

Clinical Development

Development process

Actelion's mission to bring innovative medicines to patients can only be realized when vigorous testing of the compounds in its pipeline has been performed, and the resulting data analyzed. Actelion's clinical development department aims to fully explore and describe both the benefits for patients and any potential risks of the compounds. The group works to efficiently develop and bring to the market, on a global scale, innovative pharmaceutical products.

The process is achieved through creative and targeted clinical and pharmacological research – supported by high performance strategic clinical development, biometry, drug safety, drug regulatory, life cycle, and operations functions.

Through life cycle project teams, strategic clinical development initiates and consolidates the processes, from defining the target profile to submission to regulatory authorities. These processes are required to advance innovative compounds through the different phases of clinical development in a rapid and cost-effective manner.

Actelion's clinical science function ensures that all clinical programs adhere to the highest standards of science and medicine, while also ensuring the appropriate generation of all the information required by health care authorities worldwide.

Through global, cross-functional life cycle teams organized by the development function, Actelion ensures the timely development of a product to its full potential – from entry-into-humans through to introduction to the market – and that all appropriate measures are undertaken to maximize the full value creation potential of each product until the patent expires.

The Biometry function with its expertise in the field of statistics and data management supports the development of Actelion's compounds and, together with Drug Safety, the safety monitoring of marketed products.

Development pipeline - Actelion's focus on high unmet medical needs

Phase	Compound	Indication	Study	Results expected
IV	Bosentan	Combination bosentan and sildenafil in PAH	COMPASS-2	n/a
IV	Miglustat	GD1 patients switched from ERT to miglustat	MAINTENANCE	2010
III	Almorexant	Insomnia	RESTORA	n/a
III	Clazosentan	Prevention of vasospasm-related morbidity/ mortality post aSubarachnoid Hemorrhage (SAH)	CONSCIOUS-2 CONSCIOUS-3	H2 2010 2011
III	Macitentan	Pulmonary Arterial Hypertension	SERAPHIN	H2 2012
III	Selexipag*	Pulmonary Arterial Hypertension	GRIPHON	n/a
II	CRTH2 Receptor Antagonist	Asthma	n/a	n/a
II	S1P ₁ Receptor Agonist	Multiple Sclerosis	n/a	n/a
II	S1P ₁ Receptor Agonist	Plaque psoriasis	n/a	n/a
II	Macitentan	Idiopathic Pulmonary Fibrosis (IPF)	MUSIC	n/a
I	Antibiotic	Anti-infective	n/a	n/a
I	Cardiovascular	Cardiovascular	n/a	n/a

*proposed INN

Phase IV

Bosentan

Bosentan (Tracleer®), is an oral dual endothelin receptor antagonist, which is currently approved for the treatment of pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder which severely compromises the function of the lungs and heart. In the United States, Tracleer® is approved for the treatment of PAH Functional Class II - IV to improve exercise capacity and decrease the rate of clinical worsening. Patients with class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in class II patients, which may preclude future use as their disease progresses. In Europe, it is approved for treatment of PAH Functional Class III to improve exercise capacity and symptoms, as well as PAH Functional Class II, where some improvements have also been shown. In the EU, Tracleer® is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Bosentan in development for PAH

Current status

The COMPASS program specifically evaluates safety and efficacy of the use of bosentan in combination with sildenafil. Sildenafil is an approved treatment for PAH but one which works by its effect on another pathological pathway of the disease.

Actelion has concluded COMPASS-1, the first clinical trial to provide detailed hemodynamic information on the combination of sildenafil and bosentan.

The COMPASS-2 study is ongoing to investigate the effect on morbidity and mortality of a combination of bosentan with sildenafil compared to sildenafil monotherapy.

