea, Thailand, Taiwan, and Vietnam.

Daridorexant (Simcere)

Daridorexant is licensed to Simcere in the Greater China region (Mainland China, Hong Kong, and Macau). A Phase 3 study with daridorexant in Chinese patients delivered positive results in May 2024 and an NDA for Mainland China was submitted in June 2024. The Hong Kong Department of Health granted approval for daridorexant, under the tradename QUVIVIQ, for the treatment of insomnia in May 2024.

Selatogrel and cenerimod (Viatris)

A joint development committee from Idorsia and Viatris is overseeing the development of two ongoing Phase 3 programs up to regulatory approval.

Selatogrel is a potent, fast-acting, reversible, and highly selective $P2Y_{12}$ inhibitor being developed in a Phase 3 study (NCT04957719) for the treatment of acute myocardial infarction ("SOS AMI") in patients with a recent history of AMI. It is intended to be self-administered subcutaneously via a drug delivery system (autoinjector).

Cenerimod is a highly selective S1P1 receptor modulator, given as an oral once-daily tablet, which is being developed in a Phase 3 program known as "OPUS" (NCT05648500, NCT05672576, and NCT06475742) for the treatment of systemic lupus erythematosus (SLE).

Viatris has worldwide commercialization rights for both selatogrel and cenerimod (excluding, for cenerimod only, Japan, South Korea, and certain countries in the Asia-Pacific region).

Daridorexant (DOD)

Idorsia is supporting a clinical study sponsored by the US Department of Defense (DOD) to develop new therapies for posttraumatic stress disorder (PTSD). The Phase 2 study will evaluate the safety, tolerability, and efficacy of potential therapeutic interventions, including daridorexant, in active-duty US service members and veterans with PTSD (NCT05422612).

ACT-1002-4391

Owkin has a global license to develop and commercialize ACT-1002-4391, Idorsia's novel, potent EP_2 / EP_4 receptor antagonist with antitumor efficacy, to be used both as monotherapy and in combination with other oncology agents. The compound is in preparation for Phase 1 clinical pharmacology studies. Owkin will use its proprietary AI-based data-mining platform to generate clinical trial designs and to identify patients who may benefit from, and potential targets for, the compound.

Idorsia is an independent biopharmaceutical company based on science and innovation. The company is specialized in the discovery, development, and commercialization of innovative small molecules, with the aim of transforming 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

Our Innovation

Latest update:
October 2024