Welcome and Introduction

Presenter

Katherine Greene, Forum for Collaborative Research

Time	Topic	Presenters
2:15	**Session I: Project Overview**	
2:15	Welcome and Introduction	Katherine Greene, Forum for Collaborative Research
14:25	Regulatory Perspective Updates and Remarks	Lara Dimick-Santos, U.S. Food and Drug Administration Elmer Schabel, European Medicines Agency Irene Tebbs, U.S. Food and Drug Administration Daniel Krainak, U.S. Food and Drug Administration
3:10	**Session II: Cirrhosis**	
3:10	Compensated Cirrhosis & Clinically Meaningful Benefit	Naga Chalasani, Indiana University School of Medicine
3:25	Cirrhosis Endpoints: ACLF and MELD	Rajiv Jalan, University College London
3:40	Decompensated Cirrhosis: Experience from U.S. Pivotal and Phase 2B Trials	Arun Sanyal, Virginia Commonwealth University
3:55	Group Discussion	
4:35	**Break**	

Time	Topic	Presenters
5:00	**Session III: U.S. Payer and Care Delivery Perspectives**	
5:00	Lessons Learned in HIV and HCV	Carl Schmid, *The AIDS Institute*
5:10	Medicare Coverage: A Review	Louis Jacques, ADVI
5:40	Panel Discussion	Louis Jacques, ADVI Heather Patton, Kaiser Permanente Hal Yee, LA County Department of Health Services
6:30	**Session IV: Working Groups**	
6:30	Case Definitions Working Group	Sophie Megnien, Genfit Brent Tetri, Saint Louis University
6:40	Pediatric Issues Working Group	Miriam Vos, Emory University
6:50	Placebo Arm Data Working Group	Eric Lefebvre, Allergan
7:00	Standard of Care Working Group	Manal Abdelmalek, Duke University Sven Francque, Antwerp University Hospital
7:10	**Session V: Wrap-Up**	
7:15	**Adjourn / Evening Reception**	

Liver Forum Steering Committee

Co-Chairs
- Arun Sanyal, *VCU*
- David Shapiro, *Intercept*

Regulatory
- Lara Dimick, *FDA/CDER/DGIEP*
- Ruby Mehta, *FDA/CDER/DGIEP*
- Chris Leptak, *FDA/CDER/OND*
- Elmer Schabel, *EMA/BfArM*

Patient Advocates
- William Baldyga *University Illinois at Chicago*
- Donna Cryer, *Global Liver Institute*

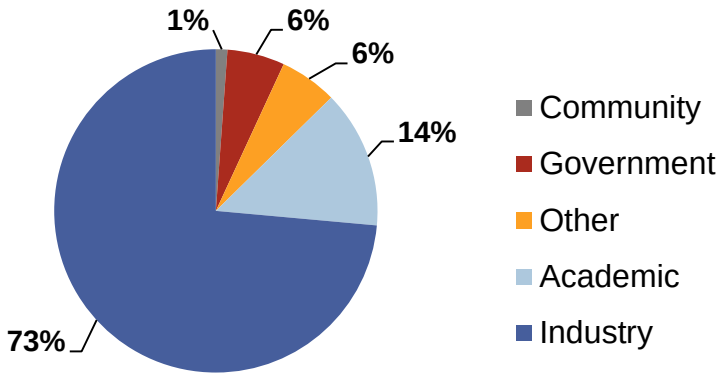
Academia
- Scott Friedman, *Mount Sinai*
- Miriam Vos, *Emory University*
- Vlad Ratziu, *Hôpital Pitié Salpêtrière*
- Detlef Schuppan, *Mainz University*
- Stephen Harrison, *Pinnacle Clinical Research*
- Laurent Castera, Hôpital Beaujon
- Tom Hemming Karlsen, *Oslo University*

Industry
- Gary Burgess, *Vectura Limited*
- Laurent Fischer, *Allergan*
- Sophie Megnien, *Genfit*
- Rob Myers, *Gilead*

