INTERNATIONAL
PROGRESSIVE MS ALLIANCE
CONNECT TO END PROGRESSIVE MS

Progressive MS Alliance Industry Forum Meeting
February 16 and 17, 2017
Washington DC, USA

Executive Summary

The International Progressive MS Alliance (Alliance) continues to bring the world together to seek solutions for those living with progressive multiple sclerosis. During the meeting of Industry Forum members, Industry and Biotech Representatives, Alliance Managing Members and the Scientific Steering Committee, FDA Regulatory Representatives and Alliance-funded Collaborative Network Lead Investigators, the Alliance facilitated review of key areas across the MS research landscape, conducted ongoing discussions towards enabling the development of therapies for progressive MS, and worked towards identifying the future Alliance research strategy – building upon our progress. This third annual Industry Forum meeting was held February 16 – 17, 2017 in Washington D.C., USA.

This meeting ensures all necessary stakeholders that change the world for people with progressive MS, come together, and with a focus on identifying the key opportunities and challenges that must be addressed. Presentations, followed by provoking discussions, stimulated conversation and encouraged collaboration towards meeting the following objectives.

Meeting objectives:

- Solidify and refine Industry Forum's role, commitment and shared objectives within the work of the Alliance.
- Advance discussions and develop actions on the key focus areas of the Industry Forum – paths to enable therapeutic development; data sharing; and pathophysiology.
- Identify opportunities and synergies to strengthen the Collaborative Networks.
- Engage regulatory authorities and gather insight towards developing solutions for people living with progressive MS.
- Provide advice to the Alliance Scientific Steering Committee.

Key outcomes:

- Strong atmosphere of collaboration with a recognition that working together will lead to more effective and timely solutions.
- Clear synergies between the Scientific Steering Committee and Industry Representatives towards the future strategies of the Alliance.
- Strong engagement with FDA Regulatory Representatives with confirmation of their willingness to collaborate.
- Agreement that the MS community must continue to seek solutions to speed up clinical trial processes and de-risk development of therapies for progressive MS.
- The progressive MS landscape is changing, progress is being made and the community must acknowledge this evolution and shift priorities accordingly.
- There is a need for mechanisms that better share clinical data among the community.

The following provides a detailed summary of the meeting and key considerations for the future Alliance scientific strategy development.

Detailed Meeting Summary *(Reference meeting slides for additional details)*

The Alliance Industry Forum provides a venue for industry to provide advice to the Alliance Scientific Steering Committee (SSC). The February 2017 meeting engaged, further committed and mobilized industry in the future direction of the Progressive MS Alliance strategy. This meeting provided the venue and time to facilitate robust discussions among key stakeholders on four key areas:

1. Collaborative data sharing
2. Path to enable therapeutic development
3. Phase III clinical trials – future direction
4. Pathophysiology

Presentation sessions were shared in these four topic areas, followed by group discussions.

Thursday, February 16

Session 1: Collaborative Data Sharing

- Session Co-Chairs: Bruno Musch and Xavier Montalban
- Presenters: Jan Hillert, Rick Rudick, Gary Cutter

Jan Hillert opened this first session of the meeting, which aimed to provide an overview of the current state of data sharing in MS. Hillert shared a synopsis of the Big Data Sharing initiative, noting the lessons learned and future goals. He noted this network provides opportunity to collaborate and use the pooled data which consists of four national registries and MS Base. Long term real world data is needed from the MS registries – emphasized the importance of collaborating to take care of established resources and sustain such a resource. Jan Hillert also presented a summary of the recommendations arising from the Patient Registries Workshop held on October 28th 2016. (See full report: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500221618.pdf).

Rick Rudick then presented the value of capturing "real world evidence" for MS research and the ability to address existing gaps through studying real world data. Real world data has many benefits – capturing comparative effectiveness information, closing disease knowledge gaps, healthcare data for future drug development and evidence-based health policy– among others. However, there are challenges in generating this data in MS including limited standardization and use of technology, relatively small cohorts, privacy and data security barriers and a healthcare system that is set-up to provide service not knowledge. An overview of the MS PATHS initiative, sponsored by Biogen, bringing together 10 healthcare institutions in US and EU to pilot a Learning Health System for MS (which merges Research data with Healthcare practice data), was shared with meeting attendees. Rudick shared lessons learned from this pilot project and the process of beginning to merge patient care with research.

Gary Cutter closed this session by describing statistical approaches to the analysis of real world data and the associated limitations. The strengths of real world databases and observational studies include real patient population data and actual treatments in practice. In contrast, the limitations often include unknown confounding variables and variable standards of treatments and the biases of patients and clinicians. Real world data can answer many questions. However, when considering big databases it is important to remember the results are only as good as the original source.

