Selected Updates and Assessment of FDA's Adoption of ASGCT's 2018-2021 Recommendations

Presenters:

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American Society of Gene + Cell Therapy

Introduction

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Presentation outline

1. ASGCT's Recommendations on Chemistry, Manufacturing, and Controls (CMC)
2. ASGCT's Recommendations on Clinical Issues
3. ASGCT's Recommendations on FDA Logistics and Procedural Issues

CMC Considerations

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Presenter disclosures

- Ravishankar Vadali is an employee and stockholder of Ocugen Inc

ASGCT appreciates FDA's efforts at providing direction on CMC expectations to CGT developers

- CGT-specific guidances with CMC components released over the last two years
  - Considerations for the Development of CAR T Cell Products draft guidance (Mar 2022)
  - Human Gene Therapy Products Incorporating Human Genome Editing draft guidance (Mar 2022)
  - CMC Information for Human Gene Therapy Products final guidance (Jan 2020)
  - Human Gene Therapy for Neurodegenerative Diseases final guidance (Oct 2022)
  - Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial final guidance (Nov 2022)

- ASGCT co-hosted a roundtable on potency assays with the Alliance for Regenerative Medicine (ARM) this fall – thank you for CBER's attention to this topic.

- Upcoming draft guidance on "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry" included in the 2022 CBER Guidance Agenda.

Comparability study expectations and manufacturing considerations remain major hurdles to CGT development

(2021) ASGCT recommendations on comparability

- FDA should allow a more flexible and pragmatic approach to manufacturing process changes and comparability assessment, providing further guidance on principles for decision making.
- It should be acceptable for characterization assays without acceptance criteria to provide relevant but difficult-to-quantify data to inform the overall assessment of comparability for attributes that are not expected to impact safety.
- Statistical analysis expectations should consider that low-replicate batches are an inherent feature of CGT investigational products. We propose greater weighting of science- and risk-based arguments and decision making that includes qualitative data.
- ‘Identicalness’ cannot be demonstrated in a comparability study given current assay limitations, natural biologic variation of complex (sometimes ‘living’) cell products, and poorly defined links to clinical benefit.
- Further guidance/clarity is required on the expectation for comparability testing of viral vectors used in genetically modified cell therapy products.
- Further guidance is needed on the parameters that FDA believes define a “change” in manufacturing that warrant comparability studies.
- The appropriate comparator for contemporaneous comparability testing following a process change should be the product manufactured using the preceding process, not all historical products and processes.

Raw Materials – Plasmid Quality + Viral Vectors for Ex-Vivo Modification of Cells

Current Policy and Ongoing Efforts

CMC for Human GT Products (Jan 2020) guidance defines master cell bank (MCB)/working cell bank (WCB) qualification and release tests for plasmid manufacture, however, based on agency feedback to sponsors, plasmids need to be GMP manufactured.

FDA does provide exceptions for Ph1 depending on situation, but GMP is preferred.

Viral vectors for ex-vivo modification of cells are treated as Drug Substance and subject to GMP manufacturing/controls (per draft guidance *Considerations for the Development of CAR T Cell Products [Mar 2022]).*

ASGCT Recommendations

FDA should adopt a policy that plasmids and viral vectors that do not directly become part of the drug substance or drug product may be defined as raw materials or reagents, and their quality ensured by supply chain control.

- Alternatively, clarity is needed regarding GMP manufacturing requirement for plasmids.

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CMC Strategy Stage 3 Process Validation (PV)

Current Policy and Ongoing Efforts

Current guidance *Process Validation: General Principles and Practice (Jan 2011*) applies to a broad range of biologics including CGTs, even though there are process considerations unique to CGTs.

ASGCT Recommendations

FDA should provide specific guidance on PV for CGT products with limited batches and those with patient specific batches/variability.

- FDA should permit concurrent PV with suitable in-process controls during pivotal trial material manufacturing instead of requiring a dedicated PPQ campaign.

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Product Specifications – Identity

Current Policy and Ongoing Efforts	ASGCT Recommendations
Gene sequence by Sanger has been the commonly accepted practice, while industry is currently moving towards next generation sequencing (NGS) methods – so uncertainty persists on NGS method selection and acceptance criteria.	ASGCT requests FDA further define the agency's acceptance of new and upcoming sequencing technologies for identity and provide considerations for resolving sequence mismatches due to assay performance.

