

Two Interviews.

Clinical trials for skipping exon 51 as a therapy for Duchenne muscular dystrophy.

Introduction by Professor Reinhardt Rüdél, University of Ulm, Germany.

Muscular dystrophy is one of the most evil diseases of the world. Its most common form, named after the French physician Guillaume Duchenne, is inherited as a recessive, X-linked trait (a mode of inheritance perhaps better known from its existence also in haemophilia): mothers are the transmitters of the disease, sons are the affected patients. Duchenne muscular dystrophy is the most common monogenetic disorder of childhood – about one in 3,500 boys is affected, new mutations are relatively common. The disease leads to a rather fast loss of force of all skeletal muscles, the affected boys become wheelchair-bound at the end of the first decade of life, and, before the introduction of assisted ventilation, they used to die from respiratory failure before the end of the second decade. The worst of all is that, up to now, there is no real cure whatsoever.

For more than 100 years after its first description, we did not know the pathology of this dreadful disease, but hoped that with the finding of the responsible gene that was mutated, and with the discovery of its unknown gene product, treatment of the disease would immediately follow.

It is now more than 20 years ago that the gene was detected, and soon after its gene product was found, and yet we have no cure today.

This is outrageous for many of the parents of Duchenne boys who desperately wait for the promised treatment while they see their sons waste away. Why does research progress so slowly? For a long time, there was really not much research into treatment of muscular dystrophy going on because the researchers just did not know from which angle to attack the disease: all the many tested classical pharmaceuticals proved to be useless.

Now, with the advent of molecular biology, intensified research at least recognised several possible routes along which new ways of treatment could be developed. But each of these routes turned out to be stony, to be much slower to negotiate than any of the researchers and doctors had anticipated. The parents became desperate or furious.

In this situation, Günter Scheuerbrandt, a German biochemist who had long been engaged with the development and application of a simple method for the early diagnosis of muscular dystrophy, decided to assume a role that might be compared to both an interpreter and a comforter of the waiting community of patients and parents.

They – experienced in the questions of every-day care of the diseased – did not understand what was going on in the research scene. They were marching through a tunnel without seeing any light. Nobody explained to them, why research did take so unexpectedly long. Günter, however, in taking to write letters in which the difficulties of research were explained in a language that was also understandable to lay people, at least gave them the reassurance that their distressed cry for strenuous investigations was heard.

For composing these letters, Günter developed his method of attending most of the relevant researcher's reunions and interview there the protagonists about their achievements, their obstacles, their own hopes. He then transcribed these interviews, sent the resulting texts to the respective interviewees for approval and then distributed them via e-mail, on his homepage and in lectures at meetings of parents' associations.

This beneficial activity, from which patients, parents, doctors as well as researchers are continually profiting, has recently been acknowledged both by parents and researchers. Upon nomination of a couple of German Duchenne parents he was awarded the Bundesverdienstkreuz (Federal Cross of Merit) by the President of the German Federal Republic in February 2009. Only one month later, he received from the Italian Gaetano Conte Academy for the Research into Striated Muscle, i.e. a doctors' and researchers' institution, the Gaetano Conte Award 2009, named after the Italian physician who was the very first to describe muscular dystrophy.

This latter prize was awarded to him at the meeting of the Mediterranean Society of Myology on Cyprus in March 2009. After the ceremony, he found the time to interview Professor Kate Bushby, Director of the European neuromuscular research network TREAT-NMD, on the present state of the development of a therapy of muscular dystrophy using antisense oligonucleotides (AOs). Not much later, at a German parents' meeting, he also interviewed Drs Hans Schikan and Judith van Deutekom, CEO and Head of Research, respectively, of the Dutch pharmaceutical enterprise Prosensa, involved in the commercial development of AONs for the treatment of muscular Dystrophy.

Read in the following Günter's two latest interviews that will update you on where research stands and at the same time illustrates Günter Scheuerbrandt's method of translating the researchers knowledge, achievements, problems and hopes into the language of lay people whom he has admittedly meanwhile taught a host of molecular biochemistry.

