

ACTELION'S CLINICAL DEVELOPMENT

DEVELOPMENT PROCESS

Actelion's mission to bring innovative medicines to patients can only be realized with rigorous testing of the compounds in its pipeline and thorough analysis and interpretation of the data.

Actelion's clinical development department aims to fully explore and describe the benefits for patients. At the same time we continuously assess and monitor the potential risks, of new drug candidates. The group works to efficiently develop and bring innovative, effective and well-tolerated pharmaceutical products to patients worldwide.

Our clinical and pharmacological research involves the close cooperation of multiple functions: clinical science, pharmacology, biostatistics and data management, drug safety, drug regulatory affairs, life cycle management, and clinical operations functions.

Life cycle teams formed from representatives of clinical development functions, preclinical and business strategy and operations ensure the timely development of a product. They guide the compounds from the definition of a target profile and entry-into-human studies through to submission of the dossier to health authorities and beyond, handling Phase IIIb / IV programs. They also ensure that all appropriate measures are undertaken to optimize the value creation potential of each product.

The collection of innovative compounds in Actelion's pipeline, in combination with each compound's different phase of clinical development, makes this work highly diverse and demanding, yet it also satisfies our expectations for speed and cost-effectiveness.

Actelion's clinical development functions collectively manage these clinical programs to the appropriate scientific, medical and operational standards to generate the information required by health authorities worldwide.

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	2013
IV	Bosentan	Pediatric pulmonary arterial hypertension	FUTURE	2014
III	Macitentan	Pulmonary arterial hypertension	SERAPHIN	Complete
III	Selexipag	Pulmonary arterial hypertension	GRIPHON	2014
III	Macitentan	Digital ulcers associated with systemic sclerosis	-	2014
II	Cadazolid	<i>Clostridium difficile</i> infection	-	2012
II	Ponesimod	Multiple sclerosis	-	Complete
II	Ponesimod	Plaque psoriasis	-	H2 2012
I	Anti-malarial	Malaria	-	-
I	Cardiovascular	Cardiovascular disorders	-	-
I	CRTH2 receptor antagonist	Asthma / Allergic disorders	-	-
I	Metabolic disease	Metabolic disease	-	-
I	Immunology	Immunological disorders	-	-
I	Macitentan	Glioblastoma	-	-
I	Orexin receptor antagonist	Insomnia	-	-
I	S1P ₁ receptor agonist	Immunological disorders	-	-

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.

BOSENTAN IN DEVELOPMENT FOR PAH

Current status: The COMPASS-2 study specifically evaluates efficacy and safety of the use of the dual endothelin receptor antagonist bosentan in combination with a phosphodiesterase type 5 inhibitor sildenafil.

COMPASS-2 is a prospective, double-blind, placebo-controlled, event-driven study evaluating the progression of PAH in two groups of patients, one receiving sildenafil monotherapy and the second group receiving a combination of sildenafil and bosentan. Sildenafil is an approved treatment for PAH but one which exerts its effect through an alternate pathological pathway of the disease as compared to bosentan.

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

COMPASS-1: Gruenig E. et al. J Clin Pharmacol 2009; 49(11):1343-52

BOSENTAN IN DEVELOPMENT FOR PEDIATRIC PAH

Current status: The FUTURE (Pediatric Formulation of bosentan in pulmonary arterial hypertension) program now includes three additional studies: FUTURE-3, FUTURE-4 and FUTURE-5.

The first study (FUTURE-3) is an open label study in 64 patients aged from 3 months to 12 years to assess the pharmacokinetics, tolerability, safety, and efficacy of the pediatric formulation of bosentan twice versus three times a day.

The second study (FUTURE-4) is randomized and placebo-controlled and investigates the use of bosentan as adjunctive therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn (PPHN).

The company is also initiating a randomized, placebo-controlled study to investigate the efficacy, safety, and tolerability of the pediatric formulation of bosentan in 130 patients aged between 3 months and 17 years (FUTURE-5).

The program is scheduled to reach conclusion in H2 2014 and could fulfill the company's commitment to Health Authorities for receiving the pediatric patent extension for Tracleer in the US and EU.

AVAILABLE CLINICAL DATA

A quadrisect, dispersible 32mg tablet formulation of Tracleer® (bosentan) has been approved in the EU for the treatment of PAH in children aged from 2 years.

FUTURE-1 an open-label study, evaluated the safety and pharmacokinetics of a new dispersible tablet formulation of Tracleer®. This study provided important pharmacokinetic and dosing information using the new pediatric formulation of Tracleer®. In FUTURE-1, the observed exposure to Tracleer® was similar to that in children who participated in BREATHE-3.

FUTURE-2, an open-label safety extension study, is ongoing to assess long-term safety and outcome data.

MILESTONES

- 2009** > Tracleer® received EU approval of pediatric formulation for the treatment of PAH

KEY SCIENTIFIC LITERATURE

FUTURE-1: Beghetti M, Haworth SG, et al. Br J Clin Pharmacol 2009;68(6):948-55

PHASE III

MACITENTAN

Macitentan is a novel dual endothelin receptor antagonist that resulted from a tailored drug discovery process. Macitentan has a number of potentially key beneficial characteristics - i.e., increased *in vivo* preclinical efficacy vs. existing ERAs resulting from sustained receptor binding and tissue penetration properties. A clinical pharmacology program indicated a low propensity of macitentan for drug-drug interactions.

