The Amyloidosis Forum: A Public-Private Partnership to Advance Drug Development in AL Amyloidosis

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BACKGROUND

- Immunoglobulin light chain (AL) Amyloidosis is a rare, multi-systemic disease with two components: an underlying plasma cell dyscrasia and the resulting organ dysfunction caused by light chain deposition.
- Currently, there are no FDA approved treatments for AL Amyloidosis and a substantial unmet need for patients.
- The Amyloidosis Research Consortium (ARC) was founded in 2015. ARC's mission is dedicated to changing the way research is being done and focuses on what will have the greatest impact on improving the lives of patients.
- ARC is accelerating the development of advanced diagnostic tools and effective new treatments for systemic amyloidosis through collaborations across industry, academia and regulatory agencies.
- In 2019, a Public Private Partnership (PPP) was formed between ARC and the US Food and Drug Administration's Center for Drug Evaluation & Research (CDER).

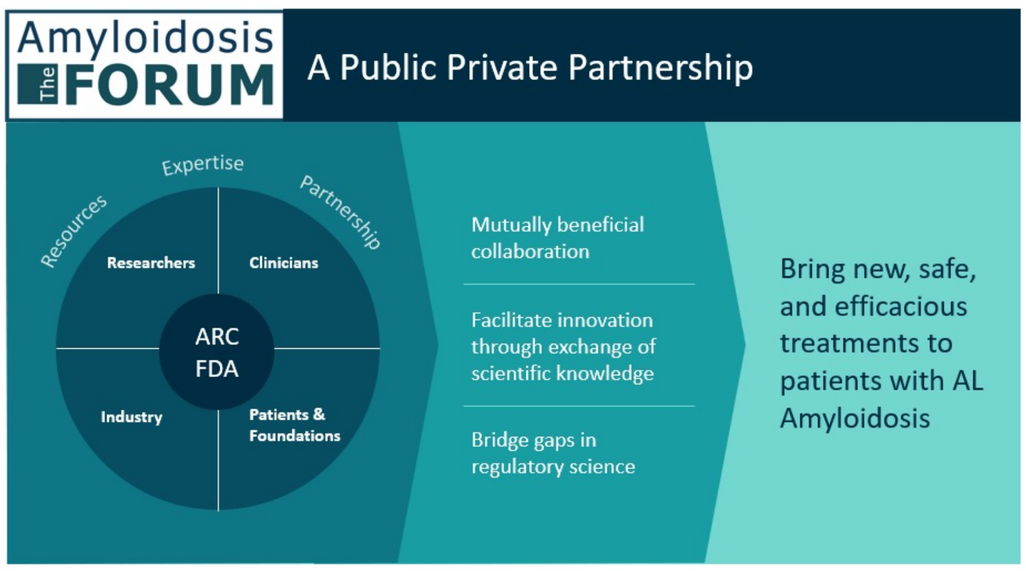
What is a Public Private Partnership (PPP)?

A PPP or a consortium is a collaborative group managed by a convening or coordinating organization involving multiple stakeholder organizations including at least one non-profit or 501(c)(3) organization (e.g., academia, government, or foundation) and at least one for-profit organization (e.g., pharmaceutical, biotechnology, or medical device company). A PPP may involve multiple committees and working groups.

OBJECTIVE

- The goal of this PPP is to identify and bridge the scientific gaps in drug discovery and development for the treatment of AL Amyloidosis.
- The PPP seeks to leverage expertise and resources of all stakeholders (academia, industry, patients, and regulatory agencies) for the conduct of mutually beneficial scientific activities in the precompetitive domain to support bringing new, safe and efficacious therapies to patients with AL Amyloidosis.
- This PPP could potentially serve as a model for other rare diseases.