Prof. Dr. Dr.h.c. Reinhardt Rüdél was, until his retirement five years ago, director of the Department of General Physiology at the University of Ulm, Germany, where he performed research on several muscle diseases, in particular on hereditary disorders of muscle excitation. For many years he was chairman of the German muscular dystrophy association, DGM, and president of EAMDA, the European Alliance of Muscular Dystrophy Associations. He is still actively engaged in writing and publicly speaking about the problems and the hopes of men, women and children who suffer from one of the many muscular diseases. He himself has one, a muscular atrophy, so he knows what it means to live and work in a wheelchair.

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Interview with Professor Kate Bushby TREAT-NMD Coordinator, Newcastle upon Tyne, UK

This interview was recorded in Nicosia on Cyprus by me, **Guenter Scheuerbrandt** PhD., on the 21st of March 2009 at the 9th Congress of the Mediterranean Society of Myology. The following text is an edited and shortened version of the spoken interview. It has been approved by Professor Bushby for the information of patients, their families, and care-givers. My questions are written in italics, the answers of Professor Bushby in normal print.

Local and systemic clinical trials for skipping exon 51 of the mRNA in Duchenne boys have been and are being performed by the Dutch company Prosensa in Leiden, Liuven, and Göteborg, and by the American company AVI BioPharma in London and Newcastle with the help of the MDEX Consortium of which you are a leading member. Professor Rudolf Korinthenberg at the Children's Hospital in Freiburg told me that he is ready to help either Prosensa or AVI to perform the next large and pivotal clinical trials with his organization of 10 German clinical centers.

The TREAT-NMD network, of which Rudolf and his team are a key partner, is very pleased about the level of industry interest in the network, in particular for feasibility inquiries, and regarding future studies. It would be fantastic if these future studies were co-ordinated via Rudolf's team.

If the companies get outside funds from public sources like health departments or so, wouldn't there be problems when they are earning money later?

There is often collaboration between drug companies and public funders for drugs to be developed. It helps to move the process forward.

Because I got the merit medal of Germany for my reports from our president Horst Köhler, I can now talk to some German politicians at a high level. I told them that we will need about two million euros for a large trial with 100 Duchenne boys. But it seems to be quite difficult to get anything outside the normal way of applications, and that takes years.

Yes, getting public money takes a long time, and also the drug companies have to agree that you go down the route of accessing public money for a collaborative project. As you know, exon skipping is mainly being done by Prosensa and AVI. They are developing the technology and they chose to do these ongoing trials. We really hope that partnerships will develop which will allow the development of new trials in the future.

I saw in a press release of AVI that your local trial has been finished, and that the results are available by now.

The results have been written up. Our manuscript is in the process of being submitted. The publication should come out soon.

Your results are positive, aren't they? Are they better than the results the Dutch got in their local trial which were published at the end of 2007 in the New England Journal of Medicine?

Yes our results are positive. We can't really compare them with the Dutch results, because the way we did the trial was slightly different. For example, we were allowed to take a biopsy from the same EDB muscle of the boy's other leg. One muscle was injected with the antisense drug and the other with only a salt solution, to have a control. The control is very important, because of the background

level of dystrophin in some Duchenne patients. It is necessary to determine that what we are seeing after the treatment is definitely higher than the background. With the low dose, our results were not so good, but with the 10 times higher dose, they were much better. Dystrophin was visible in a significant portion of the muscle fibers.

Your next trial, the systemic one, has now been started. From what Francesco Muntoni said at ActionDuchenne's meeting in London last November, I calculated that this trial will be ready in about the month of August of this year. Can anything been said already?

The trial will be finished later than August, but we hope it will be ready this year. Two patients have been injected so far. So it is a bit premature to say anything.

And will you do multiple biopsies to see whether the drug is active in possibly all muscles?

No, we are not allowed that. There will be just one biopsy afterwards, from the biceps. This will be compared with a biopsy taken before treatment.

Do you expect some improvement of the muscle function?

Not really. But because we have to check that the muscles are not damaged by the treatment we are measuring muscle function and strength. But this is not an efficacy trial. It lasts only for 12 weeks.

What will happen afterwards, will you need another trial?

Yes, and that will be the controlled trial, the trial where we have to use a placebo for determining efficacy reliably.

And this could not be made together with the Dutch to compare the two types of the drug at the same time?

From the academic point of view that would make very great sense. But I don't think the companies would do that. It is most likely that they very much would like to complete their trials independently.

But wouldn't one then need to give the placebo to much fewer children?

