ACTELION'S CLINICAL DEVELOPMENT

DEVELOPMENT PROCESS

As part of the Janssen Group of Pharmaceutical Companies of Johnson & Johnson, Actelion is committed to leverage Johnson & Johnson's global presence and commercial strength to accelerate growth and patient access to our important therapies. With its unparalleled portfolio of outcome-based PAH treatments, Actelion will continue to focus on advancing the science and patient care in PAH as well as advance pipeline products in new therapeutic areas to find additional meaningfully differentiated products to benefit patients.

Actelion's clinical development activities include the characterization of macitentan in specific PAH patient populations as well as expanding its use beyond PAH. The pipeline also includes a novel antibiotic, cadazolid, under investigation for Clostridium difficile-associated diarrhea (CDAD), and a S1P1 receptor modulator, ponesimod, investigated in multiple sclerosis.

Life cycle teams, formed from representatives of clinical development functions, technical operations and business strategy and operations, ensure an efficient development of a new medicine. They are steering the compounds through to submission of the dossier to health authorities and commercialization until loss of exclusivity of the medicine in the major markets and beyond. They also ensure that all appropriate measures are undertaken to optimize the value creation potential of each product.

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

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DEVELOPMENT PIPELINE

	Compound	Target Indication	Study	Status
Phase III	**Cadazolid**	*Clostridium difficile*-associated diarrhea	IMPACT	Complete
	Macitentan	Pediatric PAH	TOMORROW	Initiating
	Macitentan	Portopulmonary hypertension (PoPH)	PORTICO	Ongoing
	Macitentan	Fontan-palliated	RUBATO	Initiating
	Ponesimod	Multiple sclerosis	OPTIMUM	Ongoing
	Ponesimod	Multiple sclerosis	POINT	Ongoing
Phase II	**Macitentan**	Chronic thromboembolic pulmonary hypertension	MERIT	Complete

CADAZOLID

Cadazolid, a novel antibiotic, is a strong inhibitor of *Clostridium difficile* protein synthesis, leading to potent suppression of toxin and spore formation.

Cadazolid, a novel quinoxolidinone antibiotic, is a strong inhibitor of Clostridium difficile protein synthesis, leading to suppression of toxin production and spore formation. In preclinical studies, cadazolid showed potent in vitro activity against C. difficile isolates and a low propensity for resistance development. In a human gut model of CDAD (*Chlostridium difficile*-associated diarrhea), cadazolid had a very limited impact on the normal gut microflora.

Cadazolid was previously investigated in a randomized, double-blind, active reference group Phase II study, with 84 patients randomized 1:1:1:1 to 250, 500, or 1,000 mg cadazolid or oral 125 mg vancomycin. The results provided proof of concept for the efficacy and safety of cadazolid for the treatment of CDAD and supported the progression to the Phase III program with a cadazolid dose of 250 mg BID.

CURRENT STATUS

On June 8, 2017, Actelion provided an update on the Phase III program IMPACT to investigate the efficacy and safety of Actelion's novel anti-infective cadazolid versus vancomycin in the treatment of Clostridium difficile-associated diarrhea (CDAD). In the pivotal program, IMPACT 1 met its primary endpoint, while the second study IMPACT 2 did not meet the primary endpoint. The company will now work diligently to complete the analyses of the full study results, and detailed results will be made available through scientific disclosure at upcoming congresses and in peer-reviewed publications.

AVAILABLE CLINICAL DATA

The IMPACT program (International Multi-center Program Assessing Cadazolid Treatment in patients suffering from Clostridium difficile-associated diarrhea) comprised two identical Phase III studies, IMPACT 1 and IMPACT 2, that were designed as multi-center, randomized, double-blind studies to compare the efficacy and safety of cadazolid (250 mg administered orally twice daily for 10 days) versus vancomycin (125 mg administered orally four times daily for 10 days) in patients with Clostridium difficile-associated diarrhea (CDAD).

Primary endpoint of the studies was the clinical cure rate at end of treatment (+ 2 days). The clinical cure rate was defined as the resolution of diarrhea (less than or equal to 3 unformed bowel movements per days for at least 2 consecutive days) and no further need for CDAD therapy on study treatment and maintained for 2 days after the end of study treatment.

In the pivotal program, IMPACT 1 met its primary endpoint, while the second study IMPACT 2 did not meet the primary endpoint. Cadazolid demonstrated an acceptable tolerability and safety profile in the IMPACT program.

MILESTONES

2017 Completion of Phase III development

2014 Cadazolid receives US FDA QIDP & Fast Track designation for development in CDAD

2013 Initiation of Phase III development

2012 Completion of Phase II development

KEY SCIENTIFIC LITERATURE

- T. Louie et al. Antimicrob. Agents Chemother. 2015; 59(10):6266-73
- D.N. Gerding et al., J. Antimicrob. Chemother. 2016; 71(1):213-9.