Key Messages from Session 1

- Are the current data standards in the MS space adequate?
  - General standards need to be identified and agreed upon by the community. Details of the specific information the community seeks to collect needs to be identified.
  - Look into technology solutions that may be leveraged to help capture relevant data and standardize these processes.
- Does the current data that exists today allow us to answer key research questions? Or, is there a need to collect new data? What are the key questions we need to answer?
  - This is dependent on first identifying the current missing data.
  - With the existing challenges of defining progression in a precise way, it may remain challenging to focus on progressive MS alone, without also looking at relapsing MS.
  - Essential to collect the right data from the right population over an extending period of time. Databases in MS are complicated – treatments change over time, the most advance patients are on several therapies over the course of their lifetime, dropout rate is extensive.

Session 2: Path to Enable Future Therapeutic Development

- Session Co-Chairs: Bill Carroll and David Leppert
- Presenters: Bob Fox, Doug Arnold, Gordon Xu, Peter Fuhr, Richard Nicholas

Session two focused on the most encouraging pathways towards future therapeutics development in progressive MS. To begin this session, Bob Fox shared an overview of the current landscape of phase II biomarkers. Although we've seen much success in relapsing MS drug development, the lack of a phase II proof of concept outcome measure in progressive MS, remains a major challenge. Whole brain atrophy remains the most popular biomarker currently, with alternatives being imaging, biofluids and electrophysiology. Fox shared the potentials and the unknowns of these various alternative biomarkers, while noting that all have the potential to demonstrate utility towards "de-risking" phase III trials.

Doug Arnold then provided an overview of the Collaborative Network titled, 'Identifying a biomarker of disability progression for use in clinical trials'. Arnold's team is pioneering the development of MRI markers that signal disease progression, and adapting these for use in early phase II clinical trials of progressive MS treatments. The hypothesis being that disease progression is detectable through MRI prior to its clinical expression, and a novel biomarker will enable more efficient clinical trials as a primary outcome measure and predictor of progression. The aims of this project include gathering existing large database sets with MRI and clinical follow-up; develop robust image processing techniques; statistical evaluation; and a deep learning for discovery of new MRI makers – the goal being to de-risk development.

Junqian (Gordon) Xu, Peter Fuhr and Richard Nicholas shared presentations focused on additional novel techniques to phase II biomarkers. Xu presented work being conducted in the area of cervical spinal cord MRI. Fuhr then shared multimodal evoked potentials as biomarkers for progressive MS. Nicholas closed the session with a presentation on PET as a potential surrogate marker. Although a number of experimental and practical challenges remain with utilizing PET, a more standardized approach to utilizing PET is gaining traction. Although all these methods need to be validated via

exploratory trials, all also have the potential to demonstrate utility towards "de-risking" phase III trials.

Key Messages from Session 2

- What are regulatory expectations for bio-marker qualification? How do these differ for Phase II and Phase III?
  - There is a formal process to qualify biomarkers with the FDA
  - Phase II biomarker efficacy is more of sponsor question than a regulatory concern. This is typically used to determine whether to move forward with a program and de-risk for phase III
  - Clinical meaningful outcomes that address benefits to patients are preferred.
  - Regulatory stressed that drugs are indicated for a disease, not for a mechanism.
- Therapy with the potential to delay progression would be valuable to community
- Consider measuring subclinical disease to save brain tissue.
- Identify opportunities that exist to identify early predictors – this would be a benefit to patients.

Session 3: Phase III Clinical Trials - Future Direction

- Session Co-Chairs: Mike Panzara and Bob Fox
- Presenters: Xavier Montalban, Ludwig Kappos, Raj Kapoor, Volker Knappertz

Session three was dedicated to the future direction of phase III clinical trials. Xavier Montalban began the session with an overview of the current progressive MS treatment landscape and challenges. Montalban shared a history of the challenges we've seen in progressive MS trials, as well as the current landscape which includes some successful studies currently underway. Presented key learnings to date including inflammation as a frequent phenomenon in progressive patients, neuroprotective plus anti-inflammatory strategies seem to be necessary; recruitment in phase 3 trials is increasingly difficult. A biomarker for phase II trials is needed along with new and innovative trial designs.

Ludwig Kappos then presented a perspective on clinical trial designs in progressive MS. Questions remain regarding the appropriate measures in progressive MS – inflammation, myelin damage, axonal and neuronal damage. We also continue to see challenges in defining the target population. History may propose that trials should be designed to target "progressive forms of MS" rather than separated by primary progressive or secondary progressive.

