Hypertension vaccine CYT006-AngQb achieves strong blood pressure reduction during important early morning period when most adverse cardiovascular events occur

- Blood pressure reduction achieved at 8 am versus placebo: -25 / -13 mm Hg (systolic / diastolic, p<0.0001 / p=0.0035)
- Blood pressure reduction dependent on vaccine dose and induced anti-angiotensin II antibody levels
- Detailed results presented today at the Seventeenth European Meeting on Hypertension in Milan, Italy

Schlieren (Zurich), Switzerland and Milan, Italy, June 17, 2007 - Cytos Biotechnology AG (SWX:CYTN) presented today new clinical data on its hypertension vaccine CYT006-AngQb at the Seventeenth European Meeting on Hypertension in Milan, Italy. The vaccine candidate was tested in a placebo-controlled, double-blind phase IIa clinical trial in 72 patients with mild to moderate hypertension. On January 26, 2007, Cytos Biotechnology reported top-line data from this study, which showed that the 300 μg dose of the vaccine was safe, very well tolerated and efficacious in lowering day-time ambulatory blood pressure.

The new data presented today show a particularly strong efficacy of the vaccine in early morning hours, a critical time period when serious cardiovascular events frequently occur. The graph below shows the mean ambulatory blood pressure during the 24-hour measurement period 14 weeks after the first injection of the vaccine or of placebo. The early morning rise of blood pressure starting at 5 am was significantly suppressed by the vaccine, leading at 8 am to a change from baseline of the blood pressure of -25 / -13 mm Hg compared to placebo (SBP / DBP, p<0.0001 / p=0.0035).

**Figure**: Mean (SEM) ambulatory blood pressure during the 24-hour measurement period. Shown are systolic (SBP) and diastolic (DBP) blood pressure values for the vaccine-treated (300μg AngQb) and the placebo group 14 weeks after the first injection. SEM = standard error of the mean.

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The strong suppression of the early morning rise of blood pressure was associated with an exceptionally low increase in plasma renin concentration (PRC) from a mean renin concentration of 5.1 pg/ml at baseline to 6.3 pg/ml at week 14 (p=0.02). Inhibition of the renin-angiotensin system by small molecule drugs is known to induce a reactive rise of the plasma renin concentration, which is a counter-reaction of the body potentially decreasing the efficacy of current drug therapy. In contrast to small molecule inhibitors, which display large variations in serum drug levels throughout the day, the vaccine-induced anti-angiotensin II antibodies were found to decline with a half-life of about 4 months. This may lead to a practically continuous inhibition of angiotensin II for weeks, which may in part account for the minor reactive rise observed in plasma renin concentration, and to the potent effect of the vaccine in early morning hours, as is further explained in the quote of Dr. Müller below.

A further important finding of the study is the dependence of efficacy on both the dose of the vaccine and the levels of induced anti-angiotensin II antibodies. Two doses of the vaccine, 100 μg and 300 μg, were tested in the trial. The induced anti-angiotensin antibody levels were significantly higher at the 300 μg than at the 100 μg dose (p=0.0098). Accordingly, blood pressure reduction was much larger and only significant at the 300 μg dose (p=0.0498). Efficacy was thus driven by a long-lasting, although reversible antibody response.

Dr. Philipp Müller, EVP Clinical Development at CytoS Biotechnology comments on the study results: “These data highlight a very important new aspect of the vaccine CYT006-AngQb, namely its exceptionally good control of the early morning blood pressure. So far, inhibition of the renin-angiotensin system has been studied clinically only with small molecule inhibitors, which all produce a daily pattern of peaks and troughs in drug levels. Here, a trough in drug levels coincides with a natural rise of the blood pressure in early morning hours. The combination of these effects may lead to insufficient control of the early morning blood pressure surge.

An intervention with a different pharmacokinetic profile like the vaccine approach, which avoids daily peaks and troughs in drug levels as well as the reactive rise of plasma renin, may therefore achieve a better protection from adverse cardiovascular events in early morning hours. This is crucial if one considers that myocardial infarction is three times more likely to begin in the morning than during night time and that morning hypertension has been identified as the strongest independent risk factor for stroke.

Another remaining major problem of current hypertension therapy is the lack of patient compliance. More than 50% of all patients who initiate oral drug therapy either completely discontinue treatment within the first 12 months or take their drugs only partially in-line with their doctor’s guidance. A physician administered vaccine would no longer require daily self-medication by the patient. The observed half-life of the vaccine-induced antibodies suggests a treatment regimen with booster injections every four to six months. In between these periods of time, the patient is no longer burdened with daily drug therapy. These advantages should allow for a better overall control of hypertension, which is today the leading risk factor for mortality in the world.”