THE SERAPHIN STUDY

SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome) was the largest randomized, controlled study in PAH patients with a long-term treatment to include a clearly defined morbidity/mortality primary end-point [1]. The pivotal Phase III study was designed to evaluate the efficacy and safety of macitentan - a novel dual endothelin receptor antagonist that resulted from a tailored drug discovery process - through the primary endpoint of time to first morbidity and all-cause mortality event in patients with symptomatic PAH.

Global enrollment was completed in December 2009 with a total of 742 patients. Patients were randomized 1:1:1 to receive two different doses of macitentan (3 mg and 10 mg once daily) or placebo. Patients were allowed to receive PAH background therapy throughout the study, either PDE-5 inhibitors or oral/inhaled prostanoids. This event-driven study was conducted in 151 centers, from almost 40 countries in North and Latin America, Europe, Asia-Pacific and Africa and was completed in the first half of 2012, with 287 patients having an adjudicated event.

MACITENTAN IN DEVELOPMENT

Current status: In April 2012, Actelion announced that the pivotal Phase III SERAPHIN outcome study has met its primary endpoint.

Initial analysis indicated that in this long-term event-driven study in patients with PAH, and treated for up to three and a half years, macitentan, at both the 3 mg and 10 mg dose, decreased the risk of a morbidity/mortality event over the treatment period versus placebo. This risk was reduced by 45 percent in the 10 mg dose group ($p < 0.0001$). At 3 mg, the observed risk reduction was 30 percent ($p = 0.0108$).

Secondary efficacy endpoints including change from baseline to month 6 in six-minute walk-distance, change from baseline to month 6 in WHO functional class and time - over the whole treatment period - to either death due to PAH or hospitalization due to PAH also showed a dose-dependent effect ($p < 0.05$ for either dose). A trend in favor of 10 mg macitentan was observed on all-cause mortality ($p = ns$).

Macitentan is currently investigated in a pivotal Phase III program in patients with ischemic digital ulcers associated with systemic sclerosis, initiated in December 2011. Additionally, following excellent preclinical results, a Phase I/Ib open-label study was initiated with macitentan in patients with recurring glioblastoma.

SAFETY AND TOLERABILITY IN SERAPHIN

The safety set comprised 741 patients (randomized 1:1:1), who received at least one dose of study treatment. Mean exposure to study treatment was 85.3 weeks for placebo patients ($n = 249$), 99.5 weeks for patients on 3 mg ($n = 250$), and 103.9 weeks for patients on 10 mg ($n = 242$).

Macitentan in this patient population was well tolerated. The number of adverse events reported and patients discontinuing treatment due to adverse events was similar across all groups.

Elevations of liver alanine or aspartate aminotransferases greater than three times the upper limit of normal were observed in 4.5 percent of patients receiving placebo, in 3.6 percent of patients on 3 mg of macitentan and in 3.4 percent of patients on 10 mg of macitentan. In addition, no difference was observed between macitentan and placebo on fluid retention (edema).

A decrease in hemoglobin - reported as an adverse event - was observed more frequently on macitentan than placebo, with no difference in treatment discontinuation between groups.

MILESTONES

- 2012** > SERAPHIN outcome study meets its primary endpoint
- 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;327(3):736-45.

Iglarz M et al. Optimization of tissue-targeting properties of macitentan, a new dual endothelin receptor antagonist, improves its efficacy in a rat model of pulmonary fibrosis associated with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2011;183:A6445.

Sidharta PN et al. Macitentan: Entry-into-humans study with a new endothelin receptor antagonist. *Eur J Clin Pharmacol* 2011;67(10):977-84.

Bruderer S et al. Effect of cyclosporine A and rifampin on the pharmacokinetics of macitentan, a tissue-targeting dual endothelin receptor antagonist. *AAPS J* 2011 Dec 22 [Epub ahead of print].

Bruderer S et al. Absorption, distribution, metabolism, and excretion of macitentan, a dual endothelin receptor antagonist, in humans. *Amer Coll of Clin Pharmacol* 40th Annual Meeting, Sep 11-13, 2011; Chicago, USA.

SELEXIPAG

Selexipag, originally discovered and synthesized by Nippon Shinyaku, is a first-in-class, potent, orally available, selective 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.

SELEXIPAG IN DEVELOPMENT FOR PAH

Current status: Selexipag is being evaluated in the Phase III GRIPHON, (Prostacyclin (PGI₂) Receptor agonist in pulmonary arterial hypertension) trial. GRIPHON is a multicenter, double-blind, placebo-controlled trial evaluating the efficacy and safety of oral selexipag in patients with pulmonary arterial hypertension.

GRIPHON is currently enrolling a target of 1,150 patients around the world. The primary endpoint of the trial is to demonstrate the effect of selexipag on the time to first clinical event of morbidity or mortality.

