

TREAT-NMD AND SMA: ANNUAL UPDATE REPORT

The principal scope of this activity was to participate or to organize face-to-face meetings or teleconferences in order to discuss and reach consensus about relevant topics related to the organization of clinical trials in SMA.

A Joint Meeting TREAT-NMD and ENMC on spinal muscular atrophy (SMA) was held at Naarden (The Netherlands) the 12-13th May 2007 to coincide with a European Neuromuscular Centre workshop on SMA which had assembled representatives of many of the European centres caring for patients with spinal muscular atrophy for discussion of possible clinical trials. Several members of the ICC (International Coordination Committee) group for SMA attended from the USA, and collaboration was extremely fruitful. There are several activities taking place via the ICC and details of these can be found at <http://www.smafoundation.org> and <http://www.fsma.org/>. The meeting discussed important issues regarding consensus on Outcome Measures, Standards of Care and Registries related to SMA.

TREAT-NMD actively participated in other relevant meetings on SMA such as a) the 11th Annual International Spinal Muscular Atrophy Research Group Meeting, Schaumburg, Illinois, USA (presentation of the TREAT-NMD European Network, presentation of a new method to measure the levels of SMN transcripts in blood lymphocytes that reached international consensus), b) the SMA Summit on Drug Development, Bethesda, Maryland, USA (active participation to the discussion with the SMA N-American Coordination Committee for the organization of Clinical Trials in SMA), and c) the first Steering Committee Meeting held in Frankfurt in October 5th 2007 to start designing and organize a trial for treatment of SMA with the drug TRO19622. The sponsor for the trial design discussed in Frankfurt was TROPHOS.

Introduction

TREAT-NMD is focused on the identification of the open problems to be solved in designing clinical trials, and on the integration of ongoing work in SMA in Europe to obtain wide consensus and standardization of activities. Work has already begun to integrate European approaches to SMA trials. Using the resources of TREAT-NMD, we will integrate these efforts while informing and contributing to the development of the novel tools of the network.

This effort is related particularly to the following challenges: 1) agreement on a common core of information for the SMA patient databases, and biobank resources; 2) standardised assessments for each functional severity form of SMA patients (SMA type 1, 2, and 3), and 3) standards of care for the different severity functional status (non-sitting SMA patients, sitting SMA patients, and walking SMA patients). This effort is taking forward not only in Europe but is shared with the USA partners harmonized by the ICC (International Coordination Committee).

This task has to contribute in developing and thereafter assessing the framework and tools created within TREAT-NMD, ensuring that these will represent a durable resource for future clinical trials.

Moreover, after overcoming the 3 main preliminary tasks, the final effort is directed to harmonise clinical trial plans working with the TREAT-NMD Clinical Trials Co-ordination Centre (CTCC), to develop protocols for designing the backbone in order to move forward for trials in SMA. The CTCC will be assessed for its ability to help with statistical and regulatory support, liaison with orphan drugs authorities and EU clinical trials authorities.

Presentation of results

A Joint Meeting TREAT-NMD and ENMC on spinal muscular atrophy (SMA) was held in Naarden (The Netherlands) on May 12-13, 2007 to coincide with a European Neuromuscular Centre workshop on SMA,

which had assembled representatives of many of the European centres caring for patients with spinal muscular atrophy for discussion of possible clinical trials. Several members of the ICC (International Coordination Committee) group for SMA attended from the USA, and the collaboration was extremely fruitful.

The workshop was organized in 3 main sections related to the following topics: 1) Outcome measures for SMA type 1, 2 and 3; 2) Registries for SMA; 3) Standards of care, allowing the participation of all the members to all sections. Details of what was covered are described below:

Outcome measures for SMA type 1, 2 and 3

Work in the last couple of years has led to the development or the adaptation and validation of several scales for functional assessment in SMA. Over the whole spectrum of SMA, various scales are available for use now in various trial scenarios there is also scope for further development.

At the Joint Meeting TREAT-NMD and ENMC at Naarden (The Netherlands) Eugenio Mercuri (Rome, TREAT NMD WP9.1) and Michael Rose (London, WP 9.2) introduced the session with a review on why we need outcome measures and what are the shortcomings with the existing measures.

A session of the workshop was dedicated to possible functional scales in SMA1. Allan Glanzmann (Philadelphia) presented preliminary results of the validation of a scale specifically designed, in collaboration with European Centers (Rome, London) for weak infants with type 1 SMA. The scale is called CHOP-INTEND (Children's Hospital Philadelphia-International Evaluation for Neuromuscular Disorders). The validation of the scale is about to be published and has been made available to the other participants of the workshop.

