Amyloidosis Public-Private Partnership With FDA Working on Multi-Domain Endpoints, Federated Data Analytics Approach

The Amyloidosis Forum, a public-private partnership including FDA and the Amyloidosis Research Consortium, has been working on multi-domain endpoints to facilitate clinical trials in the rare disease where drug development faces the challenge of a group of conditions characterized by different manifestations.

Cardiologist Preston Dunnmon, formerly an FDA clinical team leader, noted at an FDA Rare Disease Day meeting March 4 that the Amyloidosis Forum was "born from the combination of profound medical need, fascinating science, and the frustrated energy of multiple stakeholders." Since the end of last year, Dunnmon has been a VP of R&D data sciences at Janssen.

"There was the frustration of the patients with no approved drugs to treat these debilitating and often fatal conditions," Dunnmon said. "There was the frustration of regulators – and at the time it was me – who by mandate of law must have substantial evidence of both safety and effectiveness in order to approve drugs. There was the frustration of academics whose voices on subjects like biomarkers seemed to go unheard." The discussion of the amyloidosis partnership was part of the broader theme of the meeting on FDA's interactions with patients to support rare disease drug development.

The Amyloidosis Forum has included senior FDA staff from all involved divisions, including cardiology, nephrology, neurology, gastroenterology, hematology, and clinical outcomes assessment and statistics, as well as people from the UK's MHRA. CDER's current liaison to the Amyloidosis Forum Division of Cardiology and Nephrology Medical Officer Rosalyn Adigun.

The Amyloidosis Research Consortium was founded in 2015 and held one of the first externally-led patient focused drug development meetings. *(See our April 20, 2017 note, FDA Neurology Division Is Early Adopter In Externally-Led Patient-Feedback Meetings; New Model Ramping Up In 2017.)*

The specific work described for the amyloidosis collaboration illustrates a theme of the FDA/industry PDUFA VII agreement. FDA is committing in that agreement to "conduct up to three public workshops by the end of FY 2027 to discuss various topics relevant to endpoint development for rare diseases, such as the use of multidomain analysis methods." *(See our August 25, 2021 note, PDUFA VII Rare Disease Pilot Will Offer Extensive Support On Novel Endpoints In Exchange For Public Disclosure; Opportunities To Participate Will Also Be Rare.)*

In 2018, ARC held a "research strategy roundtable convening leading experts across all stakeholder groups to identify and align around the most important priorities across the amyloidosis research and development continuum," Executive Director of Clinical Research Kristen Hsu said. She noted that Dunnmon attended the meeting in his FDA role at the time, and that it led to the Amyloidosis Forum partnership, which includes work with 23 regulators, 55 clinician experts and 16 industry representatives.

Hsu said that the group plans to expand the focus of the Amyloidosis Forum beyond light chain amyloid to include TTR (transthyretin) amyloidosis and other rare types of amyloidosis later this year.

The effort to identify a multi-domain endpoint addresses the impact of amyloidosis on several different affected organs.

"The goal behind this type of endpoint is to better take into account amyloidosis patients' unique experience with this disease and hopefully speed up drug development," Hsu said. "A multi-domain endpoint could allow for enrollment of a broader patient population, earlier detection of treatment effects, and shorter follow-up with clinical trials. We've set about this by bringing the community together to learn from other rare diseases. Establishing an organ-specific working group, with a goal of identifying and prioritizing potential components to a multi-domain endpoint.

"We're now working through the process of evaluating those components through collaborations and analysis of data collected across the community," Hsu said.

Amyloidosis Forum Statistics Working Group Chair James Signorovitch highlighted the challenge of finding endpoints for AL (light chain) amyloidosis. A "first hurdle" with AL was "developing a surrogate biomarker," Signorovitch said. "For this goal we really needed data from multiple randomized controlled trials to be able to establish a surrogate."

The forum is also focused on using "federated data analytics" to attempt to access data on potential biomarkers from multiple different clinical trials conducted by sponsors who cannot directly share data themselves.

Signorovitch suggested that there is now enough clinical trial data on amyloidosis to validate a surrogate – but that data is not readily accessible.

"In particular, the data is spread out across the world in different data silos," Signorovitch said. "Some of these are in academic centers in Europe and China, others of these data are held by different pharmaceutical manufacturers. And for a number of very understandable reasons, these data cannot be pooled all in one place any time soon for analyses. Even when investigators would wish to be able to share these data and pool them, there are significant issues around patient privacy at the national level that can really prevent data sharing." The Amyloidosis Forum is using federated analytics to learn from data without "requiring that the data leave institutions across international borders."

The federated approach allows different groups to provide analytics "that each center can run themselves, and then we can assemble all the results centrally later without sharing that patient-level data. So this allows us to learn from the data faster and reach important conclusions for drug development sooner."

Over the past four years, the first signs of successes have emerged from drug development efforts for several conditions related to amyloidosis, with four drug approvals during that period: Alnylam's *Onpattro* (patisiran) in August 2018; Akcea/Ionis' *Tegsedi* (inotersen) in October 2018; Pfizer's *Vyndaqel* (tafamidis) in May 2019; and Janssen's *Darzalex Faspro* (daratumumab) in January 2021.

Another marker on the prospects for development in the field and FDA flexibility on clinical trial design is coming up in the middle of April with the approaching PDUFA action date (April 14) for Alnylam's vutrisiran. The initial Phase 3 study (Helios-A) on that drug includes a comparison to a control group from a separate study (Apollo) on patisiran.