STARS
STRENGTHENING
REGULATORY
SCIENCE

Online course

The Winding Road from a Brilliant Idea to Drug Approval

CSA STARS

Case-study: ATMP scientific advice

23-26 February 2021

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University Medical Center Groningen

university of groningen

CBG MEB
COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

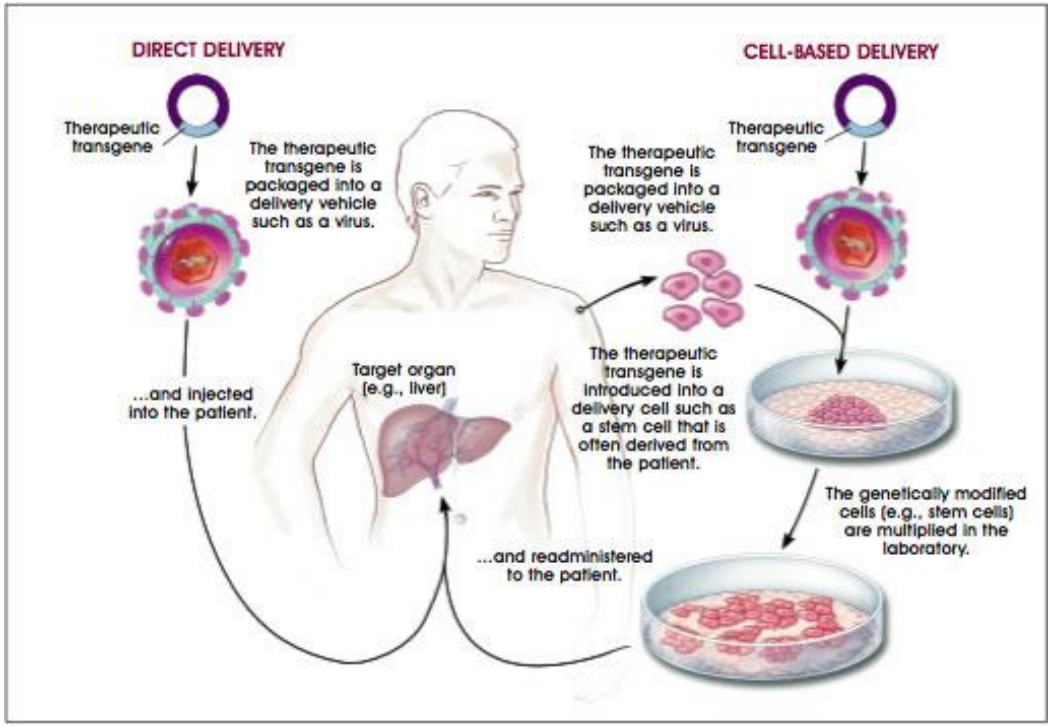
Today's program

09:00-09:40	Introduction to Day 3. How regulators work and think: the basics (Peter Mol)
09:40-09:45	Q&A
09:45-10:05	Novel regulatory tools & drug development support mechanisms (Peter Mol)
10:05-10:10	Q&A
10:10-10:25	Coffee break
10:25-10:50	Scientific advice (European & national) (Marjon Pasmooij)
10:50-10:55	Q&A
10:55-11:20	Case example – ATMP scientific advice (Viktoriia Starokozhko)
11:20-11:25	Q&A
11:25-11:40	Coffee break
11:40-12:10	Novel methodologies and Real World Evidence supporting drug regulatory decision-making
12:10-12:30	Final Q&A round (Moderator: Marjon Pasmooij)

Gene therapy

is a form of treatment that uses transfer of genetic material into the cell for therapeutic purposes

- Gene therapy
- Gene editing
- Gene silencing



(© 2001 Terese Winslow)

Gene therapy

- **Viral- based gene therapy** (LV, AAV, γ-retrovirus etc)
- Non-viral gene therapy (physical delivery, cationic lipids, nanoparticles etc)

Fields

- Oncology
- Haematology (sickle-cell disease, thalassemia, haemophilia etc)
- Immunodeficiencies
- Cystic fibrosis
- Spinal muscular atrophy
- other

