Long Term Follow Up For Gene and Cellular Therapies

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Disclosures

- Full-time employee of Allogene Therapeutics
- Equity interest in Allogene Therapeutics
- Previously an employee of Kite Pharma (Head of PV and Risk Management)

Disclaimer

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Aim of LTFU

- Identify and mitigate the long term risks to the patients receiving the GT product
- Understand the persistence of the product

Is a LTFU Study Required?

- Will depend on
  - Product characteristics e.g Propensity of GT products/vectors to modify the host genome
  - Patient related factors, life expectancy, co-morbidities
  - Pre-clinical data e.g persistence of the GT product
  - Clinical data: What has previously been observed?
- **Key questions**
  - Does your GT product utilize genome editing technology
  - Are vector sequences integrated or is the human genome otherwise genetically altered
  - Does the GT product have the potential for latency and reactivation
  - Do preclinical study results show persistence of the GT product

A dedicated Protocol required for LTFU

- Establish a dedicated LTFU protocol detailing patient schedules, sampling plan, methods of monitoring, and the clinical events of interest that will be monitored
- Patients should be consented. Informed consent document should describe purposes of research, the expected duration of the subjects participation, procedures, duration, visits. If any blood or tissue will be stored, the informed consent should state so.
- Duration of the LTFU should be sufficient to observe the subjects for risk of interest.
- Protocol should describe how the data will be recorded
- Protocol should describe steps that would be taken to assess causality for events of interest.

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Lots of Guidance on LTFU

Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

Draft Guidance for Industry

This guidance document is for comment purposes only.

Guidance for Industry

Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events

Long Term Follow-Up After Administration of Human Gene Therapy Products

Draft Guidance for Industry

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 January 2018
EMEA/149995/2008 rev.1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products

Draft

emea European Medicines Agency

London, 22 October 2009
Doc. Ref. EMEA/CHMP/GTWP/60436/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

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Guidance for RCR is Evolving Due to Increased Experience

	FDA 2006 Guidance	FDA 2018 draft guidance	EU 2009 guidance
Pre-treatment	Yes	Yes	Yes
RCR testing in 1st Year	3, 6, 12	3,6, 12	3, 6, 12
RCR testing: Subsequent years	RCR Sample collection Yearly thereafter. Samples archived	No sample collection if no positive tests in the first year	3, 6 and 12 for 5 years then yearly. Samples archived for 5 years if negative results during the first year of treatment
Clinical FU	Physical examination at the time of the annual sample collection	Yearly visits for the first 5 years by attendance at Healthcare Facility.(Hx and Physical examination) Then subsequently the yearly check up can be by phone or questionnaire	Physical attendance at clinic
Events of interest	Malignancy, neuro events, Hematologic disorders	Same as in 2006	Same as in the FDA Guidance

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Monitoring: Chimeric Antigen Receptor (CAR)-T Cell LTFU

- CAR T products are using non-replicating Gammaretroviruses or Lentiviruses to deliver CAR-encoding sequences into T cells
- These viruses can integrate or have the potential for latency followed by reactivation
- Autologus CAR T products are already in late stage development or being marketed (YESCARTA and KYMRIAH)
- Recently allogeneic CAR T products using genome editing are entering clinical studies.
- Currently there is a mandatory 15 year follow for CAR T products
- Long term monitoring for RCR is clear and specific with regards to the type of testing and the schedules
- Guidance for monitoring of insertional mutagenesis not as clear

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Post-Licensure Monitoring for CAR T Therapy

- Testing for RCR and vector integration should continue after FDA licensure.
- Using data from clinical studies to decide the extent of post-marketing testing for RCR.
  - RCR and vector persistency monitoring can be event driven: Only test in patients who develop an AE suggestive of a retrovirus-associated disease e.g Primary secondary malignancy, neurotoxicity, persistent hematological disorder
  - Centre for International Blood and Marrow Transplant Research (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT) are running post licensure LTFU for CAR-T therapies

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Suggested recommendations

- Provide more clarity on monitoring for off target effects of genome editing and insertional mutagenesis.
- Combine Is there a way of combining LTFU data from studies with the data combined from post marketing experience?
- Stakeholders should widely share the experiences and learnings from LTFU studies.

2017

2021

As more Gene Therapy products enter the clinic, it is important to harmonize conduct of LTFU studies as that will lead to better understanding of the magnitude of the risks.