Challenges and Opportunities in IBD Clinical Trial Design

Marla C. Dubinsky,[1] Rory Collins,[2,3] Maria T. Abreu,[4] on behalf of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD)

[1]Deputy Scientific Secretary IOIBD; Icahn School of Medicine at Mount Sinai, New York, New York; [2]UK Biobank, Manchester, United Kingdom; [3]Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom; [4]Chair, IOIBD; Division of Gastroenterology and Hepatology, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida

Keywords: Clinical Trials; Crohn's Disease; Ulcerative Colitis; Inflammatory Bowel Disease.

The International Organization for the Study of Inflammatory Bowel Disease held a single-day meeting focused on challenges and opportunities in trial design. The meeting included 95 registrants and consisted of 2 plenary presentations and 3 breakout sessions. The overall goals of the meeting were to identify challenges that must be met in the design of clinical studies of new and established therapies for inflammatory bowel disease (IBD).

Challenges in IBD Clinical Trials

Participants completed a survey focused on challenges in the conduct of clinical trials in IBD. The results showed that the greatest challenge in designing and completing studies in IBD was patient recruitment,[1] and it was also noted that the greatest opportunity was innovation in study design. The survey also collected opinions on the relative importance of induction and maintenance endpoints for clinical trials in IBD, and clinical remission was viewed the most important endpoint for both induction and maintenance.

The conduct of clinical trials in patients with IBD has been made more challenging by increasing complexity of regulatory demands[2] that may not always enhance study quality or safety.[3] These demands result in very complex protocols and have unintended negative consequences that include higher costs and longer times for completion of studies,[4,5] higher burden for patients,[6] fewer new treatments being developed by industry and fewer academic studies of current therapies, distortion of research agendas and reduced creative collaborations between academia and industry, and an undue focus on complying with rules rather than on innovation in the design and conduct of randomized controlled trials (RCTs).

Plenary Presentation 1: The Urgent Need to Streamline Randomized Trials: Evolve or Die

Dr Rory Collins emphasized that there is an urgent need to develop new evidence-based guidelines for the conduct of RCTs rather than replacing them with less reliable observational studies.[3] He noted that studies carried out for vaccines against severe acute respiratory syndrome coronavirus 2 and for treatment with dexamethasone during the Coronavirus Disease 2019 pandemic have shown that methodologically rigorous clinical development can be greatly streamlined and conducted much more rapidly than is typically the case. He emphasized that despite efforts to simplify the conduct of clinical trials, regulatory considerations and the pharmaceutical industry's response to them have become substantial impediments to the introduction of new medications. The high cost of RCTs and increasing difficulty in enrolling and completing them have increased pressure to consider observational evidence as an alternative source of support for drug efficacy and safety. However, there are important limitations to observational real-world studies that include significant risk for confounding and bias, and identification of apparent effects on health outcomes that are precise (ie, have small random errors) but are not causal.[3] Consequently, RCTs are needed to detect plausibly moderate beneficial or adverse effects of treatments on common health outcomes (with wide eligibility criteria yielding generalizability).[3] The conduct of RCTs can be facilitated by putting greater reliance on comparison of the experimental treatment arm with the randomly allocated control group. This is the case because missing data have little impact if losses are unbiased with respect to the allocated group.[3] Understanding the limited effects of missing or incorrectly interpreted results has the potential to decrease the need for central adjudication of study outcomes, which adds substantial cost, but typically little gain.

Appropriate guidelines for clinical trials should be based on scientific principles that focus on issues that can

Abbreviations used in this paper: **CD, Crohn's disease; CDAI, Crohn's disease Activity Index; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; RCTs, randomized controlled trials; UC, ulcerative colitis.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2021.03.065

materially affect the reliability of the results, including randomization with concealed assignment, adherence to trial intervention, completeness of follow-up, and intention-to-treat analyses.[3] In addition, these guidelines should be developed in collaboration by academia, industry, and regulators and should have the flexibility to be adapted for many different types of trials.[3] Enrollment of clinical studies can be facilitated by access to electronic health care record systems and specialized registries to identify large numbers of potentially eligible patients.[3] Unduly restrictive inclusion and exclusion criteria should be eliminated so that RCT results are relevant to a wide range of patients. Minimizing loss to follow-up and assessing long-term health outcomes can be facilitated by linkage to electronic health record systems and by incorporating technological advances (eg, smartphones and digital sensors) into clinical trial protocols.[3] The results of RCTs also can be improved by increasing adherence to study protocols and safety procedures. This can be facilitated by implementation of interactive electronic case-report forms. Patient safety and trial performance can be improved through real-time monitoring and analysis of electronic data from local trial sites.