MACITENTAN

Macitentan is an orally available endothelin receptor antagonist (ERA) that resulted from a tailored drug discovery process in Actelion's laboratories.

Macitentan (Opsumit®) 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. The product is commercially available in over 45 markets, including the US (since November 2013), Germany (since January 2014) and Japan (since June 2015). The registration process for other countries is ongoing.

CURRENT STATUS

Macitentan is currently being further evaluated in multiple studies to expanding the clinical utility of this important product in PAH and beyond.

MERIT (Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension) was a Phase II prospective, randomized, placebo-controlled, double-blind, multi-center, parallel-group study to assess the efficacy, safety and tolerability of 10 mg macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

In MERIT, 80 inoperable patients were randomized in a 1:1 ratio into 2 treatment groups (macitentan 10 mg or placebo) over a 24 week treatment period. The study started in August 2014 and was completed in September 2016.

After 16 weeks the treatment effect was a significant 16% reduction in pulmonary vascular resistance (PVR) with macitentan compared with placebo (95% CL: –30%, –1%; p=0.04 intention-to-treat (ITT)). The efficacy observed was consistent across all sub-groups, included patients receiving background PH specific therapy at baseline (61%), including PDE-5 inhibitors (59%). Mean PVR decreased from baseline in both macitentan and placebo groups (geometric mean percent ratios of Week 16/baseline 73.0% and 87.2%, respectively).

The study also showed a significant positive effect of macitentan compared to placebo on exercise capacity. After 24 weeks of treatment, the mean change in 6-minute walk distance (6-MWD) from baseline was an increase of 35 meters (m) in macitentan and 1 m in placebo. The 6-MWD least-squares mean difference at Week 24 was 34.0 meters between macitentan and placebo (95% CL: 2.9, 65.2 m; p=0.03).

Macitentan was well tolerated in this patient population and safety was in general consistent with the known safety profile for macitentan from previous clinical studies. The most frequently reported adverse events that occurred with higher frequency on macitentan vs. placebo were peripheral edema (22.5% vs. 10.0%) and events related to anemia (17.5% vs. 2.5%). Hemoglobin decreases were observed in both macitentan and placebo groups and in only one subject in each group hemoglobin values decreased below 100 g/L during the study.

PORTICO (PORtopulmonary Hypertension Treatment wIth maCitentan - a randOmized Clinical Trial) is a randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group Phase IV study to assess the safety and efficacy of macitentan in **patients with portopulmonary hypertension (PoPH)**. The primary objective of the study is to evaluate the effect of 10 mg macitentan on pulmonary vascular resistance (PVR) as compared to placebo. Secondary objectives include the evaluation of the effect of macitentan as compared to placebo on exercise capacity and WHO functional class, as well as the evaluation of the safety and tolerability of macitentan in patients with PoPH.

RUBATO is a Phase III prospective, multi-center, double-blind, placebo-controlled parallel group study is to assess the efficacy and safety of macitentan in stable Fontan-palliated adolescents and adults. The primary objective is to assess the effect of macitentan 10 mg as compared to placebo on exercise capacity through cardiopulmonary exercise testing (peak VO2). Secondary objectives include the evaluation of the safety and tolerability of macitentan as compared to placebo in stable Fontan-palliated patients. The duration of the study is expected to be approximately 28 months; the start is planned for mid-2017.

TOMORROW (pediaTric use Of Macitentan tO delay disease pRogRessiOn in PAH Worldwide) is a multicenter, controlled, randomized, open-label event-driven study to assess the efficacy, safety and pharmacokinetics of a pediatric formulation of macitentan versus standard of care in **children with PAH**. The study will enroll children between the age of 1 month and 18 years in more than 20 countries and is expected to last up to 6 years.

AVAILABLE CLINICAL DATA

Macitentan has been studied in SERAPHIN, a multicenter, double-blind, placebo-controlled, parallel-group, event-driven, Phase III outcome study in 742 patients with symptomatic PAH, who were randomized to three treatment groups (placebo [N = 250], 3 mg [N = 250] or 10 mg [N = 242] of macitentan once daily), to assess the long-term effect on morbidity or mortality.

Treatment with macitentan 10 mg resulted in a 45% risk reduction (hazard ratio [HR] 0.55; 97.5% CI: 0.39 to 0.76; logrank p < 0.0001) of the composite morbidity-mortality endpoint up to end of treatment (EOT) when compared to placebo. The treatment effect was established early and was sustained. In patients already on background therapy for PAH treatment with macitentan 10 mg resulted in a 38% risk reduction (HR 0.62; 97.5% CI: 0.43 to 0.8; logrank p=0.0094) of the composite morbidity-mortality endpoint compared to placebo.