It was also discussed that any trial in SMA1 should take into account the natural history of the condition and that the available data on natural history and early prognostic markers of severity of SMA1 are scanty. Enrico Bertini, Sabine Rudnik-Schoeneborn, and Jan Cobben presented data on cohorts of patients with SMA1 showing similar trends of survival and progression of the disease in 3 cohorts collected with similar but not identical inclusion criteria. Statistical analysis by univariate and multivariate analysis in the cohort of 38 SMA1 patients presented by Enrico Bertini demonstrated that around the age of 3-4 months a simple questionnaire can detect some factors that predict 3 different severity SMA 1 types based on age of survival: a) Neonatal SMA1 (respiratory distress and neurological signs during the first month) ; b) Classical SMA 1 form (absence of neonatal weakness but never able to achieve head control) ; c) Chronic SMA1 form (able to achieve head control). These results of this study are in press and be published in 2008 in the journal *Paediatrics and Child Health*. It has been suggested and agreed that the data available could be re-evaluated according to similar inclusion criteria and collated in a large database that may provide information on early prognostic markers in untreated children. It has also been agreed that there may be scope to develop a further prospective dataset based on the newly adopted standards of care.

A separate session was dedicated to functional scales in SMA2. Marion Main presented data on the development and validation of the Hammersmith functional scale for non ambulant children. This scale has already been validated outside UK and used in the two clinical trials using phenylbutyrate and in the ongoing trials using valproate in the States. Some of the criticism to the scale (lack of detailed instructions, order of the items) appears to be largely solved by a US modified version.

The main problems highlighted in the discussion are related to floor and ceiling effect in patients with borderline type 1/2 or type 2/3 respectively. There have been various suggestions to overcome these difficulties by having add-on modules for upper limbs in weak children or using modules of items selected by existing scales such as the GMFM, as already validated in US, or from the Duchenne Hammersmith

scale for ambulant children or North Star. This will be further investigated by the participants.

Elena Mazzone (Rome) proposed a list of items that are being used in an attempt to develop a module assessing upper limb function in weak infants. The items have been made available to the other participants to the workshop.

Carole Berard (Lyon) presented the data on the use of the MFM in SMA2. The scale has been validated for neuromuscular disorders, and is already in use outside France and offers a wide range of items assessing different domains in both ambulant and non ambulant children. It was discussed that this scale has the great advantage of being well validated and to assess a wide range of abilities that could be extremely useful in long term trials during which patients may change their functional status. The disadvantages of the scale are mainly related to the length of the examination and to the scoring system that may not be sensitive enough to detect small changes.

Birgit Stephenson (Stockholm) presented a Danish scale that provides useful information on everyday functional abilities in patients with neuromuscular disorders. It has been proposed that the scale, largely used in DMD, may be used and possibly adapted for SMA as well. The scale has been made available to all the participants with the aim of collecting some data in SMA children that could help in better understanding its value and possible changes.

Summarizing, below is the list of the scales presented during the meeting as validated motor functional outcome measures in the evaluation patients with SMA2 and 3 and DMD:

- Hammersmith Functional Motor Scale (HFMS) for use in SMA
- Modified HFMS
- Expanded HFMS using items from GMFM
- Modified HFMS with Add-on modules – fine, gross motor and timed tests
- GMFM validated in SMA
- French Motor Function Measure based on GMFM
- Danish EK scale – Measures functional ability in DMD and SMA

Anna Mayhew (SMA Representative, UK) gave an exhaustive overview and critical appraisal of the scales published and some preliminary results of a questionnaire circulated before the meeting.

In a session on quality of life in paediatric neuromuscular disorders Linda Haynes (Texas) presented some preliminary findings on the validation of the PEDSQL module for neuromuscular disorders. So far this is the only questionnaire validated for neuromuscular disorders and there have been interest from different participants and by the TREAT-NMD to discuss translation in different European languages and subsequent validation for both SMA and DMD.

Natural history studies are helping to inform the development of prognostic indicators especially in SMA1. The definition of these areas will be crucial for the execution of successful clinical trials. Three studies have collected data on survival of SMA 1, but there may be scope to develop a further prospective dataset based on the newly adopted standards of care.

Registries for SMA

Establishment of a harmonised database/registry for SMA patients is a major aim of the network, led by Hanns Lochmueller and Christophe Beroud (WP04.2). At the ENMC meeting in May we had a preliminary

discussion for setting up a registry and a data base for SMA. Other later meetings have focused exclusively in this specific deliverable for database/registry including SMA. A TREAT-NMD website (<http://www.treat-nmd.eu/biobanks/>) has been created for updating on this critical section.

