Santhera develops drugs for the treatment of Duchenne muscular dystrophy.

An interview with Thomas Meier, PhD,
Chief Scientific Officer at Santhera Pharmaceuticals Ltd.
in Liestal near Basel, Switzerland.

Dr. Günter Scheuerbrandt spoke on 11 January 2006 with Dr. Thomas Meier about the scientific developments at Santhera Pharmaceuticals which could lead to a pharmacological treatment of Duchenne muscular dystrophy (DMD) in the near future. The following text is a shortened version of the recorded interview. It was authorized by Dr. Meier for the information of the affected families and their doctors. The questions of Dr. Scheuerbrandt are written in italics.

Dr. Meier, thank you for agreeing to explain to the parents of children with Duchenne muscular dystrophy the efforts which your company is making to find medications which would slow down the muscle degeneration of this still incurable disease considerably.

Santhera has clinical and preclinical programs for the development of drugs for the treatment of Duchenne muscular dystrophy and related diseases. First, I would like to explain our preclinical program for the development of calpain inhibitors, i.e. of substances that interfere with the degradation of muscle proteins. Then, I will talk about the clinical studies with our lead-product SNT-MC17/idebenone. We have already been working for some time with SNT-MC17/idebenone in the indication Friedreich's Ataxia. Based on the mode of action of SNT-MC17/idebenone we believe that it could improve the function of the heart and skeletal muscles of Duchenne patients.

Beginning with the discussion of our calpain inhibitor program, the principal cause of DMD is the absence of functional dystrophin which is an anchor protein of the muscle cell membranes. As a consequence of dystrophin-deficiency muscle cell membrane becomes unstable and leaky allowing uncontrolled influx of calcium into muscle cells. This leads to the activation of calpain, an enzyme that cleaves muscle cell proteins. Calpains have an important function in healthy muscle cells, maintaining the equilibrium between the synthesis and the degradation of proteins. An increased activation of calpains in Duchenne muscular dystrophy leads to a dramatic degradation of muscle proteins. We were able to show in experiments with animals, that by inhibiting the calpains, one could significantly improve the typical symptoms of the disease.

We started our calpain inhibitor program about three years ago. One of the challenges that we had to solve was that inhibitors have to reach and enter the target muscle cells in order to produce the desired therapeutic effect. We therefore had to establish a comprehensive medicinal-chemistry program which allowed us to improve the inhibitors step by step. In the meantime, we have tested more than 800 different chemical compounds, most of them in cell culture and about 50 in the mdx mouse (a standard animal model for DMD). We are now advancing the most promising inhibitors into preclinical development. By applying our calpain inhibitors we aim to maintain the structural integrity of muscle proteins and cells and to improve their function.

So all, the substances you are now testing preclinically are calpain inhibitors?

Yes, all compounds that we are currently developing preclinically for the indication DMD are calpain inhibitors. They are now entering formal preclinical development and also undergoing the toxicity studies that are required by regulatory authorities. We expect that we will send the necessary documents and applications to the authorities in Europe and the United States at the beginning of 2007 so that we can begin human trials.

Up to now, we have tested our inhibitors in the mdx mouse. After a treatment of four to eight weeks, we could observe a clear improvement in the histology of different muscles. We then tested our inhibitors in long-time running experiments with mdx mice using computer-controlled running wheels. We saw that mdx mice treated with calpain inhibitors could run significantly better than untreated mice, although the improved running performance did not reach the level of healthy animals. However we must bear in mind that the mdx mouse is not an optimal model of the human disease. Compared with a sick child, the mdx mouse is really "too healthy". As a small animal with a low weight, the mouse does not stress its muscles as heavily. Thus, the typical disease symptoms are not present to the same extent as in a child. In the dog, the disease is much more severe, and in the patient even more. Despite this, the significant improvement of the musculature of the mdx mouse mediated by our calpain inhibitors is an important finding.

Early on we decided at Santhera that we will focus on pharmacological treatment options for neuromuscular diseases. In our opinion gene or stem cell therapy approaches are still too difficult and too risky at the present time. Santhera concentrates its efforts on classical pharmacological research in the field of neuromuscular diseases. Perhaps we will get less attention this way, but

we know much more precisely what authorities will have to see in order to approve a treatment for DMD. The development time is shortened this way, and a new effective compound could be developed much faster then through stem cell approaches or gene therapy.

Do the calpain inhibitors have to be injected into the blood, or could one take them as tablets?

At the moment, we are discussing whether our calpain inhibitors will be available for oral applications. The experiments are in progress at this time, in-house as well as in external institutions. But we already know that our inhibitors are effective in mice after subcutaneous application, i.e. by an injection under the skin.