Available clinical data

COMPASS-1 demonstrated that adding sildenafil to patients on long-term bosentan therapy produced significant hemodynamic improvements, including a significant reduction in mean pulmonary vascular resistance (PVR) observed 60 minutes after administration of a single dose of sildenafil 25 mg (-15.2% [95% CI: -20.8 to -9.6]; $p < 0.0001$), and a decrease in the mean total pulmonary resistance (-13.3% [95% CI: -17.0 to -9.6]; $p < 0.0001$).

Milestones

2007 COMPASS-1 study results presented at ESC
2006 COMPASS program initiated

Key scientific literature

Gruenig E. et al. Acute administration of sildenafil in patients with pulmonary arterial hypertension (PAH) treated with bosentan produced a significant hemodynamic response: results of the COMPASS-1 study. European Society of Cardiology (ESC) Congress 2007 Abstract 1012

Miglustat

Miglustat (Zavesca®) is a low molecular weight inhibitor of glucosylceramide synthase and α -glucosidase. Zavesca® is approved for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease (GD1), and may only be used in those patients for whom enzyme replacement therapy is unsuitable. It is approved for this indication in 39 countries including the US and EU since 2003. Zavesca® is also approved in the EU for the treatment of progressive neurological manifestations in adult and pediatric patients with Niemann-Pick type C disease.

Miglustat in development for type 1 Gaucher disease

Current status

The MAINTENANCE study is evaluating the long-term safety and efficacy of miglustat as maintenance therapy after a switch from enzyme replacement therapy (ERT) in mild-to-moderate adult type 1 Gaucher disease patients with stable disease. Enrollment in the MAINTENANCE trial was completed during the second quarter of 2008. Results of this study are expected to become available in 2010.

Available clinical data

Zavesca® (miglustat) 100 mg is the only oral drug available for the treatment of GD1, and was approved on the basis of three international open-label clinical trials. The rationale for the use of miglustat in GD1 is to help balance the overall level of glucosylceramide by reducing its production to a level compatible with breakdown by residual glucocerebrosidase activity, a unique mode of action known as "substrate reduction therapy". Bone manifestations of GD1 were evaluated in three open-label clinical studies in patients treated with miglustat 100 mg t.i.d. for up to two years ($n = 72$). In a pooled analysis of uncontrolled data, bone mineral density Z-scores at the lumbar spine and femoral neck increased by more than 0.1 units from baseline in 27 (57%) and 28 (65%) of the patients with longitudinal bone density measurements. There were no events of bone crisis, avascular necrosis or fracture during the treatment period.

Milestones

- 2008 EU approval for a type II variation for miglustat and bone disease in type 1 Gaucher disease
- 2004 Zavesca® launched in the US and Switzerland
- 2003 Zavesca® launched in the EU
- 2002 Zavesca® in-licensed; marketing authorization granted by European Commission

Key scientific literature

Pastores G.M. et al. Effect of miglustat on bone disease in adult patients with type 1 Gaucher disease: a pooled analysis of three multinational Open-label studies. *Clinical Therapeutics*. 29: 1645-53; 2007.

Elstein D. et al. Oral maintenance clinical trial with miglustat for type 1 Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood*. 110: 2296-2301; 2007.

Giraldo P. et al. Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica*. 91:125-8; 2006.

Elstein D. et al. Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) in type 1 Gaucher disease. *J Inherit Metab Dis* 27: 757-66; 2004.

Phase III

Almorexant

Almorexant is a first-in-class, dual orexin receptor antagonist which has the potential to shift the paradigm for treating sleep disorders. It is an oral therapy that penetrates the blood-brain barrier and is capable of inducing a transient and reversible blockade of the orexin receptors. Orexins are neuropeptides produced in the brain, or more specifically, by a very small number of specialized neurons located in the hypothalamus. Orexins play an important role in maintaining wakefulness, and therefore regulate the sleep-wake-cycle. Almorexant was discovered by Actelion scientists in an in-house research program.

Actelion and GSK entered into an exclusive worldwide (excluding Japan) collaboration in July 2008 to jointly develop and commercialize Actelion's first-in-class orexin receptor antagonist almorexant.