Raj Kapoor and Volker Knappertz then led presentations on innovative approaches to trial design. Kapoor provided a look at adaptive designs to phase III trial designs including modifications such as eligibility, sample size, randomization procedure, duration, endpoints, and dropping or adding arms. Advantages to adaptive approaches include multiple arms and hypotheses, ability to drop non-

responders and the possibility of smaller/shorter/rolling programs. Disadvantages include the potential for introducing bias, increasing type one error rate, and overestimating size of any positive effect. Knappertz presented the group with trial approaches that combined biology with technology, evoking the idea and possibility to leverage smartphones, wearable devices and heath sensors to quantify health and disease outcomes in trials. Patients are looking for a change and are motivated now, more than ever to find answers to their personal health and care. Looking to make our trials "smart" by leveraging technology may also generate more insights and lessen excess time.

Key Messages from Session 3

- What lessons have we learned from other neurodegenerative diseases?
  - Enrich trials with patients that are more likely to progress.
  - Understanding the pathophysiology is key to successful outcomes. Essential to continue to work towards understanding the pathophysiology of progressive MS.
- Defining the progressive population (Lublin classification)
  - Neurologists will embrace this both in practice and in trials.
  - Patients do not feel strongly about a classification.
  - From a regulatory perspective the indication must be supported in a patient population. The agency will move with the state of the science.
- Technology is encouraged by FDA. However, leveraging technology must be used to solve problems; not used in search of a problem
- What would it take for the agency to start considering a combined population?
  - Each endpoint must assess something clinically meaningful. Composite endpoints are perfectly reasonable, but each component should be meaningful.

Friday, February 17

Session 4: Pathophysiology

- Session Co-Chairs: Alan Jacobs and Marco Salvetti
- Presenters: Marco Salvetti, Francisco Quintana, Gianvito Martino, Fernando Dangond, Julie DeMartino

The final session of the meeting focused on pathophysiology, an essential focus area of the Industry Forum and across the field of MS, as there is still much unknown regarding the pathophysiology of this disease. Marco Salvetti opened the session with an overview of pathophysiology in MS, asking the question 'What does a complex pathophysiology imply for the development of new treatments?". Salvetti shared some of the recent advancements, not only in the field of progressive MS but also looking across trials in Huntingdons, Nasu Hakola and Alexander disease.

Francisco Qunitana provided an overview the Collaborative Network he leads, titled 'Development of a drug discovery pipeline for progressive MS'. The project is identifying drug candidates that may be effective therapies for progressive MS. The hypothesis is targeting the CNS innate immune response will provide efficacious therapeutic approaches for progressive MS. The aims of this network include evaluation of drugs targeting sphingolipid metabolism as therapeutics for PMS; unbiased screening for drugs that modify CNS innate immunity; and investigation of the molecular mechanisms that control CNS innate immunity in MS. This screening cascade can be used to evaluate compounds developed in other projects and to identify compounds acting on candidate therapeutic targets identified on other projects.

Lead investigator, Gianvito Martino, shared the Collaborative Network titled 'Bioinformatics and cell reprogramming to develop an in vitro platform to discover new drugs for progressive multiple sclerosis (BRAVEinMS)'. The BRAVEinMS team is working to design and conduct a comprehensive and well-characterized pharmacological screening to ultimately identify a handful of lead compounds with therapeutic potential for PMS. The opportunities to engage industry through the Alliance Industry Forum are many and include generating a database where hits and/or compounds already analyzed (and tested) in pre-clinical or clinical MS are listed; evaluate common target pathways of selected hits and compounds to explore 'novel' pathogenic mechanisms; create a common repository of iPSCs from MS patients; and create an Alliance specific target discovery platform for further research into MS.

Fernando Dangond and Julie DeMartino explored the application of tools of computation and analysis to capture and interpret biological data. They presented an example of the application of bioinformatics in identifying targets in the development of novel designer targeted drugs such as imatinib mesylate (Gleevec), which interferes with the abnormal protein made in chronic myeloid leukemia. The ability to identify and target specific genetic markers by using bioinformatic tools facilitated the discovery of this drug. Exploring abnormal regulatory networks underlying Progressive MS pathophysiology may makes sense, the challenge is identifying the specific focus. Key lessons were shared in target selection, including urging the Alliance to forge a path towards the public sharing on negative clinical trial outcomes.

Key Messages from Session 4

- The Alliance may collaborate with industry and regulators in developing ways towards faster and more standardized screening – a more efficient and reproducible approach is needed.
- We need to connect the linkages between clinical and target discovery (Clintrials.gov and ex novo design of experimental medicine trials could be a potential source).
- There may be untapped value in IP literature.
- Biology models that reflect progression over time would be very useful. Challenges with this approach include with blood samples and the need for a large patient population.