Standards of care

TREAT-NMD has an activity to develop and disseminate standards of care in SMA. An international working group (SCC-Standards of Care Committee) has already used literature review and expert consensus via the Delphi technique to generate Care Standards. A first document on International Consensus for Standards of Care for SMA, written with the collaboration of some TREAT-NMD members, has been published in August 2008 in the Journal of Child Neurology. The workshop participants were able to share this document ahead of publication, and there was general agreement that this is an excellent and very thorough starting point for the development of care standards to be adopted and disseminated via the network, though some areas require further work which will be carried out with the original members of the ICC working group. A short has been derived from the full version of this manuscript and has been proposed in the TREAT-NMD website (<http://www.treat-nmd.eu/soc/eng/sma/index.htm>).

General areas for development

The TREAT-NMD group is committed to seeking opportunities to move forward with clinical trials in SMA in collaboration with other similar efforts, such as those based in the USA. Specific examples where there is already active feedback include the collaborations with the ICC (International Coordination Committee) on outcome measures and standards of care, and cross talk with the Indianapolis Registry. With the ICC TREAT-NMD is actively participating to a teleconference, monthly, to harmonise decisions on the different developing areas.

The collaboration with the ICC has already produced a web based survey directed to parents with children affected by SMA. The survey has been translated in Italian, French, German, Spanish and Dutch collecting more than 900 responders in 24 months. The survey will be closed for the end December 2007 and statistical analysis will follow. The goals of this survey are to: 1) identify how similarly or differently care is given to children with SMA around the world; 2) see how care for SMA has changed over the past 20 years; 3) obtain information from parents /caregivers about what is important to them in the care of their child, how they now obtain such care and identify where the doctors and therapists can do better; 4) obtain information to help us construct the best possible clinical trials in SMA. The result of this study will be available at the end of the next 12 months, in 2008.

Other areas to be developed include sharing of data from previous and ongoing trials to allow cross validation of control data and the systematic testing of new target molecules.

TREAT-NMD has participated to all the teleconferences organized monthly by ICC and led by Cynthia Joyce to harmonise actions with the N-American Network. In addition TREAT-NMD has participated to the 11th Annual International on Spinal Muscular Atrophy Research Group Meeting, held the 21st, 22nd, & 23rd, June 2007 in Schaumburg, Illinois, USA and also has participated to the SMA Summit on Drug Development, held the 28-29th September 2007 in Bethesda, Maryland, USA. TREAT-NMD was represented by Enrico Bertini, Louis Viollet, Marion main, Anita Simmons, Michael Rose, and Jean-Luis Abtibol at the SMA Summit. The main goals of the Summit were the following: 1) to gain a better understanding of the clinical and regulatory requirements for approval of SMA clinical trials; 2) update on the status of drug development; 3) identify challenges and gaps in current effort for drug development. There is growing interest from pharmaceutical industry and academic institutions for phase 2/3 testing in SMA.

The meeting started with a comprehensive overview on SMA biology by Charlotte Sumner concluding

with some critical questions related to therapeutic strategies in SMA: a) Why are some motor neurons selectively vulnerable in SMN deficiency (sparing some like the ones innervating the diaphragmatic muscles for example); 2) is SMA a cell autonomous disease?; c) what is the therapeutic window in SMA? Many questions related to SMA biology still require explanation and further work is to be done studying the available tissue of patients. Collecting tissues for bank repositories is of paramount importance to advance in SMA research.

The second session was dedicated to overcoming regulatory challenges in translational research and drug development for SMA. Tan Nguyen from the FDA office on Orphan drugs highlighted current legislation in USA (Orphan Drug Act approved in 1983) giving incentives to industry for developing promising drugs for rare diseases. The incentives include: protocol assistance; tax credits equal to 50% of the qualified clinical testing expenses; release of marketing application fee; grant funding for clinical studies; seven years marketing exclusivity once the drug is approved by FDA. A new drug, a new orphan indication of a previously approved drug, or the same drug as a previously approved drug, but potentially clinically superior, are eligible for designation for use in rare diseases. Updated cumulative lists of designated and approved orphan drugs are available at <http://www.fda.gov/orphan>. Applicants may apply for orphan product development (OPD) electronically via <http://www.grants.gov>. Applications are open for domestic and foreign, public or private, non profit or for profit entities, State and local units of government and non-HHS federal agencies. To date OPD grants have supported clinical development of 41 approved orphan drugs and medical devices. Jean Temeck from the FDA spoke about Regulatory requirements for Pediatric Drug Development. Two important acts have been approved in the last years in USA. The BPCA (Best Pharmaceuticals for Children Act) that has renewed the pediatric exclusivity incentive, providing process for “off-patent” drug development, and the PREA (Pediatric Research Equity Act) that has established the Pediatric Advisory Committee, requiring pediatric assessment for certain applications unless waived or deferred. The general principles are that the pediatric population has unique pediatric safety concerns and development of new products should include pediatric studies, although they should not delay adult advances in adults. Pediatric patients should be given medicines that have been properly evaluated for their use in the intended population. Ethical considerations are always important in pediatric trials and are becoming more defined in the US. Since 1997 more than 200 products have been studied for pediatric purposes in USA.