Product Specifications – Sterility

Current Policy and Ongoing Efforts	ASGCT Recommendations
21 CFR 610.12 and USP sterility chapters do not address sampling volume requirements for cell therapy products specifically; low-volume products typically encounter challenges under the current system.	ASGCT requests that FDA utilize the flexibility intended in the revision of 21 CFR 610.12 to allow for greater flexibility in volume requirements for sterility sampling.

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Product Specifications – Acceptance Criteria/ Range

Current Policy and Ongoing Efforts

Based on *ICH Q6B* – "….Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data".

FDA often prefers utilizing manufacturing capability as primary data set to set the specification ranges.

This presents a challenge for some gene therapy products in which the number of manufacturing batches are very limited. *[Sometimes (n=1) batches for Ph 1 and Ph 3 manufacturing campaigns for rare diseases].*

ASGCT Recommendations

FDA should facilitate a public meeting to discuss the challenges of setting and/or updating phase-appropriate specifications and acceptance criteria for CGT products. The unique nature of CGT products presents particular challenges in setting specifications (due to batch sizes, number of batches, complexity of the product, etc.), for which guidance documents may not always meet sponsor needs. ASGCT believes an open dialogue on this issue, rather than confining the discussion to individual meetings with sponsors, would have significant value.

Product Specifications – Impurities + HCP and DNA Levels

Current Policy and Ongoing Efforts

ICH Q3A and *Q3B* focused on process derived impurities for Drug Substances and Drug Products broadly.

70th Meeting of the Cellular, Tissue and Gene Therapies Advisory Committee on toxicity risks of adeno-associated virus (AAV) vector-based gene therapy products included a discussion question on AAV empty capsids as impurities.

FDA and EUA guidances for DNA impurities refer to *WHO TRS 878-pg 27* and the 10ng/dose level. FDA routinely waives or relaxes this based on justification provided by the sponsor, leading to uncertainty among developers.

ASGCT Recommendations

ASGCT recommends FDA organize meetings/workshops to develop a roadmap for defining process and product-related impurities and calculating/setting specs for specific classes of CGTs, in particular -

- Specific request – Provide a roadmap to quantify risk of product related impurities and process related impurities with accompanying spec justification.
- Considerations for empty, partial, and/or non-functional viral vectors.
- How to quantify risks of process-related impurities vs specific specs (i.e. 10ng/dose DNA).

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Clinical Considerations

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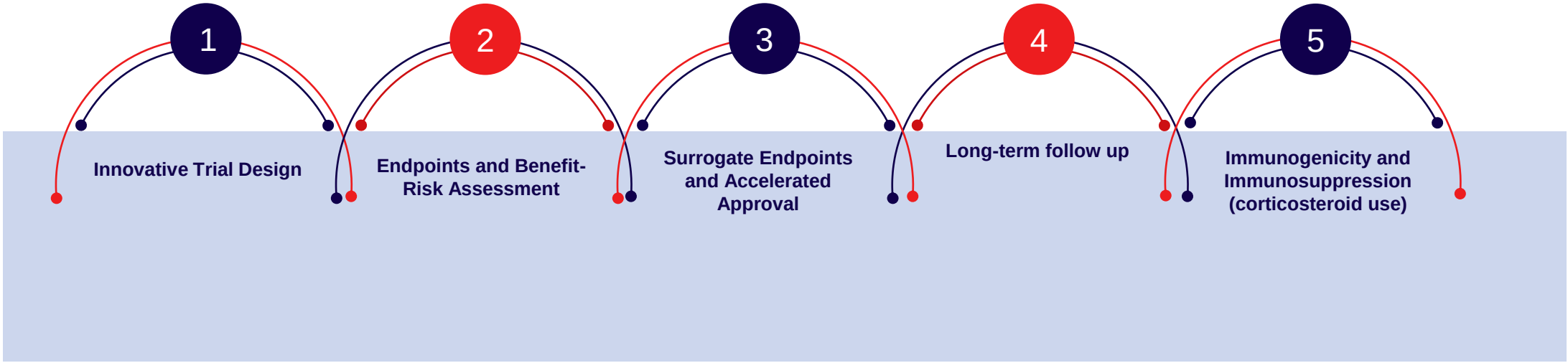
Presenter disclosures

- Jack Brownrigg is an employee and stockholder of BioMarin Pharmaceutical Inc.

Clinical Considerations: Topics



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Innovative Trial Design

Current Policy and Ongoing Efforts

- Draft Guidance on Natural History Studies for rare diseases
- Draft Guidance on Substantial Evidence of Effectiveness
- Finalized Guidance on Multiple Endpoints in Clinical Trials is welcomed. ASGCT appreciates the clarity provided on acceptable approaches for controlling Type I error, when and how multiplicity due to multiple endpoints should be managed, and instances where descriptive analyses can be considered for inclusion in labeling without presenting p-values.

