

Cortendo Press Release

New findings offer promise in the treatment of stress-related disease

Gothenburg, 29th April 2002 – Cortendo today announced that the company's Phase IIa study with lead compound CORT001 shows significant beneficial clinical effects in the treatment of Metabolic Syndrome. This is a serious and increasingly common disorder characterised by the association of hypertension, hyperlipidaemia, abdominal obesity, and insulin resistance/type 2 diabetes. Cortendo is pioneering a totally new therapeutic approach to the treatment of Metabolic Syndrome based on the hypothesis that prolonged exposure to elevated levels of the stress hormone, cortisol, is a key factor underlying the development of this serious multifactorial disease.

Beneficial clinical effects of Cortendo's lead compound confirmed in Metabolic Syndrome

The 12-week study, which included 72 patients at 3 centres (University of California at Los Angeles (UCLA) and University of California at San Diego (UCSD) in the US, and the University of Tromsø in Norway) was designed to investigate the effect of normalising cortisol levels on a number of key disease characteristics, including insulin resistance, blood glucose levels, hepatic steatosis, blood pressure, and lipids. The glucose-lowering potential of CORT001 is indicated by mean HbA_{1c}, which showed a significant reduction from baseline at the 400mg dose ($p < 0.001$), and evidence of a dose-dependent effect, with mean reductions from baseline of 0.67%, 0.10%, and 0.27% in the 400mg, 200mg, and placebo groups, respectively.

At the 400mg dose, CORT001 significantly reduced mean supine systolic blood pressure (SBP) by 11.0 mmHg compared with placebo ($p = 0.002$). This reduction in blood pressure took patients below the threshold generally agreed to offer renal protection in diabetes¹. The lower dose of 200mg produced a 4.2 mmHg reduction in SBP, however this was not statistically significant versus placebo. Both the 400mg and 200 mg doses of CORT001 produced statistically significant reductions in mean total cholesterol of approximately 16.6% ($p = 0.017$) and 10.0% ($p = 0.026$) respectively, compared with placebo. Interestingly, despite evidence of improvement

in insulin-dependent clinical variables, no change was recorded in peripheral insulin resistance over the 3-month period of the study, suggesting that the effects were mediated via central mechanisms. The treatment was generally well tolerated, with no apparent dose-related incidence of adverse events.

Findings support a central effect of CORT001

These results are consistent with a central effect of CORT001 and compare favourably with individual symptomatic treatment using existing agents. The glitazones have a dose-dependent effect on glucose control, with reductions of HbA_{1c} in the range 0.5-1.5%²; an angiotensin-II-antagonist achieves dose-dependent reductions in SBP of 6-12.5 mmHg³; and statins may be expected to reduce total cholesterol by 20-33%⁴ over a similar, or longer timeframe. Commenting on the findings, Professor Robert Henry, the Principal Investigator at the UCSD study centre said: “These data are supportive of Cortendo’s hypothesis that cortisol is centrally involved in the abnormal lipid and glucose metabolism of Metabolic Syndrome”. Professor Jon Florholmen, Principal Investigator at the University of Tromsø, added that: “With this drug we are able to improve most of the important clinical characteristics of Metabolic Syndrome”.

Cortendo will now build on these results with the further clinical development of CORT001 and the company’s follow-up compounds for the treatment of metabolic disorders and other diseases potentially associated with cortisol hypersecretion. In the near-term, a larger and longer study is planned to confirm and extend the current findings.

Metabolic Syndrome – an area of high unmet medical need

Each of the disorders that comprise Metabolic Syndrome is an independent and well-established risk factor for cardiovascular disease, which accounts for approximately 17 million deaths worldwide, annually⁵. In the US, where there are an estimated 47 million individuals with Metabolic Syndrome⁶, the National Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults has highlighted the importance of treating Metabolic Syndrome in order to prevent cardiovascular disease⁷. Yet, there is currently no single treatment for Metabolic Syndrome, which is sub-optimally controlled on a symptomatic basis with agents targeting the component diseases and disorders.

About Cortendo

Cortendo is a pharmaceutical research and development company currently focused on introducing the first treatment for Metabolic Syndrome based on a totally new therapeutic strategy – cortisol regulation. In parallel, Cortendo is investigating the potential of extending this therapeutic approach to other diseases and disorders that may be associated with hypersecretion of cortisol, with near-term focus on heart failure. The first patent for the concept of cortisol synthesis inhibition in the treatment of Metabolic Syndrome was filed in 1994 and Cortendo was formally established in late 1996. The company has raised approximately SEK 127 million by private placement in three rounds of financing.

References

1. Hansson L. Assessment of hypertension organ damage, chapter 5.2. Mancia G, *et al.*, eds. Hypertension. New York, Harcourt, 2002.
2. Fuchtenbusch M, Standl E, Schatz H. *Exp Clin Endocrinol Diabetes* 2000; **108** (3): 151-163
3. Elmfeldt D, George M, Hübner R, *et al.* *J Hum Hypertens* 1997; **11** (Suppl 2): S49-53
4. Feher MD, Richmond W. Lipid disorders. London, Gower, 1990.
5. WHO 2001 Cardiovascular Diseases Web Site: www.who.int/ncd/cvd
6. Ford E, Giles W, Dietz W. *JAMA* 2002; **287**: 356-359.
7. National Institutes of Health. Bethesda, Md; National Institutes of Health 2001. NIH Publication 01-3670.

