

## Evolva reports additional Phase IIa data on EV-077

Reinach, Switzerland, 28 August 2012 - Evolva Holding SA (SIX: EVE) today announces further data for the first 32 patients enrolled in the Phase IIa study of its investigational drug, EV-077, a novel, reversible antagonist of isoprostanes and prostanoids. 16 patients received EV-077 and 16 patients received placebo.

The data indicate that 300mg EV-077 given orally twice daily to patients with type 2 diabetes provided anti-platelet activity, reduced exercise-induced proteinuria and increased forearm blood flow. This was achieved with only a slight increase in bleeding time. The analysis also indicates that EV-077 was generally well tolerated, with adverse events mostly limited to increases in liver enzymes, which were transient or resolved after discontinuation.

### Key Highlights of the Data

#### Efficacy

##### **Platelet Aggregation**

EV-077 achieved a consistent, substantial, inhibition of platelet aggregation induced by arachidonic acid and U-46619 (measured in whole blood and in platelet-rich plasma). This occurred at all time points. This was the primary efficacy parameter of the study and statistical significance was achieved ( $p=0.001$ ).

##### **Peripheral Blood Flow**

Though not powered to reach statistical significance and against a background of high variation, EV-077 shows a consistent trend to improvement of vascular endothelial function (both macrovascular and microvascular) after 4 weeks of treatment on top of anti-hypertensive therapy.

<i>Change on day 29 versus baseline</i>	EV-077	Placebo
Macrovascular endothelial function	+43%	+20%
Microvascular endothelial function	+108%	+25%

Vascular endothelial dysfunction precedes atherosclerosis and is a common feature of diabetes. Impaired post-occlusive reactive hyperaemia (PORH) is an accepted indicator of vascular endothelial function. In this study PORH was investigated by flow-mediated dilatation of the brachial artery (macrovascular) and by forearm skin dilatation (microvascular).

### Exercise Induced Proteinuria

Though not powered to reach statistical significance and against a background of high variation, EV-077 shows a consistent trend to improvement (a decrease) in the level of protein in the urine after exercise.

<i>Change on day 29 versus baseline</i>	EV-077	Placebo
Peak albuminuria – all patients	-34%	+12%
Peak albuminuria – exercise completers <sup>*)</sup>	-54%	+10%

<sup>\*)</sup> not all individuals completed the exercise test, and such individuals would not be expected to show a full response (EV-077, baseline n=12, day 29 n= 10; placebo, baseline n= 13, day 29 n=11)

Exercise induced proteinuria is an early marker of loss of kidney function, which is one of the most important complications of diabetes from both a medical and an economic standpoint.

### Safety

#### Bleeding Time Increases

Bleeding time increased from 4.4 minutes at baseline to 8.6 minutes on day 29 for patients receiving study drug, compared with an increase from 4.9 minutes to 5.9 minutes in the placebo arm. The increase measured for EV-077 is not considered to be clinically relevant and is similar or lower than that of several marketed drugs for chronic use (notably aspirin and clopidogrel).

#### Adverse Events

EV-077 was generally well-tolerated; no serious adverse events occurred in the study. Mild-to-moderate adverse events were largely limited to increases in transaminases (liver enzymes), which were transient or resolved after discontinuation.

<b>Adverse Events</b>	EV-077	Placebo
Serious adverse events	0	0
Patients reporting one or more adverse events	10	6
Transaminase increase	4	0

Of the four cases of transaminase increase three were increases of less than 3x the upper limit of normal. These either resolved whilst remaining on EV-077 (one case) or occurred on the last day of treatment (two cases) and resolved after the study. In one case the increase was more than 8x the upper limit of normal, and the patient was withdrawn from the study. This case also resolved after discontinuation.

As stated in the media release of 17 August 2012, Evolva is exploring, in consultation with the German regulatory authority BfArM, how to best address the liver enzyme elevations, for example by using lower doses in a next group of patients.

An analysis of pharmacokinetic and pharmacodynamic data support the hypothesis that substantially lower doses (10-30mg) of EV-077 will also demonstrate efficacy. Contrary to the media release of 17 August the data was not presented at a satellite symposium of the ESC Congress 2012, as in consultation with the two co-chairs of the symposium it was decided that discussions with the BfArM should take precedence.

**Norbert Bender**, CMO of Evolva commented, "We believe the data underpin the potential of EV-077 as a potentially valuable tool in the prevention and treatment of important vascular complications in patients with type 2 diabetes. We are looking forward to discussing the next steps with the German regulatory authority."

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### **About the Phase IIa study**

The Phase IIa study is designed to assess to safety, tolerability and pharmacokinetics of 28 days EV-077 treatment (300mg, given orally, twice-daily), and its effects on platelet function, vascular inflammation and oxidative stress in type 2 diabetics. It is a single-centre study, conducted in Germany. The study is randomised, double-blind and placebo-controlled. Measurements include oxidative stress, vascular inflammation, blood flow and platelet reactivity, as well as markers of the function of organs that are often impaired in diabetes (e.g. kidney).

### **About Evolva**

Evolva's mission is to discover and provide **innovative, sustainable ingredients for health, nutrition and wellness**. Evolva uses biosynthetic and evolutionary technologies to create and optimise small molecule compounds and their production routes. We are active in consumer healthcare and nutrition as well as in pharma. In both areas we have partnered projects as well as proprietary programmes. For more information see [www.evolva.com](http://www.evolva.com).

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Glossary	
Albuminuria	Condition wherein a protein called albumin is present in the urine. It is a type of proteinuria.
Proteinuria	Presence of an excess of proteins in the urine.
Microvascular	Concerning small blood vessels - the portion of the circulatory system that is composed of the capillary network.
Macrovascular	Concerning large blood vessels.
Transaminase	An enzyme in the blood. Whilst mild elevations of transaminases (<3 times the Upper Limit of Normal) following statin therapy are not known to lead to any significant liver toxicity over time, then their presence can, in other cases, be an indicator of liver damage
Arachidonic acid, U46619	Substances often used to test platelet aggregation.
Vascular endothelial cells	Cells, lining the entire circulatory system, from the heart to the smallest capillaries.