This second session was concluded by Jill Heemskerk who spoke about the role of the NIH in Translational Research. She presented the SMA Project: A New Approach to Therapy Development at NIH, a \$22MM NINDS therapeutics program for Spinal Muscular Atrophy (SMA) with the goal to find new drugs for testing in SMA patients. The project has a Steering committee composed of Academics, NIH members and Industry advisors, and moves along 4 branches of research by a lead development team: 1) Chemical Optimization; 2) In vitro Testing; 3) Pharmacology and Toxicity; 4) Mouse Model Testing. In this manner the project moves with the expertise of a Steering committee, with and industry-style operation and with an intensive project management with internal expertise (lead development team). The project is already working on an Indoprofen analogue optimization with promising results, to increase potency, eliminate toxicity (Cox Inhibition), and improve BBB penetration.

The third session summarized the current resources for SMA Clinical Trials. Chin Wang from the Stanford University (USA) presented the summary of the document recently published on Standards of Care, followed by Jaqueline Jackson, who reviewed the International Spinal Muscular Atrophy Patient Registry established in USA at the Department of Medical and Molecular Genetics at Indiana University School of Medicine, established in 1986 at the request of the Families of SMA. The Registry is now guided by ICC. Family and clinical history information is collected from self report questionnaires and

medical records. Data from 1,640 patients are stored in the registry. Proposed research studies must have Institutional Review Board (IRB) approval and are subject to review by the International Spinal Muscular Atrophy Patient Registry Oversight Committee. The registry has fulfilled numerous requests for statistical data and assisted in the recruitment of hundreds of participants for research studies. The registry is also organized to provide DNA banking and research recruitment. Richard Finkel, Director of the Neuromuscular Program at the Children's Hospital of Philadelphia (USA) presented preliminary and interesting data on the parental survey that has been translated in several languages. More than 1000 responses have been collected through August 2007 (404 in USA, 120 from UK, 95 from Italy, 91 from Germany, 64 from France, and 21, 19 and 17 respectively from Canada, New Zealand/Australia and Spain. Responders are caregivers of children with SMA type 1 (36%), SMA type 2 (48%), SMA type 3 (16%). Data are collected on patient demographics and clinical features, parental burden, diagnostic testing, clinical care modalities (therapies, orthopedic, pulmonary, medications), clinical trial experience and opinion, and SMA resources. For example a frequent gastrointestinal complaint in children is constipation and it is seen more often than symptoms related to gastrointestinal reflux. The collection of data will be stopped for the end of 2007 followed by detailed statistical analysis. Susan Lannaccone began the discussion of SMA clinical research networks with a presentation of the AmSMART (American SMA Randomized Trial) network. This multicenter group (with 11 sites) has organized several trials: 1) Development of outcome measures for children with SMA ages 2-18 years, evaluated with GMFM (Gross Motor Function Measure), quantitative muscle testing (QMT), pulmonary function tests (PFTs), and quality of life tool (PedsQL Neuromuscular module). Except for GMFM all the other measures were stratified for age. AmSMART in 2003-2004 completed a Phase II trial using creatine (5 sites, primary outcome measures GMFM/QMT) showing reliability of outcome measures. In addition AmSMART conducted a Phase I/II trial in type 1 infants during 2004-2007, using TIMP, MUNE, PedQL, pharmacokinetics (PK) for riluzole, SMN mRNA and safety blood chemistry (enrolment was low and drop out high). The current work of AmSMART is to complete a pilot comparison of the QMT and the hand held myometer and the validity study for the PedsQL Neuromuscular Module. Darryl De Vivo described the PNCR (Pediatric Neuromuscular Clinical Research Network) for SMA Clinical Trials established in 2004. Supported by the SMA Foundation is completing a 3 year natural history study enrolling 100 patients by August 2007. Four sites from USA East Coast participate (Columbia, Harvard, UPenn, URochester) and the network has been dedicated to SMA clinical research and is poised to implement studies advancing treatment trials, biomarker studies, neuropathological studies, outcome measure research, and high quality clinical care. The natural history study has the aim to reassess the changing clinical profile, validate several outcome measures, and build a tissue culture repository that will be shared with other investigators who are involved in related translational initiatives. Innovative study designs are being explored as the network team prepares for phase 1, 2 and 3 clinical trials. An expanded HFMS (Hammermith functional Motor Scale) has been developed by the network team to facilitate clinical trials involving SMA types 2/3 (O'Hagen et al., 2007) and the changing natural history profile of SMA type 1 during the recent decade has been highlighted with changing of standards of care (Oskoui et al., 2007). Kathryn Swoboda summarized activities of Project Cure SMA that was launched in 2000 in collaboration with Families of SMA. Achievements include the validation of the modified HFMS for SMA, biomarker assays including a quantitative real time PCR assay for SMN mRNA, electrophysiological measures of motor nerve function (MUNE, CMAP), and measures of nutritional status, lean body mass status and bone density. The Project Cure SMA has 6 sites and is completing the multicenter SMA CARN-VAL trial, a phase II double-blind placebo-controlled trial to assess safety and efficacy of combined regimen of carnitine and valproic acid in children with SMA. This year two other trials were launched :a) the VALIANT SMA TRIAL for a phase II double-blind placebo-controlled study of valproic acid in ambulatory patients and b) STOP SMA, an open label study of sodium phenylbutyrate targeted to presymptomatic patients. After the presentation of Enrico Bertini summarizing the efforts