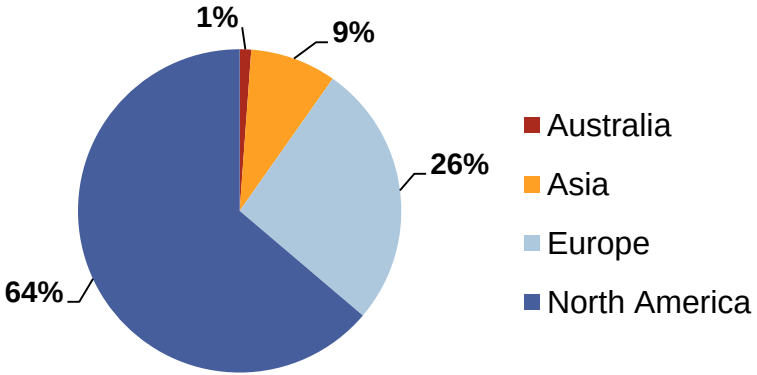
Liver Forum 6

- Liver Forum 6, Amsterdam, The Netherlands
  - 174 attendees: 124 in-person, 47 remote

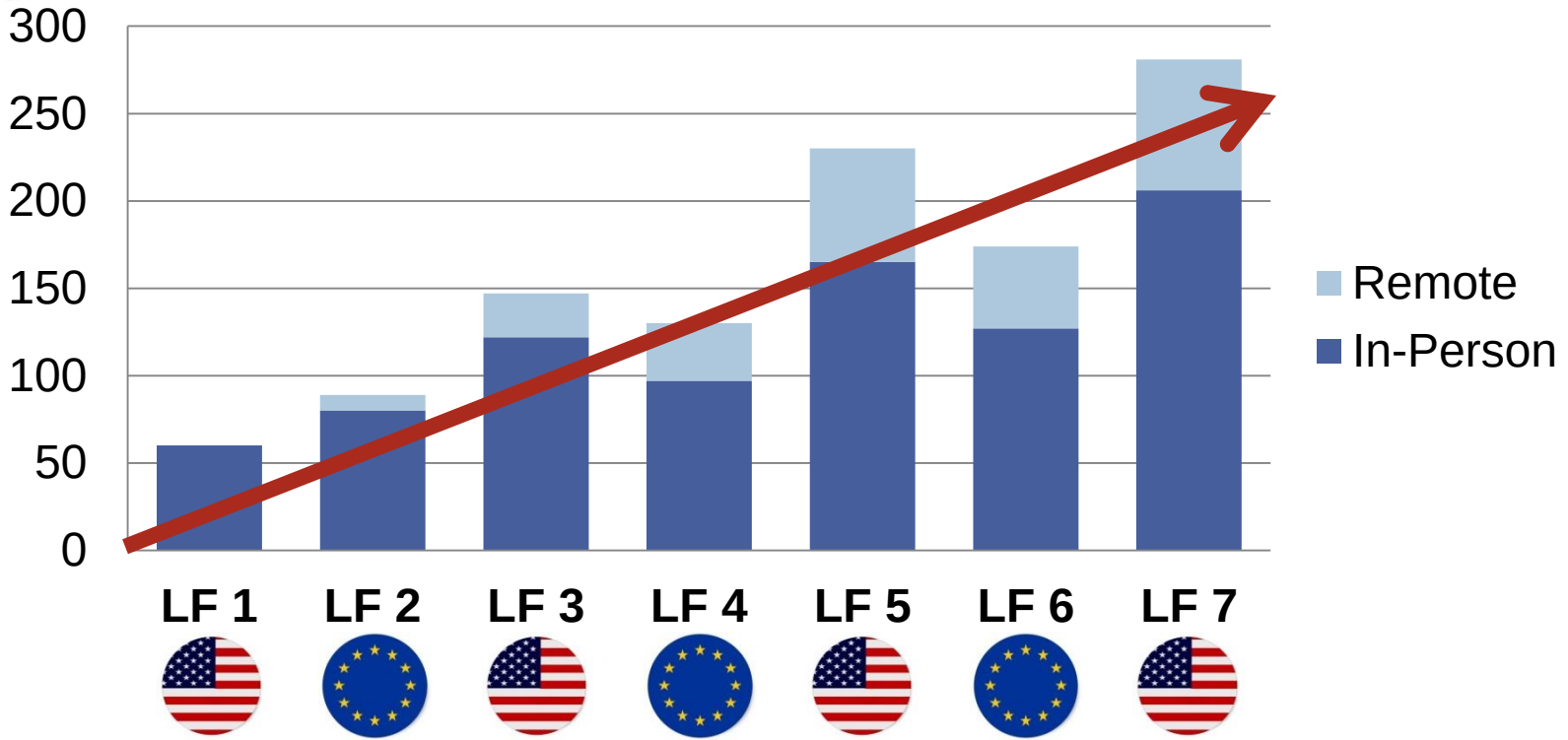
Attendance by Organization



Attendance by Region



Participation Over Time



Reminders

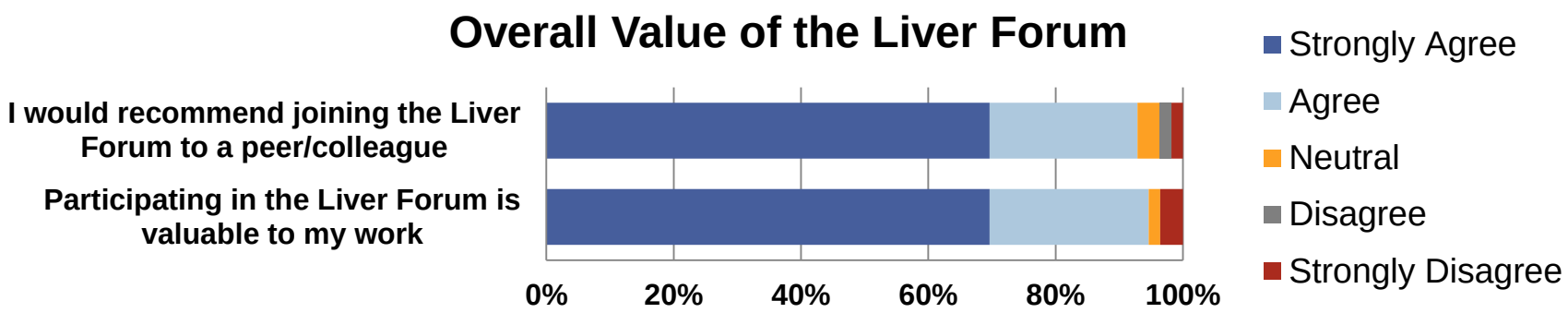
- **Attendance Rules:**
  - Meetings are closed/ not public
  - 2 individuals in-person per company
  - No marketing/commercial staff in-person
  - **No investors**

Reminders