Plenary Session 2: Biomarker Discovery a Deep Dive in Clinical Trials

Studies focused on genetics have greatly increased our understanding of immunologic diseases, but it is also important to understand that these conditions arise from a complex interplay between genetic and environmental factors that often lead to tissue-damaging responses.[7,8] Genomic studies have helped to identify important targets in immunologic diseases, but they require enormous mobilization of homogeneous patient cohorts. It is also important to understand that cells rather than genes lead to disease and that a better understanding of cell-specific molecular defects in diseases should help identify relevant drug targets. Genetic studies have identified >200 IBD susceptibility loci thought to control host-environmental interactions,[9] but they fail to explain IBD clinical heterogeneity and do not predict response to treatment.[10,11] It has become clear that disease archetypes arise from a combination of gene defects, environment exposures, and cellular networks. This realization has increased our understanding of Crohn's disease (CD) and led to identification of patients expressing a unique cellular module in inflamed tissues that consists of immunoglobulin G plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells (termed the GIMATS module). This module has been shown to be present in subsets of patients in 4 independent ileal CD cohorts and its presence was significantly correlated with failure to achieve durable corticosteroid-free remission with anti-tumor necrosis factor therapy.[12] This approach has the potential to redefine disease using cellular and molecular rather than histological criteria, and to maximize therapeutic responses by identification of biomarkers predicting treatment response and resistance. It can also facilitate identification of new therapeutic targets by assessing cellular and molecular responses or resistance to treatment.

Workshop 1: Inclusion/Exclusion Criteria and the Real World

Drs. Severine Vermeire, James Lindsay, and Siddarth Singh led the discussion of these issues with meeting participants.

Diagnosis/Demographics

The justification for stringent inclusion and exclusion criteria is not clear and it is important to aspire for trial populations representative of patients seen in clinical practice.[6] Exclusion criteria should be limited to factors that might induce errors in analysis of the primary study endpoint. There has been an evolution from clinical inclusion criteria to those based on endoscopy and histology. As a result, many patients who would be included in RCTs based on clinical presentation are now excluded based on endoscopic or histologic entry criteria. It was also suggested that there should be no restrictions on patient age for RCT enrollment and that large-scale studies can permit a high degree of patient heterogeneity.[5,13] There should also be reconsideration of other factors that typically result in exclusion of patients with IBD from clinical studies. For example, patients with stomas should be included if the stoma does not interfere with endpoint evaluation and those with fistulas should not be excluded as long as there are no abscesses. Laboratory abnormalities likely to result from IBD or its treatment (eg, anemia, low lymphocyte levels) should not result in exclusion. Relaxation of entry restrictions related to cancer history, particularly for solid tumors, also may be appropriate. It is important to gain input from oncologists regarding this issue as trial designs are being developed.

Prior/Concomitant Medications

The most important challenge related to this topic is the fact that washouts for medications being discontinued before entry into clinical trials are very long. This nearly universal aspect of trial design has several important negative consequences.[14] First, long washouts result in patients being treated with steroids only for extended periods, which has potential negative consequences. Second, this requirement is inconsistent with clinical practice in which treatment switches are made without intervening washout periods. Third, long washout periods have the potential to result in worsening patients' condition such that they no longer meet the entry criteria of the trial in question. Finally, there should be no limitations on prior medications for patients enrolled in clinical trials or restrictions regarding continuation of a biologic agent when another is being initiated.[14]

Workshop 2: Relevant Endpoints for Clinical Trials and the Real World

This workshop was led by Drs Remo Panaccione, Vipul Jairath, and Corey Siegel. Its goals were to review current

endpoints for studies of patients with CD and ulcerative colitis (UC), discuss their pros and cons, and consider the relevance of real-world studies for drug development. There are differences between US Food and Drug Administration (FDA) and European Medications Agency recommendations regarding endpoints, which also have very heterogeneous definitions.