The risk of PAH related death or hospitalization for PAH up to EOT was reduced by 50% (HR 0.50; 97.5% CI: 0.34 to 0.75; logrank p < 0.0001) in patients receiving macitentan 10 mg (50 events) compared to placebo.

Efficacy of macitentan 10 mg on the primary endpoint was consistent across subgroups of age, sex, ethnic origin, geographical region, aetiology, by monotherapy or in combination with another PAH therapy and by WHO FC (I/II and III/IV).

The most commonly reported adverse drug reactions are nasopharyngitis (14.0%), headache (13.6%) and anaemia (13.2%, see section 4.4). The majority of adverse reactions are mild to moderate in intensity.

MILESTONES

2013 Opsumit approved by the US FDA and the EU Commission
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

- Pulido T et al.N Engl J Med 2013; 369:809-18.
- Iglarz M. et al. J Pharmacol Exp Ther. 2008; 327(3):736-45.
- Iglarz M et al. Am J Respir Crit Care Med 2011; 183:A6445.
- Sidharta PN et al. 2011; 67(10):977-84.
- Bruderer S et al. AAPS J 2012; 14(1):68-78.

PONESIMOD

Ponesimod is a potent orally active, selective sphingosine-1-phosphate receptor 1 (S1P1) immunomodulator.

Ponesimod prevents lymphocytes from leaving lymph nodes, thereby reducing circulating blood lymphocyte counts and preventing infiltration of lymphocytes into target tissues. The lymphocyte count reduction is rapid, dose-dependent, sustained upon continued dosing, and quickly reversible upon discontinuation. Initial data suggest that ponesimod does not cause lymphotoxicity by destroying/depleting lymphocytes or interfering with their cellular function. Other blood cells e.g. cells of the innate immune system are largely unaffected. Ponesimod is therefore considered a promising new oral agent for the treatment of a variety of autoimmune disorders.

CURRENT STATUS

OPTIMUM (Oral Ponesimod versus Teriflunomide In relapsing MUltiple sclerosis) is a Phase III multi-center, randomized, double-blind, parallel-group, active-controlled superiority study to compare the efficacy and safety of ponesimod to teriflunomide (Aubagio®) in patients with relapsing multiple sclerosis (RMS). The study aims to determine whether ponesimod is more efficacious than teriflunomide in reducing relapses. The study, which is expected to last about 4 years, completed recruitment in March 2017, with 1133 patients randomized into the trial in 2 groups to receive ponesimod 20 mg/day or teriflunomide 14 mg/day.

POINT (POnesImod aNd Tecfidera) is a prospective, multicenter, randomized, double-blind, parallel group, add-on, placebo-controlled, superiority study with ponesimod in patients with RMS. The study is designed to compare the efficacy, safety, and tolerability of add-on therapy with ponesimod 20 mg vs. placebo in adult patients with active RMS who are treated with dimethyl fumarate (Tecfidera®). Approximately 600 patients receiving dimethyl fumarate twice daily for at least 6 months will be randomized in a 1:1 ratio to ponesimod 20 mg or placebo. Treatment will be given until the last patient enrolled into the study has been treated for 60 weeks, with expected average treatment duration of 2 years, and for a maximum duration of 3.3 years. Enrollment has commenced, with the first patient randomized in March 2017, and the study is being conducted under a Special Protocol Assessment (SPA) agreement with the FDA.

AVAILABLE CLINICAL DATA

The decision to move into Phase III development was based on the Phase IIb dose-finding study with ponesimod in patients with relapsing-remitting multiple sclerosis. A total of 464 patients were randomized into this study and the efficacy, safety and tolerability of three ponesimod doses (10, 20, and 40 mg/day) versus placebo, administered once daily for 24 weeks.

The primary endpoint of this study was defined as the cumulative number of new gadolinium-enhancing lesions on T1-weighted magnetic resonance imaging (MRI) scans at weeks 12, 16, 20, and 24 after study drug initiation. A key secondary endpoint of this study was the annualized relapse rate over 24 weeks of treatment. Patients who completed 24 weeks of treatment were offered the opportunity to enter into an extension study. This ongoing trial is investigating the long-term safety, tolerability, and efficacy of 10 and 20 mg/day of ponesimod in patients with relapsing-remitting multiple sclerosis, in a double-blind fashion. Following a recommendation by the IDMC, patients on 10 mg are being switched to 20 mg as of March 2017. The study continues to provide extensive safety and efficacy information for ponesimod in this indication, with some patients treated for more than 6 years. The safety database from all studies with ponesimod now comprises more than 1,300 patients and healthy volunteers.

MILESTONES

2015 Phase III program in multiple sclerosis initiated
2011 Phase IIb dose-finding study in multiple sclerosis successfully completed
2006 Entry-into-humans
2004 Preclinical development initiated

KEY SCIENTIFIC LITERATURE

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Latest Update: June 2017

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