Advanced Therapy Medicinal Products:
from Promise to Reality

Regulatory path for translation of research
to commercial medicinal products

Nonclinical Development of Gene Therapy Medicinal Products

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Non Clinical Studies

Objectives

- To demonstrate proof-of-principle,
- Define effects transposable to Humans
  - -wanted
  - -unwanted

Prior to FIH trials AND through clinical development

Aspects to Address for GTMP

- Pharm … nodel(s)
- Bio-di …
- Recor … cheme to be …
- Identi …
- Identi … ctivity …
- Identi … ed clinic …
- Identi …

Most May be Needed

Before FIH Administration

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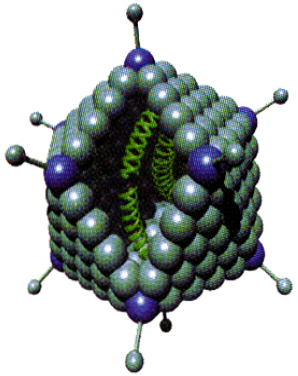
Non Clinical Studies

Principles



- should be performed in relevant (animal) models appropriately justified.
- The rationale of the NC Program must be justified.
- Conventional studies may not be appropriate for GTMPs.

The Concept of Relevance

Reflection paper on quality, non-clinical and clinical issues related to the development of recombinant adeno-associated viral vectors

Choice of Animal Model

- **Species specificity of the vector:**

  Eg : AAV is a species specific virus, therefore it is possible that the biodistribution of a human serotype derived vector in eg a mouse or rat and humans may not correlate.

- **Therefore Use of a serotype of virus that is specific to the animal model of choice, rather than the human serotype that will be used in clinical studies is justifiable .**

The Concept of Relevance

Reflection paper on quality, non-clinical and clinical issues related to the development of recombinant adeno-associated viral vectors

Choice of Animal Model.

- **Species specificity of the transgene product**: the impact of immune responses to the transgene product will also need to be factored into the assessment of the suitability of the animal model particularly as the gene of interest is likely to be of human origin,

- **Therefore Use a rAAV containing the appropriate homologous animal gene rather than the human transgene that will be used clinically is justifiable..**

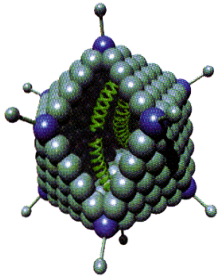
e “Basic” Nonclinical Development “Package”

- **Pharmacodynamics**
  - Primary (POC/MOA)
  - Secondary
  - Safety
- **Fate in the Body: ADME**
- **Toxicity / Safety**
  - General
  - Reproductive
  - Genotoxicity / Tumorigenicity

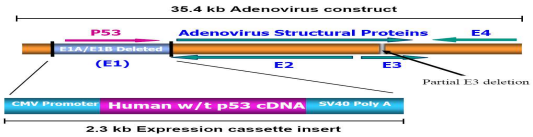
Gene Therapy Medicines
Type of Products

- Plasmid
- DNA
- viral vectors
- non-viral vectors
- genetically modified viruses
- genetically modified cells
- …

Active Components of GTMP



- delivery system/vector particle/virus,
- the transgene(s)/expression vector



- and the gene product(s).

- Supportive studies should in principle investigate the vector particle/delivery system and the therapeutic transgene(s) as included in the GTMP,

Pharmacodynamic Studies

- **Pharmacodynamic "proof of concept" in non-clinical model(s)**
  - In vitro **(animal / human)**
  - In vivo
- Expression /control of expression and production of the "correct" transgene product in the appropriate target organ must be demonstrated

- If production of any aberrant gene product is foreseen, its biological consequences need evaluation

Pharmacodynamic Studies (add safety?)

In vivo Studies

- Animal model of disease if possible
- Homologus models encouraged

Biodistribution Studies

- **Should provide data on all organs (target/non target)**
- **Should include investigation on**
  - GTMP persistence,
  - mobilization
  - and shedding (data form Tg/expression vector is generally sufficient).