Figure 1. The Amyloidosis Forum Structure and Goals



METHODS

- In the first of a series of meetings at the FDA, the inaugural Amyloidosis Forum focused on achieving a broad understanding of AL Amyloidosis.
- A cross-stakeholder panel was convened, comprised of a team of multi-disciplinary physicians from medical institutions in the US and Europe, health outcomes professionals, representatives from ARC, representatives from pharmaceutical companies, and representatives from 6 divisions of the FDA (the Divisions of Hematologic Malignancies 2; Gastroenterology and Inborn Errors Products; Cardiovascular and Renal Products; Neurology Products, Clinical Outcomes Assessments and the Rare Diseases Program).
- The panel presented and discussed overview of AL Amyloidosis, including its pathobiology, clinical features, epidemiology, staging systems; burden of illness and the degree to which the disease and various treatment options impact patient quality of life; the FDA's regulatory perspectives in the context of rare diseases and clinical outcomes assessments; and the challenges in designing clinical trials for AL Amyloidosis.
- Three patients shared their journeys and highlighted the varying degree to which AL Amyloidosis is a multi-systemic disease posing myriad challenges.

RESULTS

Community Engagement

- The Inaugural Amyloidosis Forum was held on 12 November 2019 as a public meeting on the FDA White Oaks campus.
- The meeting was attended in person by a range of physicians, representatives from the FDA, representatives from pharmaceutical companies, patients, and their caregivers and family members.

Hematologic Response vs. Organ Response

- Hematological characteristics, staging systems, and response criteria were examined with clear consensus that a "deep response" to plasma cell clone-directed treatments was critical to overall survival and organ response.
- Emphasis was placed on the heterogeneous clinical phenotypes of AL Amyloidosis, including impacts on the cardiovascular, renal, neurological, and gastrointestinal systems which all substantially impact morbidity, but lack validated organ response criteria acceptable to both the FDA and the amyloid community in most systems.

Table 1: Meeting Attendees

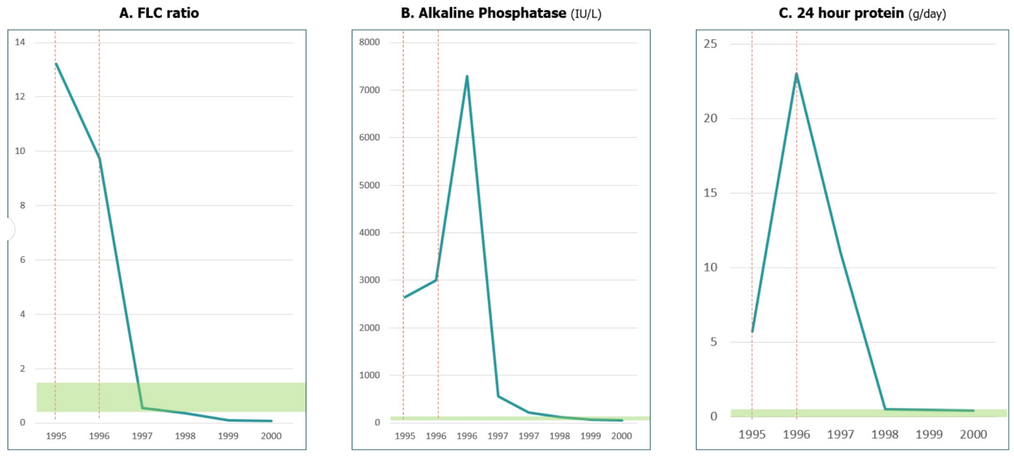
	Attendees, N	(%)
Panelists	**n=24**	
Academia	11	(46%)
FDA	7	(29%)
Industry	3	(13%)
Health Outcomes	2	(8%)
ARC	1	(4%)
Meeting Attendees	**n=139**	
FDA	21	(15%)
ARC	7	(5%)
Physicians	18	(13%)
Industry	35	(25%)
Patients	23	(17%)
Family/Caregivers	13	(9%)
Other	22	(16%)
Webcast Viewers	**n=151**	

To learn more about the Amyloidosis Forum or to view a recording of the meeting please visit: www.amyloidosisforum.org

Patient Perspectives: A Tale of Two Diseases

- Patients provided important perspectives on the path to diagnosis, challenges of rigorous treatment, and the burden of disease.
- Patient perspectives highlighted the challenges of treating two different diseases: the underlying plasma cell dyscrasia and the resulting organ system disfunction.
- While each patient's experience was unique, commonality could be seen in that AL Amyloidosis and current treatment options both significantly and broadly impact health-related quality of life (HRQOL).
- The impact on HRQOL during treatment is primarily due to rigorous therapeutic regimens that are very difficult for patients to tolerate.