About early morning blood pressure
Blood pressure is not static but undergoes natural variations which follow a circadian pattern. Highest levels are reached during the morning, which then decline to reach a trough value at about midnight. In the early morning, a steep increase in blood pressure occurs. It has been suggested that this morning surge in blood pressure triggers adverse cardiovascular events. Each year in the United States alone acute myocardial infarction develops in over 600,000 persons who were previously free of cardiac symptoms. A large study has revealed a marked circadian periodicity in the onset of myocardial infarction with the primary peak incidence being in the morning. At this time, myocardial infarction is three times as likely to occur as during the night. The same periodicity was observed in the onset of stroke. Striking evidence suggests that the morning surge in blood pressure is crucial in determining the rupture of critically weakened arterial walls and subjects with a large surge in morning blood pressure have a significantly elevated risk of intracerebral hemorrhage and stroke.
Current hypertension therapy therefore aims at a full 24-hour blood pressure control. Commonly used angiotensin II receptor blockers (ARBs) were reported to achieve an ambulatory blood pressure reduction from baseline in the early morning hours of (SBP / DPB) - 8.7 / - 5.8 mm Hg (valsartan) and - 11.0 / - 7.6 mmHg (telmisartan), respectively.\(^5\)

**About hypertension**

Hypertension, also termed high blood pressure, is a medical condition where the blood pressure is chronically elevated. Although asymptomatic in nature and in itself rarely an acute problem, persistent hypertension is one of the most important preventable causes of premature death worldwide and contributes to around half of all cardiovascular disease.\(^6\) It is one of the major risk factors for stroke, myocardial infarction, heart failure, and arterial aneurysm, and is a leading cause of chronic renal failure. Genetic predisposition and lifestyle habits such as inadequate physical activity, high fat diet, and high salt intake promote high blood pressure. Up to 30% of adults in most countries suffer from hypertension.\(^7\) Despite effective and relatively inexpensive treatment available, a health survey in the UK revealed that only 9% of hypertensive individuals have their blood pressure controlled successfully.\(^7\) This poor overall treatment success is mainly attributed to the asymptomatic nature of hypertension and the necessity for long-term treatment with medications that require at least once daily self-administration.

**About CYT006-AngQb**

CYT006-AngQb is a therapeutic vaccine in development for treatment of hypertension. It is designed to instruct the patient’s immune system to produce an antibody response against angiotensin II. Angiotensin II is a small peptide in the body and part of the so-called renin-angiotensin system (RAS), an important regulator of blood pressure. Angiotensin II causes blood vessels to narrow, resulting in increased blood pressure. In a phase IIa clinical trial, vaccination with CYT006-AngQb has been shown to reduce blood pressure by induction of antibodies that bind angiotensin II. Thereby, binding of angiotensin II to its receptors and subsequent narrowing of blood vessels should be decreased. The RAS has already been successfully targeted by three major classes of antihypertensive drugs on the market: inhibitors of the angiotensin-converting-enzyme (ACE), antagonists of the angiotensin II type I receptor (ARBs) and renin inhibitors. Like other antihypertensive drugs these also come with the need for daily dosing and fail to provide a solution for improving patient compliance. Treatment with CYT006-AngQb should allow for convenient dosing schedules and smooth control of blood pressure due to a sustained antibody response induced by vaccination.

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**About Cytos Biotechnology AG**

Cytos Biotechnology AG is a public Swiss biotechnology company that specializes in the discovery, development and commercialization of a new class of biopharmaceutical products – the Immunodrugs™. Immunodrugs™ are intended for use in the treatment and prevention of common chronic diseases, which afflict millions of people worldwide. Immunodrugs™ are designed to instruct the patient’s immune system to produce desired therapeutic antibody or T cell responses that modulate chronic disease processes. Taking advantage of the high flexibility of its Immunodrug™ platform, Cytos Biotechnology has built a pipeline of different Immunodrug™ candidates in various disease areas, of which 6 are currently in clinical development. The Immunodrug™ candidates are developed both in-house and together with Novartis and Pfizer Animal Health. Founded in 1999 as a spin-off from the Swiss Federal Institute of Technology (ETH) in Zurich, the company is located in Schlieren (Zurich). Currently, the company has 130 employees. Cytos Biotechnology AG has been listed on the SWX Swiss Exchange (SWX:CYTN) since October 2002.
Booster injection: refers to a vaccination given after a previous vaccination. Helps to maintain or increase an immune response.

Asymptomatic: without symptoms.

Antihypertensive drugs: a class of drugs used for treatment of high blood pressure. Also be directed against the body’s own disease-associated molecules (e.g. angiotensin II).