Consideration of endpoints used in studies of CD by Dr Jairath indicated that the CD Activity Index (CDAI) was associated with very high placebo response rates and that this creates a need for very large sample sizes.[15,16] The FDA recommended moving away from the CDAI in 2015. This resulted in development of a number of interim measures, including assessment of abdominal pain and stool frequency. Patient-reported outcome measures are now in development, including one from Peter Higgins and colleagues[17] and one from Parambir Dulai and his collaborators.[18] However, these instruments are still exploratory and the CDAI will continue to be used.

The CD Endoscopic Index of Severity and the Simple Endoscopic Score for CD have become the gold standard for clinical trials, but they have important limitations, including assessment of stenosis and differences in measurement outcomes as a function of disease subtype and location. Endoscopy results and patient-reported outcomes are now typically used as co-primary endpoints in clinical trials. Magnetic resonance enterography has many potential advantages as an endpoint, but it has not been used extensively in clinical trials. There are also important limitations with respect to the use of histology as an endpoint, including uncertainties regarding where to biopsy and a lack of validated scoring systems.

The modified Mayo Clinic Score remains the gold standard for clinical trials in UC, and placebo response rates for this measure are very low. There is increasing interest in histopathologic outcomes for patients with UC and recent results have indicated that histologic remission is a strong predictor of long-term clinical outcomes.[19] However, there are limitations with respect to the use of histopathology in studies of UC, including lack of validated instruments, disagreement among pathologists regarding ratings for severity of inflammation, sampling error, and the time lag between symptom relief and endoscopic remission vs histologic remission of inflammation.

Development of new endpoints for studies of novel and established treatments for CD must take into account the hierarchy of patient needs. The most important goals for patients (eg, being able to leave the house, go to work, eat and maintain weight, persistence with treatment, cost of care) are not well aligned with endpoints used in RCTs. In addition, goals may differ from one patient to another, and individualization of endpoints may be most appropriate. Scales need to be developed to capture the impact of treatment on patients' lives and personalized endpoints might be included in clinical trials as exploratory endpoints. It is most important to assess disease-specific quality of life in patients being treated for IBD, but effects of treatment on quality of life alone will not support drug approval. A new measure, the Overall Disease Severity Index, is currently being validated.

Workshop 3: Creative Clinical Trial Design in IBD

This session was moderated by Drs Bruce Sands (chair), James Lewis, Siew Ng, and Julian Panes. It was emphasized that there are clear limitations in traditional designs for RCTs that may be overcome with adaptive designs (Figure 1).[20] There are many different ways in which designs may be adapted based on interim data analysis (eg, continual reassessment, multiarm/multistage, population enrichment, biomarker adaptive, adaptive hypothesis

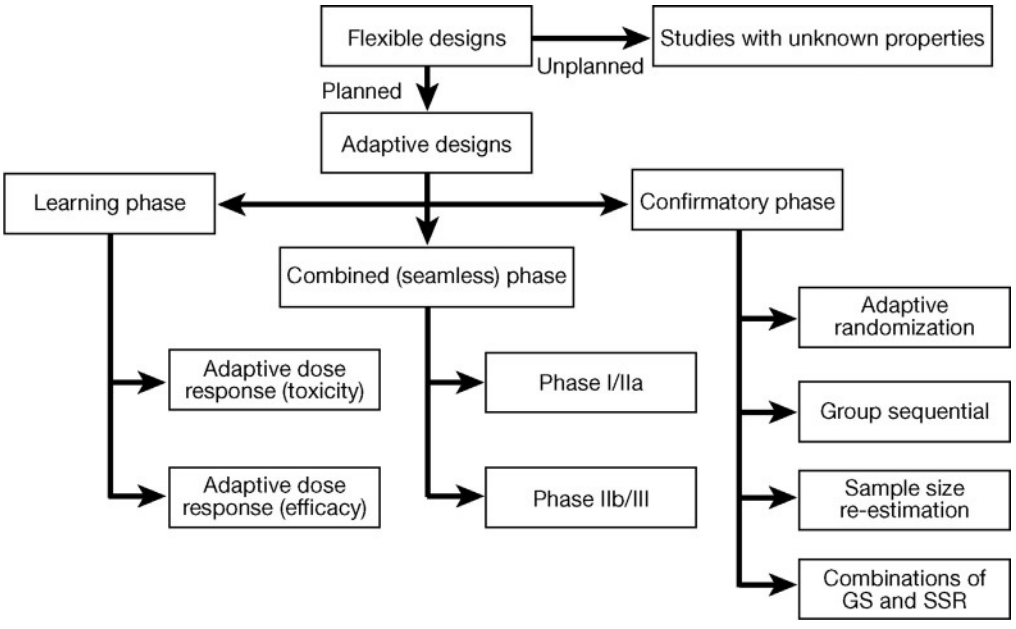

Figure 1. Summary of adaptive clinical trial designs.[20] GS, group sequential; SSR, sample size re-estimation. (Image obtained from Kairalla JA, Coffey CS, Thomann MA, et al. Adaptive trial designs: a review of barriers and opportunities. Trials 2012;13:145.)

