

# ACTELION'S 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 new compounds. The group works to efficiently develop and bring innovative pharmaceutical products to patients worldwide.

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 inno-

vative 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.

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	-
IV	Bosentan	Pediatric pulmonary arterial hypertension	FUTURE	-
III	Macitentan	Pulmonary arterial hypertension	SERAPHIN	H1 2012
III	Selexipag	Pulmonary arterial hypertension	GRIPHON	2014
III	Macitentan	Digital ulcers associated with systemic sclerosis	-	-
III	Setipiprant	Allergic rhinitis	-	-
II	Cadazolid	<i>Clostridium difficile</i> infection	-	2012
II	Ponesimod	Multiple sclerosis	-	Complete
II	Ponesimod	Plaque psoriasis	-	H2 2012
II	Setipiprant	Asthma	CONTROL	H1 2012
II	Cardiovascular	Essential hypertension	-	-
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 <sub>1</sub> 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.

In the United States, Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Considerations for use: Patients with WHO 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 WHO 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

# PHASE III

## 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. The study is event-driven and, based on the progress observed, results could become available in the first half of 2012.

In addition, Actelion has initiated a pivotal Phase III program with macitentan in patients with ischemic digital ulcers associated with systemic sclerosis in December 2011.

### AVAILABLE CLINICAL DATA

In a Phase II dose-ranging 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.

In an exploratory Phase II study in 178 patients with idiopathic pulmonary fibrosis (IPF) macitentan was generally well tolerated. The safety set comprised 178 patients (randomized 2:1) who received at least one dose of study treatment. Although the study did not meet the primary objective, exposure to study treatment was similar in each treatment group, with an average duration of 14.3 months in the macitentan group (n = 119) and 15.4 months in the placebo group (n = 59).

### 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.

### SELEXIPAG IN DEVELOPMENT FOR PAH

**Current status:** Selexipag is being evaluated in the Phase III GRIPHON, (Prostacyclin (PGI<sub>2</sub>) 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, 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.

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

- 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

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

## 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

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.

### PONESIMOD

Actelion has identified novel small molecules for clinical development on the basis of their S1P<sub>1</sub> 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 S1P<sub>1</sub> 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 S1P<sub>1</sub> 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 and 24, with the most effective dose with statistical significance ( $p < 0.001$ ).

Despite the small overall number of confirmed relapses in this study, there was also clinically meaningful effect observed on annualized relapse rate, an important secondary endpoint. Multiple sclerosis is most commonly diagnosed in young adults and is associated with diverse recurrent neurological symptoms.

#### 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.

## 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

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.

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

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## SETIPIPRANT

Actelion's CRTH2 receptor antagonist, setipiprant, blocks the effects of prostaglandin D2 (PGD<sub>2</sub>) 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.

### SETIPIPRANT IN DEVELOPMENT FOR ASTHMA AND ALLERGIC RHINITIS

**Current status:** A Phase II study with Actelion's orally-active CRTH2 antagonist, setipiprant, in seasonal allergic rhinitis has met its primary endpoint with statistical significance ( $p < 0.05$ ).

The study assessed the efficacy and tolerability of various doses of this novel CRTH2 antagonist in 579 adult patients with seasonal allergic rhinitis ("hay fever") due to mountain cedar pollen.

Patients were treated for two weeks, with the primary outcome measure to demonstrate efficacy versus placebo being the mean change from baseline in Day-time Nasal Symptom Score over the entire treatment period.

Treatment in the study was well tolerated across all treatment groups and no serious adverse events were reported.

Capitalizing on these positive results and building the evidence to support value creation with this asset, Actelion initiated the first Phase III profiling study in allergic rhinitis in December 2011. The future development path and optimal partner selection is dependent on the ongoing Phase II dose-finding study results in asthma, which are expected in H1 2012.

## AVAILABLE CLINICAL DATA

Positive data have been obtained in a proof-of-mechanism study with Actelion's orally-active CRTH2 receptor antagonist in mild asthma. In the 18-patient crossover double-blind placebo-controlled study, the primary endpoint (FEV1) was met, and the compound was well tolerated.

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

## MILESTONES

- 2011** > Positive Phase II in seasonal allergic rhinitis
- 2009** > Positive proof-of-mechanism in asthma
- 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 PGD<sub>2</sub> receptors CRTH2 and DP. *J allergy clin immunol* 108 (6), 982-8; 2001.

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## 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:** Actelion has initiated a proof-of-concept study with its novel cardiovascular compound in essential hypertension.

### MILESTONES

- 2010** > Phase II proof-of concept initiation
- 2009** > Novel cardiovascular compound enters man

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## PHASE I

Actelion currently has eight compounds in Phase I clinical development.

These include a follow-up compound to the S1P<sub>1</sub> 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: January 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).

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