Given current recruitment rates, the target enrollment is predicted to be completed by the end of 2012. Consequently, final results are expected to be available mid-2014. There will be an interim analysis for efficacy and futility at around two thirds of the total number of required events.

AVAILABLE CLINICAL DATA

Results of the Phase II, 43-patient, placebo-controlled, double-blind study, where patients were randomized in a 3:1 ratio receiving selexipag or placebo on top of PDE5 and/or ERA, showed a statistically significant reduction in pulmonary vascular resistance (PVR; primary parameter for the study). The treatment effect was shown to be 30.3 percent after 17 weeks of treatment (p=0.0045). Results also showed an encouraging numerical improvement in 6-minute walk distance (6MWD), which was a secondary endpoint of this trial. Selexipag was well tolerated and the safety profile was in-line with the expected pharmacologic effect.

Selexipag was well tolerated in healthy subjects exposed to the drug in the Phase I program. No clinically relevant or significant safety issues have emerged to date in healthy subjects exposed to selexipag in the Phase I program.

MILESTONES

- 2010** > Positive Phase II study with selexipag presented at ATS
- 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

Morrison K, et al. *J Pharmacol Exp Ther* 2010;335:249–55.

Simonneau et al., *Am J Respir Crit Care Med.* 2010;181:A2515.

PHASE II

CADAZOLID

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.

CADAZOLID IN *CLOSTRIDIUM DIFFICILE* INFECTION

Current status: Actelion's first potent, novel antibiotic, cadazolid, is investigated in a Phase II study in patients with *Clostridium difficile* infection (CDI).

The study is designed to investigate the efficacy, safety & tolerability of three doses of drug in an estimated 92 patients.

AVAILABLE CLINICAL DATA

The compound was well tolerated in healthy human volunteers and no safety signals were apparent.

MILESTONES

2009 > Actelion's first antibiotic enters man

KEY SCIENTIFIC LITERATURE

Lo Vecchio A, Zacur GM. *Clostridium difficile* infection: an update on epidemiology, risk factors, and therapeutic options. *Curr Opin Gastroenterol* 28 (1):1-9, 2012.

Khanna S and Pardi DS. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. *Expert Rev. Gastroenterol. Hepatol* 4(4), 409-416, 2010.

PONESIMOD

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.

The compounds 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 first selective S1P₁ receptor agonist, ponesimod, is currently in development, as an immunomodulator with the potential for once-a-day oral dosing, for multiple autoimmune disorders.

PONESIMOD IN DEVELOPMENT FOR MULTIPLE SCLEROSIS

Current status: A Phase IIb dose-finding study with ponesimod in multiple sclerosis was successfully completed in July 2011.

The study assessed efficacy, safety and tolerability of three ponesimod doses (10 mg, 20 mg or 40 mg) versus placebo, administered orally once daily for 24 weeks. With 464 patients enrolled, this is the largest ever dose-finding study conducted in this autoimmune disorder of the central nervous system.

In this study, ponesimod significantly reduced the cumulative number of new active lesions on monthly magnetic resonance imaging (MRI) brain scans performed from weeks 12 to 24, with the most effective dose showing statistical significance ($p < 0.0001$).

Despite the small overall number of confirmed relapses in this study, there was also a clinically meaningful effect observed on annualized relapse rate, an important secondary endpoint.

Ponesimod exhibited an adverse event pattern in this study that, if confirmed in the upcoming Phase III program, would give ponesimod a competitive safety and tolerability profile.

PONESIMOD IN DEVELOPMENT FOR PSORIASIS

Current status: Actelion has commenced a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of two doses of ponesimod in patients with moderate to severe chronic plaque psoriasis.

The study is estimated to enroll 320 patients and study drug will be administered for up to 28 weeks.

AVAILABLE CLINICAL DATA

Given the marked lymphocyte lowering effects, the Phase I data support further exploration of ponesimod in patients.

MILESTONES

- 2011** > Phase IIb dose-finding study in multiple sclerosis successfully completed
- 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

Piali L, Froidevaux S, Hess P, et al. The selective S1P₁ receptor agonist ponesimod protects from lymphocyte-mediated tissue inflammation. *J Pharmacol Exp Ther* 337(2):547-56, 2011

Bolli MH, Abele S, Binkert C, et al. 2-imino-thiazolidin-4-one derivatives as potent, orally active S1P₁ receptor agonists. *J Med Chem*. 53(10):4198-211, 2010

Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 362(5):387-401, 2010
Phys Res Coms. 316, 1009-14; 2004.

PHASE I

Actelion currently has eight compounds in Phase I clinical development.

These include a follow-up compound to the S1P₁ receptor agonist ponesimod, a more potent CRTH2 antagonist (follow-up compound to setipiprant), a cardiovascular compound, an immunology compound, a dual orexin receptor antagonist (follow-up compound to almorexant), a compound addressing a metabolic disease and an anti-malarial compound.

Finally, following excellent preclinical results, a Phase I open-label study was initiated with macitentan in patients with recurring glioblastoma.

Latest update: April 2012

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).

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.