Antibody: class of blood proteins generated by the immune system to bind and neutralize foreign materials such as bacteria or viruses. Can also be directed against the body’s own disease-associated molecules (e.g. angiotensin II).

Antihypertensive drugs: a class of drugs used for treatment of high blood pressure. Asymptomatic: without symptoms.

Booster injection: refers to a vaccination given after a previous vaccination. Helps to maintain or increase an immune response. Cardiovascular events: refer to conditions affecting the cardiovascular system, which comprises the heart, the blood vessels, and the cells and plasma that make up the blood.

Circadian: a circadian rhythm is a roughly 24-hour cycle in the physiological processes of living beings.

Compliance: a patient’s adherence to a recommended course of treatment.

DBP: diastolic blood pressure.

Diastolic blood pressure: the lowest pressure within the arterial blood stream occurring during each heart beat. The term “diastolic” is used to refer to the relaxation of the heart between muscle contractions.

Double-blind: a set-up often applied in clinical trials where neither the doctor nor the patient knows if placebo or the active drug substance is applied.

Enzyme: protein that acts as a catalyst and enables or enhances chemical reactions within cells.

Half-life: time required in which half the amount of a biological substance (e.g. antibodies) is removed from the organism.

Hypertension: high blood pressure.

Intracerebral hemorrhage: occurs when a diseased blood vessel within the brain bursts, allowing blood to leak inside the brain. The most common cause of intracerebral hemorrhage is high blood pressure.

mm Hg: blood pressure values are universally stated in millimetres of mercury (mm Hg).

Myocardial infarction: commonly known as a heart attack; is a disease state that occurs when the blood supply to a part of the heart is interrupted.

Peptide: a fragment of a protein comprised of two or more amino acids.

Phase IIa: a clinical trial that examines a new drug candidate’s safety and exploratory efficacy and may involve between 10 and 100 patients.


Plasma renin concentration (PRC): refers to the concentration of renin in the plasma; does not include prorenin, which is the precursor molecule of renin.

RAS: renin-angiotensin system. A hormone system that regulates long-term blood pressure and blood volume in the body.

Receptor: a protein molecule that binds and responds to a certain interaction partner such as hormones, immune mediators or other substances.

Renin: enzyme that catalyzes the formation of angiotensin I (Ang I) from its precursor angiotensinogen and thus initiates the renin-angiotensin system cascade.

Run-in period: time window during which blood pressure monitoring devices are placed at the participants by specialized staff and first measurements begin. During this time window blood pressure values can be influenced by the general handling and the contact with the doctor (so called “white coat effect”).

SBP: systolic blood pressure.

Small molecule drugs: low molecular weight chemical compounds. Many pharmaceutical drugs are small molecules.

Stroke: a sudden interruption in the blood supply of the brain. Most strokes are caused by an abrupt blockage of arteries leading to the brain; others are caused by bleeding into brain tissue when a blood vessel bursts (see also intracerebral hemorrhage).

Systolic blood pressure: the highest pressure within the arterial blood stream occurring during each heart beat. “Systolic” refers to the contraction of the heart muscle.

Therapeutic vaccine: a preparation of disease-related molecules (antigens) of foreign or self origin that is capable of activating the immune system against such antigens with the goal to modulate disease processes.

References

Glossary
Ambulatory blood pressure: blood pressure measured continuously during a normally active day; takes numerous automatic readings over a 24-hour period or longer and applies non-invasive ambulatory blood pressure monitoring devices.

Angiotensin II: a molecule of the RAS inducing vasoconstriction of blood vessels and other effects to raise blood pressure.

Antibody: class of blood proteins generated by the immune system to bind and neutralize foreign materials such as bacteria or viruses. Can also be directed against the body’s own disease-associated molecules (e.g. angiotensin II).

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This foregoing press release may contain forward-looking statements that include words or phrases such as “potentially”, “may”, “would”, “suggest”, “should”, “might”, “designed”, “intend” or other similar expressions. These forward-looking statements are subject to a variety of significant uncertainties, including scientific, business, economic and financial factors, and therefore actual results may differ significantly from those presented. There can be no assurance that any other therapeutic entities will enter clinical trials, that clinical trial results will be predictive for future results, that therapeutic entities will be the subject of filings for regulatory approval, that any drug candidates will receive marketing approval from the U.S. Food and Drug Administration or equivalent regulatory authorities, or that drugs will be marketed successfully. Against the background of these uncertainties readers should not rely on forward-looking statements. The company assumes no responsibility to update forward-looking statements or adapt them to future events or developments. This document does not constitute an offer or invitation to subscribe or purchase any securities of Cytos Biotechnology AG.