

22 May 2017

Actelion provides an update on the progress towards launching Idorsia – Key results for pipeline assets to be developed by Idorsia

- Positive dose-finding results with ACT-132577 asset to progress to Phase 3 development in resistant hypertension
- Positive safety study with cenerimod asset to progress into larger Phase 2 development in systemic lupus erythematosus
- Investor webcast to discuss Idorsia's strategy and pipeline today at 15:00 hrs

ALLSCHWIL/BASEL, SWITZERLAND – 22 May 2017 – Actelion Ltd (SIX: ATLN) today provides an update on the progress being made to bring Idorsia Ltd to the SIX Swiss Exchange. Following the successful tender offer by Johnson & Johnson for Actelion, the approval of the Actelion shareholders to demerge the drug discovery and early clinical pipeline business, and progress with the anti-trust regulatory approvals, the transaction is on track to complete by the end of the second quarter of 2017.

Jean-Paul Clozel, M.D. and Chief Executive Officer at Actelion, commented: "I am very excited by the progress we are making with bringing Idorsia to life. Idorsia will have an experienced team of highly qualified professionals, a full research and development pipeline, state-of-the-art facilities, and CHF 1 billion in cash at inception – the crucial elements for transforming research and development into successful medicines."

Jean-Paul Clozel concluded: "The future for Idorsia is looking bright. Realizing our ambition to develop Idorsia into one of Europe's leading biopharmaceutical company, with a strong scientific core, certainly won't be an easy undertaking but we have all the ingredients for success. We are starting on the right track with positive clinical results from two of the assets that will be developed by Idorsia, both progressing to the next stage of their development."

ACT-132577 IN DEVELOPMENT FOR RESISTANT HYPERTENSION

Actelion has completed a multi-center, double-blind, double-dummy, randomized, placebo-controlled with an active-reference arm, parallel group, dose-finding study with ACT-132577, an orally active dual endothelin receptor antagonist, in patients with essential hypertension. The study evaluated the efficacy, safety and tolerability of a oncea-day oral regimen of 4 dose levels of ACT-132577 (5, 10, 25, and 50mg) to identify the optimal doses for further studies. In this study 490 patients were randomized to receive either ACT-132577 5, 10, 25, 50 mg, placebo, or lisinopril 20 mg once daily. After 8 weeks of treatment the mean reduction from baseline in diastolic blood pressure – as measured at trough with a novel automated office blood pressure device – was between 6.3 and 12.0 mmHg in a statistically significant dose-dependent manner for the ACT-132577 groups versus a decrease of 4.9 mmHg in the placebo group and a decrease of 8.4 mmHg in the lisinopril group (in the per-protocol population comprised of 410 patients).

Systolic blood pressure reductions ranged from 10.3 to 18.5 mmHg in a statistically significant dose-dependent manner in the ACT-132577 groups and were 7.7 and 12.8 mmHg in the placebo and lisinopril groups, respectively.

These findings were confirmed in all randomized patients (Intent-to-Treat principle) and by 24 hours Ambulatory Blood Pressure Monitoring.

The safety population included 327 patients in the ACT-132577 groups, 82 patients in the placebo group and 81 in the lisinopril group. ACT-132577 was well tolerated across all four doses in this patient population. Discontinuation from study treatment due to an adverse event ranged between 1.2% and 3.7% for the ACT-132577 groups versus 6.1% in the placebo group and 3.7% in the lisinopril group. The overall frequency of adverse events was similar to those observed in the placebo group. In this study, there were two cases of increased liver enzymes above three times the upper limit of the normal range, one in the placebo and one in the ACT-132577 5 mg group. Four cases of peripheral edema were observed, two in the ACT-132577 25 mg group and two in the ACT-132577 50 mg group. Mean body weight remained unchanged from baseline in the ACT-132577 5, and 10 mg groups, increased by 0.4 Kg in the ACT-132577 25 and 50 mg groups, and by 0.3 Kg in the placebo group and decreased by 0.3 Kg on lisinopril. There was an expected dose related decrease from baseline in the hemoglobin concentration in the ACT-132577 groups (ranging from 1.3 to 6.7 g/L) versus increases of 2.2 and 0.1 g/L in the placebo and lisinopril groups, respectively.

The company will now discuss with health authorities the design of a Phase 3 program which will consist of two studies evaluating the effect of ACT-132577 on systolic and diastolic blood pressure in patients with true resistant hypertension i.e. uncontrolled hypertension despite three antihypertensive drug therapies from different classes at optimal doses including a diuretic. The program will also provide long-term safety information. If successful the program will provide the basis for registration and differentiation of the product.

Guy Braunstein, Head of Global Clinical Development at Actelion, commented: "The results of our pharmacology program together with this study give us great confidence that we have all the information we need to design the Phase 3 confirmatory program in resistant hypertension. The need for another mechanism of action in treating resistant

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hypertension has long been stressed by the medical community and ACT-132577 has great potential in this indication. Idorsia will prioritize the Phase 3 development of this important asset and proceed as quickly as possible."