Almorexant in development for insomnia

Current status

Almorexant is currently being investigated in the comprehensive Phase III program RESTORA (REstore physiological Sleep with The Orexin Receptor antagonist Almorexant). The first phase III study, RESTORA 1 met its primary endpoint, superiority of the dual orexin receptor antagonist almorexant compared to placebo on objective and subjective wake after sleep onset (WASO). The finding was highly significant ($p < 0.001$). In addition, several secondary endpoints of the study were met with statistical significance.

In RESTORA 1, the use of almorexant was well-tolerated. However, in this study as well as in the ongoing non-pivotal program, certain safety observations were made that will require further evaluation and assessment in longer-term Phase III studies. The Phase III studies are currently in preparation - in both adults and elderly patients suffering from primary insomnia - and will evaluate long-term efficacy and safety.

Additional studies are being planned to further establish the clinical profile of almorexant. The Actelion/GSK collaboration will explore aspects of sleep quality, absence of addiction and improved next-day performance. Chronic use studies in both adults and elderly will further evaluate the safety profile of this innovative agent.

Available clinical data

RESTORA 1 was a multi-center, double-blind, randomized, placebo-controlled, active reference (zolpidem), parallel-

group polysomnography study to evaluate efficacy and safety of 16-day oral administration of almorexant 200mg and 100mg in adult 709 patients with chronic primary insomnia. Enrolment took place in 90 clinical study centers in Australia, Europe and Israel.

A proof-of-concept/dose-ranging study in patients with primary insomnia indicated that almorexant significantly improved the primary parameter of sleep efficiency (the time asleep during the night divided by the time spent in bed), as measured by polysomnography (PSG), in a dose-dependent manner.

Milestones

2009	RESTORA 1 meets primary end-point in two week Phase III study
2008	Exclusive world-wide (excluding Japan) collaboration with GlaxoSmithKline initiated
2007	Phase III RESTORA study initiated
2005	Entry-into-man study initiated
1998	Project initiated in-house in 1998

Key scientific literature

Hoever P, et al. Multiple-dose pharmacokinetics, pharmacodynamics, safety and tolerability of the orexin receptor antagonist almorexant in healthy subjects. Poster presentation at SLEEP 2008 22nd Annual Meeting of the Associated Professional Sleep Societies, LLC (APSS) June 7-12, 2008.

Dingemans J et al. Proof-of-concept study in primary insomnia patients with almorexant (ACT-078573), a dual orexin receptor antagonist. Poster and oral presentation at the 5th World Congress of the World Federation of Sleep Research and Sleep Medicine Societies, Cairns, Australia, 2-6 September 2007; P0653-J.

Brisbare-Roch C. et al. Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nat Med.* 13(2):150-5; 2007.

Hoever P, et al. Entry-into-humans study with almorexant (ACT-078573), a dual orexin receptor antagonist: tolerability, safety and pharmacokinetics. Poster presentation at the 5th World Congress of the World Federation of Sleep Research and Sleep Medicine Societies, Cairns, Australia, 2-6 September 2007; P0444.

Hoever P, et al. Entry-into-humans study with almorexant (ACT-078573), a dual orexin receptor antagonist: pharmacodynamics. Poster presentation at the 5th World Congress of the World Federation of Sleep Research and Sleep Medicine Societies, Cairns, Australia, 2-6 September 2007; P0443.

Clazosentan

Clazosentan (Pivlaz®) is an intravenous endothelin receptor antagonist added to Actelion's pipeline through the acquisition of Axovan in 2003. It is currently being evaluated in a Phase III program investigating its impact on vasospasm-related morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). The product was granted orphan medicinal product status in Europe in 2003, and in the US in 2006.

Clazosentan in development for the prevention of vasospasm-related morbidity/mortality post aneurysmal subarachnoid hemorrhage

Current status

Clazosentan is currently being investigated in the pivotal Phase III study CONSCIOUS-2 (Clazosentan to Overcome Neurological iSchemia and Infarct Occurring after Subarachnoid hemorrhage). The study will measure the clinical benefits of clazosentan through the primary endpoint of vasospasm-related morbidity and all-cause mortality, which includes neurological deterioration, new brain infarcts, introduction of vasospasm rescue therapy, or death from any cause.