Possibly, it would depend on the design of the trial. It is more likely that when both drugs are ready and on the market, the academics could do a comparison.

The Dutch have just published a paper on the comparison of the two types of the drug where they say that their effect was about the same.

They were tests, done in the laboratory and with mice but not with humans. And that is not the final answer. It is however very reassuring to see promise with both drugs.

The Dutch have a so-called first list for the next exons to be skipped. Didn't AVI say in their press release that their next exon whose skipping they will develop will be exon 50?

It does seem like this is the case. They have told me that they are looking at the deletions of the different patients to determine the next important group of patients

whose exons should be skipped.

Hasn't this already been done by Annemieke Aartsma-Rus in Leiden?

Our list is slightly different, because it is based on the results of the TREAT-NMD global registry. Around 30 countries are in partnership with TREAT-NMD to contribute to the DMD global database which now has over 8,500 registrants. All of the patients enrolled on these registries are interested in taking part in trials, and some basic clinical information on them is also available. An overview of the information held will be available on the TREAT-NMD website very soon.

Will you need new approvals for the next trial?

For every trial, you need specific approval. From the local to the systemic trial that was quite straightforward. It went faster than for the first trial where we had a new drug and a new technology. The approval for the second, the systemic trial, was much easier for us.

Do you think that the next steps will also be easier?

Yes, they will be easier. The regulators would not have approved an early trial if it had not a prospect. So it is important that there are more trials in the pipeline. We will discuss the regulation of the antisense treatment with the EMEA and the FDA agencies next autumn in a meeting led by TREAT-NMD.

So the talks are going on, and how do they look? Are the regulators interested?

We are talking to them, but we don't know what will happen. But sure, they are interested in helping us.

Who are the people who decide to approve or not a clinical trial?

They are very highly competent pharmacologists and pediatricians. They are experienced people. We know this from the discussions about trials for spinal muscular atrophy.

Didn't AVI try to do their trials in the United States also?

I am sure that they have plans to move their trials into the US also. Up until now, the FDA in the States has been less easy to engage on this issue than the European EMEA.

Is that the reason you are doing the two trials in the UK?

Yes, partly.

In the next trials, can children from outside the UK participate?

For the current trial, I don't think that it is practical to come from another country, because the children have to be there every week for injections. They have to have lots of blood samples taken. The families have to live near the clinical centers. It would be better to have more trial sites in other countries especially as we move into efficacy studies. Possible trial sites are being identified and screened by TREAT-NMD. We see how complicated it is to take part in a trial with the PTC trial. Families have to put their whole life on hold, even if they live close by. Even for them it is difficult to participate.

I get requests from all over the world. Even people from Siberia and Argentina would like to come.

I can imagine that, but they should realize that the trials are only trials. In the efficacy trials, their child could even be on placebo. It may not help them and there may be unforeseen side effects. Trials are really hard work.

I always tell them, that the children participating do not get any direct benefit. But if they stay in contact with me, they will get my reports. I have more than 1,000 addresses on my English, German, and Spanish e-mailing lists, so they would find out fast when something is ready for their children.

I would even say that the people in the trials are almost at a disadvantage. Because they have to go through a hassle to get to something everybody else will profit from later provided it is proven to work. We are very grateful indeed to the families and boys who take all the time and effort to take part in these studies, which we really hope will move things forward for everyone..



Professor Kate Bushby, MD.

Can you say about how long it will take until the first exon-51 skipping drug will be ready? Gerard Platenburg said in my interview with him last Jul, it would take about four years.

Yes it might be something like that. But it is very hard to give even an estimate.

If one could skip almost all exons, one could treat 83% of all Duchenne boys. But there are other treatment possibilities, like upregulation of utrophin, which then could even be combined with exon skipping.

Yes, this kind of combination will be one way to enhance efficacy. For the development of potential antisense drugs for the smaller target groups, maybe some private investors or foundations could provide the funds for developing exon skipping drugs for small groups of patients, if the commercial companies cannot do this.

And the morpholinos are more expensive than the 2'O-methyls, yes?

They are both expensive. The company Genzyme sells their drug for the rare neuromuscular Pompe's disease for many thousands of dollars per year. Who knows - exon skipping might be similarly expensive, or it might be much cheaper. If the systemic trials produce spectacular results, then, maybe, some private investors will come along. But when they are not spectacular, this might not happen. Up

to now everything is just an experiment for a large group of related new drugs. PTC124 is different, that is just one small molecule the manufacturer has to take care of.