ET-1 participates in blood pressure regulation in response to salt and volume expansion, and is inversely correlated with plasma renin activity. Resistant hypertension is frequently associated with volume expansion in man, which is a feature of salt-sensitive hypertension. Endothelin receptor antagonists (ERA) demonstrate greater efficacy in salt-dependent / low renin than in high / normal renin non-clinical models of hypertension. Selecting an ERA for resistant hypertension and difficult-to-treat hypertension relies on extensive non-clinical and clinical foundations.

As a dual ET_A/ET_B receptor antagonist, ACT-132577 represents a novel mechanism of action in patients with resistant hypertension. The ET-1 peptide, and possibly ET-2 and ET-3 peptides, via their two receptors, ET_A and ET_B , mediate biological processes that contribute to the pathogenesis of hypertension. ET-1 is a potent vasoconstrictor that also causes neurohormonal activation, vascular hypertrophy and remodeling, cardiac hypertrophy and fibrosis, and endothelial dysfunction. Dual ERAs have been shown to counteract these deleterious effects in animal models of hypertension and provide significant benefits on top of existing therapies (e.g. renin angiotensin system blockers).

Janssen Biotech, Inc. (an indirect subsidiary of Johnson & Johnson) and Idorsia have entered into a collaboration agreement in respect of the development and commercialization of ACT-132577 and any of its derivative compounds or products. Following completion of the Phase 2 study, Janssen Biotech, Inc. may opt in to the collaboration by paying Idorsia a milestone payment of USD 230 million. If Janssen Biotech, Inc. opts in, the parties will have joint development rights over ACT-132577, while Janssen Biotech, Inc will have the sole manufacturing and commercialization rights. A cost-sharing arrangement is in place in relation to development costs.

CENERIMOD IN DEVELOPMENT FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Cenerimod is a selective sphingosine-1-phosphate receptor 1 (S1P₁) modulator, which was investigated in a Phase 2 safety study in adult patients with systemic lupus erythematosus. Cenerimod blocks the egress of lymphocytes from lymphoid organs, thereby reducing the availability of circulating effector T and B cells that can invade target organs. This pharmacodynamic effect is sustained with once daily oral dosing, with no need for up-titration, and is reversible upon drug discontinuation.

The main objective of the prospective, multicenter, multinational, randomized, doubleblind, placebo-controlled, dose-response study was to investigate the pharmacodynamics, safety, and tolerability of cenerimod in adult patients with SLE. The study enrolled 67 patients to receive either 0.5, 1, 2 or 4 mg/day of cenerimod over a treatment period of 12 weeks. The investigated study population was representative for SLE and balanced across the 4 tested dose levels and placebo.

Cenerimod induces a dose dependent reduction in lymphocyte count and was well tolerated at all dose levels. The occurrence of adverse events was similar in all five treatment groups. Based on these results, cenerimod is ready to move into an exploratory Phase 2 dose-finding study to deliver all the information required to design the Phase 3 program.

IDORSIA'S CLINICAL DEVELOPMENT PIPELINE

Idorsia will have a diversified and balanced clinical development pipeline in multiple therapeutic areas, including central nervous system disorders, cardiovascular disorders, immunological disorders, and orphan diseases.

Status	Compound	Mechanism of Action	Target Indication
Phase 2	ACT-132577	Endothelin receptor antagonist	Resistant hypertension
	ACT-541468	Dual orexin receptor antagonist	Insomnia
	Clazosentan	Endothelin receptor antagonist	Vasospasm associated with aneurysmal subarachnoid hemorrhage
	Cenerimod	S1P ₁ receptor modulator	Systemic lupus erythematosus
Phase 1b	Lucerastat	Glucosylceramide synthase inhibitor	Fabry disease
Phase 1	ACT-246475	P2Y12 receptor antagonist	Acute coronary syndrome
	ACT-774312	CRTH2 receptor antagonist	Asthma and allergy disorders
	ACT-539313	Selective orexin 1 receptor antagonist	Anxiety
	ACT-709478	T-type calcium channel blocker	Epilepsy

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Notes to the Editor

ACT-541568 IN DEVELOPMENT FOR INSOMNIA

ACT-541568 is a new dual orexin receptor antagonist (DORA) which targets the orexin system and is intended to treat insomnia. Based on preclinical data, dual orexin receptor antagonism maintains natural sleep architecture. Preclinical data suggests that DORA will have a low potential for abuse. Data from a

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comprehensive Phase 1 program indicates that DORA has an ideal pharmacokinetic and pharmacodynamic profile to deliver fast onset of sleep, a duration of action which is well-suited for appropriate sleep maintenance, and no next day "hangover effect". These properties are being explored clinically and, if confirmed, will give DORA the potential to be differentiated from current sleep medications.

