

Executive Summary: SMA Summit of Drug Development

The SMA Summit on Drug Development was held on September 28th and 29th 2007 in Bethesda, MD. The event was hosted by the Patient Advisory Group (PAG) of the International Coordinating Committee for SMA clinical trials (ICC), which includes Families of SMA, Fight SMA, MDA, and the SMA Foundation. The ICC is a volunteer committee composed of stakeholders from the Spinal Muscular Atrophy (SMA) community who work together to address the opportunities and challenges associated with effectively organizing clinical trials of new treatments for SMA. The ICC consists of six working groups: the Patient Advisory Group, the Outcomes Measures Group, the Protocol Design Group, the Standard of Care Group, the Biomarkers Group, and the Registry / Database Group.

The SMA Summit on Drug Development was convened in anticipation of major drug efficacy trials for SMA in order to foster dialogue between stakeholders, to identify barriers to successful drug development, and to develop strategies to address these gaps in the pathway to regulatory approval. Attendees included representatives from the biotech and pharmaceutical industries, international advocacy groups, clinicians, and government. Participants discussed the currently available clinical infrastructure, the existing SMA therapeutic pipeline, and the regulatory requirements for evaluating new SMA treatments.

In order to bring SMA clinical trials to fruition in the most expedient and successful manner, the Summit Steering Committee has generated a summary of key points emerging from the conference discussion, including action items for the SMA community. These will be discussed in the meeting summary below in order of importance as deemed by the steering committee.

Clinical Trial Endpoints

Of utmost significance is the need to identify and consolidate clinical endpoints, including decisions on what *core data* on safety and effectiveness endpoints should be uniformly collected at all clinical trials (taking into account the drugs and their potential target populations) for future cross comparison purposes. Due to the wide spectrum of clinical presentation in SMA, it is difficult to pinpoint an ideal clinical endpoint that can be utilized with every patient at diverse sites across the US and Europe. Thus, the current debate has focused on perfecting functional scales and determining their reliability over time and between sites.

However the Summit clearly highlighted that, for purposes of drug approval, regulatory agencies (FDA, EMEA) desire study endpoints that reflect clinical benefit to patients. For this, it is a good idea to examine endpoints that have been established in trials of previously approved drugs for neuromuscular or other related diseases. In the case of Type I and Type III SMA patients, the use of clinical parameters such as concomitant morbidities (e.g. incidence / severity / duration of significant respiratory events such as hypoxia, pneumonia, etc.) and measures such as walk tests may be considered clinically relevant and meaningful endpoints. A drug's clinical benefit can be directly demonstrated with these types of outcome measures, in conjunction with the functional scales used extensively in previous clinical trials involving the Type II and non-ambulatory Type III patients. It is essential to establish a convincing association between the improvements measured by these functional scales and the clinically meaningful benefit to patients, if these scales are to be used alone as primary endpoints in pivotal drug trials. **Several actions items arose during the summit to help overcome this barrier, including the following: (1) to convene a meeting between parents and clinical investigators to define what parameters are clinically meaningful to patients and families; (2) to initiate discussions using the ICC forum among clinical investigators to determine what changes in functional scales reflect clinically meaningful benefit (not just statistical benefit); and (3) to hold meetings with the FDA/EMEA to receive formal feedback on the use of acceptable endpoints prior to future drug trials.**

Industry Needs in SMA Drug Development

Drug Pipeline Development

The steering committee was impressed by the growth of the SMA drug pipeline and the increased participation of the biotech industry. Nine companies gave presentations on their SMA drug programs, and 13 helped financially sponsor this event. While the SMA drug pipeline is developing at a healthy pace, the drug development process is very high risk. Therefore, the SMA drug pipeline needs continued growth (similar to what has been done in CF), and ideally the number of novel programs should at least double over the next three to five years. **Clearly early investment by industry is taking place for SMA discovery programs (as evidenced by the fact that 8 of the 9 pipeline presentations were at the preclinical stage and only one focused on clinical development), but one of the goals of the SMA community should be to actively encourage industry investment into the later and more expensive stages of clinical development by finding ways to de-risk the process of SMA drug development.** Financial support from both the NIH (for the SMA Project) and Advocacy Groups continues to be the critical incentive for pre-clinical SMA translational research, but this source of funding is limited. Finally, because industry will be at the forefront of obtaining FDA approval for new SMA drugs, it is hoped that industry will begin to take a more active leadership role in the community and in the development of clinical trial infrastructure, a major goal of the Summit.