And it is only for 15% of the patients. Is PTC124 really working?

Nobody knows yet. We have to wait until the end of the trial.

Sometimes I am approached by Becker patients. They are already there where the Duchenne boys want to be. But the pharmacological methods might help them.

Yes, that is true. But they want to improve their situation also.

Thank you for answering my questions. Would you please conclude this interview with some final words to the

Duchenne patients and their families who will read this interview?

I would just like to say that we have waited for many years to be able to talk about ongoing clinical trials. This is a very exciting new era for this condition.

Professor Kate Bushby, MD.

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Interview with Hans Schikan PharmD, Chief Executive Officer, and Judith van Deutekom PhD, Head of Research, Prosensa BV, Leiden, the Netherlands.

This interview was recorded by me, **Guenter Scheuerbrandt PhD.**, on the 16th of May 2009 at the annual meeting of the German Parent Project Muscular Dystrophy **Aktion Benni & Co.** in Bochum in Germany. The following text is an edited and shortened version of the spoken interview. It has been approved by Drs. Schikan and van Deutekom for the information of patients, their families, and care-givers. My questions are written in italics, the answers are in normal print.

The exon skipping technique and the present state of the clinical trials for skipping exon 51 in the messenger RNA of the human dystrophin gene are described in detail in my new research report which can be seen on my internet pages www.duchenne-information.eu and the readers of the interview should first look at that report. Here, I would like to discuss the future, the further development of your exon skipping approach for a therapy of Duchenne muscular dystrophy.

So, let us start with your second clinical trial, the systemic one, where the potential drugs, the antisense oligos, were injected into the blood circulation of the boys. Has this trial been finished now?

All 12 boys have now been treated with subcutaneous injections and all biopsies are taken. We all are still validating the results, analyzing the biopsies and the blood samples. To get all the data together will take a couple of months.

This was a systemic trial to see whether the antisense oligos have reached all the muscles, also those of the heart and the lung function. Did you obtain biopsies after the treatment from several muscles?

We only biopsied one muscle, the shin muscle tibialis anterior to keep the burden for the boys as minimal as possible. If we find new dystrophin there, we may conclude that new dystrophin is expressed, synthesized, in other muscles as well.

But you wouldn't have a scientific proof that all muscles got new dystrophin.

That is right. You would have real scientific proof if you showed improvement of the muscle function in every single muscle. From our systemic studies in mice, we knew that there was dystrophin expression everywhere. Also, before entering this study, we found correct exon skipping effects in different tissues in the monkeys that were used to perform the necessary toxicity studies. That

gave us the confident feeling that oligos would spread throughout the body in patients.

But did you measure the muscle function, too? Did you see an improvement?

That was too early because we made only five injections. This builds up a steady state after a certain time, and we had not reached that level yet. It would be too early to draw conclusions there. In the next large trial, we will have the possibility to measure muscle function effectively.

So at the moment, there is not really an improvement of function?

Well, we don't want to create any hope if we don't have all the data in. To come out too early with any data without having analyzed everything in depth would not be justified. We expect to present the data at the World Muscle Society meeting in Geneva in September.

When will you publish the results of your systemic trial?

The publication will follow after the announcement in Geneva. We hope it will not take again one year until the publication on our first trial appeared in the New England Journal of Medicine in December 2007. But that was an intramuscular study which was not aimed at showing clinical benefit. However, we got a lot of citations by other researchers. We will probably submit our new manuscript again to a leading medical journal.

Now, for the next and larger study with 100-150 patients, you must be confident that the systemic treatment with the 2'O-methyls really works.

The intramuscular trial, the local one, as you know, gave very nice results. Provided that the systemic trial will also given nice results, the most important next step will be to show that dystrophin expression will lead to functional improvement. How many boys we will be treating is now in discussion, but it will be a larger trial.

This will be an international trial, yes? We are very

much interested that patients from Germany will participate. There is not much Duchenne research going on in Germany. One exception was the cyclosporin study which Professor Korinthenberg in Freiburg performed with 150 patients.

I think that Germany should be included because it is one of the largest countries in Europe. But we want to know how many patients are really available there and who live close to a clinic, so that they don't have to travel long distances. We want to minimize the burden of participation as much as possible.



