

welcome

Welcome to the latest TREAT-NMD newsletter. This edition features a report on a meeting TREAT-NMD held with EMEA on outcome measures for SMA clinical trials, and news of the launch of the International SMA Patient Registry in Indiana.

As always, we hope you enjoy the newsletter and look forward to hearing your comments - write to info@treat-nmd.eu with anything you'd like to say. Feel free to forward this message to anybody you think might find it of interest, or invite them to sign up to receive the newsletter by visiting our website. Back-issues of this newsletter can be found on our website at <http://www.treat-nmd.eu/patients/news/ezine-archive/>

Best wishes,

Katie, Volker, Steve, Emma, Rachel and Samantha: the Newcastle TREAT-NMD team

at a glance...

[14-16 Nov 2008 Best Practice Meeting: molecular diagnostics of Duchenne and Becker muscular dystrophies](#)

[16-18 Nov 2008 Inherited Neuromuscular Diseases: Translation from Pathomechanisms to Therapies](#)

[06-09 Jan 2009 Workshop: The Multiple Faces of Lamins in Aging and Disease](#)

[02-04 Feb 2009 TREAT-NMD Governing Board and Science and Technology Advisory Council Meetings](#)



TREAT-NMD--EMEA workshop on clinical outcome measures in SMA signals collaborative approach to future clinical trials

TREAT-NMD, an EU-funded 'network of excellence' that aims to accelerate cutting-edge treatments for rare inherited neuromuscular diseases, announces a successful meeting on spinal muscular atrophy (SMA) outcome measures with the European Medicines Agency (EMA).



A TREAT-NMD-led workshop hosted at the offices of the EMA in London helped set the collaborative agenda for future trials in SMA. Participants included 50 representatives from the neuromuscular field, including healthcare professionals, scientists, patients and pharmaceutical industry representatives. EMA representatives included the chairs of the Medicines, Paediatric, Orphan Drug and Scientific Assessment committees. There was active participation from all parties. Input from the International Care Committee (ICC) for SMA ensured that there was global representation at the meeting, the outcomes of which will also be shared with the US Food and Drug Administration (FDA).

In a new development for the neuromuscular field, the workshop focused not on discussing product-specific issues but on establishing broader common ground between the regulatory authorities and those interested in running clinical trials in SMA. In order for trials to move through the approval process without delays, consensus between trial planners and regulators on endpoints and novel methodologies is essential.

The SMA community is working extensively together and the meeting demonstrated this close link as all present spoke with a united voice on the most appropriate outcome measures for particular clinical situations. The community was complimented on its proactive approach to regulatory topics, its organisation and its international teamwork in addressing clinical trial questions for SMA.

Reactions to the presentations and discussions were positive. Meeting outcomes included the following:

SMA Type I

Using time-to-event as a primary outcome measures seem reasonable. Continued development of secondary outcome measures and protocols suitable for this population is necessary.

SMA Type II (non-ambulant)

It is important to demonstrate internal consistency, clinical meaningfulness and responder profiles for the functional scales intended to be used. Secondary measures trending in the same direction will be of critical importance.

SMA Type III (ambulant)

The 6 minute walk test seems reasonable – but the clinical meaning of an improvement needs to be carefully described. Secondary measures will need to be further defined.

Across all patient types, quality of life and caregiver burden scales will be important. It is also important to educate the regulators about disease mechanism and disease phenotypes. The EMA and FDA are willing to work with the SMA community on biomarker qualification using the new guidance published June 30. EMA encourages the organisations to seek a Scientific Advice meeting on specific questions relating to SMA.

The EMA leadership expressed its appreciation for this type of organised, harmonised input from specialists in the field, which is something that is particularly valuable when addressing rare diseases such as SMA. This meeting was a key milestone in the process of developing consensus on outcome measures and endpoints and can be seen as the start of a longer dialogue on regulatory issues

relating not only to SMA but also to other rare neuromuscular disorders. A full meeting report is in preparation and will be available via the workshop organisers at www.treat-nmd.eu.

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Indiana SMA patient registry launches new website

The [International Spinal Muscular Atrophy Patient Registry](#), a US-based initiative that is working with TREAT-NMD to provide data to the TREAT-NMD Global SMA registry, has launched a new website that allows full online interaction.



The registry sponsors have released the following announcement:

Indianapolis, IN, October 15, 2008.

After many months of anticipation we are pleased to announce the unveiling of the new International Spinal Muscular Atrophy Patient Registry Website! The Website now allows individuals to participate in the Registry completely through on-line interaction including registering, completing questionnaires, learning about and signing up for new research study opportunities and completing annual information updates.

We are excited about the enormous improvement in the speed with which we will be able to communicate with both the research and family community and hope that you will take a moment to visit our new website. Please email any comments on the SMA Registry to: smareg@iupui.edu

This project is supported by the Patient Advisory Group of the International Coordinating Committee for SMA Clinical Trials which includes: Families of SMA, Fight SMA, Muscular Dystrophy Association, SMA Foundation, and other SMA advocacy groups.