CONSCIOUS-2 is a global study which will include over 1,100 patients with aSAH and aneurysmal surgical clipping, from more than 100 centers, randomized 2:1 to receive either 5 mg/h of clazosentan, or placebo. The centers are in over 25 countries in the EU, North America and region. CONSCIOUS-2 results are expected to become available in the second half of 2010. If successful, Actelion will approach health authorities for filing.

Enrollment is ongoing in another Phase III study with clazosentan, CONSCIOUS-3. This 1,500 patient study evaluates the efficacy and safety of two doses (5 or 15 mg/h) of clazosentan versus placebo in patients post-aSAH treated by endovascular coiling. The primary endpoint is identical to that of CONSCIOUS 2.

Available clinical data

Clazosentan has been studied in a Phase II program consisting of two studies.

The first was a proof-of-concept Phase IIa placebo-controlled study of prevention of vasospasm after clipping for aSAH, published in 2005. Fewer cases of vasospasm and less severe vasospasm were observed in the clazosentan group compared with the placebo group. There were also fewer patients with new cerebral infarcts in the clazosentan-treated group.

CONSCIOUS-1 was a multi-center, international, double-blind, randomized, placebo-controlled, parallel-group, dose-finding study to evaluate the efficacy of three dose levels of clazosentan (15, 5 and 1mg/hour) in preventing the occurrence of cerebral vasospasm following aSAH in patients who underwent either clipping or coiling to stop the initial bleed, assessed by angiography.

CONSCIOUS-1 showed a strong treatment effect on the primary endpoint. Clazosentan significantly reduced moderate/severe vasospasm at all tested doses, with a relative risk reduction compared to placebo of 65% at the highest dose. A post-hoc analysis showed a trend in favor of reducing morbidity/mortality related to vasospasm using central assessment.

Milestones

2009	Phase III CONSCIOUS-3 study initiation
2007	Phase III CONSCIOUS-2 study initiation
2006	Orphan status granted in US
2005	Proof-of-concept published
2003	Orphan status granted in Europe
2003	Axovan acquisition

Key scientific literature

Macdonald R L, Kassell N F, Mayer S et al. Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1). *Stroke* 39: 3015–3021; 2008.

Vajkoczy P, Meyer B, Weidauer S et al. Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled, multicenter, Phase IIa study. *Journal of Neurosurgery* 103, 9-17; 2005.

Roux S. et al. Ro-61-1790, a new hydrosoluble endothelin antagonist: general pharmacology and effects on experimental cerebral vasospasm. *J Pharmacol Exp Ther* 283, 1110-1118; 1997.

Macitentan

Macitentan is a highly potent, tissue-targeting endothelin receptor antagonist discovered in an in-house research program. Through complete blockade of tissular endothelin, macitentan is expected to protect tissue from the damaging effect of elevated endothelin, specifically in the cardiovascular system. In preclinical studies, macitentan also exhibited effects suggesting that it maintains the integrity of the vascular wall and improves long-term outcome. Accordingly, macitentan may provide therapeutic benefit in a wide range of cardiovascular indications.

Macitentan in development for PAH

Current status

Macitentan is currently being investigated in the Phase III study SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome). This study is designed to evaluate the safety and efficacy of this highly potent tissue-targeting endothelin receptor antagonist through the primary endpoint of morbidity and all-cause mortality in patients with symptomatic PAH. Global enrollment was completed in December 2009 with a total of 742 patients.

Patients are randomized 1:1:1 to receive two different doses of macitentan (3 mg and 10 mg once daily) or placebo. With around 180 centers participating, in over 40 countries in North and South America, Europe, Asia-Pacific and Africa, this is the largest study in PAH patients and the first to include, from the beginning, a clearly defined morbidity/mortality primary end-point. Study results could become available before the end of 2012.