and goals of the TREAT-NMD network, Michael Rose gave a general discussion on outcome measures and the plans by TREAT-NMD to set up a registry for outcome measures to facilitate harmonization and informed choice of outcome measures for neuromuscular disease trials and facilitates meta-analysis of randomized controlled trials. The good quality of information relies on reliability, validity and sensitivity of outcome measures. The TREAT-NMD Registry of Outcome Measures will encourage and facilitate the entry of data on outcome measures by the clinical trials community itself. The results of this effort will be made freely available as a web-based database. The database web site will also serve as a portal for information on all aspects of outcome measures for neuromuscular diseases trials. Finally Susan Iannaccone, the session coordinator, summarized current knowledge on the natural history of SMA. It is well known that the disease has onset after birth in most cases, after a disease-free period. In some patients, after the appearance of symptoms we observe a transitory improvement of strength, with a sort of biphasic behaviour. We have no markers at the moment to recognize with certainty when the acute phase begins, and when these events are still reversible.

The following 4th session was dedicated to the clinical trial design. The overview of the topic was given by Petra Kaufmann. We have no current drug treatment to effectively alter the underlying disease process. To match the recent advance in preclinical SMA research with positive human drug trials and overcome the bottleneck of low number of patients with a numerous number of drugs to test, we need to optimize clinical trials and consider several issues: 1) efficient Phase II trials designs (example futility studies, selection procedures, adaptive and seamless designs) ; 2) biomarkers and surrogate endpoints can improve the efficiency of early drug development; 3) reliable and sensitive clinical measures are needed for the success evaluation of novel SMA therapies; 4) adaptive designs can accelerate efficacy testing of new drugs; efficacy trials need to be blinded and placebo-controlled because historical controls may not be suitable; 5) web-based data management and trial communication systems can facilitate the availability of high quality data in multi-center trials; 6) recruitment can be facilitated by increasing the proportion of SMA patients enrolled in clinical trials through patient education and collaboration of a sufficiently large number of clinical trial sites with adequate geographic distribution. The inclusion criteria have to be wide enough to allow for timely recruitment; 7) the availability of high quality data facilitates clinical trial design. A data repository with placebo group data elements from completed trials can support the planning of future trials.

This presentation was followed by a presentation of the Industry perspectives on SMA Clinical Trials by Alfred Sandrock, Senior Vice President, Medical Research-Neurology at Biogen Idec, Inc in Cambridge, Mass, USA. After an introduction noting that research in Neurological disorders is considered a high risk area for obtaining results by the Industry, Dr. Sandrock said that the most important element for advancing in clinical trials is to obtain validated targets of the disease with good clinical proof of concept, by human genetics, human tissue studies, and well understood molecular pathophysiology. He spoke about a portfolio strategy, matching information on target validity with information on target *drugability*. It is important to consider adaptive designs for designing trials concerning continuous drug evaluation, and trying to obtain good and reliable biological markers and other surrogate endpoints that reflect the pathophysiology of the disease. Moreover biological markers have to be validated against the clinical outcome. It is recommend to perform small phase Ib and II studies in the targeted population prior to large efficacy trials obtaining some surrogate endpoints reflecting the biological status of the disease that can be turned into important measures for larger phase III trials. The first day was concluded by a very important speech of Robert Beal, President of the Cystic Fibrosis Foundation. Under his leadership the CF Foundation has been recognized for its innovative approaches to bring new therapies to CF patients, and the Foundation has been able to reach a general consensus on standards of care and outcome measures for clinical trials for CF patients.

