

TREAT-NMD AND DMD: ANNUAL UPDATE REPORT

TREAT-NMD aims to encourage collaboration between activity leaders, industrial partners and experts in the field to ensure the tools TREAT-NMD are developing and utilising throughout the network are relevant for DMD as well as being relevant to and accepted by the regulatory authorities.

Two meetings, one focusing on the flagship antisense oligonucleotide project, and the other on more general outcome measures for early therapeutic trials in DMD, were arranged and took place within the first 6 months of the network. These two meetings were reported upon in the first 6 month deliverable report therefore this 12 month deliverable report serves to update on the work which has been carried out since the second workshop.

A Round table meeting was organised in collaboration with PPUK, to coincide with the PPUK (Action Duchenne) Annual conference, on the 2nd November 2007. The meeting provided an opportunity for several TREAT-NMD Activity leaders to meet with other international researchers and industrial representatives to update, discuss and plan the future direction of the Exon Skipping clinical trials. Specifically TREAT-NMD presented an update on the network tools and discussions focused on how the tools could help with recruitment for future clinical trials.

Additionally, several Activity Leaders including IC, UNEW, FTELE and MD-NET have held conference calls and attended meetings to discuss the relevance of the network tools they are currently developing. A brief description of and significant results from these meetings are detailed in this report.

Introduction

TREAT-NMD aims to establish an infrastructure across Europe that will prepare the neuromuscular community including industry, patient organisations, basic researchers and clinicians to cope with the challenges of new, cutting edge, therapeutic developments in a coordinated and integrated fashion. The aim of this deliverable is therefore to demonstrate that the existing and planned network tools do and will address and overcome the currently existing areas of fragmentation by applying them to the DMD Antisense Oligonucleotide Trials.

Areas where TREAT-NMD aims to assist include in the development of standardised assessment protocols for patients, defining outcome measures for clinical trials, standardising molecular diagnosis, developing common standards of care, facilitating communication between clinicians, patients and patient organisations and developing an infrastructure so that scientists may collaborate and interface with one another so as to accelerate clinical trials.

The main objectives to be reached within the first 18 months include co-ordinating efforts within Europe towards a Phase I/II study of AON in DMD. To achieve this aim, regular meetings must be held between Imperial College and other activity leaders to ensure relevance of tools in DMD. Two such meetings were held in Naarden, the first **“Planning Phase I/II Clinical trials Using Systemically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy”** in February 2007 and the second **“Outcome Measures for Experimental Studies in Duchenne Muscular Dystrophy”** in July 2007. The aims and outcomes of these meetings were detailed in the 6 month deliverable report, the second workshop, serving as the deliverable for month 12, taking place ahead of schedule.

In addition to these two larger meetings a smaller Exon Skipping Round Table Meeting was arranged to coincide with the PPUK Annual Conference in November 2007 and throughout the last 6 month period regular focused meetings and conference calls have occurred between several Activity leaders, in which

IC has participated, to discuss the development of the network tools and their relevance to DMD.

Presentation of results

The primary results for this deliverable consist of two workshop reports from the workshops held in February and July 2007. These workshops were reported on in full in the previous deliverable report therefore only a brief update on the progress of the workshop reports will be given in this deliverable report. In addition several meetings and conference calls have taken place between the activity leaders involved in developing the network tools, including an exon skipping round table meeting and a step activity meeting, the results are presented below.

Planning Phase I/II Clinical trials Using Systemically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy –update on Workshop report

The first of the two workshops was a joint TREAT-NMD and ENMC meeting organised by Prof. Francesco Muntoni, Prof. Kate Bushby and Prof. Gertjan van Ommen and was held in Naarden, The Netherlands on 23rd to 25th February to discuss “Planning Phase I/II Clinical trials Using Systemically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy” A workshop report was written and presented in the previous deliverable report. The report has now been accepted for publication by Neuromuscular Disorders and is currently in press. It is due to be published in the first quarter of 2008 and may be cited as;

Muntoni F et al., 149th ENMC International Workshop and 1st TREAT-NMD Workshop on: “Planning Phase I/II Clinical trials using Systemically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy

Neuromuscular Disorders (2007), doi:10.1016/j.nmd.2007.11.010

Outcome measures in experimental trials for DMD – update on Workshop report

The second of the TREAT-NMD workshops ‘Outcome measures in experimental trials for DMD’ was held in Naarden 30th June- 1st July 2007, with the support of DRCI (UPPMD, PPM, MDA and AFM). A preliminary report was prepared in situ and was presented in the previous deliverable report and is available online via the TREAT-NMD website. http://www.treat-nmd.eu/assets/documents/REPORT_13.pdf. This, in addition to the notes taken by TREAT-NMD members will be used to produce a report for publication in 2008.

