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TREAT-NMD newsletter no. 42
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welcome

Welcome to the latest TREAT-NMD newsletter. This edition features an update on the exciting development of the TREAT-NMD trial sites registry into a "network of patient care and clinical trial sites", plus a report on the development of models for predicting DMD progression, and a call for research proposals on the topic of nemaline myopathy.

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...

Sign up to the TREAT-NMD network of clinical trial and patient care sites

The TREAT-NMD trial sites registry is developing

The TREAT-NMD trial sites registry now has more than 100 trial sites registered worldwide. If you represent a clinical site that cares for neuromuscular patients or that has been involved in clinical trials, please consider signing up to the TREAT-NMD network of patient care and clinical trial sites. Here's why.

TREAT-NMD and trial-readiness

Clinical trials in certain neuromuscular conditions such as Duchenne muscular dystrophy are already starting to take place, and others are on the horizon. However, there are still many barriers to getting a trial in a rare disorder off the ground. To obtain a suitably sized patient cohort for a treatment perhaps targeting only a small subset of a patient population, trials often have to be multinational, multicentre studies, with all the added complexity this entails in terms of locating appropriate patients and taking into account differences in treatment and care standards that may potentially compromise the comparability of results. Lack of information about the location of suitable patients and about specialist clinical centres with the expertise to run a trial means that patient recruitment is a slow process, sometimes taking literally years to complete. All of this means that running a neuromuscular clinical trial is an expensive and time-consuming business, and not one that is very attractive to pharmaceutical companies.

TREAT-NMD aims to change all this by setting up the infrastructure that makes it much easier to find both the centres to conduct the trials and the patients to recruit into them. Together with the patient registries initiative, the network of trial sites that we are planning is a key part of this “trial-readiness” strategy.

A network of sites with neuromuscular expertise is not only valuable in terms of clinical trials, but also as a platform for disseminating best practice in patient care. TREAT-NMD has worked with international specialist groups such as the International Care Committee for Spinal Muscular Atrophy and the US Centres for Disease Control and Prevention to draw up consensus documents on standards of care. For the first time, there is real international agreement on the care that every patient with these conditions should receive. Most of the recommendations are not for expensive or hard-to-obtain treatments but rather for a unified and multidisciplinary approach to care that combines input from different fields (e.g. physiotherapy, cardiology, orthopaedics and nutrition) and represents the best practice that the best centres for neuromuscular care across the world are already close to achieving. By promoting these standards through centres of expertise, we can help ensure that all patients receive the best care for their condition.

To read more, visit http://www.treat-nmd.eu/userfiles/file/general/Join_the_TREAT-NMD_trial_sites_network.pdf

To register your clinical site, visit http://www.treat-nmd.eu/trialsites

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A Predictive Method for Assessing Treatment Effectiveness in Neuromuscular Disease Clinical Trials: II

A Predictive Method for Assessing Treatment Effectiveness in Neuromuscular Disease Clinical Trials: II
– by MW Munn

We have continued the research on development of predictive models for Duchenne Dystrophy progression first reported in TREAT-NMD newsletter #18, 5 October 2007. There we showed that strength loss and decay of muscle fibers could be modeled with relatively simple equations. That is, with some longitudinal data for a given patient, future progression could be predicted via models regressed to the data available. The objective is to reduce the number of patients and length of time required in clinical trials via application of predictable decay features of DMD.

Prior to reviewing this latest modeling, we suggest readers refer to the previous note at: http://www.treat-nmd.eu/userfiles/file/news/TREAT-NMD_Newsletter_No18.pdf

Since then, the model effort has expanded to include other types of data. In particular progression trajectories have been found for creatinine (Cr), creatine kinase (CK), absolute muscle mass, and a related quantity-the creatinine height index (CHI). The models have been baselined using data from the CIDD database of Duchenne dystrophy patient strength. In addition, we correlated that strength data to time sequenced progression of creatine kinase and creatinine height index. We determined that the creatinine height index is identical to the Beasley muscle fiber fraction (MFF) which we utilized in the October 2007 note.

Normal growth trajectories, e.g. height, weight, muscle mass…., are well known. Ours are completely analogous except that they represent disturbed growth trajectories for DMD and other dystrophies. CHI, for example, is referenced to such a standard “normal” trajectory.

Figure l shows a sample of progression trajectories for CIDD Patient 246. The right hand scale is muscle mass in kg. The left hand scale is for CHI = MFF, MRC, and CK normalized to unity at the peak. In this case, the patient’s growth was normal till about 3.5 years after conception. A precipitous rise in CK levels and decline in CHI begin at that point. Once data for CHI or MFF are known, one can fit an exponential decay curve (See the 5 Oct, 2007 note) to that and trace back to find when decay actually began. In this case independent measurements were available for CHI and MFF. It is evident that the two types of data agree with one another. In many cases decay onset is delayed as much as 10 years post-birth. Note the pubertal growth spurt which is evident in MRC and CHI data. It is important for researchers to be aware of this effect so that it does not confound possible improvements due to interventions. This patient never attained more than about 5.5 kg of muscle mass.