The second day of the meeting was dedicated to topics related to drug regulatory requirement and drug pipeline discoveries. The regulatory requirements were summarized by Wilson Bryan, formerly of the FDA. Drug development usually begins with in vitro studies and non-clinical proof-of-concept animal studies. These nonclinical studies precede clinical trials which progress from Phase 1 safety studies through Phase 3 efficacy (and safety) studies. In order to guide the design of subsequent clinical trials, preclinical studies can assess varying dose levels of the study drug(s) as well as various routes (e.g., oral, intravenous, or intraventricular) and regimens (e.g., daily, weekly, or monthly) of administration. Preclinical studies should mimic, as closely as feasible, the planned disease state, as well as the proposed route and regimen for human administration. Phase 1 trials usually involve the initial introduction of an investigational new drug into humans. These trials usually have a small sample size (generally 20–80 subjects) and often use a sequential group, dose-escalation design, i.e., starting with a relatively low dose that is expected to be safe, with sequential escalation to higher doses. The primary goals are safety and pharmacokinetic assessments. Phase 1 trials can detect very common adverse events and laboratory abnormalities. Phase 2 trials, which are usually moderate in size (up to several hundred subjects), can be useful to define activity, find the optimal dose and regimen, assess the magnitude of any treatment effect, and evaluate potential efficacy endpoints for a subsequent Phase 3 trial. By virtue of being larger than the preceding Phase 1 trials, Phase 2 trials may provide safety information regarding less common adverse events that were not detectable in the smaller Phase 1 trial(s). The most common problem with Phase 2 trials is that they are not conducted. Sponsors often jump from Phase 1 to Phase 3, neglecting the opportunity to find the optimal dose, route, and regimen that may give the study drug the greatest opportunity for success. This approach often leads to Phase 3 trials that use a suboptimal dose, regimen, or study population, and are retrospectively regarded as oversized, expensive, and inefficient Phase 2 trials. The goal of Phase 3 trials is to provide substantial evidence of safety and efficacy. Phase 3 trials are usually large, including several hundred to several thousand subjects, and ideally have the ability to detect the association of the study drug with less common adverse events. The success of a Phase 3 trial depends on the activity of the drug and on the design and conduct of the trial. An endpoint is a specific outcome measure or event, at a specific timepoint in a clinical trial, using a specific analysis method. The choice of endpoints for a clinical trial should consider the characteristics (see below) of the candidate endpoints, the goals of the clinical trial (including the stage of drug development), and the roles the endpoints will play in the clinical trial. It is not recommended to use quality of life questionnaires as primary endpoints. The different concepts between valid and ideal endpoints were discussed in his presentation. A video presentation by Agnes St. Raymond of the EMEA discussed European regulations regarding pediatric and orphan drug development in the EU. The incentives for drug development in these areas are considerable.

This session was followed by a sequence of brief announcements on new compounds being evaluated for potential effectiveness in SMA: optimization of Indoprofen by Jill Heemskerk (NINDS, USA); use of Drosophila SMA model for a high throughput small molecule screen by Jon Tinsley (Summit, plc, UK); use of Caenorhabditis elegans for identification of novel SMA drug targets and therapeutics by Leo Liu (Cambria Biosciences); use of sodium phenylbutyrate analogues as potential treatments for SMA by Lou Barbato (Tikvah Therapeutics, USA); C5 substituted quinazolines drug discovery program by Mark Gurney (deCODE genetics, Inc, USA); identification of tetracycline compounds that correct defective SMN2 splicing, by Paul Higgins, (Paratek Pharmaceuticals, USA); TRO19622 with neuroprotective and regenerative properties is expected to delay disease progression in SMA patients by Rebecca Pruss (Trophos, France); brain-penetrant, isotype selective HDAC inhibitors as novel therapeutic agents for spinal muscular atrophy, by Zuomei Li (MethylGene, USA); innovative and integrated approach to identify compounds that modulate SMN protein expression at the post-transcriptional level by Sergey Paushkin, PTC Therapeutics, Inc, USA). This exciting session was followed by a panel discussion chaired by Darryl