Exon Skipping Round Table Meeting

The PPUK annual conference, held from the 2nd - 3rd November provided an ideal forum for international researchers and industrial representatives to meet. Therefore TREAT-NMD in collaboration with PPUK organised an exon skipping round table meeting around the conference so that researchers could give a brief update on their research and discuss the future direction of the exon skipping work. It also provided several TREAT-NMD partners (IC, UNEW, LUMC and MRC) with an opportunity to update each other and the other 20 researchers and industrial representatives on the network tools currently being developed which will help with recruitment into clinical trials. These tools include the development of the Global patient registry (MD-NET) and the effort to map the Clinical Trials sites across Europe (MD-NET / CTCC).

A secure webpage was set up on the TREAT-NMD website so that participants could upload their presentations and review summary documents, including reports from previous meetings (listed in the attached agenda), in preparation for the meeting.

Discussions during the meeting concentrated on key points from the research and focused on the following questions:

- 1) What are current plans for clinical trials? How do we ensure these are comparable and complementary?
- 2) Where is pre-clinical work directing further development?
- 3) What could be the realistic timeline for your approach succeeding as a therapy for Duchenne if all trials go well? How would your approach cater for the majority if not all of the gene variations? What might be the timeline for that work?
- 4) How do you envisage large scale production of your product? Who is going to provide large scale production and at what cost per patient?

The meeting was recorded and Guenter Scheuerbrandt has been commissioned to write a report for families affected by DMD on the outcomes of the Round Table Meeting. The report will be available in early 2008 and will be distributed using the TREAT-NMD network dissemination tools (including the newsletter and website).

Meetings and conference calls with other activity leaders to develop network tools

MD-NET - Patient registries for DMD. WP6.1 has been involved in the development of national patient registries for DMD and the global database. Specifically this WP has worked closely with the patient organisation PPUK to develop and promote the UK DMD national registry. Furthermore the project coordinator attended the first curators training course in Montpellier from the 7th-9th November to meet with and offer support to the other 51 participants concerned with developing patient registries across the globe. Material and presentations from the training course are available via the TREAT-NMD website at <http://www.treat-nmd.eu/registries.htm>.

Clinical Trials Coordination Centre (CTCC) / MD-NET - Map Clinical Trial Sites across Europe. This work package worked closely with the CTCC to map clinical trial sites across Europe. Initially a questionnaire was designed for partners to complete to help identify national contacts across Europe. Using the feedback received from Partners individual researchers and PI's were contacted and asked to complete the on-line feasibility questionnaire so as to register their sites interest in participating in future clinical trials. The questionnaire is available at <http://skl14e.ukl.uni-freiburg.de/eu.treatnmd.fq.web/register.jsf>. So far there has been an encouraging response, with over 65 sites from 19 countries registering their interest in the first 2 months. A network in action conference call took place on Wednesday 14th November 2007 in which representatives from IC, UNEW and MD-NET took part. Participants from KI and FTELE were invited to take part but were unable to due to other commitments. The aim of the call was to discuss what the network should do next with the data collected via the online feasibility questionnaire to ensure it is relevant and useful for upcoming clinical trials. Action points from the call include;

- identify national curators to help recruit additional centre and identify the centres of excellence in their country
- involve and engage industry to ensure that the data will be useful for future clinical trials

- facilitate future workshops / meetings to help develop SOPs, procedures, protocols and discuss practical arrangements and bring together PI's involved in similar trials to encourage harmonisation i.e. European workshop in collaboration with PTC for the PTC 124 trial.

The possibility of linking the registered centres so that they can start to devise ways to develop standard operation procedures and protocols for things such as muscle biopsies was discussed during the call and this is one of the areas where future work will focus. IC will continue discussions with the CTCC, industry and relevant activity leaders regarding the best way of utilising the feasibility questionnaire data so as to effectively accelerate clinical trials.