Approved gene therapies, EMA

Trade name	Product	Condition	Vector	EMA approval
Glybera®	Alipogene tiparvovec	Lipoprotein lipase deficiency	AAV1-LPL ^{S447X}	10/2012 $^{\dagger 2017}$
Imlygic®	Talimogene laherparepvec	Regionally or distantly metastatic unresectable melanoma	HSV-1/GM-CSF	12/2015
Strimvelis®	Autologous CD34+ cells transduced to express ADA	Adenosine deaminase deficiency (ADA)	ϒ-retrovirus/ADA	05/2016
Yescarta®	Axicabtagene ciloleucel (CAR-T)	Relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma; Some types of non-Hodgkin lymphoma	ϒ-retrovirus	08/2018
Kymriah®	Tisagenlecleucel	Relapsed or refractory B-cell acute lymphoblastic Leukaemia; Relapsed or refractory diffuse large B-cell lymphoma	LV-CAR (CD19R)	09/2018
Luxturna®	Voretigene neparvovec	Inherited retinal dystrophy caused by biallelic RPE65 mutations	AAV2-RPE65	11/2018
Zynteglo®	Autologous CD34+ cells encoding βA-T87Q-globin gene	β-thalassemia with regular blood transfusions	LV-ß-globin	05/2019
Zolgensma ®	onasemnogene abeparvovec	muscular atrophy with a bi-allelic mutation in the SMN1 gene	AAV9-SMN	05/2020
Libmeldy ®	autologous CD34+ cell encoding the human arylsulfatase A gene	metachromatic leukodystrophy characterized by biallelic mutations in the arysulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity	LV-ARSA	12/2020
Tecartus ®	Autologous peripheral blood T cells transduced with anti-CD19 CD28/CD3-zeta chimeric antigen receptor	relapsed or refractory mantle cell lymphoma	retrovirus	12/2020

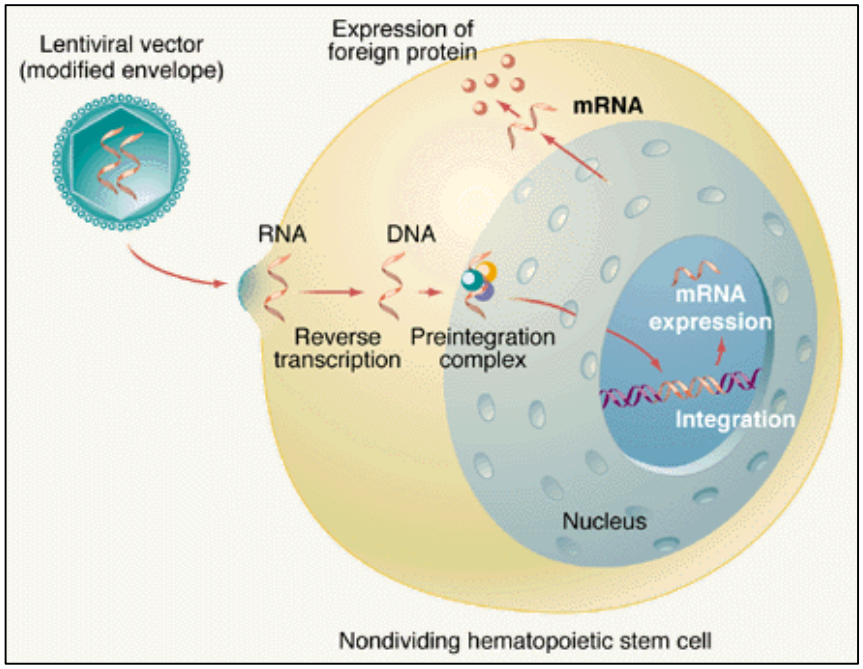
Scientific advice -scope

To get advice on the drug development program:

- Questions on Chemical, Pharmaceutical and Biological development
- Questions on non-clinical development
- Questions on clinical development
- Questions on regulatory/registration strategy
- Questions on significant benefit

Case-example: LV- based gene therapy for haemoglobinopathy

- integrating vector
- in-vitro transduction of CD34+ haematopoietic stem/progenitor cells
- introduction of a new gene



Amado & Chen, Science, 1999

Aim of the treatment:

disease cure

Example of questions on Chemical, Pharmaceutical and Biological development (1)

- **Definition for drug product, drug substance and starting materials**
  - raw material vs starting material: vectors, patient cells
  - drug substance: genetically modified cells
  - drug product: final formulation of the drug substance including excipients in the immediate container

- **Production of the LV**
  - source, exact steps

- **Characterization tests of the starting material**

Example of questions on Chemical, Pharmaceutical and Biological development (2)

