

Gene Transfer Studies: PreClinical and Clinical Challenges

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To Improve Prospects for Success

- Keep safety in mind
- Seek FDA advice, keep us informed
- Adapt strategies to account for new developments
- Formulate a development plan
- Characterize mechanism of action
- Begin with a label in mind
- Maintain focus
 - **“Clinical effectiveness at a reasonable risk”**

Preclinical Investigations

- The first step in developing products for clinical use is to establish that they are reasonably safe to test in humans
 - To make a scientific determination that safety has been established, FDA reviewers ask to see all of the relevant preclinical data

PreClinical Safety Questions

Q: What is a safe starting clinical dose?

Q: What is a safe scheme for dose escalation?

Q: Can clinical benefit be obtained without excessive toxicity?

Initial Clinical Dose : NOAEL*

Tentative Safety Factor [tSF]

*No-Observable-Adverse-Effect-Level

Preclinical Investigations

What is the scientific basis for your clinical study?

- Rationale/proof of concept
- Have you established
 - A pharmacologically effective dose (or doses)?
 - An optimal route of administration?
 - An optimal regimen?
 - Species/model for activity/toxicity assessment?

Preclinical Investigations

Have you provided adequate preclinical data to support your proposed clinical trial? Do you have data to support

- an acceptable starting dose and dose escalation scheme?
- target tissue(s) of toxicity/activity?
- clinical parameters to monitor?
- subject eligibility criteria?

Preclinical Investigations

- Are your Preclinical and Clinical study designs similar with respect to their
 - Schedule and/or duration of treatment?
 - Route of administration?
 - Appropriate controls and dose levels?
 - Collection of appropriate safety and activity endpoints?
 - Study duration?

Preclinical Investigations

- Have your preclinical studies been performed using a
 - Clinically relevant product (i.e., same vector sequence)?
 - Relevant animal species/animal model of disease?
- Have you evaluated your vector for biodistribution and persistence?

Clinical Development

- **Two kinds of Studies**
 - Exploratory Studies
(Phase 1 and 2)
 - Confirmatory Studies
(Phase 2 and 3)

Exploratory Studies (Phase 1 and 2)

- Usual Objectives: Safety, Tolerability, Feasibility, Dose exploration, Activity
- Is the activity likely to predict for a clinical benefit?
- Have you considered measuring a clinical benefit in your exploratory studies?

Safety in Exploratory Studies

- Preclinical data may not predict clinical risk of gene transfer if
 - Vector specific for human cells
 - Risk related to insertion site in human genome
 - Gene product only active or toxic in humans

Hint: If the clinical risk of gene transfer is unpredictable, use low doses and proceed slowly.

Safety in Exploratory Studies

- Is the risk large and the potential benefit small?

Hints: If the risk is large

- Can benefit(s) be enhanced or the risk lowered?
- Are there alternative less toxic options?

Safety in Exploratory Studies

- Have you defined an optimal population that is predicted to have the largest likelihood of benefit at the smallest risk?
 - Is the predicted activity of the gene therapy confined to a subpopulation of study subjects?
 - Are subjects in whom the gene therapy is predicted to be inactive at substantial risk?

Safety in Exploratory Studies

- What are the effects of the gene in normal tissue?
 - Pharmacodynamics
 - Pharmacokinetics
- What are the effects of gene in abnormal tissue?
 - Related to target disease entity
 - Unrelated to target disease entity

Confirmatory Studies (Phase 2 and 3)

- Objectives
 - Efficacy – Is the activity associated with a meaningful, measurable clinical benefit?
 - Surrogate for Efficacy – Is the activity reasonably likely to predict clinical benefit? What is the evidence?
- Have your exploratory trials shown robust clinical activity?
- Have you selected an appropriate control population?

Confirmatory Studies

(Phase 2 and 3)

- Why do confirmatory studies fail to achieve their primary endpoints?
 - Clinical Benefit issues
 - Study Design issues
 - Statistical concerns – dropouts, bias, sample size
 - Open label vs. blinding

Clinical Benefit in Confirmatory Studies

- Did the exploratory study measure an activity or a clinical benefit? The activity may not have been predictive of a benefit.
- *Hints*
 - To maximize predictability,
 - perform proof-of-concept studies early
 - scrutinize the mechanism of action
 - Design an exploratory study to look for evidence of activity that will predict for clinical benefit

Confirmatory Studies

- Did you extrapolate based on a small sample?

Hints: Increase likelihood of achieving primary endpoint by

- Expanding the sample size
- Eliminating opportunities for bias
- Anticipating confounding issues

Study Design: Advantages of Larger Sample Size

- Responses in study arm may be less than expected
- Responses in control arm may be greater than expected
- Drop outs may be greater than expected
- Compliance may be inconsistent
- Participants with poor prognoses may enroll
- New regimens may emerge during the trial

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Extra Slides –

- **General Information Regarding FDA Assistance in Design of Preclinical and Clinical Studies and Product Development**

Role of FDA in Product Development

- Preclinical and clinical advice
 - preIND
 - Preclinical pharmacology and toxicology studies
 - Exploratory and confirmatory study design
 - Statistical plan
 - Special Protocol Assessment (SPA) for Phase 3 trials (details on next slide)

Special Protocol Assessment (SPA) for Phase 3 studies

- Available for phase 3
- The review:
 - FDA has 45 days to review
 - FDA concurs or does not concur
 - If we concur, FDA has agreed that design is sufficient to meet study objectives.

Special Protocol Assessment (SPA) *Hints:*

- For Help submitting an SPA:
<http://www.fda.gov/cber/gdlns/protocol.pdf>
- Optimal design for confirmatory study:
 - Randomized, double-blind, placebo or standard of care control, dose and schedule planned for label
 - Other designs
- Statistical plan
 - Well-designed
 - Avoids bias

Special Protocol Assessment (SPA) *Hints:*

- Primary and secondary objectives
 - Clinical benefit should be obvious
 - Sharply defined.
- As applicable
 - Independent Data Monitoring Committee
 - Blinded centralized review
 - Imaging and pathological material
- Questions with submission
- Submit a draft first

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