Hans GCP Schikan, PharmD

Professor Korinthenberg said that to determine which German patients could participate one should look into the data banks of TREAT-NMD. About 13% of the possibly 2,500 German patients would need skipping of exon 51. But, obviously, participation will depend on their age and whether they must still be able to walk.

Yes, we will listen to the advice of TREAT-NMD. We are still discussing the inclusion criteria which will be specific. This also counts for the age criteria. The purpose of the trial is to study in a very well defined patient population whether we can show significant functional improvement compared to a placebo treatment. And the results of the present trial will be taken into account and also those from other trials like the large one with PTC124.

One of the most important outcome parameters in clinical trials for neuromuscular diseases is the standardized 6-minutes-walk test, which is widely used in many trials for muscle diseases. If this is one of the outcome parameters we need, then, ambulation would be a requisite. Again, we have not made our final decisions yet

So the boys must still be ambulant and able to walk for 6 minutes.

Yes, probably, but I would like to make a comment as well; I (Hans Schikan) come from Genzyme and used to work there with Myozyme the drug against Pompe disease.

One of the things we saw when parents wanted to have their children participating in clinical trials – which I understand very well – and when there was a certain minimum distance to walk, some families trained their children to become eligible for the trial. But then the children are very good at the beginning but later perform less well, and this makes the results unreliable.

So it is important, that we discuss the right conditions for the trial. And we must really work closely together, the patient's associations and the investigators to arrive at the best possible study.

In what way can German patients participate?

We will not select the patients ourselves. As a sponsor of the trial, we will design it together with the investigators. Then certain clinical sites will be identified, which might be helping us to perform the trial and which have the right experience in doing the measurements. We will have to know how many patients live in their vicinity, who are eligible for skipping exon 51. The investigators there, not we, will then start looking at that patient population and select the boys who will be invited to participate.

Will you also have a committee for this large trial like the British have for their trials?

Yes, that is the normal way of coordinating a trial. There will be a supervisory committee, and a special safety committee to avoid any mistakes.

Has your trial already been approved by the European Medicine Agency EMEA?

We don't need approval from the EMEA, but from ethical committees in the different countries where the trial will be done. There is no pan European approval necessary at the moment. But we have already discussions with regulatory authorities to see what the best planning might be. They look at the design early on, and if we have results from an earlier study, they are likely to say "go ahead" more easily. Our exon skipping drug has received an orphan drug designation. Therefore there is big support by the regulatory authorities to help us in designing the study in the most optimal way.

You have a so-called "first list" of 8 exons, 51 and 7 others, for which you like to develop the skipping drugs. Would you have to go through all the three phases of clinical trials for each of these exons? Or will the regulatory authorities relax their requirements for the later ones?

There will be meetings, organized by TREAT-NMD, with EMEA to discuss the outcome parameters and perhaps also whether the entire clinical development has to be repeated for each exon. Perhaps there are ways in which all exon skipping agents could become available more quickly. The most important thing is the safety of our patients, therefore pre-clinical safety studies have to be done for every exon. But one can imagine, when the safety is established, that functional improvement can be assumed when a certain level of dystrophin expression has been found. We think it is excellent, that these discussions are taking place, because for the more rare mutations, the number of patients will be so small that it will be practically impossible to do a normal application for only 50 patients or less. One would have also have challenges to locate the patients with very rare mutations.

Our peak priority is now to show that skipping of exon 51 will really work and that it will lead to a functional improvement. If that is there, it would help to speed up the

whole approval process.

But it might take 3 or 4 years to get exon-51 skipping to the point where the regulators say “go ahead, make it and market it”.

The development of any drug takes a long time, sometimes 15 years. We are already working with exon skipping for a long time, more than 10 years. If you look of how the development is going, there is basis for hope, that indeed within a few years, there will be something there that can really work.

We have about 20,000 other genes. Even if the authorities allow you to go ahead after you first proved that it is not toxic, something may happen later with one of the other genes.

Regarding specificity in the genome, we can look at the now known sequence of the entire human genome and check whether one or the other antisense oligos we prepared for most of the dystrophin exons would attach to sequences elsewhere in the genome. If it does, we could just lengthen its sequence somewhat or not use that particular oligo for further development.

The skipping of which exon will you develop next, 44?