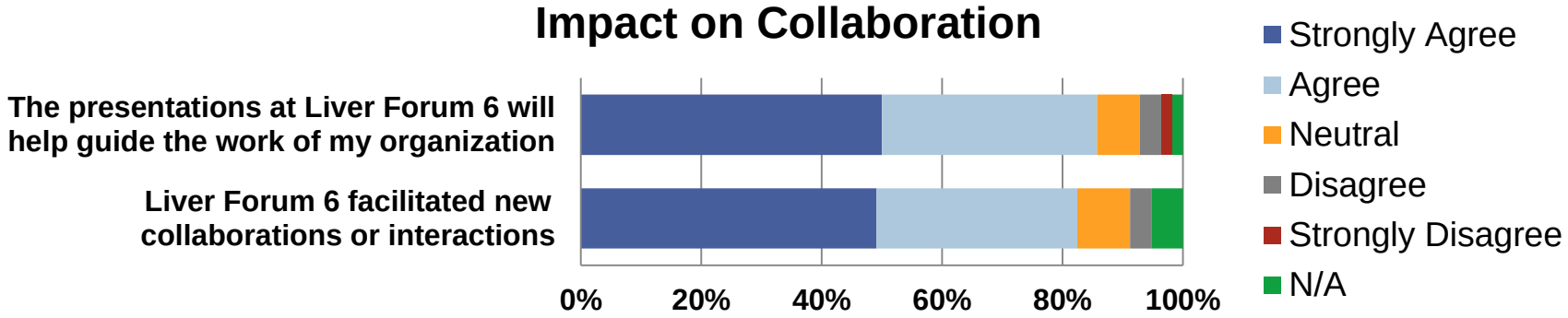
- **Membership**:
  - We restrict participation to experts with the necessary scientific knowledge from organizations or entities with a clear commitment to advancing the diagnostic and therapeutic field of NASH and liver fibrosis.
  - We recruit project members meeting the scientific expertise criteria from the various stakeholder groups.
  - We expect all meeting participants to engage in discussion, and discourage the presence of passive observers.

