Actelion to enter Phase II clinical development with new dual orexin receptor antagonist in patients with insomnia

- Investor webcast to provide background information on Actelion’s new DORA to be broadcast 07 July 2016 at 14:00 hrs CEST

ALLSCHWIL, SWITZERLAND – 07 July 2016 – Actelion Ltd (SIX: ATLN) announced today that the company is initiating a Phase II program with its new dual orexin receptor antagonist (DORA) in patients with insomnia.

The decision to move into a Phase II program is based on excellent data collected from the preclinical and Phase I clinical program, as well as a thorough understanding of the potential of dual orexin receptor antagonism on sleep efficacy and architecture. Information gathered on the optimal profile for a DORA has resulted in the discovery of a compound that demonstrates fast onset of CNS effects and natural physiologic sleep architecture in animal models. Data from an extensive Phase I program have confirmed the optimal pharmacokinetic and pharmacodynamic profile for a sleep medication, together with excellent safety and tolerability.

Jean-Paul Clozel, MD and Chief Executive Officer, commented: “Insomnia is not a lifestyle complaint, but a medical condition that can affect our physical, mental, and social health. Actelion has a rich experience with dual orexin receptor antagonism which has demonstrated how this mechanism can restore natural sleep. Actelion’s drug discovery efforts have now resulted in a compound that could deliver on the potential that this mechanism offers. Our new DORA is an excellent example of how our innovative drug discovery is creating significant potential.”

ABOUT THE PHASE II PROGRAM
The Phase II program consists of two studies, one in adult and one in elderly patients. It is designed to evaluate the effect of Actelion’s DORA versus placebo on sleep maintenance and sleep initiation, as well as next-day residual effect and next-day performance. The adult study will also include an active reference arm with zolpidem, as the most widely used insomnia treatment targeting GABA-A receptors. Both studies will also generate information on sleep architecture and sleep quality.

The first study is a multi-center, double-blind, randomized, placebo-controlled, active reference, parallel-group, dose-response study to evaluate the efficacy and safety of
Actelion’s DORA. The study is expected to commence enrollment in Q4 2016 and will recruit approximately 300 adult patients diagnosed with insomnia. The study will comprise 6 treatment arms: placebo; zolpidem; 5, 10, 25, and 50 mg of Actelion’s DORA. Treatment duration is 4 weeks. The primary endpoint is wake-time after sleep onset (WASO) at day 1 & 2.

The second study is a multi-center, double-blind, randomized, placebo-controlled, crossover, dose-response study to evaluate the efficacy and safety of Actelion’s DORA. The study is also expected to commence enrollment in Q4 2016 and will recruit approximately 50 elderly patients diagnosed with insomnia. The study has a 5-period crossover design with 5 treatment arms: placebo; 5, 10, 25 and 50 mg of Actelion’s DORA. Treatment duration in each period is 2 days. The primary endpoint is WASO at day 1 & 2.

Secondary objectives of both studies include evaluation of Actelion’s DORA versus placebo on latency to persistent sleep (LPS) as well as subjective latency to sleep onset (sLSO) and subjective WASO (sWASO). Safety and tolerability will also be evaluated.

Guy Braunstein, MD and Head of Global Clinical Development, commented: “In a little over one year, we have evaluated this very promising compound in a Phase I program which provided us with a wealth of data. The pharmacokinetic and pharmacodynamic profiles suggest that our compound offers an optimal combination of the desired effect on sleep and a low potential to impact next-day performance. The Phase II program should provide the data required to design a Phase III program to differentiate this new product.”

Martine Clozel, MD and Chief Scientific Officer, concluded: “With our understanding of the potential that a dual orexin receptor antagonist has to offer, we have been very motivated to continue our drug discovery efforts. Taking into account what we have learned from our research and from available clinical data, we were able to define the optimal profile of a new DORA. Importantly, we were looking for a highly potent compound with a fast onset, and a duration of action which would not exceed a normal night’s sleep. With our robust selection criteria in place we believe we have created and selected the optimal compound to transform the way sleep disorders are treated.”
**PIPELINE UPDATE**

In addition to progressing Actelion’s new DORA into Phase II development, enrollment into the current Phase III studies for cadazolid and ponesimod is progressing well and on target to be completed by the end of 2016. The MERIT study with macitentan in patients with chronic thromboembolic pulmonary hypertension (CTEPH) has completed enrollment and is on schedule to deliver results by the end of the year.