About the Registry:

The International Spinal Muscular Atrophy Patient Registry (the Registry) was founded in 1986 at Indiana University. The Registry connects patients and families interested in participating in research and researchers interested in studying SMA. The Registry contains information from over 1,600 families and over 1,700 individuals with SMA from all over the world and continues to grow. The Registry has helped recruit participants for clinical trials and has provided data for important SMA research studies. The Registry helps centralize information on this rare genetic disease, provides families a way to learn about research studies and provides researchers a way to find research participants.

Individuals and families affected by SMA are invited to join the Registry. Participants are asked to complete questionnaires about the symptoms, treatment, medications, and other experiences with SMA.

Participant information is stored in a secure database. Researchers who are interested in studying SMA can request two types of data from the Registry, de-identified information and identifiable information. De-identified information does not contain any names or personal identifiers, and can be given to researchers without having to contact Registry families. Identifiable information includes information that can identify you and will never be released without getting your written permission to do so. Identifiable information includes data such as names and dates of birth. Some researchers may also request contact with families to obtain specific information or to request participation in a research study. In these instances, the Registry will contact each potential participant to ask if they are willing to share their identifiable information for a research project.

In 2008 the Registry joined TREAT-NMD (Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases) in a global collaboration to further the research goals of the neuromuscular disease community.

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New and updated Cochrane reviews

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New review - Calcium antagonists in Duchenne muscular dystrophy published October 2008



The review authors identified 5 randomised controlled trials of different calcium antagonists involving 196 participants in total. The trials were not sufficiently comparable to undertake a meta-analysis.

The review authors conclude:

'There is no evidence from RCTs for significant benefit from calcium antagonists in DMD. However, there is evidence of harmful cardiac side effects. There is a theoretical basis for use of calcium antagonists in DMD, due to a myoprotective effect in vitro, although there remains uncertainty because of the differing effects in vivo of calcium antagonists on intracellular calcium concentration. Any possible effect may be small, but could act synergistically with other modes of treatment. Further trials should avoid diltiazem and verapamil, because of their

effects on sinus node function and atrioventricular conduction and consider drugs such as amlodipine because of its possible cardioprotective effect and lack of association with sympathetic activation. They should be sufficiently powered to detect a difference in function (activity) and not just in muscle strength, and should specifically record cardiovascular parameters, such as conduction block and left ventricular function by use of ECG and echocardiography, both to detect specific side effects and to detect any cardioprotective effect. As any effect would be protective, this suggests that trials starting at a young age would show the greatest benefit. If a minor effect were shown, where clinical significance were uncertain, a combination trial with other drugs affecting outcome, such as steroids, could be considered.

Phillips MF, Quinlivan R. Calcium antagonists for Duchenne muscular dystrophy. Cochrane Database of Systematic Reviews 2008, Issue 4. <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004571/frame.html>

Updated review - Treatment for swallowing difficulties (dysphagia) in chronic muscle disease.

This review was first published in 2004. The authors re-ran searches of key databases to see if any new trials had been published and updated the results accordingly.

They concluded:

'There are no trials that have adequately evaluated different treatments in the management of dysphagia for chronic muscle disease. It is therefore not possible to decide on the most appropriate treatment for a given individual based on current evidence. However, observational studies do suggest that people with moderate or severe dysphagia secondary to oculopharyngeal muscular dystrophy do benefit from either cricopharyngeal myotomy or upper oesophageal dilatation. In the absence of comparative randomised trials it not possible to say which of these procedures is superior in terms of efficacy and safety, or if other interventions such as dietary manipulation and/or swallowing advice would be equally beneficial. A single observational study also suggests that enteral feeding via gastrostomy is beneficial in children with congenital myopathy. Dietary and swallowing advice alone did not appear to benefit this subject group. While there is clearly a need for well designed research into the most appropriate management of dysphagia for chronic muscle disease, there are a number of areas of uncertainty that should be addressed first such as the natural history of feeding difficulties in chronic muscle disease and the most appropriate method of assessing subjects with dysphagia before and after a given intervention'.

Hill M, Hughes T, Milford C. Treatment for swallowing difficulties (dysphagia) in chronic muscle disease. Cochrane Database of Systematic Reviews, Issue 4 2008. <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004303/frame.html>

Cochrane Neuromuscular Disease Group

The editorial base of the Cochrane Neuromuscular Disease Group has moved. We can now be contacted at:

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AVI BioPharma's Drug for Duchenne Muscular Dystrophy Recommended for Orphan Drug Status in EU and Receiving Provisional GTAC Approval for Clinical Trial in UK

AVI BioPharma, Inc, a developer of RNA-based drugs, announced that the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) adopted a positive opinion recommending orphan medicinal product designation for AVI-4658 to treat Duchenne muscular dystrophy (DMD). Additionally, the Company received notification from the Gene Therapy Advisory Committee (GTAC) in the UK granting provisional approval for the Company's planned clinical trial for systemic delivery of AVI-4658 to treat DMD. AVI expect to comply with the conditions required for final GTAC approval by the end of the year.



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