Evaluation Highlights

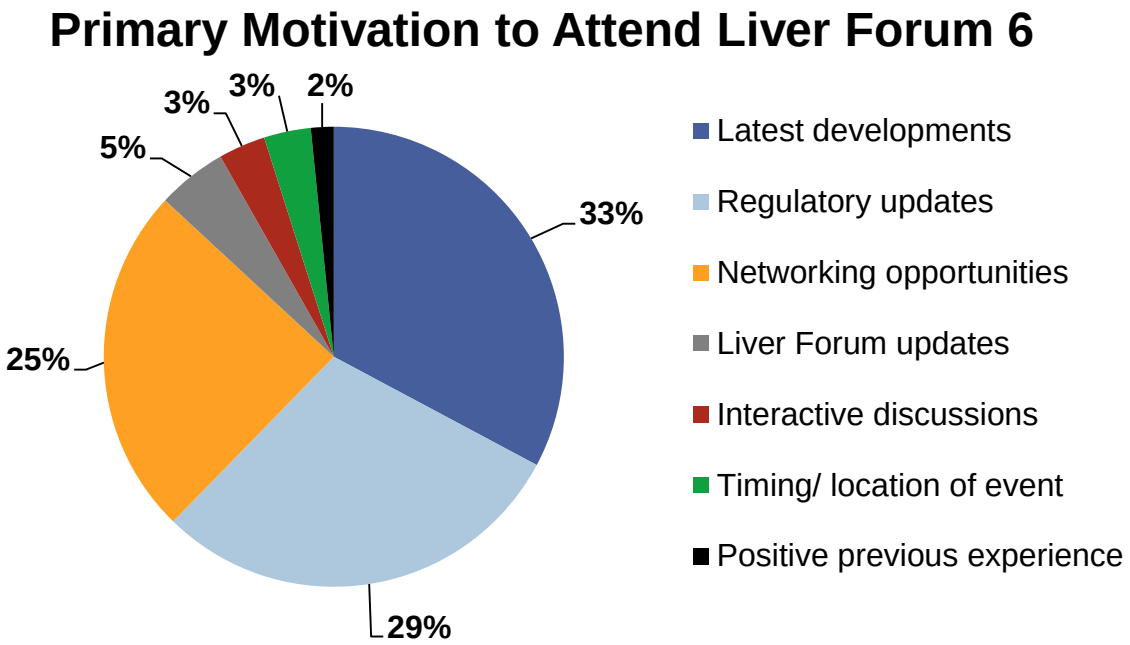
Overall Value of the Liver Forum



Impact on Collaboration



Evaluation Highlights



Liver Forum 6→7

- **Placebo Arm Data Working Group**
- **Standard of Care Working Group**
- **2017 NASH Biomarkers Workshop**
- **Statistics Workshops**
  - **Adaptive Enrichment (link)**
  - **Causal Inference (link)**

Liver Forum 6→7

- **Outreach to Regulatory Agencies**
- **Launch of PSC Forum**
  - **Separate Forum**
  - **Jessica Weber: jweber@forumresearch.org**
- **Manuscript Submissions & Publications**

Manuscript Updates

- **Accepted:**
  - Baseline parameters in clinical trials for nonalcoholic steatohepatitis: Recommendations from the Liver Forum
  - Case definitions for inclusion and analysis of endpoints in clinical trials for NASH
- **In Preparation / Under Review:**
  - Defining improvement in NAFLD for treatment trial endpoints: Recommendations from the Liver Forum
  - Regulatory considerations for clinical trials in pediatric nonalcoholic fatty liver disease




Baseline Parameters

Baseline Parameters in Clinical Trials for Nonalcoholic Steatohepatitis: Recommendations From the Liver Forum

Yuval Patel, Joanne Imperial, Andrew Muir, Quentin Anstee, David DeBrota, Lara Dimick-Santos, Claudia Filozof, Ruby Mehta, Arun Sanyal, Elmer Schabel, Brent Neuschwander-Tetri, and Veronica Miller, *on behalf of the Liver Forum's Data Standardization Working Group*