Table 1. Advantages and Disadvantages of Adaptive Clinical Trial Designs[21]

Potential advantages
• Statistical efficiency: o Greater chance to detect a true drug effect. • May provide same statistical power with a smaller expected sample size or shorter expected duration. • Ethical considerations: o Stop early if unlikely to demonstrate efficacy, exposing fewer patients to ineffective treatment. • Acceptability to stakeholders (sponsors, patients).
Potential limitations
• Require specific analytical methods to avoid increasing the chance of erroneous conclusion and introducing bias estimates. o Complex designs may require simulations. • Gains in efficiency may be offset by other losses: o More effort at the design stage. • Logistical challenges to trial conduct and integrity. • Smaller sample size = less reliable safety evaluation. • Resul]ts after adaptation may be different from those before adaptation.

design, alteration of endpoint, adaptive switching). The advantages and disadvantages of adaptive designs noted by the FDA are summarized in Table 1. Adaptive designs might be particularly useful in studies of patients with mild disease in which there is a potential for high placebo response rates and difficulty in carrying out power analysis. They might also be beneficial in settings in which there is high uncertainty about appropriate endpoints and/or responses to treatment.

The group considered additional approaches that might speed drug approval. Combining phases 2 and 3 of clinical development has the potential to decrease unwanted pauses in this process. This approach is being used by several sponsors, but none have proceeded to registration. Dose selection in phase 2 has been a continuing problem in studies of new treatments for IBD that might be solved with an adaptive trial design in which ineffective doses were dropped and sample sizes for arms with effective doses were increased.

There are barriers to the use of adaptive designs. At present, we do not know the best first-line therapy for any condition. In addition, focusing on patients with moderate-to-severe disease leads to inclusion of patients refractory to numerous agents. More studies of first-line treatment are needed. The plenary presentations suggested that there are 2 distinct treatment development pathways: (1) A "deep dive" into individual patients; and (2) large studies with heterogeneous patient populations focusing on generalizability of results. The latter approach includes umbrella trials recruiting patients with all disease severities, and this was strongly supported.

Conclusions

All of those involved in the management of patients with IBD have a responsibility to move the field forward and improve patient outcomes. It is essential to streamline inclusion/exclusion criteria to make RCTs easier to enroll and more representative of the full range of patients seen in the clinic and to consider trial designs with the potential to speed drug/biologic approval. It is the intent of IOIBD to develop standardized clinical trial designs that include the input of relevant stakeholders to achieve these goals.

References

1. Danese S, Schabel E, Ainsworth MA, et al. Challenges and opportunities for IBD drug development: from early stage to regulatory approval. Gut 2020;69:1157–1161.
2. Khanna R, Jairath V, Vande Casteele N, et al. Efficient early drug development for ulcerative colitis. Gastroenterology 2016;150:1056–1060.
3. Collins R, Bowman L, Landray M, et al. The magic of randomization versus the myth of real-world evidence. N Engl J Med 2020;382:674–678.
4. Harris MS, Wichary J, Zadnik M, et al. Competition for clinical trials in inflammatory bowel diseases. Gastroenterology 2019;157:1457–1461.e2.
5. Johnson C, Barnes EL, Zhang X, et al. Trends and characteristics of clinical trials participation for inflammatory bowel disease in the United States: a report from IBD partners. Crohns Colitis 2020;360(2):otaa023.
6. Sharp D, Ringer S, Park KT, et al. Listening to the patient: improving the design and conduct of clinical trials in inflammatory bowel diseases. Crohns Colitis 2020;360(2):otaa011.
7. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3:e297.
8. Neurath MF. Cytokines in inflammatory bowel disease. Nat Rev Immunol 2014;14:329–342.
9. Momozawa Y, Dmitrieva J, Théâtre E, et al. IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. Nat Commun 2018;9:2427.
10. Torres J, Colombel JF. Genetics and phenotypes in inflammatory bowel disease. Lancet 2016;387:98–100.
11. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–1035.
12. Martin JC, Chang C, Boschetti G, et al. Single-cell analysis of Crohn's disease lesions identifies a pathogenic cellular module associated with resistance to anti-TNF therapy. Cell 2019;178:1493–1508.e20.
13. Ha C, Ullman TA, Siegel CA, et al. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clin Gastroenterol Hepatol 2012;10:1002–1007. quiz e78.
14. Abreu MT. Combining biologic agents in inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2019;15:549–551.
15. Jairath V, Zou G, Parker CE, et al. Systematic review with meta-analysis: placebo rates in induction and