Figure 2: A Patient's Journey: Before, During and After Autologous Stem Cell transplant (aSCT)



Burden of Illness- Health Related Quality of Life

- The panel reviewed a conceptual model built for AL Amyloidosis, depicting that the impact of disease on HRQOL ranges from physical function impairment to emotional distress.
- The panel focused on use of the SF-36 (or SF-12) to 1) compare impact of disease relative to a general population and to other conditions with known morbidity; 2) quantify the benefit of new treatments from the patient's point of view; 3) examine changes in HRQOL over time; and 4) predict other outcomes such as job loss, work productivity, and healthcare expenditures.
- The importance of patient reported outcomes (PROs) as one type of clinical outcomes assessment in AL Amyloidosis trials was discussed. According to the FDA, PROs for rare diseases are typically tailored to the concept of interest, and the use of general HRQOL instruments are generally considered secondary/supportive.
- The challenges of the temporal disconnect between a drug exhibiting activity, the associated worsening of symptoms due to treatment side-effects, and the timing of detecting clinically meaningful improvements in HRQOL for the AL Amyloidosis population were also discussed.

FDA Perspectives

- FDA representatives discussed regulatory perspectives regarding the demonstration of clinical benefits of investigational therapies in the context of a rare disease with multi-systemic manifestations.
- Understanding the natural history of the various manifestations of AL Amyloidosis, the development of appropriate multi-domain responder indices (for the plasma cell dyscrasia and organ system effects), and the application of robust statistical methodologies for analysis of the responder indices were highlighted as important enablers of future treatment development efforts.
- The panel also highlighted the potential importance of well-designed health-related quality of life instruments, reliable quantification metrics of system organ effects and the potential of advanced imaging technologies, and survival prediction models.

Challenges in Trial Design: Endpoints

- Treatments for AL Amyloidosis generally either target the cause (i.e. clonal plasma cell production of excess serum free light chains) or the downstream effects (i.e. amyloid deposition, organ damage, and progressive organ failure).
- Trial endpoints must consider the drug's intended mechanism of action and must also demonstrate clinical benefit.
- Chemotherapy, autologous stem cell transplantation (aSCT), immunotherapy and other investigational agents that target the underlying clonal disorder should assess the hematological response and the difference between involved/uninvolved free light chain (dFLC) as appropriate endpoints.
- Therapeutic approaches targeting amyloid deposition and organ function should assess organ response (heart, kidney, liver, gut, or other organs) with organ-relevant objective functional and/or quality of life measures.
- Currently, only anti-plasma cell therapies have demonstrated clinical benefit and there remains much to learn about assessment of "anti-amyloid" treatments.

Figure 3: Patient Hematologic Responses vs Organ Responses

Response criteria	Clear and novel endpoints
Hematologic response **Response to underlying clonal disorder** • Complete response • Very good partial response • Partial response • No response	**Clear Endpoints** • Overall survival • Hematological response • Progression to dialysis
Organ response **Reduction in amyloid deposits and improvement in organ function** • Cardiac response • Renal response • Liver • Gut response • Other organ response	**Incorporate Novel Endpoints** • Improved cardiac biomarkers • Improved markers of organ function • Structural cardiac changes • Improvement on imaging • Quality of life measures

CONCLUSIONS

- The inaugural Amyloidosis Forum resulted in clear consensus on several areas for further discussion and exploration:
  - Natural history studies, the role of imaging to assess burden of disease and response to therapy, and importance of disease-specific patient reported outcome measures;
  - Additional topics for future discussion included novel trial designs and endpoints.
- The 2nd Amyloidosis Forum will be held on **05 May 2020** at the FDA White Oak Campus
  - Proposed topics include natural history data and development of hierarchical or multimodal endpoints

XVII International Symposium on Amyloidosis; 01 – 05 March 2020; Tarragona SPAIN