Gastroenterology. 2017;153(3), 621-625.e7
https://doi.org/10.1053/j.gastro.2017.07.024

COMMENTARIES

Baseline Parameters in Clinical Trials for Nonalcoholic Steatohepatitis: Recommendations From the Liver Forum

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent form of chronic liver disease in the world, affecting an estimated 25% of the global adult population.[1] Liver-related morbidity and mortality attributed to NAFLD are substantial, and fibrosis seems to be the strongest independent predictor of outcome.[2] Fibrosis develops among patients with the nonalcoholic steatohepatitis (NASH) phenotype, making it the biologically relevant focus of drug development.[1] Currently, there are no approved therapies to treat NASH, although many drugs are in development. Multiple challenges exist in drug development for NASH, including the inconsistent measurement of baseline parameters, which makes interpretation and comparison of trial data difficult. As drug development proceeds, there is a need to standardize data collected as well as aspects of study design (eg, stratification factors) to make datasets comparable and assist the regulatory agencies' efforts to determine efficacy and safety.

To support efforts in NASH drug development, the Liver Forum first convened after the 2013 American Association for the Study of Liver Diseases and US Food and Drug Administration co-sponsored conference on clinical trial designs and endpoints in NASH.[4] The Liver Forum is an independent collaborative drug development and regulatory science project focused on diagnostics and treatments for NASH based on the established model of the Forum for Collaborative HIV Research.[5] For this particular effort, the Liver Forum invited experts from stakeholder groups in academic medicine, regulatory agencies, the pharmaceutical and medical diagnostics industries, and patient advocacy organizations to develop consensus recommendations for standardized baseline parameters for NASH-related clinical trials.

Methods

A working group of the Liver Forum assessed the state of the science in clinical trials for NASH and made specific recommendations for the categories of data to include in eligibility determinations and baseline assessments. As a first step, we reviewed recent and current placebo-controlled randomized clinical studies registered at clinicaltrials.gov for general patterns of study entry criteria and baseline data collection. For the purposes of this report, we defined broad categories of parameters to recommend for baseline data collection, including demographics and genetics; diet and activity including alcohol, tobacco, and substance use; concomitant medications; laboratory tests; and histology. Further recommendations regarding comorbidities and surgical history, anthropometrics, specialized biomarkers, imaging and other noninvasive diagnostics, and quality of life are available in the Supplementary Materials. For each category, specific variables were assessed for their relevancy with regard to therapeutic goal (ie, whether the drug target is liver fibrosis versus steatohepatitis), phase of trial, and whether the measure is essential, ideal, or should be considered. We further developed consensus strategy for stratified randomization for use in NASH-related trials (Supplementary Materials).

Results

Demographics and Genetics

Age, sex, and ethnicity are known risk modifiers for NAFLD and NASH (Supplementary Table 1). These factors are essential to capture as baseline parameters regardless of trial phase or mechanism of action. Epidemiologic studies suggest that NAFLD is more prevalent in males compared with females, which may be owing to different factors including insulin resistance, visceral adiposity, lifestyle, and sex hormones.[6] Age is a risk factor for NAFLD fibrosis progression and of comorbid conditions such as cardiovascular disease.[7] Aging effects on the liver include decreased volume, blood flow, and mitochondrial dysfunction. Race and ethnicity, often surrogates for unknown genetic polymorphisms, are considered important parameters to capture for proof-of-concept (POC) and phase II trials, and are recommended as essential components for phase III trials. These are typically self-reported given the current lack of better tools to characterize the underlying genetic factors that might contribute to NASH pathogenesis. The prevalence of NAFLD has been shown to vary by race and ethnicity, which is not fully explained by lifestyle or metabolic risk factors.[8]

Genetic polymorphisms in genes including *PNPLA3*, *TM6SF2*, and *GCKR* have been robustly associated with liver disease severity and/or cardiovascular risk in NAFLD.[9] These variants have specific ethnic distributions, with *PNPLA3* accounting for ≤72% of interethnic variation in hepatic triglyceride content in the Dallas Heart Study.[10] DNA (venous blood or extracted from tissue) should be collected and the informed consent process should include the ability to genotype these candidate genes as well as "genome-wide" analyses for future analysis. This is particularly important for phase III trials given their larger size. Genetic testing would also be useful for identifying genes that may predict risk of drug-induced liver injury for study drugs. Furthermore, determining the presence of genetic polymorphisms associated with NASH in trial patients will be essential for evaluating the impact of these polymorphisms on treatment response. Current candidates include *PNPLA3* I148M and *TM6SF2* E167K.[11]