Available clinical data

In a Phase II study with 379 hypertensive patients, macitentan was significantly better than placebo and better than enalapril in reducing blood pressure 24 hours after drug intake. In this patient population, macitentan was generally well tolerated. The overall frequency of adverse events was similar to those observed in the placebo group. Similar to other endothelin receptor antagonists, macitentan may potentially exhibit known class effects such as a propensity for elevated liver enzymes, which will be monitored in the SERAPHIN study. Additional interaction studies concluded prior to the start of the SERAPHIN study have shown no clinically relevant interaction with warfarin, sildenafil, or ketoconazole (CYP 3A4 inhibitors).

Milestones

2007	Initiation of Phase III SERAPHIN study in PAH patients
2005	Initiation of Phase II dose ranging study
2004	Entry-into-man
2003	Selection of Macitentan for initiation of preclinical studies

Key scientific literature

Iglarz M. et al. Pharmacology of Macitentan, an orally active tissue targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther*. 2008 Sep 9.

Selexipag*

Selexipag (previously known as ACT-293987 or NS-304), originally discovered and synthesized by Nippon Shinyaku, is a long-lasting orally-available drug that is converted to the active principle, a potent non-prostanoid IP receptor agonist which exerts vasodilating effects. Selexipag has major potential as a novel treatment of pulmonary arterial hypertension.

In April 2008, Actelion and Nippon Shinyaku signed a licensing agreement, under which Actelion will be responsible for the global development and commercialization of selexipag outside Japan, and the two companies will co-develop and co-commercialize the drug in Japan.

* proposed INN

Selexipag in development for PAH

Current status

Actelion's first-in-class, orally active, non-prostanoid IP receptor agonist successfully completed a Phase IIa, placebo-controlled study to assess efficacy, safety and tolerability of this compound in 43 patients suffering from PAH and already receiving standard care with oral PAH medications.

The primary endpoint of pulmonary vascular resistance (PVR) change from baseline was met with high statistical significance ($p < 0.01$). The compound was well tolerated.

Based on these results, Actelion has progressed selexipag into a Phase III morbidity/mortality study in pulmonary arterial hypertension, enrolling the first patient in late 2009.

Available clinical data

Data from the Phase I study indicated that multiple doses up to 600 µg bid were well tolerated. There was no clinically relevant pharmacokinetic or pharmacodynamic interaction with warfarin.

Milestones

- 2009 First patient enrolled in Phase III morbidity / mortality study
- 2009 Positive Phase IIa data obtained - primary endpoint met with statistical significance
- 2008 Actelion in-licensed selexipag
- 2008 Phase II study initiated

Key scientific literature

Kuwano et al (2007). NS-304, an orally available and long-acting prostacyclin receptor agonist prodrug. *J Pharmacol Exp Ther* 322: 1181-1188.

Kuwano et al (2008). A long-acting and highly selective prostacyclin receptor agonist prodrug, NS-304, ameliorates rat pulmonary hypertension with unique relaxant responses of its active form MRE-269 on rat pulmonary artery. *J Pharmacol Exp Ther* 326: 691-699.

Phase II

Actelion's CRTH2 receptor antagonist

As a CRTH2 receptor antagonist, ACT-129968 blocks the effects of prostaglandin D₂ (PGD₂) role in inflammation and, in consequence, the amplification and maintenance of allergic reactions. It targets the allergic inflammation at the beginning of the cascade, with potential to be used as a controller therapy in both asthma and/or allergic rhinitis, as well as in multiple potential indications that are based on allergic inflammation.

Actelion's CRTH2 receptor antagonist in development for Asthma

Current status

Positive data have been obtained in a proof-of-mechanism study with Actelion's orally active CRTH2 receptor antagonist in mild asthma. In preclinical studies, this compound inhibited migration and activation of fundamental cell types involved in allergic inflammation. In the 18-patient crossover double-blind placebo-controlled study, the primary endpoint (FEV₁) was met, and the compound was well tolerated.