ASGCT Recommendations

ASGCT would like to reiterate several recommendations we made in 2020:

- Existing Rare Diseases guidance could be strengthened through addressing development situations characterized by sample size restriction, to acknowledge the shortcomings of randomization with small sample sizes, and to clarify methods for aggregating data across concurrent and historical controls and pre-treatment disease trajectory.
- Update guidance to provide examples of when p-values >0.05 may be used as a success criterion.
- ASGCT recommends that Draft Guidance on Natural History Studies for rare diseases could benefit from specifying its relevance for Cell and Gene Therapy trials.

Endpoints and Benefit-Risk Assessment

Current Policy and Ongoing Efforts

- FDA Workshop and Guidance development on benefit-risk assessment
- PFDD guidance series development

ASGCT Recommendations

ASGCT would like to reiterate several recommendations we made in 2020:

- FDA should adopt the use of tools such as modeling and simulation, and Bayesian Statistics in supporting the understanding of durability leveraging pre-approval data, while ongoing clinical assessments can continue in the post-approval setting (e.g., while a therapy may spare loss of life early in a condition [such as SMA], approval should be provided long before durability is established).
- Incorporate patient voice into the determination of unmet need, or unrealized unmet need into benefit/risk decision making to support decision to expedite regulatory approval. Greater clarity is needed overall on how to demonstrate a “meaningful advantage over other therapies,” especially in the context of accelerated approval.
- Explain how and when the agency deems it appropriate to incorporate comparison of pre- and post-treatment disease course into evaluation of efficacy to complement use of external or concurrent controls.

Updated recommendation for 2022:

- Leverage opportunities for dialogue (e.g., Type C surrogate endpoint discussion meetings).

Surrogate Endpoints and Accelerated Approval

Current Policy and Ongoing Efforts

- Expedited Programs Guidance
- Guidance documents on cell and gene therapy development

ASGCT Recommendations

ASGCT would like to reiterate several recommendations we made in 2020:

- FDA guidance should be expanded to clarify how measures of gene expression can serve as surrogate endpoints to support accelerated approval.
- Demonstration, through use of a reliable and reproducible assay(s), that a gene therapy can express or restore a functional version of a protein that is known to be causative for the target disease should be considered a surrogate endpoint that is reasonably likely to predict clinical benefit, provided that the functional activity is adequately characterized (i.e., quantity, location, biological relevance).
- FDA guidance should be expanded to articulate the use of intermediate clinical endpoints with continued clinical assessment post approval.

Long-term Follow-up

Current Policy and Ongoing Efforts

Guidance development efforts:

- 2018: RWD/RWE final guidance
- 2019: Submitting Documents Using RWD and RWE to FDA
- 2020: GT LTFU final guidance
- 2021: RWD: Assessing Electronic Health Records and Medical Claims Data
- 2021: Data Standards for Drug and Biological Product Submissions Containing RWD
- 2021: RWD: Assessing Registries

ASGCT Recommendations

ASGCT would like to reiterate several recommendations we made in 2020:

- Recommendation: Inclusion in a registry should be an acceptable alternative for LTFU.
- As articulated in the guidance document, it is rational to have reporting requirements that are vector and disease-specific, with some requiring long-term observation and others short-term or no observation at the end of the clinical protocol.
- It would be useful for the FDA to publish a data-driven document of the 15-year monitoring data generated over the past 25 years.

Updated recommendations for 2022:

- ASGCT recommends that LTFU duration that starts pre-approval, post-administration of the product should inform the LTFU requirements post-approval. Accordingly, the duration and body of LTFU data collected pre-approval should be considered as the body of LTFU evidence together with the LTFU requirements and commitments for the products post-approval.
- We understand that REMS is suitable for certain products, e.g., for products with risk for immediate and severe allergic reactions. However, REMS may not be the best-suited tool for long-term safety data collection and safety surveillance. ASGCT recommends that resource-intensive REMS are not appropriate where existing tools for ensuring post-marketing safety suffice to ensure appropriate LTFU and continued safety data collection, and recommends FDA not require REMS in those cases.

Immunogenicity and Immunosuppression (Corticosteroid Use)

Current Policy and Ongoing Efforts

- FDA co-hosting a public workshop on AAV immunogenicity issues with ASGCT in Q1 2023

ASGCT Recommendations

ASGCT would like to reiterate a recommendation we made in 2020:

- FDA should issue immunogenicity recommendations, which are updated regularly to reflect progression and learnings in the field to provide developers with a clear risk-based framework, to facilitate cell and gene therapy product development.