That means, if tablets cannot be used, the drugs would have to be injected under the skin. Would that then influence only those muscles which are close to the injection site?

No, our calpain inhibitors are active systemically, i.e. in the whole body. If we inject them into the neck region of the mouse they are also active in the leg muscle for example.

What are your plans for this year?

We are working on an acceptable formulation for our calpain inhibitors that could ultimately be used in patients. We also have to prepare much larger quantities of the substances than before, especially for the toxicity tests required by the authorities. This is actually the program for this year. We expect to have the preclinical results available by end of this year and if they are all positive we will submit the required documentation to the regulatory authorities for examination. Clinical studies in humans can be initiated as soon as the regulatory authorities have accepted the data package for our inhibitors.

Where will you perform these clinical studies?

We are already talking to different clinicians in Europe and in the United States and are discussing the possible design of the clinical program. Eventually, we hope to carry out the studies in both regions simultaneously. It is too early to say in which countries we will start clinical development. We also need to discuss with the authorities whether we have to perform clinical tests with healthy volunteers before we can begin studies with Duchenne patients.

And how old will the children who participate in the trials be?

The age of the participants in the trials will depend on many factors, including the nature of any side effects. But it is still too early to discuss the details of clinical details.

So much then about your work with the calpain inhibitors. Let us now talk about your more advanced program with idebenone.

Idebenone, internally known as SNT-MC17, is now in clinical trials for Friedreich's Ataxia (FRDA). Cardiomyopathy, a disease of the heart muscle, is frequently diagnosed in patients with FRDA where in many cases it becomes a life-threatening condition. Our company is now performing the clinical studies necessary for approval in Europe and in the United States in that indication. At the moment, a phase-III study with about 200 FRDA patients is underway in Germany, the United Kingdom and in the Netherlands.

But the heart muscle is also affected in older Duchenne patients. Therefore, we have also initiated a clinical program with SNT-MC17 for the treatment of cardiomyopathy in DMD patients. In October last year we started a clinical phase-IIa study in Belgium. We intend to enrol 21 Duchenne boys into this study of which 14 patients will receiving SNT-MC17/idebenone for one year while 7 patients receive placebo, a look-alike preparation without effect. This is a double blind study with placebo control, which must be done for every potential new drug.

Here, too, there is the question of whether the drug will have to be injected.

SNT-MC17 is orally available and will be given as a tablet. The dosage we are currently testing is one tablet three times per day.

How old will the children be?

In this study we include children between 10 and 16 years of age. We cannot include very young patients because a minimal cardiomyopathy must be diagnosed at the start of the study to enable us to detect the potential therapeutic effect of the study medication. We measure the heart function in these Duchenne patients using very sensitive methods which allow us to follow functional changes during the duration of the study. In addition, we carefully analyze any potential therapeutic effect on the muscle strength of the patients of SNT-MC17 by monitoring various parameters

Where have these techniques been developed?

This technique has been developed mainly at the University of Leuven (Belgium) where it was used in a study with Friedreich's Ataxia patients. The professors at this hospital are very experienced in the method of tissue Doppler imaging which we also apply in this study.

And where will the study be performed?

Also at the University of Leuven with Professor Gunnar Buyse as principal investigator. We expect to finish recruiting the patients shortly, then it will take one year until the last patient has completed the protocol.

That will then be the beginning of 2007, and then the data will have to be analyzed.

We hope this will be relatively fast given we have only 21 patients. The evaluation will be done by a recognized clinical research organization. We expect to know about

eight weeks after the end of the study whether we have an effect or not.
But you hope that idebenone will not only be good for the heart but also for the skeletal muscles, after all, the heart is also a muscle.

Yes, the primary endpoint of our study is the improvement of heart function. However we are also investigating the effect of the study medication on the function of skeletal muscles. The clinicians at the University of Leuven are using quantitative muscle strength measurements. For example, with one of these instruments, the child has to lift a leg against a resistance and at the same time he can see on a screen how a ball moves or a plane flies over mountains. This helps to motivate the children to perform these exercise tests. The methods used by the team of clinicians are standardized and fully validated and are applied in many other hospitals. In addition, we also have the manual muscle strength measurements performed by physical therapists, and a whole series of other secondary endpoints like the creatine kinase (CK) values and other clinical blood parameters. But the most interesting result will possibly be a positive influence of SNT-MC17 on muscle strength and the endurance of the musculature.

If you see positive results at that stage, does that mean that you will already be seeing therapeutic effects?