maintenance trials of Crohn's disease. Aliment Pharmacol Ther 2017;45:1021–1042.
16. Ma C, Guizzetti L, Jairath V. Improving clinical trial efficiency in gastroenterology. Gastroenterology 2019; 157:892–893.
17. Higgins PDR, Harding G, Leidy NK, et al. Development and validation of the Crohn's disease patient-reported outcomes signs and symptoms (CD-PRO/SS) diary. J Patient Rep Outcomes 2017;2:24.
18. Dulai PS, Jairath V, Khanna R, et al. Development of the symptoms and impacts questionnaire for Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2020; 51:1047–1066.
19. Ozaki R, Kobayashi T, Okabayashi S, et al. Histological risk factors to predict clinical relapse in ulcerative colitis with endoscopically normal mucosa. J Crohns Colitis 2018;12:1288–1294.
20. Kairalla JA, Coffey CS, Thomann MA, et al. Adaptive trial designs: a review of barriers and opportunities. Trials 2012;13:145.
21. US Food and Drug Administration. Adaptive designs for clinical trials of drugs and biologics. Guidance for industry. Available at: https://www.fda.gov/media/78495/download Accessed January 8, 2021.

Received March 15, 2021. Accepted March 21, 2021.

Correspondence
Address correspondence to: Marla C. Dubinsky, MD, Division of Pediatric Gastroenterology and Nutrition, Icahn School of Medicine, 17 East 102nd Street, New York, New York. e-mail: marla.dubinsky@mssm.edu; or Maria T. Abreu, MD, Department of Medicine, Division of Gastroenterology, Crohn's & Colitis Center, University of Miami Miller School of Medicine, 1011 North West 15th Street (D-149), Gautier Building, Suite 510, Miami, Florida. e-mail: mabreu1@med.miami.edu; fax: (305) 243–6125.

Acknowledgments
The IOIBD Challenges and Opportunities in IBD Clinical Trial Design Group represents expert speakers and panelists who participated in the meeting and who also served as authors in the development of the Meeting Summary.

The speaker banner is as follows:
Maria T. Abreu, University of Miami;
Rory Collins, British Heart Foundation, University of Oxford (UK);
Marla C. Dubinsky, Icahn School of Medicine, New York;
Vipul Jairath, Western University Ontario;
James D. Lewis, Perelman School of Medicine, University of Pennsylvania;
James Lindsay, Barts Health NHS Trust, Royal London Hospital;
Miriam Merad, Icahn School of Medicine, New York;
Siew Ng, Chinese University of Hong Kong, Prince Wales Hospital;
Remo Panaccione, Cumming School of Medicine, University of Calgary;
Julian Panes, Clinic Barcelona, Hospital University;
Bruce Sands, Icahn School of Medicine, New York;
Corey A. Siegal, Dartmouth-Hitchcock Medical Center;
Siddarth Singh, UC San Diego Health; and
Severine Vermeire, KU Leuven.