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**FURTHER R&D NEWSFLOW IN 2016**

Lucerastat future development
Cardiovascular pipeline update with MERIT results
Cadazolid Phase III program update
Ponesimod Phase III program update

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NOTES TO THE EDITOR

ABOUT ACTELION’S DORA
As part of its drug discovery efforts on G-Protein Coupled Receptors, Actelion has built a library of potent dual oral orexin receptor antagonists (DORAs). These compounds are active on both OX1 and OX2, the receptors which mediate the actions of orexins. Actelion’s work with dual orexin receptor antagonism has demonstrated that blocking the activity of the orexin receptors offers the potential to restore normal physiological sleep. The company’s new DORA is orally active, effectively crosses the blood-brain barrier and is currently evaluated as a treatment for insomnia.

Other properties of dual orexin receptor antagonism could translate into better next-day performance (decreased hangover effect), absence of tolerance and rebound insomnia, less cognitive impairment and no respiratory depression.

ABOUT OREXINS
Orexins are neuropeptide modulators - small protein-like molecules used by nerve cells (or neurons) to communicate with each other in the brain. Orexins act functionally at the interface of alertness, energy homeostasis and reward:aversion systems, essentially to regulate vigilance and alertness states. Defects of the orexin peptides, or their receptors, are associated with wakefulness and sleep disorders.

The anatomical distribution of orexin receptors in the brain supports the essential role that orexin plays in promoting alertness and maintaining wakefulness under situations of high motivational relevance, e.g. circadian vigilance states, reward opportunities or exposure to threats. Orexins and their receptors are highly conserved across vertebrate species.

ABOUT INSOMNIA
Medically, a lack of sleep can have a significant negative impact on daily functioning, and physical and mental health. According to the 2013 Diagnostic and Statistical Manual (DSM-5) and the International Classification of Sleep Disorders (ICSD-3, 2013), insomnia (also referred to as insomnia disorder) is defined as a combination of both dissatisfaction with sleep and a significant negative impact on daytime functioning. Dissatisfaction with sleep describes the difficulty to initiate and/or maintain sleep on at least three nights per week for at least 3 months, despite adequate opportunity to sleep. The impact on daytime functioning can include fatigue, sleepiness, poor concentration, low mood, or impaired ability to perform social or occupational tasks. Rather than applying primary and secondary causal attribution labels, insomnia is now recognized as a condition that requires independent clinical attention, irrespective of other medical problems the patient might have.

Insomnia is, worldwide, the most commonly reported sleep disorder. As the prevalence of insomnia depends on the specific case definition, estimates for the prevalence of insomnia symptoms vary from 30% to 5–10% for specific insomnia disorders. Current treatment of insomnia includes behavioral therapy, sleep hygiene recommendations, and pharmacotherapy. Most sleep disorder products on the market enhance the effects of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Such medications suffer from a major trade-off: the greater the efficacy, the greater the "hangover" effect the next day in terms of impaired mental and physical performance. Usually, hypnotics decrease the length of the REM (rapid
eye movement) sleep phase, which – together with non-REM sleep – is hypothesized to be important for memory consolidation.

References:

3. Citrome L. Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014;68(12):1426-41.

INVESTOR WEBCAST

An investor conference call and webcast will be held at 14:00 hrs CEST to discuss today's announcement.

**Date/Time:**

7 July 2016
14:00 hrs – 15:15 hrs Basel
13:00 hrs – 14:15 hrs London
08:00 hrs – 09:15 hrs New York

**Conference Call Connect #:**

Dial-in participants should start calling the number below 10-15 minutes before the conference is due to start.

Dial:
Europe: +41 (0) 44 583 18 01
UK: +44 (0) 203 194 05 61
US: +1 855 402 77 67

**Participant’s mode:**

Listen-Only with possibility to open individual lines during Q&A session. Participants will be asked for their name and company.

**Webcast Access:**

Webcast participants should go to the Actelion website http://www.actelion.com 10-15 minutes before the conference is due to start. **Participant’s mode:** Listen-Only

**Webcast Replay:**

The archived Investor Webcast will be available for replay through http://www.actelion.com/ approximately 60 minutes after the call has ended.
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 also 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 2,500 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.

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®). All trademarks are legally protected.

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