Yes.

Do you then need a phase-III study?

We will discuss this with the authorities as soon as we have analyzed the data of the IIa trial. We will probably have to perform another trial, because, at the moment, we are testing only one dosage of SNT-MC17. Perhaps the authorities will ask us to test additional dose groups and to repeat the study with more patients. I would be surprised if SNT-MC17 would be approved based on a single phase-IIa study. This would be very unusual.

Would the phase-III study last about as long?

If we obtain clear effects after six months, we would certainly have the possibility of shortening the following study. At this moment, we have deliberately planned for a long study duration in order to maximize our chances to detect therapeutic effects.

That means, if everything goes well, one could, in about three years and with a question mark, think about an introduction of idebenone as a Duchenne medication.

Yes, but all I can only say with any certainty today is that the results of the present phase-IIa study will, in all likelihood, be available in the second quarter of. 2007.

What the families will also be interested in is, providing everything goes well and you are successful, how will the drug then reach the patients?

We are planning to fully develop SNT-MC17 for the treatment of DMD, file for approval and market the drug ourselves.

And you plan for approval of SNT-MC17 both in Europe and the United States?

That is correct. At the present time, our SNT-MC17 Duchenne study is being performed in Europe. If we are successful, the next step would be to agree with the European authorities on a centralized procedure for approval as it is mandatory for rare diseases. Then we must, as already mentioned, probably plan another phase-III trial which, because of the large number of patients needed would possibly have to be performed simultaneously in different countries, perhaps even simultaneously in the United States and in Europe.

Can you also manufacture the drug SNT-MC17/idebenone?

Yes, we have the production for SNT-MC17 in place and have already produced several hundred kilograms. For the present and the planned clinical studies, tablets are available in two different dose strengths. The technical development is almost completed. What is missing is only the proof of efficacy for us to press forwards towards approval.

Will SNT-MC17 be very expensive? And will health care insurance pay for it?

At this time, we cannot say anything about the costs of the drug. But you also ask whether a drug for Duchenne muscular dystrophy would be paid for by health care insurance. Personally I am convinced that the health care insurers will refund the price for an approved drug with proven safety and efficacy. The insurers will not be in a position to deny their patients an effective medication. The situation would not be comparable to a 17th headache tablet to be brought to the market. SNT-MC17 would hopefully be a therapy for a severe disease of children which, until now, cannot be treated efficiently.

In fact, you are not changing the molecular basis of the disease. You are not altering the gene.

Correct. As already mentioned, Santhera does not engage in gene-therapy strategies or stem-cell based therapy approaches. With our pharmacological methods, with SNT-MC17 and also with the calpain inhibitors, we want to slow down the course of the disease, more exactly, the muscle weakness in Duchenne muscular dystrophy. I do not believe that we will be able to stop the disease completely. But if we would succeed in keeping the sick children ambulant for a few extra years, this would be an enormous success.

Even if it will not be a complete cure, the children would gain more time for waiting for a comprehensive therapy, isn't that so?

Yes, but, in addition, our therapy could also improve the quality of life for the patients. I would like to stress that in our opinion more than one medication or treatment method

could eventually be useful for the Duchenne disease. Let me look far into the future: Perhaps, one day, we will have an exon skipping treatment with the result that a certain amount of dystrophin can again be made by the muscles. Such a therapy could then be combined with a calpain inhibitor which would slow down the degradation of cell proteins including dystrophin. SNT-MC17 would then, via a third mechanism, improve the heart function and reduce the general muscle weakness. This approach to interfere simultaneously with several cellular and biochemical pathways is still far in the future for Duchenne muscular dystrophy, however, it is already being discussed by researchers and clinicians. It will be a challenge for them to develop an optimal program using all the techniques that will hopefully be available in the future.

The scientists at Santhera are now concentrating their efforts on obtaining the approval of the therapeutic approaches mentioned in order to make these therapeutic interventions available to the thousands of Duchenne boys everywhere in the world.

On behalf of the many families with Duchenne children, I would like to thank you very much for this interview. And I am wishing, like all of us, that you and your team will be successful so that all our wishes will become true.

Santhera Pharmaceuticals AG is a biopharmaceutical company in Switzerland specialized on the discovery, development and marketing of new therapies for the treatment of neuromuscular diseases. The company was formed in 2004 through the merger of MyoContract AG and Graffinity Pharmaceuticals AG, providing it with a fully integrated platform for the discovery and development of drug candidates. Santhera has production and research facilities in Liestal near Basel and in Heidelberg and has about 60 employees. Detailed information can be found on the internet at www.santhera.com.