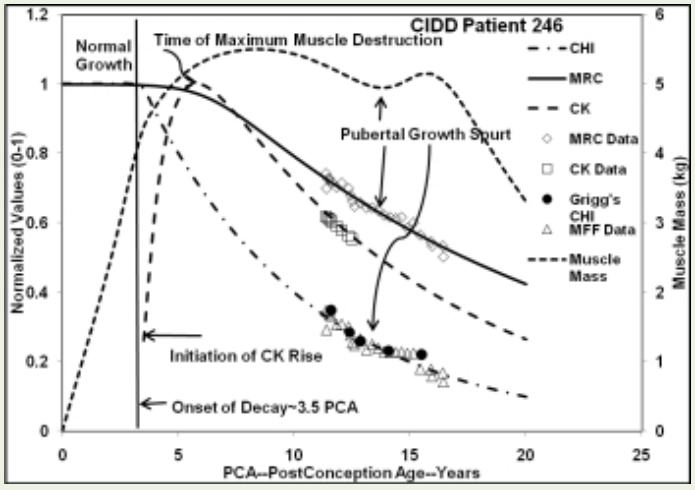

Figure 1. Typical Disturbed Growth Trajectories for Duchenne Dystrophy

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If you would like to participate in an e-mail discussion forum to help forward the work in this area, please email emma.heslop@treat-nmd.eu who will be happy to add you to the discussion list. We suggest that TREAT-NMD partners involved in assessment tools and outcome measures may be interested to participate as well as people from the wider neuromuscular community. You may also contact Dr. Munn directly at mwmunn44@azwildblue.com to discuss further or to obtain model equations for all these trajectories.

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Nemaline Myopathy Research Grant - Request for Proposals

A Foundation Building Strength (www.buildingstrength.org) is a public charity started in January 2008 to advance the science of treating myopathies while supporting the families of NM with information, resources and solutions. The charity has just announced its first request for proposals aimed at scientists who perform either basic science or clinical research related to Nemaline Myopathy. Work that is treatment related is of especial interest. Funding for an initial one year award period

will be for as much as $75,000, with the expectation of renewing funding for additional year(s) at an increased level. The deadline for applications is January 31st, 2009.

For further information please download the full RFP at http://www.buildingstrength.org/RFP_2008.pdf.

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Acceleron Initiates Phase 1 Clinical Trial for ACE-031 to Treat Diseases Involving Muscle Loss

Acceleron Initiates Phase 1 Clinical Trial for ACE-031 to Treat Diseases Involving Muscle Loss

CAMBRIDGE, Mass. – October 20, 2008 - Acceleron Pharma, Inc., a biopharmaceutical company developing novel therapeutics that modulate the growth of tissues including bone and muscle, today announced the initiation of a Phase 1 clinical study of ACE-031, its lead compound for treating diseases involving the loss of muscle mass and function. The Phase 1 trial is a randomized, placebo-controlled single-dose, dose-escalating study to evaluate the safety and pharmacokinetics of ACE-031. This clinical trial is the first-in-human study in the global development of ACE-031 and will be conducted in Canada.

“There is a tremendous unmet medical need to treat patients suffering from a wide array of diseases involving the loss of muscle strength and function. ACE-031 has the potential to be a very important new approach to treat these serious and life-threatening conditions,” said Matthew Sherman, M.D., Chief Medical Officer of Acceleron.

“The start of this ACE-031 Phase 1 trial is another important clinical milestone for Acceleron,” said John Knopf, Ph.D., Chief Executive Officer of Acceleron. “Last week we announced the start of a Phase 2 clinical trial in patients with multiple myeloma bone disease with ACE-011, the lead compound in our bone program, and today we are proud to announce the start of the first clinical trial for ACE-031, the lead compound in our muscle program. The Acceleron pipeline continues to mature and expand, and most notably, the company remains in a strong financial position to deliver on our clinical goals. We look forward to several data presentations at major medical meetings before the end of the year that will demonstrate the progress of our pipeline.”

Muscle is increasingly recognized as central to many biological processes and plays a major role in human health. The loss of muscle mass and strength is ultimately directly related to the cause of death in neuromuscular diseases such as muscular dystrophy and amyotrophic lateral sclerosis (ALS). Severe muscle loss in cancer leads to serious complications and a poor prognosis. Muscle loss is a natural consequence of aging, similar to bone loss, resulting in decreased muscle strength (frailty), reduced mobility and an increased risk of a fall and broken bones. In metabolic diseases, an imbalance of diet, energy utilization and skeletal muscle leads to poor metabolic function. By increasing muscle mass there is a corresponding decrease in fat mass and improvements in metabolic function.

About ACE-031

ACE-031, a soluble molecule based on the activin receptor type IIB (ActRIIB), is a biologic therapeutic that inhibits signaling through the ActRIIB receptor. By blocking signaling though ActRIIB, ACE-031 increases muscle mass and strength. In numerous and varied animal models of disease, ACE-031 significantly increased muscle mass and muscle strength. ACE-031 has shown encouraging preclinical results in animal models of age-related muscle loss, neuromuscular disease, cancer treatment-related muscle loss and metabolic diseases.

About Acceleron

Acceleron is a privately held biopharmaceutical company committed to discover, develop, manufacture and commercialize novel biotherapeutics that modulate the growth of bone, muscle, fat and the vasculature to treat musculoskeletal, metabolic and cancer-related diseases. Acceleron’s scientific approach takes advantage of its unique insight into the regenerative powers of the Growth and Differentiation Factor (GDF) family of proteins. ACE-011, a novel bone forming compound, is the Company’s lead compound and is being developed to reverse bone loss in diseases such as cancer-related bone loss in a strategic alliance with the multinational biopharmaceutical company Celgene Corporation. ACE-031, a novel muscle building compound, is being developed to increase muscle mass and strength. In addition, the company is advancing through preclinical development product candidates that control angiogenesis and inhibit fat accumulation. Acceleron utilizes proven biotherapeutic technologies and capitalizes on the company’s internal Good Manufacturing Practice (GMP) manufacturing capability to rapidly and efficiently advance its therapeutic programs. The investors in Acceleron are Advanced Technology Ventures, Bessemer Ventures, Flagship Ventures, MPM BioEquities, OrbiMed Advisors, Polaris Ventures, QVT Financial, Sutter Hill Ventures and Venrock. For more information, visit www.acceleronpharma.com.

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