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Procedural Considerations

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Advanced CGT Regulatory Consultant

OTAT Growth Program

Primary Goals

- Expedite advances in cell and gene therapy
- Improve staff satisfaction and sustainability

FDA elevates OTAT to "Super Office" within CBER

Regulatory News | 30 September 2022 | By Joanne S. Eglovitch

2022 Center for Biologics Evaluation and Research (CBER) Science Symposium

CBER OTAT Listening Session

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PDUFA VII commitment letter: RWE, rare diseases see renewed attention

TOWN HALL

OTAT Town Hall: Gene Therapy Chemistry, Manufacturing, and Controls

SEPTEMBER 29, 2022

Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2022

(Updated June 2022)

Human Gene Therapy Products Incorporating Human Genome Editing

Draft Guidance for Industry

FDA U.S. FOOD & DRUG ADMINISTRATION

OTAT – Sponsor Communications

American Society of Gene & Cell Therapy (ASGCT)
Effective Regulatory Interactions

Listening Sessions + OTAT Growth Program

Current Policy and Ongoing Efforts

ASGCT is excited about the “Super Office” in CBER to meet growing demands and dedicated exclusively to cell and gene therapy workload.

ASGCT is honored that we were among the early groups to have the OTAT Growth Program shared with us.

ASGCT Recommendations

ASGCT recommends that FDA repeat the 2021 listening sessions after one to two years to assess the extent to which the learnings from the OTAT Growth Program made a difference in OTAT-sponsor interactions.

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Direct Collaboration Opportunities with ASGCT

Current Policy and Ongoing Efforts

October OTAT-ASGCT-ARM roundtable on potency assays

Upcoming FDA-ASGCT Workshop on AAV Immunogenicity

FDA participation at ASGCT Annual Meetings and Policy Summits

Annual ASGCT-FDA Liaison meetings

ASGCT Recommendations

FDA is encouraged to, while preserving confidential commercial information (CCI), incorporate lessons learned which are generally applicable to many or all sponsors in its public presentations or FAQs. A summary of top/common causes for clinical holds and what sponsors can do to avoid them would be of particular value (i.e. on immunogenicity, clinical translation of non-clinical findings, total viral load on empty/full capsid levels, etc.).

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Information Sharing and Workshops

Current Policy and Ongoing Efforts

ASGCT is especially enthusiastic about the recent OTAT town hall format on CMC as a model for future multidisciplinary events.

- Increased communication is beneficial to stakeholders and patients.
- Reduces delays in advancing clinical programs.

ASGCT Recommendations

We encourage FDA to continue hosting events outside of the formal Advisory Committee structure, to broaden the pool of SMEs who may participate and increase audience interaction with presenters, given the challenges involved in sourcing non-conflicted speakers in the formal Advisory Committee process.

Generally, as FDA is considering additional outreach and education, we recommend the agency give particular attention to efforts that address the following elements:

- Cutting-edge technologies
- New treatment modalities
- Topics that apply to a class of gene therapy products
- Leveraging the regulatory landscape and drug approval

Advisory Committees

Current Policy and Ongoing Efforts	ASGCT Recommendations
Cellular, Tissue and Gene Therapies Advisory Committee meeting on toxicity risks of adeno-associated virus (AAV) vector-based gene therapy products. • ASGCT appreciates that FDA focused on a number of critical topics in the AAV field at this AdComm.	ASGCT recommends that OTAT consider convening a meeting of the *Cellular, Tissue and Gene Therapies Advisory Committee* on clinical translation of findings.

RMAT Guidance

Current Policy and Ongoing Efforts	ASGCT Recommendations
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Guidance for Industry (2019). • FDA has done a good job putting out regular public updates with information on approvals and denials.	FDA should include a publicly posted FAQ or host a town hall with stakeholders to discuss the common reasons for denial of RMAT application. We note that there is a persistently high denial rate for applications, which suggests there is a gap in understanding among sponsors.

PDUFA VII – New Meeting Types

Current Policy and Ongoing Efforts

Positive Highlights:

- OTAT has in the past been thoughtful and responsive in evolving INTERACT to meet sponsor needs after its initial introduction.
- We are excited to see the inclusion of Type D and Type C meetings in PDUFA commitments.
- We look forward to the revised Formal Meetings guidance included in PDUFA commitments, as well as the opportunities for clarifying follow-up questions.

