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

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, Liiven, 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 Action Duchenne’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 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.

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 atrophin, 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.

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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.