De Vivo, on the evaluation of pre-clinical and clinical compounds with the participation of Frank Bennett, from Isis Pharmaceuticals (USA), John McCall, from the PharMac LLC company (USA), Paul McGonigle from PsychoGenics, Inc (USA), Thomas Meier, from Santhera Pharmaceuticals, Inc (Switzerland), Robert Pacifici, from CHDI, Inc (USA), and Charlotte Sumner from the John Hopkins University. The speakers agreed that the most important considerations for SMA drug development are strategies for preclinical testing that include more and better data from animal models (accelerate these studies) and the rapid development of consensus on primary outcome measures and surrogate outcome measures. The speakers agreed that a Clinical Research Organization (CRO) style approach to preclinical research can accelerate the research process and facilitate decisions regarding lead candidates.

The following topic of the second day was chaired by Leslie Morrison and summarized current knowledge on endpoints for SMA trials. Kristin Krosschell, working at the Northwestern University together with Susan Iannaccone (USA) summarized her experience on the validation and reliability of GMFM module for neuromuscular disorders, highlighting the need for functional outcome measures to be tested for inter-rater and intra-rater reliability, concurrent validity and discriminate validity. Her group has also collaborated to create and validate the recent Expanded HMFS that can cover the evaluation of SMA type 2 and 3 patients.

Kathryn Swoboda, from the University of Utah (USA) presented her experience with the electrophysiological endpoints, particularly CMAP and MUNE. She nicely demonstrated the utility of using MUNE in SMA type 1 children in a presymptomatic phase showing a catastrophic decline of motor units in the first 2 months after onset of symptoms. These data demonstrate that MUNE is an endpoint targeted to the pathophysiology of disease and she recommends MUNE for evaluating SMA type 1 children, while CMAP can be used in the more chronic forms of mild severity in SMA type 3 patients to monitor reinnervation.

Marion Main, the head physiotherapist at Hammersmith Hospital in London (UK) presented an overview on Type II/III-specific outcome measures, strength and walking, and discussed the pros and cons of each of these measures. She concluded that it is important to ensure that a range of reliable and validated outcome measures is available to develop the most appropriate tests for the age and functional level of the patients in specific trials.

Richard Finkel presented the development of a specific measure for patients with SMA type 1 and weak type 2. Validity and sensitivity tests are on the way to conclusion. Anita Simmonds, a world-renowned Pulmonary Physician in the clinical and academic Dept of Sleep & Breathing at the Royal Brompton Hospital in London (UK), summarized the minimum of the pulmonary assessments for clinical trials (FVC, Peak cough flow, spot SpO₂, overnight oximetry) and standard of care for patients. She highlighted the importance of standardization of routine pulmonary care: acute and chronic indications, non-invasive ventilation and cough assistance. Lynda Hynan, a biostatistician working together with Susan Iannaccone, presented the Peds-QL Neuromuscular Module for the development of a secondary outcome measure for SMA patients. Investigators are testing the validity and reliability of this measure by analyzing data from 320 patients with SMA.

The activity on finding a sensitive and valid biomarker/surrogate marker for SMA trials was presented by Louise Simard, from the University of Manitoba (Canada). A promising biomarker looking at the absolute measurement of mRNA in leucocytes will be published shortly by the group of Christina Brahe working at the Human Genetic Institute of the Catholic University in Rome (Italy).

Seward Rutkove, from the Harvard University Medical School (USA) summarized the preliminary and encouraging results obtained with a new methodology called Electrical Impedance Myography (EIM) showing that with an instrument able to measure the impedance, resistance and capacitance of muscle,

you can obtain information on the diseased muscle. The method is relatively of simple application to patients and is painless.

The last panel discussion was chaired by Kenneth Fischbeck and centered on resource allocation and funding priorities for advancing therapeutic developments in SMA. All the panel discussants agreed on the importance of creating a centralized infrastructure for clinical trials in USA, of the need to standardize SMA severity forms, to standardize measures and parameters, standardize the measure of muscle strength, creating multiple centers with a standardized network using a standardized template (monitoring trials, common data bases and recruitment methodology). They agreed that the field would benefit greatly from increased investment of resources in clinical trial infrastructure and proposed that optimal funding might appear as a 50% allocation towards support of basic sciences, at least 25% for developing pre-clinical studies and remaining 25% dedicated to multi-centre clinical research networks.