- **Release tests for the drug product**
  - important!
  - total and CD34+ cell count and viability, cellular impurities, transduction efficiency (including VCN), potency test, sterility

- **Drug product manufacturing process: characterization and validation strategy**

- **Drug product characterization and comparability strategy for a change to commercial manufacturer**
  - if the commercial product differs from the product used in the clinical trials

Example of questions on Chemical, Pharmaceutical and Biological development (3)

- **Potency assay**
  - **measures the function of both the transgene and the cellular component (CD34-enriched cells) of the final product**

- **Usage of transduction enhancers**

- **Cryopreservation**

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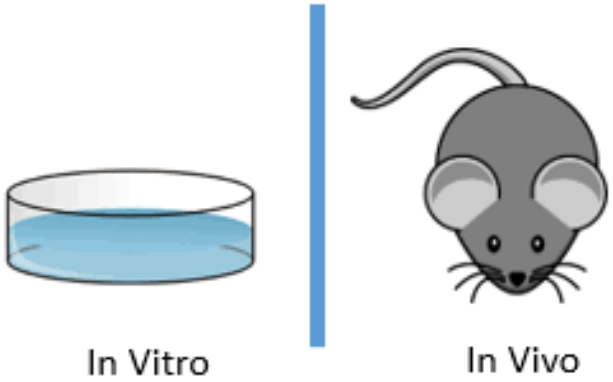

Questions on non-clinical development
Questions on Toxico-Pharmacological development

- **General suitability of the non-clinical package**
- **Determination of the clinical starting dose**
- **Biodistribution studies**

  - expression of the transgene in different organs
- **Mutagenicity studies**
- **Suitability of the animal models**

  - how representative is the model?
  - are certain studies really needed?
  - what species?

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Examples of questions on clinical development

- **Single pivotal trial**
  - is clinical effect outstanding?
  - external & internal validity is essential
  - see EMA Points to Consider on application with one pivotal study

- **Trial design: single arm trial *vs* (randomized) controlled trial**
  - is RCT feasible?
  - delayed start design
  - historical control (data quality?)
  - innovative trial designs

Play a role:
Natural course of the disease
Rarity of the disease
Effect size

Examples of questions on clinical development

- **Study population**
  - severity
  - genotypes
  - ages

  } influence indication!
  - geographical study location (USA, EU, Asia etc)

- **Sample size**
  - rarity of the patients (disease severity)
  - sufficient efficacy & safety data sets: sample size based on efficacy endpoint only might not be accepted

- **Dose**
  - minimum/maximum dose

Examples of questions on clinical development

- **Primary endpoint**
  - PD marker
  - hard clinical outcome
  - which is the most relevant for this specific drug & population?

- **Secondary endpoints:**
  - PD markers
  - healthcare burden (e.g. hospitalizations, transfusions) – important for HTA, reimbursement
  - patient-reported outcomes (PRO)

- **Statistical analysis plan**

Examples of questions on clinical development

- **Long-term efficacy & safety data**
  - Post-marketing studies: safety, efficacy
  - Registries: study design, data quality, data entry

Marketing of Zynteglo suspended as precaution due to potential cancer risk

bluebird bio has chosen to suspend sales of Zynteglo while they investigate whether safety concerns identified with a related investigational gene therapy may apply to the licenced medicine.

By Hannah Balfo
Pharmaceutic
19 Februar
No comments yet
SHARES

Orchard Therapeutics' gene therapy Strimvelis linked to a leukemia case

by Angus Liu | Nov 2, 2020 12:27pm

Product registry, e.g. Zynteglo ®

Disease registry (e.g. cystic fibrosis)

Procedure registry (e.g. EBMT)

Nancy Finn, 2017

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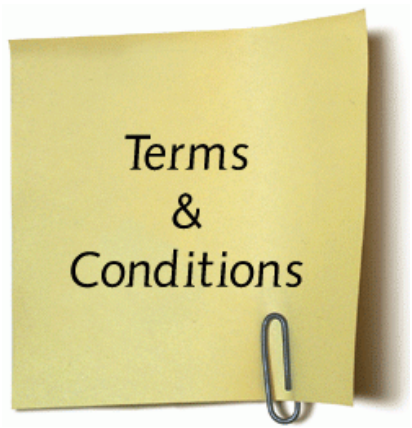
Examples of questions on regulatory/ submission strategy