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- **Dosing**
  - Should include clinical use (with safety margins)
  - Should cover administration schedules

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  - Should include clinical use (with safety margins)
  - Should cover administration schedules
- **Observation time**
  - should cover persistence of signal (i.e.duration of transgene expression and activity)
  - and include time-points for which there is no signal detection, if applicable.
- **Data might also contribute to the environmental risk assessment (ERA).**

Toxicity Evaluation

- **Should address the whole GTMP construct** (virus or other micro-organism or vector particle and/or delivery system + expression vector including cassette + transgene

- **Should address possibility of aberrant gene to be expressed**

- **Should consider intracellular positioning** (e.g. mitochondrial or nuclear chromosomal positioning) and the number of expression vector / transgene copies (e.g., with a view to insertional oncogenesis).

- **Should also Include the transgene product**
  - To determine any consequences of its over-expression
  - Immunogenicity
  - or unwanted pharmacological effects.

Toxicity Studies

The toxic potential of a GTMP is influenced by eg

- the number of vector particles,
- structural particle components, eg viral coat proteins
- the expression/integration of the delivered gene(s). (to be estimated for dose determination)

Dose determination should be based on the proportion of infective/transducing viral particles relative to total viral particle count

Toxicity Studies (1)

- **CPMP/SWP/1042/99 to be followed together with ICH M3 R2**
  - Species selection
  - Dose
  - **Study duration**
  - **Histopathology**
  - **Reversibility testing**
  - … …

  With case-based scientifically justified adaptations

Toxicity Studies (2)

- To Use the clinical route and method of administration
- Dosing based on the clinical and appropriate safety margins.
- Species Selection : should be relevant
- **Study Duration should be in line with ICHM3-R2.**
- **Single dose / persistent transgene expression the duration of observation should at least reflect the duration of the expression.**

Toxicity Studies (3)

- Integration studies
- Germline transmission
- Target tissue selectivity
- Immunogenicity and immunotoxicity
- Reproductive Toxicity
- Carcinogenicity/oncogenicity/tumorigenicity

(in silico/in vitro/in vivo)

- Environmental risk/shedding

e Gene Therapy Successes

In J Kaiser, Science, vol334, 29, October 2011

Disorder	Disease type	Patients benefiting	First publication
X-SCID	Immunodeficiency	17/20	2000
ADA-SCID	Immunodeficiency	26/37	2002
Adrenoleukodystrophy	Neurologic	2/4*	2009
Leber's congenital amaurosis	Blindness	28/30	2008
Wiskott-Aldrich syndrome	Immunodeficiency	8/10	2010
β-thalassemia	Hemoglobinopathy	1/1	2010
Hemophilia	Coagulation	6/6	2011?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Refusal of the marketing authorisation for Glybera (alipogene tiparvovec)

Outcome of re-examination

What did the company present to support its application?

The effects of Glybera were first tested in experimental models before being studied in humans. The company's clinical programme included 27 patients with lipoprotein lipase deficiency on a low-fat diet.

What were the CHMP's main concerns that led to the refusal?

During the re-examination, the CAT concluded that these concerns could be addressed with additional post-marketing studies. Whilst the CHMP still considers Glybera to be potentially valuable in the treatment of this very rare disease, it took a different view and concluded that the benefits of the medicine did not outweigh its risks due to questions over the medicine's benefits. The initial recommendation that Glybera should not be granted marketing authorisation was therefore maintained.

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Final Remarks

- Gene Therapy Medicinal Products constitute a Hope in the Context of Public Health improvement.
- Progress Towards Safer and more Efficient Delivery Systems Will Facilitate Their Success.
- **The Global Testing Strategies May Need Refinement**
- Early Dialogue with Regulatory Authorities May Facilitate The Development Process. And is Highly Encouraged.

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THANK YOU