The meeting was really exciting, covering all the aspects of therapeutic development for SMA, from basic science, pre-clinical studies, and methodology of discovering new drugs, to trials design, standards of care for patients, and outcome measures that are available at the moment. All the stakeholders were present: FDA, Academia, Foundations, Patient support groups, Public health Institutions, Networks related to Spinal Muscular Atrophy, and Industry, and each shared perspectives on clinical drug development. Feedback from participants confirmed that the goals of the meeting were reached – everyone learned something fundamental and something new at this meeting. There was strong support for the work on development, standardization and harmonization efforts that are already underway by our organizations and great enthusiasm for moving forward quickly. It can be considered a hallmark in advancing methodology discussions for forthcoming clinical trials.

Finally the first Steering Committee Meeting was held in Frankfurt on October 5th 2007 to design and organize a trial for treatment of SMA. The sponsor for the trial design discussed in Frankfurt is TROPHOS, a small biopharmaceutical company dedicated to develop therapeutic strategies for degenerative diseases of the central nervous system. The Clinical Trial is proposing the drug TRO19622 for administration to patients affected by Spinal Muscular Atrophy. TROPHOS has shown interest for SMA and has already performed a preclinical research study on animal models and a 1b study for safety and pharmacokinetics. In this first meeting TROPHOS was seeking advice from TREAT-NMD to design a pivotal phase 2/3 trial for TRO19622.

The current status for clinical trials in SMA is that there are no guidelines from regulatory authorities for drug development in Spinal Muscular atrophy in Europe. The Steering Committee in Frankfurt was committed to decide on the Trial design and who to conduct the clinical trial.

The local organizer was Dr. Jan Kirschner representing A05 for implementation of the European Clinical Trials Co-ordination Centre (CTCC) (Rudolf Korinthenberg, Jan Kirschner, and Angela Stanescu). Other participants were Prof. Francesco Muntoni and Prof. Volker Straub for A06 (Network in Action: applying TREAT-NMD integrated tools), Prof. Enrico Bertini for WP06.2: Spinal Muscular Atrophy, Prof. Eugenio Mercuri for WP09.1 Select and elaborate assessment tools for neuromuscular patients and define outcome measures. This first meeting will be followed by teleconferences and further meetings in the forthcoming year 2008.

Analysis of TREAT-NMD impact in SMA

The ENMC meeting held in 2007 represents an important step towards harmonisation of activities aimed at developing clinical studies on SMA. The working group has highlighted a number of areas of interventions in all three aspects addressed: 1) outcome measures; 2) registries and 3) standard of care.

During this first year of activity we have made progress in achieving consensus in functional outcome measures for SMA type II and III, however validation has to be completed for some of the functional scales, including the hand-held myometer versus the QMT. In addition a functional outcome measure for SMA type 1 (CHOP-INTEND) will be completed and validated during the second year of the project. The close collaboration with the North American network of the ICC has been very useful for accelerating results in this area.

Concurrently, progress has been achieved also in the area of Standard of Care for SMA with the production of a consensus on a guideline for care of SMA patients, and also in creating the Registry. We have now obtained a general agreement on a common core of items for collecting information for a Registry for SMA patients, and we are thus ready for recruiting patients.

We have started discussing on the design of a first trial with TROPHOS, and this will be developed in the 2nd years of the project. In the mean time the French community will finish recruiting patients for the riluzole trial by the end of December 2007. The trial will have 2 years duration, and at the end of this study they will have results in using the MFM (Measure de fonction Motrice) in a RCT trial.

Conclusion

TREAT-NMD will be working in several areas to evaluate, improve and train centres in use of specific outcome measures:

1. Evaluation of myometry in extended range of muscle groups in SMA (discussion forum to be set up and moderated by Marion Main- WP09.1) and validation of the hand held myometry versus the QMT (Eugenio Mercuri WP9.1)
2. Assessment of activity monitoring as an outcome measure in SMA (discussion forum to be set up and moderated by Sonia Messina- WP09.1)
3. Develop an active working group to interact with the ICC outcome measures group (Eugenio Mercuri- WP09.1).
4. Explore plans to get European translations of neuromuscular module of PedsQOL (WP09.1)
5. Provide resources for teaching materials and exchange visits for evaluators via the education and training network in conjunction with the outcomes measures group (WP12.1 and WP12.2)
6. Application of systematic reviews for selection of the most efficient outcome measures to use in clinical trials (Michael Rose WP09.2)

In addition TREAT-NMD has made relevant progress in the dissemination of guidelines for Standards of Care in SMA with the pivotal activity of Thomas Sejersen (WP 10.1), and is engaged in the organization of a European Clinical trial with the coordination of Dr. Jan Kirschner representing A05 for implementation of the European Clinical Trials Co-ordination Centre (CTCC).

Collection of patients for the registry on SMA can now start after the agreement of a common core of information framework created by Hanns Lochmueller and Christophe Beroud (WP04.2).