The results of the call were disseminated to all relevant activity leaders, including FTELE and KI. The minutes are available in the additional information section of this report.

FTELE - Select and elaborate assessment tools for NM patients and define Outcome Measures. Representatives from this WP have been involved in numerous teleconferences and meeting organised by activity leaders to discuss elaborating assessment tools for NMD patients and defining Outcome Measures. The OM workshop organised by this WP and attended by other activity leaders in Naarden on the 30th June is one example as well as the Step Activity monitor meeting held in Paris in July and the Quality of Life conference call which took place in September.

KI - Facilitate the development of DMD Standards of Care and identify a dissemination plan for the patient community. DMD Standards of Care are currently being developed and it is important that these standards are adopted across Europe so that each patient has the same chances of being involved in European clinical trials when they are ready to recruit. CDC are developing standards which aim to be ready for mid 2008 and KI are working to develop a précis of these standards in parallel so that they may be disseminated as soon as the CDC guidelines are agreed. KI are leading this effort however this WP will be involved in the discussions regarding the drafting of and dissemination of the précis document. A meeting between KI, IC, UNEW and patient organisation representatives has been arranged for the 14th January 2008, in Milan, to discuss the plan of action for developing and disseminating the précis document as efficiently as possible.

UNEW - International collaborations with research groups. This work package participates in and contributes to the quarterly DRICI conference calls with the aim of promoting international research collaborations. In the last conference call held on the 11th December ethical points for consideration at the next PEC meeting, regarding recruiting children into clinical trials, were discussed as well as the potential for collaboration on a 'Clearing House' for DMD trials initiative and development of the DMD Standards of care development and dissemination.

ENMC - Develop internal/external personnel training. TREAT-NMD have initiated discussion with PTC Therapeutics regarding the establishment of a training programme for the Principal investigators and physiotherapists involved in the PTC 124 trial and PTC approached TREAT-NMD to coordinate the European training activities for the upcoming trial with DMD patients. UNEW, IC, KI, AFM, FTELE and MD-NET have been selected as potential trials sites and the European training may potentially take place at UNEW in March 2008. A conference call to discuss the logistical possibility took place on the 11th December 2007 and the next call to further define timelines and requirements is scheduled for the 4th January 2008.

Critical analysis of results

The two meetings (AON and OM workshops), presented in the previous report, represent the significant

work being done towards harmonising efforts not only in Europe but also globally, in the development of criteria for clinical trials in DMD. A critical analysis of the results from AON and OM workshops were presented in the previous report however results from the additional meetings, detailed above and in the additional information, show that work has continued in a number of areas to ensure the relevance of the network tools to DMD trials. We can highlight the major achievements towards the objective by summarising how TREAT-NMD has been working in several areas to develop the network tools;

1. A TREAT-NMD activity led by the University of Basel and Santhera will produce recommendations on the strengths and weaknesses of available models and the assessment procedures available and how they can be standardised. An animal models workshop was held by the WP leaders earlier in the year and a consensus meeting will be held in Milan in January, a report will be produced in Month 16 which will be made available via the TREAT-NMD network. Data on the clinical value of animal models treated with corticosteroids will be gathered from the literature and from amongst the workshop participants. This data will be shared via the TREAT-NMD network (Activity 07)
2. Information relating to early and current trials can provide useful information which can inform future developments. TREAT-NMD will begin to collect this kind of information systematically as a resource for the community in collaboration with the teams performing these studies (Activity 09).
3. Functional tests may be influenced by standards of care and the TREAT-NMD activity can feed in here to assuage these concerns (Activity 10)
4. The role of TREAT-NMD in assessing and harmonising clinical endpoints is in establishing the value and limitations of the existing scales with or without adaptation, and training in the available techniques (North Star ambulatory assessment, MFM, Functional scales). TREAT-NMD (Activity 12) will address the value of existing scales through workshops and offer training and education making use of the TREAT-NMD website and infrastructure. Activity monitoring has had some work done in DMD and should ultimately be useful to measure activity levels and intensity of activity. Correlation with other measures and longitudinal data are also necessary. A TREAT-NMD meeting on the use of activity monitors was held on July 11th 2007 (Activity 09)
5. TREAT-NMD could have an important role to play in talking to and liaising with regulators and funding bodies.
6. In collaboration with Industry TREAT-NMD advisory boards have been set up to help progress early Phase I/II clinical trials as and when the need arises.
7. TREAT-NMD can and has started to facilitate trial coordination in Europe to harmonise efforts via the Clinical Trials Coordination Centre (Activity 05)
8. TREAT-NMD can map the clinical trial sites capable of conducting cutting edge clinical trials across Europe and display this information on the website thereby providing a resource for the wider neuromuscular community (Activity 05).
9. TREAT-NMD can help accelerate clinical trial by facilitating recruitment into trials using the Global Patient Database (Activity 04).
10. The TREAT-NMD communication infrastructure now in place has proven to be an invaluable tool with regards to dissemination and sharing of data (Activity 01 and 02)
11. DRCI (Duchenne Research Collaborative International) is currently working on developing a Clinical