Plans for initiating a Phase II dose-finding study in asthma are ongoing.

Available clinical data

In Phase I studies, the compound was well tolerated and showed an appropriate pharmacological profile.

Milestones

2009	Positive proof-of-mechanism - primary endpoint met with statistical significance
2008	Phase II proof-of-mechanism study initiated
2007	Entry-into-man study initiated
2006	Preclinical development initiated

Key scientific literature

Pettipher R. Review: The roles of the prostaglandin D₂ receptors DP1 and CRTH2 in promoting allergic responses. *Brit. J. Pharmacol.* 1-9; 2007.

Tanaka K., et al. Effects of prostaglandin D₂ on helper T cell functions. *Biochem & Biophys Res Coms.* 316, 1009-14; 2004.

Iwasaki M., et al. Association of a new-type prostaglandin D₂ receptor CRTH2 with circulating T helper cells in patients with atopic dermatitis. *J. Invest. Dermatol.* 119:609-16; 2002.

Hirai H., et al. Prostaglandin D₂ selectivity induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. *J. Exp. Med* 193(2) 255-261; 2001.

Gervais F., et al. Selective modulation of chemkinesis, degranulation, and apoptosis in eosinophils through the PGD₂ receptors CRTH2 and DP. *J allergy clin immunol* 108 (6), 982-8; 2001.

Actelion's selective S1P₁ receptor agonist

Actelion has identified novel small molecules for clinical development on the basis of their S1P₁ receptor selectivity. These molecules also have high potency and a favorable pharmacokinetic profile after oral dosing, resulting in a substantial and rapidly reversible depletion of circulating lymphocytes. They are effective in animal models of T cell mediated inflammation. Actelion's selective S1P₁ receptor agonists are potential therapeutic agents for immune disorders in which activated T cells play a critical role. In these pathological situations, traditional immunosuppressants have a high potential for toxicity, slow reversibility, and may increase the risk of infection or malignancy.

Actelion's selective S1P₁ receptor agonist is currently in development, as an immunomodulator with the potential for once-a-day oral dosing, for multiple autoimmune disorders.

Actelion's selective S1P₁ receptor agonist in development for Multiple Sclerosis

Current status

Following a successful Phase I program, Actelion's first-in-class selective S1P₁ receptor agonist is currently investigated in a Phase IIb dose-finding study in patients with multiple sclerosis.

Actelion's selective S1P₁ receptor agonist in development for Psoriasis

Actelion has advanced its selective S1P₁ receptor agonist for the treatment of psoriasis based on a Phase IIa proof-of-concept study. While this short term study did not reach statistical significance, sufficient information was obtained to proceed with a first pivotal study in psoriasis.

The Phase IIa study also extended the safety information of Actelion's selective S1P₁ receptor agonist, previously established in healthy volunteers, to a larger group of psoriasis patients for up to six weeks of treatment. Full study results will become available through future presentation at major scientific meetings and subsequent scientific publication.

Available clinical data

Given the marked lymphocyte lowering effects, the Phase I data support further exploration of Actelion's S1P₁ receptor agonist in patients.

Milestones

- 2009 Initiation of dose-finding study in multiple sclerosis
- 2008 Initiation of proof of concept study in psoriasis
- 2006 Entry-into-humans
- 2004 Preclinical development initiated

Key scientific literature

Waubant E. Emerging therapies for MS. *Rev Neurol (Paris)*. 163(6-7):688-96; 2007.

Brinkmann V. Sphingosine 1-phosphate receptors in health and disease: mechanistic insights from gene deletion studies and reverse pharmacology. *Pharmacol Ther*. 115(1):84-105; 2007.

Rosen H. et al. Tipping the gatekeeper: S1P regulation of endothelial barrier function. *Trends Immunol*. 28(3):102-7; 2007.