The physician members are as follows:
Vineet Ahuja, All India Institute of Medical Sciences;
Matthieu Allez, Hôpital Saint-Louis–Paris;
Ashwin Ananthakrishnan, Harvard Medical School/Harvard School of Dental Medicine;
Willem Bemelman, Amsterdam UMC;
Jonathan Braun, IRIBI, Cedars Sinai Medical Center;
Jean-Frederic Colombel, Icahn School of Medicine at Mount Sinai NY;
Silvio Danese, Humanitas Research Hospital–Milano;
Geert D'Haens, Amsterdam UMC;
André D'Hoore, UZ Leuven;
Axel Dignass, Agaplesion Markus Hospital;
Iris Dotan, Rabin Medical Center & the Sackler Faculty of Medicine–Tel Aviv;
Miguel Angel Gassul, IGTP Germans Trias i Pujol Foundation–Spain;
Anne Griffiths, SickKids Hospital Toronto;
Jonas Halfvarson, Örebro University Hospital–Sweden;
Stephen Hanauer, Northwestern University;
Paulo Kotze, Cajuru University Hospital of the Catholic University–Brazil;
Ioannis Koutroubakis, University Hospital Heraklion–Greece;
Edward Loftus, Mayo Clinic;
Edouard Louis, University Hospital CHU Liege;
Fernando Magro, Instituto de Farmacologia Porto;
Gerassimos Mantzaris, Evangilismos Hospital Athens;
Jean-Yves Mary, INSERM Hospital Saint-Louis;
Dermot McGovern, Cedars-Sinai Medical Center;
Pia Munkholm, Danish Center for eHealth & Epidemiology (DEEP);
Colm O'Morain, Beacon Consultants Clinic Dublin;
Yves Panis, Beaujon Hospital;
Laurent Peyrin-Biroulet, CHU de Nancy;
Cosimo Prantera, Ospedale San Camilo-Forlanini–Rome;
Zhihua Ran, Shanghai IBD Research Center;
Britta Siegmund, Charité - Universitätsmedizin Berlin;
Mark Silverberg, Mount Sinai Hospital Toronto;
Eduard Stange, Robert-Bosch Krankenhaus, Stuttgart;
Stephan Targan, Cedars-Sinai Medical Center;
Curt Tysk, Örebro University Hospital–Sweden;
Simon Travis, Oxford University Hospital;
Morton Vatn, University of Oslo; and
Yesus Yamamoto-Furusho, National Institute of Medical Sciences and Nutrition–Mexico.

Additional meeting participants are as follows:
Janske Aarts, Pfizer Inc.;
Brihad Abhyankar, Theravance Biopharma Ireland Ltd.;
Harris Ahmad, Bristol-Myers Squibb;
Richard Aranda, Gossamer BIO;
Vipin Arora, Eli Lilly & Company;
Jalil Benjacoub, Nestle Health Science;
Sofie Berg, AbbVie Inc.;
Robin Besuyen, Galapagos;
Daniela Bojic, F. Hoffmann-La Roche AG;
Valerio Carriero, AbbVie Inc.;
Fabio Cataldi, Arena Pharmaceuticals Inc.;
Laurence D'Agay, Celgene Int.;
Silvia Delgado-Aros, Boehringer-Ingelheim;
Paul Giannasca, Nestle Health Science;
Kavitha Goyal, Janssen Pharmaceuticals;
Roland Greinwald, Dr. Falk Pharma GmbH;
Savion Gropper, Boehringer-Ingelheim;
Shunsuke Kageyama, EA Pharma Co. Ltd.;
Raphaël Laoun, Tillotts Pharma AG;
Barrett Levesque, Gossamer BIO;
Trevor Lissoos, Eli Lilly & Company;
Irene Modesto, Pfizer Inc.;
Ralf Mohrbacher, Dr. Falk Pharma GmbH;
Ralph Mueller, Dr. Falk Pharma GmbH;
April Naegeli, Eli Lilly & Company;
Snehal Naik, Arena Pharmaceuticals Inc.;
Deanne Nguyen, Theravance Biopharma Ireland Ltd.;
Wojciech Niezychowski, Pfizer Inc.;
Caitriona O'Brien, Gilead;
Irina Odnoletkova, Galapagos;
Alessandra Oortwijn, Galapagos;
Kun KT Park, F. Hoffmann-La Roche AG;
Waldemar Radziszewski, Amgen; Camilla Rowan, Janssen Pharmaceuticals;
Leonardo Salese, Pfizer Inc.; Johannes Spleiss, Tillotts Pharma AG;
Andrea Stancati, Takeda; Amanda Tatro, F. Hoffmann-La Roche AG;
Jennifer Thompson, Boehringer-Ingelheim; Robert Hofmann, Tillotts Pharma AG;
Javier Zambrano, AbbVie Inc.;
Wen Zhou, AbbVie Inc.; and
Ellen Zigmont, Gossamer BIO.☆