- Full marketing authorization
- Conditional marketing authorization
- Exceptional circumstances



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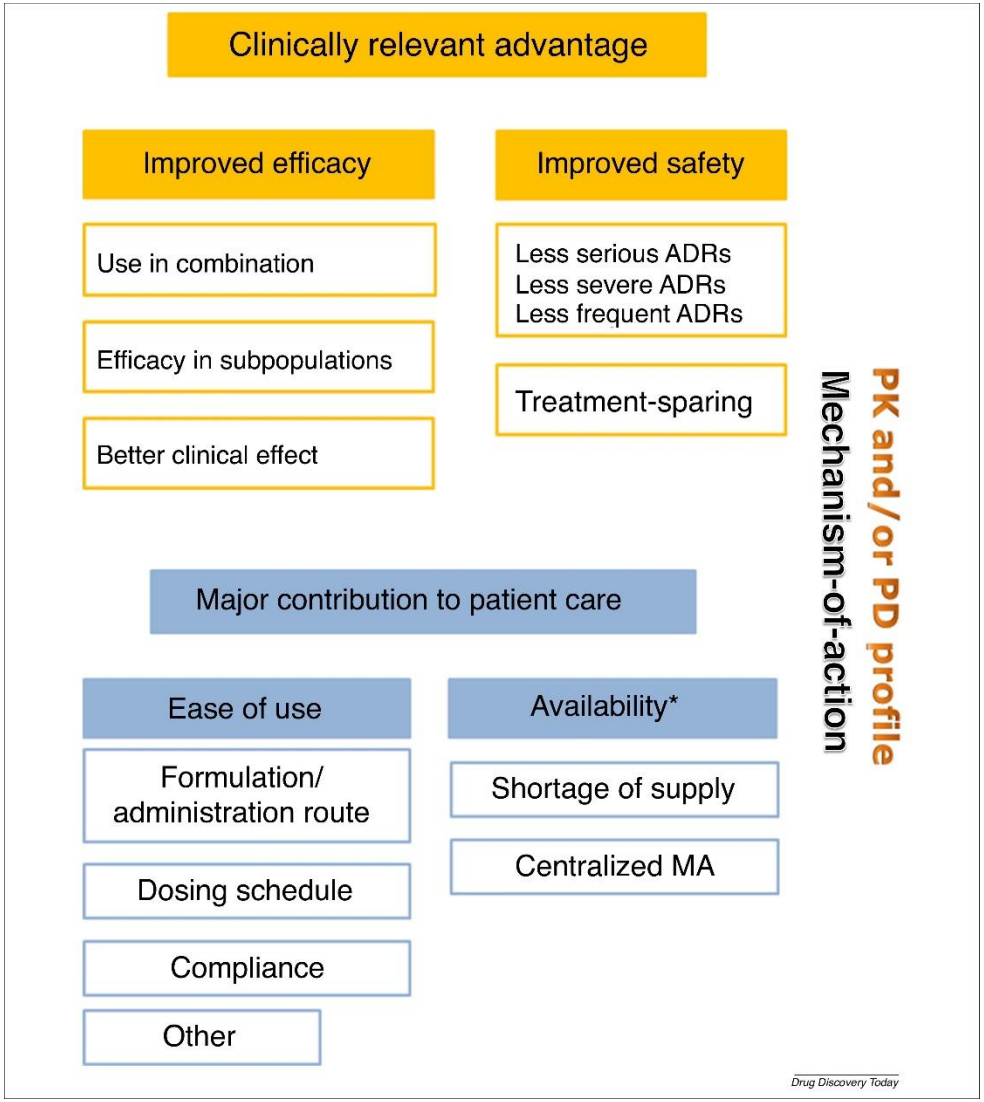
Significant benefit

- In the EU, demonstration of 'significant benefit' is mandatory if satisfactory methods exist for a disease targeted by a new orphan medicinal product.

- Will generated evidence be sufficient to demonstrate a benefit of new treatment over existing therapies?

- Important for the patient access to new therapies!

  - HTA, payers, reimbursement



Fregonese et al, 2018

Take home message

- During scientific advice you can ask questions on (almost) all aspects of drug development
- Open dialogue with regulators → thinking together
- Exceptions from the current regulation can be discussed

- Special advice procedure for biomarkers and novel methodologies – qualification advice

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GOOD MEDICINES USED BETTER

Thank you for your attention
Questions?