Yes, 44, we are about to start a systemic phase I-IIA trial similar to the present 51-trial. We will not do a local, intramuscular trial.

How about the other exons 45, 53, 46, 52, 50, and 43 on your priority list?

We really have to allocate all our resources to making sure that the first products can come to patients. The company can then grow and we can look for many more possibilities of exon skipping in Duchenne or other diseases and RNA modulation as well. But our first priority is really to make sure that we can bring something to patients soon.

You are using the 2’O-methyl oligos because you have so much experience with them. But sometimes, the morpholinos seem to be more efficient. And you published results that both types are more or less similarly active in mice. Will you continue to use 2’O-methyls?

In our 2008 paper, we directly compared the efficiency of 2’O-methyls and morpholinos to skip exon 23 in the mdx mouse. For skipping that exon, the morpholino seemed to be slightly better than the 2’O-methyl, but this was in a mouse model. It does not seem to be true for other exons. We also looked at the biodistribution and accumulation of the compounds in other tissues. We saw that more morpholinos were going into the kidney and the liver than the 2’O-methyls. That increases the risk of side effects. Thus, we feel still quite comfortable with the 2’O-methyls. And the results for the human exons do not give us a reason to switch over.

The 2’O-methyls go better into the heart, isn’t it?

Yes, that seems so. But also that was only studied in mice. We have to be careful of generalizing the data we found so far in mice.

There are now three more types of antisense oligos, the third one just published, the octa-guanidine morpholinos.

If we look back in 20 years from now to all the different approaches towards Duchenne exon skipping, we will see that so much more research activities were attracted. And there might possibly be better ones that achieve better outcomes as well. But it will also take several years to optimize and modify these other oligos.



Judith C. T. van Deutekom, PhD

How about the financing of your next large study? Will Prosensa pay for everything? Do you need extra money?

We don’t have enough money, because we do not yet generate any revenues from research. The whole development is very costly. We have a number of top-tier venture companies, which are backing us up and, of course, the help of Aktion Benni, of Cure Duchenne, and of many other organizations, but we still need more. Also for orphan drugs, the whole development until approval is very costly. And then, after the regulatory approval, there will be more follow-up research, for instance to find different dosages to improve efficiency. And that has to be financed, too. Yes, we still need more resources for the long-term growth of Prosensa to bring this research further ahead.

But for the next trial we are talking about, is its funding assured? In February of this year, the German minister of Research, Annette Schavan, told me that you got an 18 million euro investment.

The 18 million were the last investment in December of 2008. But to bring the product eventually to registry approval, that the first patients can use it, we need much more.

Do you have private investors in addition to the associations?

Yes, we have a number of very esteemed and well established investment companies, which are backing us up. We are confident they will continue doing it. We want to be a sustainable company on the long term. We aim at bringing treatments for as many patients as possible.

But these private investors expect return, they want something back. How about the associations which give you money, does this money also have to go back?

We would be happy if the outcome of all this work, of all these partnerships, would be an effective treatment for the boys. That would be the biggest return we could hope to give to the patients and to their organizations as well.

How expensive will an exon skipping treatment be?

We could look at Genzyme's drug against Pompe disease as an example, which is a drug for worldwide less than 10.000 patients. This drug was launched at an average price of 300,000 euros per patient per year.

There are half a million Duchenne boys in the world. That is easy to calculate if you know the total population, the birth rate, the average life time and the frequency of Duchenne.

It depends also whether all of them will be accessible. Many are in countries without an optimal healthcare system. Pompe may serve as a reference in the Western world. Obviously, the development and manufacturing costs are high and need to be shared by all accessible patients, therefore the fewer patients there are with a certain disease, the higher the cost per patient will be.

Let us approach this from a different perspective. Treatment of Pompe patients requires high per patient costs. There is no discussion about that. If you look at the number of patients who are actually treated, the impact on the overall health care budgets is quite small. There are diseases where tens of thousands of people are treated at a certain price. There are rare diseases where there are very few patients treated at a higher price. Should one help people with more common diseases more than people with rare diseases? People who have a rare disease and the knowledge is available to treat them, have the same right for treatment as people with a more common disease.

And that was actually written down?