Doggrell SA. Is fingolimod an advancement in the treatment of multiple sclerosis? *Expert Opin Pharmacother*. 8(3):383-6; 2007.

Kappos L. et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med* 355(11):1124-40; 2006.

Macitentan

Macitentan is a highly potent, tissue-targeting endothelin receptor antagonist discovered in an in-house research program. Through complete blockade of tissular endothelin, macitentan is expected to protect tissue from the damaging effect of elevated endothelin, specifically in the cardiovascular system. In preclinical studies, macitentan also exhibited effects suggesting that it maintains the integrity of the vascular wall and improves long-term outcome. Accordingly, macitentan may provide therapeutic benefit in a wide range of cardiovascular indications.

Macitentan in development for IPF

Current status

Macitentan is currently being investigated in a double-blind, randomized, multicenter study evaluating efficacy and safety in patients with idiopathic pulmonary fibrosis.

Available clinical data

In a Phase II study with 379 hypertensive patients, macitentan was significantly better than placebo and better than enalapril in reducing blood pressure 24 hours after drug intake. In this patient population, macitentan was generally well tolerated. The overall frequency of adverse events was similar to those observed in the placebo group. Similar to other endothelin receptor antagonists, macitentan may potentially exhibit known class effects such as a propensity for elevated liver enzymes, which will be monitored in the SERAPHIN study. Additional interaction studies concluded prior to the start of the SERAPHIN study have shown no clinically relevant interaction with warfarin, sildenafil, or ketoconazole (CYP 3A4 inhibitors).

Milestones

- 2009 Initiation of Phase II pilot study in IPF patients
- 2007 Initiation of Phase III SERAPHIN study in PAH patients
- 2004 Entry-into-man
- 2003 Selection of macitentan for initiation of preclinical studies

Key scientific literature

Iglarz M. et al. Pharmacology of macitentan, an orally active tissue targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther*. 2008 Sep 9.

Phase I

Actelion's novel antibiotic

Actelion 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.

The development of antibiotic resistance and the emergence of new pathogenic bacterial strains mean that infections that were once treatable with antibiotics are becoming increasingly difficult or impossible to treat. This makes new antibiotics based on new chemical scaffolds and with new mechanisms of action highly sought after.

Actelion's novel antibiotic in development

Current status

Actelion's focus on developing novel classes of potent antibiotics, highly active against problematic and multi-resistant pathogens, with a low propensity for resistance development, has resulted in our first antibiotic entering clinical studies. The decision to progress this potent, novel antibiotic into clinical development was supported by comprehensive pre-clinical tests.

Milestones

2009 Actelion's first antibiotic enters man

Key scientific literature

Spellberg B. et al. *Clinical Infectious Diseases* 46(2), 155-164; 2008.

Talbot G.H. *Expert Rev. Anti Infect. Ther.* 6(1), 39-49; 2008.

Keck W., Hubschwerlen C. *Pathogenic bacteria: How to get them back into the line of fire?* *Current Opinion in Investigational Drugs* 6(2), 139-40; 2005.

Disclaimer:

This fact sheet has the sole purpose to provide members of the public with general information about the activities of Actelion Ltd and its associated companies. 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.

Actelion's novel cardiovascular compound

Cardiovascular disorders encompass all conditions where there is a disturbance in the function of the heart or blood vessels. Cardiovascular disease accounts for more than one death in three in industrialized countries, and accounts for an increasing proportion of death in the developing world.

Actelion's cardiovascular compound in development

Current status

Comprehensive preclinical tests support progressing this innovative compound into clinical development.

Milestones

2009 Novel cardiovascular compound enters man

Latest update: March 2010

Actelion Pharmaceuticals Ltd is a global biopharmaceutical company headquartered in Allschwil/Basel, Switzerland. Actelion concentrates on discovering, developing and marketing innovative drugs for high unmet medical needs. The company is quoted on the SIX Swiss Exchange (tickersymbol: ATLN).