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Backgrounder: Cortisol regulation – a novel therapeutic concept

Cortendo's therapeutic concept for the treatment of Metabolic Syndrome is based on the finding that long-term exposure to elevated levels of cortisol results in a significant increase in the amount of visceral fat, giving rise to a characteristic abdominal obesity^{1,2}. It is Cortendo's hypothesis that this is the trigger mechanism that starts a disease cascade resulting in the spectrum of disorders that comprise Metabolic Syndrome.

In this hypothesis, the enlarged abdominal fat store, stimulated by cortisol, leaks increasing amounts of free fatty acids, which travel directly to the liver through the portal vein. The metabolism of these fatty acids reduces the action of insulin in the liver with the result that:

- ✍ Glucose levels in the body rise
- ✍ Insulin leaves the liver, exposing tissues throughout the body to abnormally high levels of this hormone. This leads in turn to peripheral insulin resistance, mainly in muscle tissue
- ✍ Free fatty acids are metabolised in the liver and distributed throughout the body resulting in elevated blood lipid levels.

With lead development compound CORT001, Cortendo aims to normalise cortisol synthesis and re-establish the normal action of insulin in the liver, thereby resolving Metabolic Syndrome and related disorders at an early stage in the disease process (Figure 1 - overleaf).

A relationship between stress, cortisol levels, and disease is increasingly recognised amongst scientists and clinicians, with mounting evidence to support the role of cortisol in the development of metabolic disorders. For example, in an epidemiological study of more than 8,000 subjects, Professor Claes-Göran Östenson, Karolinska Institute, Stockholm, Sweden, has shown that different forms of mental stress can increase the risk of developing type 2 diabetes by as much as four-fold³. The findings remained statistically significant after correcting for other known risk factors, such as obesity, smoking, and genetic factors, suggesting an association between stress, cortisol, and diabetes.

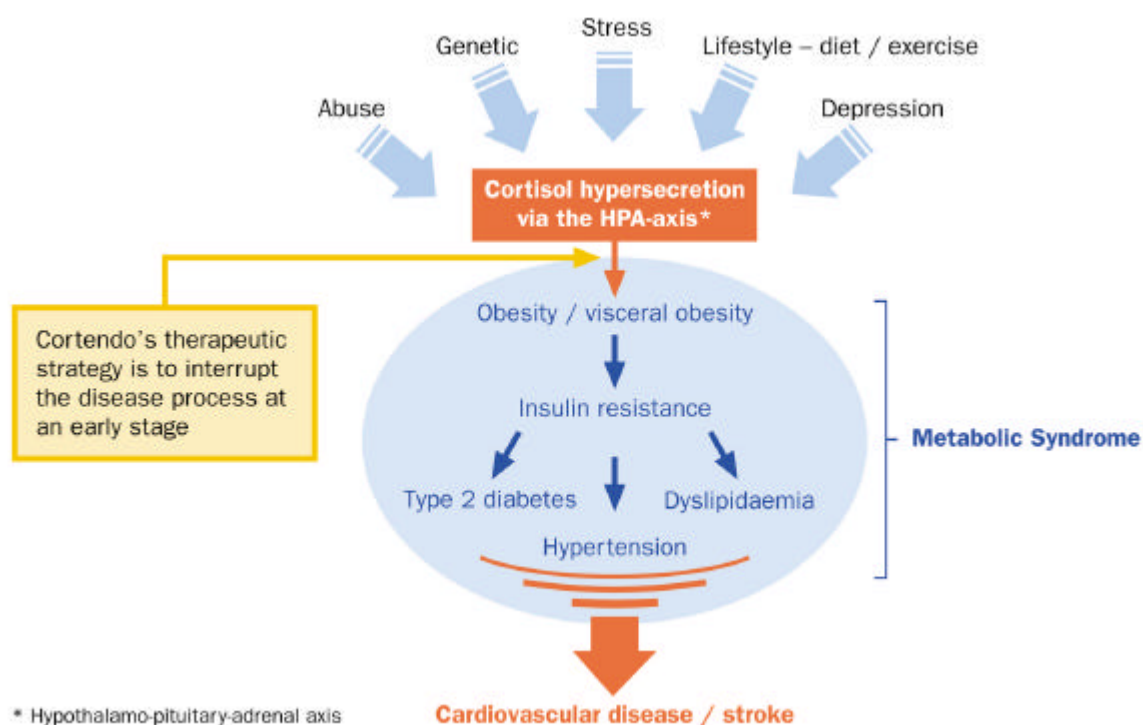


Figure 1: The basis of Cortendo's therapeutic concept is that long-term exposure to high levels of cortisol triggers a disease cascade resulting in Metabolic Syndrome. Hence, treatment is aimed at interrupting the cascade at an early stage in order to resolve the disease by normalising cortisol synthesis.

References

1. Mårin P, Darin N, Amemiya T, *et al.* *Metabolism* 1992; **41**: 882-885
2. Björntorp P. *Int J Obes Relat Metab Disord* 1996; **20**: 291-302.
3. Pers Comm, and reported in the Norwegian Press, *Dagsavisen* 19th January 2002