New data supporting gradual up-titration of ponesimod to mitigate first-dose cardiodynamic effects to be presented at EACPT 2015

ALLSCHWIL, SWITZERLAND – 25 June 2015 – Actelion Ltd (SIX: ATLN) today announced that data supporting a gradual up-titration dose regimen of ponesimod will be presented at the 12th Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT 2015). The congress will take place in Madrid, Spain from the 27-30 June 2015 and the poster abstract can be found on page 37 of the on-line pdf.

The poster presentation summarizes the results of a clinical study comparing the effects of ponesimod on heart rate and AV-conduction using a new gradual up-titration regimen verses the up-titration regimen previously used in clinical investigation. The ponesimod up-titration regimens are based on preclinical investigations [1], pharmacokinetic-pharmacodynamic modeling and simulations, and clinical experience.

The authors conclude that the cardiodynamic first-dose effects of ponesimod are mitigated by the new gradual up-titration.

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Notes to Editor:

PONESIMOD AT EACPT 2015
Poster number 341.00:
A novel gradual up-titration regimen mitigates the first-dose effects of ponesimod, a selective S1P₁ receptor modulator.
Monday June 29, 2015, 12:30 to 14:00, Screen 2, Poster Area, Hotel Meliá Castilla, Madrid.

ABOUT PONESIMOD
Ponesimod, an investigational drug, 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.

ABOUT PONESIMOD IN MULTIPLE SCLEROSIS

Actelion has initiated Phase III development of ponesimod in patients suffering from relapsing multiple sclerosis.

OPTIMUM, is a multicenter, randomized, double-blind, parallel-group, active-controlled superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis. The study aims to determine whether ponesimod is more efficacious than teriflunomide in reducing relapses. The study is expected to enroll approximately 1’100 subjects, randomized in 2 groups in a 1:1 ratio to receive ponesimod 20 mg/day or teriflunomide 14 mg/day, and is expected to last a little over 3 years.

An additional study to further characterize the utility and differentiation of ponesimod in multiple sclerosis is being discussed with Health Authorities.

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, was evaluated.

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. The results of this study have been published. [2]

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. The study continues to provide extensive safety and efficacy information for ponesimod in this indication, with some patients treated for more than 5 years.

PONESIMOD IN OTHER INDICATIONS

Actelion is initiating a Phase II study with ponesimod in patients suffering from chronic graft versus host disease.

The study has an open-label, single-arm, intra-subject dose-escalation design to investigate the biological activity, safety, tolerability, and pharmacokinetics of ponesimod in subjects with symptomatic moderate or severe chronic graft vs. host disease inadequately responding to first- or second-line therapy. The study will also investigate the clinical response to ponesimod treatment in these patients. Approximately 30 subjects will be enrolled to receive ponesimod in escalating doses of 5, 10, and 20 mg/day over the course of 24 weeks. The study will be conducted at approximately 10 sites in the US and is expected to last approximately 18 months.
References
1. Rey M et al. Desensitization by progressive up-titration prevents first-dose effects on the heart: guinea pig study with ponesimod, a selective S1P1 receptor modulator. PLoS One. 2013 Sep 12;8(9):e74285.

ACTELION LTD
Actelion Ltd. is a leading biopharmaceutical company focused on the discovery, development and commercialization of innovative drugs for diseases with significant unmet medical needs.

Actelion is a leader in the field of pulmonary arterial hypertension (PAH). Our portfolio of PAH treatments covers the spectrum of disease, from WHO Functional Class (FC) II through to FC IV, with oral, inhaled and intravenous medications. Although not available in all countries, Actelion has treatments approved by health authorities for a number of specialist diseases including Type 1 Gaucher disease, Niemann-Pick type C disease, Digital Ulcers in patients suffering from systemic sclerosis, and mycosis fungoides type cutaneous T-cell lymphoma.

Founded in late 1997, with now over 2,400 dedicated professionals covering all key markets around the world including Europe, the US, Japan, China, Russia and Mexico, Actelion has its corporate headquarters in Allschwil / Basel, Switzerland.

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