A Phase 2 program was announced in July 2016, with studies in adults and elderly patients underway to assess sleep maintenance, sleep initiation and next day residual effects and performance. The program should provide the data required to design a Phase 3 program to differentiate this new product and is well on track, with results expected in the second half of 2017.

LUCERASTAT IN DEVELOPMENT FOR FABRY DISEASE

Lucerastat is a small molecule iminosugar that inhibits glucosylceramide synthase and has the potential to provide substrate reduction therapy for the oral treatment of certain lysosomal storage disorders. It is being evaluated for the treatment of Fabry disease, a X-linked genetic disorder that is estimated to impact approximately 5,600 patients in the US and 5 major EU countries.

In an exploratory clinical study in patients suffering from Fabry disease receiving enzyme replacement therapy, treatment with oral lucerastat demonstrated a marked decrease in the plasma levels of metabolic substrates thought to be related to the development of the disease. Lucerastat is an oral monotherapy that has potential for patients with Fabry disease regardless of their mutation. The design of a pivotal Phase 3 study, expected to start in 2018, is currently under discussions with health authorities.

Lucerastat for Fabry disease has received Orphan Drug designation in the US and in the EU.

CLAZOSENTAN IN DEVELOPMENT FOR CEREBRAL VASOSPASM SECONDARY TO ANEURYSMAL SUBARACHNOID HEMORRHAGE (aSAH)

Clazosentan is an endothelin receptor antagonist in development as an intravenous infusion for cerebral vasospasm secondary to aSAH. Clazosentan was granted orphan status in Europe in 2003 and in the US in 2006. Idorsia believes clazosentan can decrease the need for invasive intervention (i.e. angioplasty), which is currently used in such conditions at high cost and with high medical risk.

Currently, clazosentan is being investigated in a Phase 2 study, REVERSE, which evaluates whether clazosentan has a rapid effect in reversing angiographically confirmed cerebral vasospasm in patients with aSAH treated by endovascular coiling or surgical clipping. Results are expected to be discussed with health authorities by the end of 2017.

COMPOUNDS IN DEVELOPMENT IN PHASE 1

ACT-246475 is a P2Y12 receptor antagonist in development for the prevention of myocardial damage in acute coronary syndrome and is targeted for individuals at risk of a myocardial infarction or the recurrence of a myocardial event. The compound meets a very specific pharmacokinetic profile, which requires the product to be well-absorbed subcutaneously after self-administration, with a rapid onset of action and 3 to 4 hours duration of action. ACT-246475 has completed Phase 1, and the study design for Phase 2 is currently being developed.

ACT-774312 is an oral CRTH2 antagonist developed for the treatment of moderate to severe uncontrolled asthma. Idorsia believes there is a significant unmet need for new therapies to treat asthma patients whose disease is not fully controlled with conventional therapies. Current evidence suggests that treatment with a CRTH2 antagonist can contribute to the better management of asthma. ACT-774312 has entered Phase 1 and a decision to move into Phase 2 is expected in the second half of 2017.

SORA is a selective orexin 1 receptor antagonist which is being investigated for the potential treatment of anxiety disorders. It is a potent antagonist, brain-penetrating, and has shown anxiolytic (anxiety-inhibiting) effects after oral administration in four different preclinical models representing specific sub-types of anxiety disorders. In these models, it does not induce sleep at anxiolytic doses. Phase 1 trials are ongoing, with a decision to move into Phase 2 expected in the second half of 2017.

ACT-709478 is a potent, brain-penetrating, selective triple calcium T-channel blocker for potential use in generalized epilepsy. The compound has shown efficacy after oral administration in two animal models of generalized epilepsy. A pharmacology study in patients is expected to be initiated in the second half of 2017.

INVESTOR CONFERENCE CALL / WEBCAST

Actelion will host an investor conference call and webcast to introduce Idorsia's strategy and pipeline. Jean-Paul Clozel, CEO of Actelion and Guy Braunstein, Head of Global Clinical Development at Actelion will present.

Date/Time

22 May 2017	15:00 hrs - 16:00 hrs	Basel
	14:00 hrs - 15:00 hrs	London
	09:00 hrs - 10:00 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)203 009 24 60	
	US:	+1 855 228 38 74	

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

<u>Webcast Access</u>: Webcast participants should go to the Actelion website <u>http://www.actelion.com</u> 10-15 minutes before the conference is due to start.

<u>Webcast Replay</u>: The archived Investor Webcast will be available for replay through <u>http://www.actelion.com</u>/ approximately 60 minutes after the call has ended.

ABOUT 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 need.

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 2,500 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 currently traded on the SIX Swiss Exchange (ticker symbol: ATLN). All trademarks are legally protected.

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