Trial Network Database to record data on current trials specifically targeted to NMD. They record items such as principal investigators, funding bodies and the centres conducting clinical trials. They are keen to take this initiative to an international level and are also in talks with the TREAT-NMD regarding cross-linking their 'clearing house' database with the outcome measures database being created by WP9.2 so as to ensure that there is no duplication of effort. (Activity 9)

12. The experience of the various labs in the assessment of muscle biopsies will be shared to develop standardised operating procedures (Activity 07)

Ethical issues

Ethical issues regarding clinical trials were addressed at the first meeting of the Project Ethics Council (PEC). Topics for discussion arose from the previous discussions of the AON and OM Workshop held as part of this work package. Specific issues discussed include:

- access to clinical trials
- recruitment of patients to clinical trials, given that there is little likelihood of direct benefit to the individual participant
- issues around consent, given that most trial participants are young people requiring proxy parental consent
- highlighting the importance for the network to tackle fragmentation in research in parallel to maintaining concern with Quality of Life issues.

Issues relating to recruiting children into clinical trials will be addressed and discussed with ethical experts and patient organisation representatives.

Conclusion

Conclusions from the Planning Phase I/II Trials Workshop- update

A report has been prepared and is in Press for this workshop. (submitted to Neuromuscular Disorders). Collaboration between all of the workshop participants, especially amongst the two research groups Prosensa and MDEX consortium were necessary in the development of this report.

Conclusions from Outcome Measures Workshop- update

A full report regarding this workshop is currently being prepared and will be distributed to all participants and published in a peer reviewed Journal in 2008.

Conclusion from TREAT-NMD – PPUK Exon Skipping Round Table

12 TREAT-NMD partners participated in the Exon Skipping Round Table Meeting.

UNEW (University of Newcastle, Newcastle, UK)

Kate Bushby (UNEW)

Emma Heslop (UNEW/IC)

IC (Imperial College, London, UK)

Francesco Muntoni (IC)

Ganeshaguru Kanagasabai (IC)

Dominic Wells (IC)

Jenny Morgan (IC)

Jinhong Meng (IC)

Maria Kinali (IC)

MRC (MRC, Oxford, UK)

Aurelie Goyenville (MRC)

Arran Babbs (MRC)

Kay Davies (MRC)

LUMC (Leiden University, The Netherlands)

Annemieke Aartsma-Rus (LUMC)

The remaining 11 participants included representatives from Industry (AVI and Prosensa), research (MDEX consortium) and patient organisations (PPUK) all of whom participated in the presentations and or discussions. It was clear from the discussions at the meeting that TREAT-NMD has an important role to play in facilitating clinical trials in DMD with exon skipping being an example of one such trial. TREAT-NMD can utilise the network tools, in particular the global patient database, the list of competent clinical trial sites and the communication infrastructure to do so.

Conclusions from Meetings with Activity Leaders

Numerous collaborations with the majority of the partners involved in developing the network tools have taken place over previous 6 months. These collaborations are a good indication that the network tools are being developed with consideration so as to be as effective as necessary as possible.

Participants at the various meetings and conference calls include representatives from IC (Francesco Muntoni, Emma Heslop), UNEW (Stephen Lynn, Kate Busby, Volker Straub), ENMC (Pauline Evers), MD-NET (Angela Stanescu, Jan Kirschner), FTELE (Enrico Bertini, Eugenio Mercuri), KI (Thomas Sejersen), AFM (Hervé Laouenan). Action points from these meetings are being followed up throughout the network on a daily basis.