Actelion’s ponesimod successful in mid-stage trial in patients with moderate to severe chronic plaque psoriasis – Ponesimod to proceed to Phase III clinical development in psoriasis

ALLSCHWIL/BASEL, SWITZERLAND – 18 December 2012 – Actelion (SIX: ATLN) announced today that its selective S1P1 modulator, ponesimod, successfully met the primary endpoint – the proportion of patients with at least 75% improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI 75) at week 16 - in a double blind, placebo-controlled study conducted in 326 patients with moderate to severe chronic plaque psoriasis.

Results of the primary endpoint were highly statistically significant with both tested doses. With Ponesimod 20 mg, 46% of patients improved by at least 75% at week 16 (p<0.0001 versus placebo). With Ponesimod 40 mg, 48.1% of patients improved by at least 75% at week 16 (p<0.0001 versus placebo). An improvement by at least 75% was observed at week 16 in 13.4% of the placebo treated patients. Both doses were administered once daily.

At the end of induction, ponesimod patients improving at least 50% or more in their PASI score at week 16 were re-randomized to either continuation of the same dose of ponesimod, or to placebo.

After the initial 16 week induction phase of the study, further improvement was seen with ponesimod during the 12-week double-blind, placebo-controlled maintenance period. Among patients continuing on ponesimod 20 and 40mg, 71% and 77% achieved PASI75 at the end of the study, respectively.

Efficacy was also demonstrated across other endpoints of the study, including Physician Global Assessment (PGA) at week 16.
Guy Braunstein, M.D. and Head of Clinical Development at Actelion commented: "This is the first time that this mechanism has demonstrated efficacy with psoriasis patients. Analysis during the maintenance period of the study showed patients continued to improve beyond the initial 16 week induction phase. Having conducted such a large Phase II study we have the information we need for the design of the pivotal Phase III program."

Safety and tolerability data from the study are consistent with the safety profile of ponesimod observed in previous studies conducted including the Phase II study with multiple sclerosis patients.[3] At initiation of ponesimod treatment, transient reductions in heart rate and less frequently, a transient effect on atrioventricular conduction were observed in the study as expected. The most frequent adverse events (AEs) reported for ponesimod was dose-dependent dyspnea and asymptomatic liver enzyme elevations. Overall, there were no indications of an increased infection rate with ponesimod in the study with the exposure to ponesimod up to 28 weeks. The safety data-base from all studies with ponesimod, now comprises more than 1,100 patients and healthy volunteers with some patients treated for up to 3.3 years.

Jean-Paul Clozel, M.D. and Chief Executive Officer commented: "We are excited to now know that ponesimod, originating from Actelion's discovery effort, has the potential to become an important treatment option in immune-mediated disorders in addition to multiple sclerosis. Actelion will rapidly move forward with the preparation of the pivotal program and discussions with health authorities for the psoriasis indication."

Once full data analysis has been concluded, Actelion will discuss the details of the upcoming Phase III program with health authorities. Actelion will present the results of this dose-finding study through scientific presentations and publications.

Notes to the Editor

About ponesimod in psoriasis
Ponesimod was studied in patients with moderate-to-severe psoriasis in a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial that evaluated the efficacy, safety and tolerability of 2 dose levels of ponesimod administered during 16 weeks. This induction period was followed by a 12-week maintenance period during which patients treated with ponesimod and reaching PASI50 at week 16 were treated either with ponesimod or placebo, for a total of up to 28 weeks. This 326-patient study started enrollment in 2010 and was completed in November of 2012.

About the efficacy measurements used in the study
Efficacy of a potential therapy for psoriasis is commonly measured using the Psoriasis Area and Severity Index (PASI). A reduction of at least 75% in PASI from baseline is typically considered clinically meaningful by the CHMP and clinicians [EMEA 2004]. The CHMP [EMEA 2004] recommends using two endpoints to assess
efficacy: PASI in conjunction with a validated, standardized global score such as Physician’s Global Assessment (PGA). In this mid stage dose-finding study PASI has been chosen as the primary efficacy endpoint and PGA as the secondary endpoint.

About Psoriasis

Psoriasis is a chronic, relapsing, inflammatory and immune-mediated skin disease affecting about 1-3% of the population worldwide. Plaque psoriasis is the most common form of psoriasis, constituting ~ 85% of cases. The most characteristic skin lesions of chronic plaque psoriasis are sharply demarcated erythematous plaques, covered by silvery white scales, which most commonly occur on the elbows, knees, scalp, umbilicus, and lumbar area. Children, adolescents, and adults are affected.

About the Phase IIb study with ponesimod in multiple sclerosis [1,2,3]

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 dose levels (10 mg, 20 mg or 40 mg) versus placebo, administered orally once daily for 24 weeks with 464 patients.

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. As compared to placebo, the primary endpoint was reduced by 43% (p<0.05), 83% (p<0.0001) and 77% (p<0.0001) with ponesimod 10, 20 and 40 mg, respectively.

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

About S1P receptors

Sphingosine-1-phosphate (S1P) is a sphingolipid released by erythrocytes, platelets, mast cells and other cell types. It is currently established that S1P stimulates at least five different cell surface resident G-protein coupled receptors (GPCRs) - S1P1,2,3,4, and 5. Activation of these GPCRs mediates a complex variety of biological responses such as lymphocyte migration, endothelial cell proliferation, blood vessel constriction and heart rate modulation.

About the selective S1P1 immunomodulator ponesimod

Ponesimod is an 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-responsive, is sustained with continued dosing and quickly reversed upon discontinuation. Ponesimod does not cause lymphotoxicity: it does not destroy lymphocytes or interfere with their cellular function. Other blood cells e.g. cells of the innate immune system are unaffected and remain available to fight off infection. Ponesimod is therefore considered a promising new oral agent for the treatment of a variety of autoimmune disorders.

About Actelion and selective S1P1 immunomodulators

Actelion’s efforts in the field of selective S1P1 receptor immunomodulators started in 1999 by focusing on GPCRs found on the endothelium, the inner lining of blood vessels. The result of these research efforts is Actelion’s orally active selective S1P1 receptor agonist, ponesimod.
References

5. Matloubian M et al; 2004; Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 427:355-360.

Actelion Ltd.

Actelion Ltd is a biopharmaceutical company with its corporate headquarters in Allschwil/Basel, Switzerland. Actelion's first drug Tracleer®, an orally available dual endothelin receptor antagonist, has been approved as a therapy for pulmonary arterial hypertension. Actelion markets Tracleer® through its own subsidiaries in key markets worldwide, including the United States (based in South San Francisco), the European Union, Japan, Canada, Australia and Switzerland. Actelion, founded in late 1997, is a leading player in innovative science related to the endothelium - the single layer of cells separating every blood vessel from the blood stream. Actelion's over 2,400 employees focus on the discovery, development and marketing of innovative drugs for significant unmet medical needs. Actelion shares are traded on the SIX Swiss Exchange (ticker symbol: ATLN) as part of the Swiss blue-chip index SMI (Swiss Market Index SMI®).

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