Safeguarding public health

EMEA First Workshop on Advanced Therapy Medicinal Products (ATMP)

Requirements for gene therapy products: Non-clinical and clinical aspects

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Non-clinical requirements

Pharmacology

In vitro and *in vivo* pharmacodynamic “proof of concept”studies

- appropriate models and relevant animal species
- Target selectivity

Pharmacokinetics:

- Biodistribution studies
  - persistence, clearance and mobilisation
  - germ line transmission

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Non-clinical requirements

Toxicology:

- Unintended effects on the physiological function
- Repeated toxicity where single dosing may result in prolonged functionality
- Reproductive and developmental toxicity
- Integration studies
- Immunogenicity and immunotoxicity

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CLINICAL

Pharmacokinetics:

shedding studies

biodistribution studies, including distribution to gonads

pharmacokinetics of the product and the gene expression moieties *e.g.* expressed proteins

Pharmacodynamics:

expression

function

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Pivotal factors for success (where can it all go wrong?)

- Concept i.e., assumptions
- Quality of the product
- Specificity of the product
- Dose
- Posology
  - Method
  - Route
  - Duration
  - Frequency
- Target group
- Current therapies

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Regulatory requirements for approval

- Unequivocal efficacy
- Acceptable safety

Leading to **positive clinical benefit**

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DOSE & POSOLOGY

- Minimal effective dose
- Optimal dose
- Dose interval
- Effect of dose increment
- Dose related toxicity
- Therapeutic margin

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DOSE FINDING STUDIES

Extremely important, often poorly done

- Basis of chosen dose for MAA
- Maximal tolerated dose (MTD)
- Minimum Active Biological Effect Level (MABEL)
- Availability of PD markers
  - Are they valid?
- Can the planned studies support efficacy/ safety evaluation?

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Proof-of-concept studies

If necessary

- End-points
- Homogenous patient group
- Duration
- Comparator
- Supportive value

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Confirmatory trial (s)

- Single or multiple studies?
- Choice of countries/ centres
- Number of regions/ countries/ centres

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Trial design

End-points:

- Clinically meaningful
- If using surrogate, its validity
- Objective vs. subjective
- Efficacy is usually primary
- Safety could be an end-point, usually secondary

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Trial design contd.

Test Product

Use of commercial batches recommended. If not feasible, address comparability issues thoroughly

Comparator

- Placebo
- Active comparator
  i. Choice
  ii. Applicability

Active and placebo comparison

Blinding issues

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Are any special procedures involved?

Training to investigators
- Ensure consistency
- External validity when employed more widely
- Use might be restricted to specialists
- Description of procedure in protocol
- Problems with blinding
- Safety aspects of the procedure
- Can it be a confounding variable?

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Trial design contd.

Type of trial e.g.,

- Double-blind
- Randomised
- Controlled
- Parallel group

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Trial design contd.

Minimising bias

- Method of randomisation
  - Stratify, if necessary
- If open-label, choose objective end-points
- Consider independent efficacy evaluation
- Method of blinding, if applicable
- Avoid single-arm trial

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Trial design contd.

Statistical methods

Superiority/ equivalence/ non-inferiority

- Choice of delta (depends on the assumptions on efficacy)
- Power – e.g., 90 or 95%? (not a regulatory concern)
- If underpowered, how will the results be analysed?
- Sub-group analysis

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Trial design contd.

Analysis plan

- Interim analysis
- Stoppage rules for efficacy or futility
- Dropouts/ withdrawals handling
- Deviations/ violations handling
- Alpha spending effect

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Trial design contd.

SAFETY – General

Expected
Unexpected
On-target
Off-target

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Trial design contd.

Causality assessment

Minimise bias
Role of blinding
Safety monitoring committee
Scientific plausibility
Pattern of AEs

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Trial design contd.

Safety – specific

Emergence of replication competent vector
Emergence of new strains
Re-assortment of existing genomic sequences
Tumour development
Long-term safety

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RESULTS

Clinical benefit should be demonstrated

Statistical significance alone insufficient

Post-approval commitments may be necessary, based on the results

Post-hoc sub-group analysis usually not favoured –can be hypothesis generating at best!