Yes, if you look at what the European Commission is trying to do in terms of stimulating companies to do research development for rare diseases, many steps have been taken already, but much work still needs to be done there. In the United States, the Orphan Drugs Act was established back in 1983, many years before it was started in Europe. And right now, there are over 3,000 designations for therapeutic developments for rare diseases in the United States and around 300 orphan drugs are already available for patients. If you look to Europe, where regulation came much later, only some 50 orphan drugs are currently available for patients, but companies are working on more such drugs. So we have to catch up in Europe. A continued support for medical research for orphan diseases is needed.

Now, let's look into the future. The parents are waiting, and many are thinking and even saying openly that it does not really matter whether there is still a risk with the antisense drugs. Even if they are not 100% safe, Duchenne is so bad and progressing so fast that we need a therapy for our boys before it is too late for them.

We need to work together. We need to work with patient associations, with physicians, with investigators, with the authorities and with academic researchers in universities. We need to work with all of them to ensure that patients can get access as quickly as possible once safety and efficacy have been established. We really need to work together in partnership.

We are talking about a new field here. Twenty years ago, rare diseases including Duchenne, were not treated. And now, we see lots of activities for finding therapies for rare diseases, also for Duchenne. We have to make sure, that we develop the most optimal pathway that the fruits of research and development become accessible to patients as

soon as possible. So working together is number one. And I would like to say to the parents, that at our company, we remind ourselves every day, that there are people outside waiting for the results of our efforts. We are very much aware of that. We feel we have a huge responsibility. There are many players in this field whose partnership is essential and we are only one of them. We will use our best efforts to hopefully bring something to the patients in the next few years which will be helping them. In drug development, "we cannot break iron with hands", as we say in Dutch. We have to do a number of steps one after the other to go ahead.

In my opinion, the exon skipping technique is the farthest ahead of all the about 40 different research approaches I am aware of. When I talk to lay people about gene technology, they are afraid of everything connected with the word gene. Then I tell them about exon skipping and ask them: "What would you do when you had a boy with Duchenne dystrophy, cystic fibrosis or even cancer for whom that kind of gene technology would be the only help he could get?"

With exon skipping we do not change the gene itself, we only change the faulty genetic message, the messenger RNA, we actually repair it.



Henry and Emil

You know that last February, I got the merit medal of Germany, the Bundesverdienstkreuz, from our president Horst Köhler. I found out who asked the president three years ago to give it to me: A family with two Duchenne boys, one 6 years old, the other 3 years. After the first boy was diagnosed, the mother had a genetic test which showed that she is not a carrier. She got a second Duchenne child anyway. So, one assumes that she has a mosaic of germ cells with and without the mutation. Such a genetic mosaic cannot be diagnosed, but it brings a risk of about 10% for a repetition of the disease.

I am now talking to a number of politicians in high places, and also to the wife of the president, to Eva-Luise Köhler, who takes care of children with rare diseases. I

talk also to our Minister of Health, Ulla Schmidt, and the Minister of Research, Annette Schavan, and to 6 members of the Bundestag, our federal parliament. I told all of these influential people that we need about 2 million euros for your large trial with German participation. But they only said that we have to go through the usual bureaucratic steps. And this might take years. What can I do more to convince these politicians, I can write to them and some of whom I am going to meet personally?

What you are doing already, and the way you are talking and writing about the disease and about what is happening in the research field is giving hope to the families.

I am very careful not to raise unreasonable hope.

That is most important. And that is why we are very cautious of what we are saying as well. To get more public awareness of Duchenne dystrophy is also very important.

Here we can think about the very successful telethons in France and the United States.

The French association AFM is very active. Every year, their telethon is bringing more than 100 million euros.

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They are also sponsoring companies and helping them in the field of muscular diseases.

Our association, Aktion Benni & Co, was named after Benni Over who is now 20 years old and not doing well. I suggested this name to Benni's parents who started this association when Benni was 2 or 3 years old. All the efforts of this family and of the about 700 families now belonging to us was and still is going to raise money for research. This is also one point: what can individual parents really achieve? They try to get 500 euros scraped together and give that to Benni & C., and then most of it goes to you. If you look at your 18 million, how much can 500 euros or 1,000 really help?

We are really very grateful for all the support we receive in our strive to find a treatment for Duchenne. All contributions can help. Together, in partnership, we hopefully will be able to find a solution for Duchenne.

Thank you very much for this interview, also on behalf of the parents and all others who will read it.

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