Diet and Lifestyle

The appropriate standard of care for dietary and activity counseling should be provided to NAFLD patients before enrollment in clinical trials, not only because research ethics require that all patients receive standard-of-care treatment, but also to normalize

Gastroenterology 2017;153:621–625

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- Andrew Muir

Case Definitions

Case definitions for inclusion and analysis of endpoints in clinical trials for NASH through the lens of regulatory science

M. Shadab Siddiqui, Stephen Harrison, Manal Abdelmalek, Quentin Anstee, Pierre Bedossa, Laurent Castera, Lara Dimick-Santos, Scott Friedman, Katherine Greene, David Kleiner, Sophie Megnien, Brent Neuschwander-Tetri, Vlad Ratziu, Elmer Schabel, Veronica Miller, Arun Sanyal, *on behalf of the Liver Forum Case Definitions Working Group*

Hepatology. 2017;xx(x), xx-xx


Hepatology

HEPATOLOGY

Case definitions for inclusion and analysis of endpoints in clinical trials for NASH through the lens of regulatory science

Journal:	Hepatology
Manuscript ID	HEP-17-0183.R2
Wiley - Manuscript type:	Special Article
Date Submitted by the Author:	28-Sep-2017
Complete List of Authors:	Siddiqui, Mohammad; Virginia Commonwealth University Harrison, Stephen; Pinnacle Clinical Research Abdelmalek, Manal; Duke University, Medicine; Gastroenterology Anstee, Quentin; Newcastle University, Institute of Cellular Medicine Bedossa, Pierre; Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, Paris University - Paris Diderot, Department of Pathology Castera, Laurent; Hôpital Beaujon, Department of Hepatology Dimick-Santos, Lara; Food and Drug Administration, Center for Drug Evaluation and Research Friedman, Scott; Mount Sinai School of Medicine, Division of Liver Diseases Greene, Katherine; University of California Berkeley, Forum for Collaborative Research Kleiner, David; NCI, NIH, Laboratory of Pathology Megnien, Sophie; Genfit Corp Neuschwander-Tetri, Brent; St. Louis University, Division of Gastroenterology and Hepatology Ratziu, Vlad; Université Pierre et Marie Curie, Assistance Publique Hôpitaux de Paris, Hôpital Pitié Salpêtrière, INSERM UMR_S 938 Schabel, Elmer; Bundesinstitut fur Arzneimittel und Medizinprodukte, Gastroenterology & Hepatology Unit Miller, Veronica; University of California Berkeley School of Public Health, Forum for Collaborative Research Sanyal, Arun; Virginia Commonwealth University, Chief, Division of Gastroenterology, Hepatology, and Nutrition
Keywords:	Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Drug development, Regulatory science, Clinical trial endpoints

Accepted Oct. 2017

SCHOLARONE™
Manuscripts

Hepatology

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- Brent Tetri
- Chinweike Ukomadu
- Viktor Voros
- Miriam Vos
- Jessica Williams
- Teresa Wright

Working Group Chairs

- Stephen Harrison
- Sophie Megnien

Member & Sponsor Update

- **Total Industry Members**: 120
- **New Industry Members Since LF6**: 9
- **Total Current Sponsors**: 50
- **New Sponsors Since LF6**: 3
  - GSK
  - Janssen
  - Perspectum Diagnostics Ltd.

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Many Thanks

- **Forum Staff**
  - Malene Cobourne
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  - Luis Javier Hernandez
  - Jeffrey Kaminski
  - Victoria Mason
  - Veronica Miller
  - Brenda Rodriguez
  - Ken Taymor
  - Jessica Weber
- **Prism Event Management**
  - Paula Blay
  - Rachel Heitkamp
  - Graham Hill
  - Mairead O'Reilly
  - Sarah Sanderson
  - George Seaton

Thank You!

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