Efficacy Biomarkers for Go / No-go Decision Points in Drug Development

When choosing which projects to move into clinical development, drug companies value measurements of desired bioactivity (for instance increased SMN levels in accessible cell types) in early stage human trials. This allows determination of whether a drug is doing what it was designed to do at the molecular level in patients before launching into more expensive efficacy trials. Therefore the development of reliable biomarkers in patients, including SMN expression, is key to encouraging industry interest in SMA drug development and clinical trials. Additional types of biomarkers should also be considered. For example biomarkers using electrophysiological techniques to assess denervation, particularly in type I patients who enroll in trials prior to the acute stage of denervation could be very illuminating (with the advent of newborn screening, these patients will be enrolled routinely within 5 years). In addition from the industry perspective, it is equally critical to understand why a particular therapy fails either in clinical trials or in pre-clinical animal studies and biomarkers will be particularly helpful in this regard. Depending on the class of drug, different measurements of drug activity will be most appropriate and enabling to early stage clinical trials. These could include measurements of SMN levels, of denervation, of HDAC inhibition, and of snRNP assembly. **In summary, while the regulatory agencies may not accept biomarkers that have not been proven to predict clinical benefit as primary endpoints in the drug approval process, companies will have a difficult time moving forward without markers of molecular efficacy for internal assessments.** Therefore, this issue has particular important in attracting drug companies to invest in SMA clinical development.

Evaluation of Pre-Clinical Compounds in the SMA Drug Pipeline

The panel discussion on evaluating pre-clinical and clinical compounds was also very informative. **Although companies will internally decide whether to move propriety compounds into the clinic, as a community it would be desirable to develop a general consensus on what minimal findings -- be it effects in animal models (survival, weight gain, increased motor function, increased SMN expression), effects in SMA cellular models (increased SMN expression, increased neuronal survival, the ability to form stable synapses in vitro), or biomarker measurements in animal or open-label Phase I studies -- will be sufficient to comfortably move forward with clinical trials in SMA patients for each different class of drugs (HDAC inhibitors, neuroprotectants, SMN enhancers, etc).** While this set of criteria will be the most clear-cut for SMN enhancing drugs, it is just as critical to develop guidelines for other drug classes as well.

Clinical Trial Infrastructure

Centralized Natural History and Placebo Database

One of the top priorities in the area of clinical trial infrastructure is establishing a consensus on how clinical trial data will be collected, stored, retrieved, and transmitted. Within this domain, harmonizing natural history data collection and central storage of this data is the most pressing issue. This needs to include agreement on the functional scales to be used and common fields for data collection. In most cases, industry will maintain and utilize their own databases for drug trials, but a database of de-identified natural history or placebo data from each of the clinical networks in the US would be an extremely valuable resource for clinical researchers as well as for industry partners.

Patient Recruitment for SMA Clinical Trials

Increasing awareness and patient participation in the International SMA Patient Registry at Indiana University is key for successful clinical trials (<http://www.iupui.edu/~medgen/hereditary/sma.html>). Currently this resource is open to all in the SMA community, and finding the means to fund the registry and increase its enrollment must be a priority for the entire community. In addition, the affected questionnaire, which is being updated currently, should have the active participation of SMA trialists in order to reflect the needs of the clinical trial community. **Having a fully functioning patient database will be a big advantage and incentive to drug companies conducting SMA clinical trials.**

Clinical Care during SMA Trials

With the recent publication of the Consensus Statement for Standard of Care of SMA (generated by the ICC Standard of Care Committee) the SMA community is poised to use this opportunity to educate all SMA stakeholder groups about the many considerations in caring for patients with SMA, including those clinicians who are less familiar with SMA. **This document provides an opportunity for outreach to referring physicians with two specific goals: 1. Identifying new patients for clinical trial recruitment 2. Reducing variability of care for patients enrolled in trials. Advocates, families, and clinicians all need to help with the effort to educate and communicate the care choices for SMA.**

Conclusions and Future Goals

As this meeting demonstrated, our community is currently cohesive and actively working together to advance SMA drug development. Currently, three major SMA Clinical Networks are established in the US. Dialogues are ongoing among all the networks in the US and in Europe on reaching consensus regarding the methods with which to conduct SMA trials, particularly pivotal trials for novel drugs attempting to obtain regulatory approval. Through the ICC, representatives of all major groups meet monthly. In addition, representatives from the major trial groups in both the US and Europe form the basis of the five main ICC working groups: the Outcomes Measures Group, the Protocol Design Group, the Standard of Care Group, the Biomarker Group, and the Registry / Database Group. During the course of the Summit, the SMA stakeholders voiced a number of key points, outlined in this summary, and the ICC forum can be used to effectively to address these issues. **As a community, we are dedicated to building on our success in integrating and consolidating the manner in which clinical trials are conducted, including in the areas of consistent endpoint selection, patient recruitment, implementation of clinical care standards, data collection harmonization, operational experience in conducting trials, and the development of shared and accessible natural history databases.** Achieving these goals will be critical for a coherent network with adequate sites to emerge for the large pivotal trials required for SMA drug approval and commercial clinical investment. Funding with dedicated NIH, Advocacy Group, and Industry support will be key to our success.

By Jill Jarecki, PhD (Chair PAG of the ICC; Families of SMA) on the behalf of Steering Committee for the SMA Summit on Drug Development.

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