ASGCT Recommendations

ASGCT is eager for the implementation of the Type C surrogate endpoints meetings, new Type D meetings, and the formalization of INTERACT meetings.

- We encourage OTAT take full advantage, to the extent staffing allows, of these interactions over the course of this user fee cycle.
- We encourage FDA to update the communications and meetings guidance to reflect the PDUFA VII agreement.

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PDUFA VII – OTAT Learn

Current Policy and Ongoing Efforts

Positive Highlights:

- The site is an excellent resource for new stakeholders
- Course content includes a number of relevant topics
- Multidisciplinary approach
- Appreciate that presentations are updated as information becomes available
- We are glad that suggestions for additional topics have been welcomed by OTAT

ASGCT Recommendations

FDA should ensure that the CBER Q&A guidance to promote the development of cell and gene therapies under PDUFA VII is produced in concert with an update to the OTAT Learn website.

- In addition, we encourage OTAT to evaluate the Learn website for inconsistencies with existing Agency policy and to align with existing practices to the greatest extent possible (e.g., OTAT Learn states that video conference will not be used for sponsor meetings while it is used routinely by other Offices and Centers).

PDUFA VII – SOPPs and MaPPs

Current Policy and Ongoing Efforts

Positive Highlights:

- Increased frequency of INTERACT meeting granted with successful outcomes
- Guidance is valuable in pIND Type B meeting request or IND submissions

ASGCT Recommendations

We encourage OTAT to provide links to CBER- or OTAT-specific SOPPs and MaPPs and to indicate which CDER processes are leveraged by OTAT. Currently, CDER SOPPs and MaPPs are readily available, but corresponding documents for CBER are often hard to find or not available publicly.

Summary: Procedural considerations

- *2018 Recommendation: When serious issues arise that the agency is aware of that may alter protocol design and manufacturing practices, it would be of significant help to provide information to the community of the FDA's concerns that can have major implications to programs based on long term commitments.*

- **2022 Key Message #1:** ASGCT members' request of FDA on this point stands. ASGCT recommends that FDA consider avenues to publicly share information that: is gathered through the Agency's standard review process; could be aggregated and/or generalized, such that it is not product-specific; and would benefit or impact a significant subset of sponsors or development programs through disclosure.

    - Such information might be conveyed as part of opportunities for additional high-quality interactions through the product lifecycle.
    - Additional stakeholder interactions from the agency, as much as is reasonable with FDA's resources, would be valuable.

- **2022 Key Message #2: <u>ASGCT would like to sincerely thank OTAT for your responsiveness to new ideas and willingness to work with sponsors and problem solve</u>.** ASGCT especially appreciate OTAT's goal to be fully staffed under PDUFA VII by 2023; the Society would like to play a positive, proactive role to work with OTAT to advance the field.

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Acknowledgements

Work group members

- Diane Berry, PhD, Sarepta Therapeutics
- Jack Brownrigg, MD, PhD, BioMarin
- Megan Zoschg Canniere, PharmD, Spark Therapeutics
- Nimi Chhina, PhD, BioMarin
- Daniela Drago, PhD, NDA Partners
- Sofia Hakansson-Buch, PhD, Novo Nordisk
- Hans-Peter Kiem, MD, PhD, Fred Hutch Cancer Center
- Sadik Kassim, PhD, DH Life Sciences
- Dan Leblanc, Ensoma
- January McKee, PhD, Castle Creek Biosciences
- Adora Ndu, PharmD, JD, BridgeBio
- Natalia Shunmugan, PhD, Ultragenyx
- Rachel Smith, PhD, Stride Bio
- Kaye Spratt, PhD, Independent Regulatory Consultant
- John Tomtishen, Cellares
- Ravishankar Vadali, PhD, Ocugen
- Kristin Van Goor, PhD, Vertex Pharmaceuticals
- Angela Whatley, PhD, PTC Therapeutics
- Keith Wonnacott, PhD, LEXEO Therapeutics
- Fraser Wright, PhD, Stanford University

Thank you!

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Appendix

Links to Previous ASGCT Recommendations Referenced in this Presentation:

(2018) Manufacturing considerations

(2018) *In vivo* gene therapy with DNA vectors

(2018) Long term follow up in recipients of HSCs and immune effector cells modified by retroviral or lentiviral vectors

(2019) Surrogate endpoints to accelerate gene therapy product development

(2020) Innovative Clinical Study Design for Gene and Cell Therapies

(2020) Immunogenicity testing requirements for AAV gene therapy

(2021) Recommendations on CMC Expectations for Gene and Cell Therapy Products

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