Clinical Trials of Cell Therapies for Parkinson’s Disease

CIRM Webinar
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Cell Therapies for Parkinson’s Disease (PD)

• First-in-Human (FIH) Clinical Trials
  – Trial Design
  – Example: Product is a cell, or genetically-modified cell, for intra-cerebral administration

• Expedited Programs for Serious Conditions
  – Breakthrough Designation
FIH Clinical Trial

- Objectives
- Basic Design
- Study Population (Eligibility Criteria)
- Dose / administration
- Monitoring
- Endpoints
FIH Trial – Objectives to assess:

1) Safety
2) Tolerability
3) Dose-exploration
   a) Maximum Tolerated Dose (MTD)
   b) Maximum Feasible Dose
   c) Optimum Biologic Dose
FIH Trial – Objectives to assess:

4) Feasibility, including:
   a) Logistics
   b) Recruitment

5) Preliminary Efficacy – better to fail early than to fail late(?)
FIH Trial – Basic Design

• Proof-of-concept
  – From non-clinical studies (animal models)
  – Helps justify risks to subjects
  – Helps guide the clinical study design

• Cohorts
  – Sequential
  – Size
FIH Trial – Basic Design

• Controls
  – Improve assessments of safety and efficacy
  – Historical; no treatment; sham surgery; placebo

• Randomization (if concurrent control)

• Blinding (particularly if sham surgery or placebo control)
FIH Trial – Eligibility Criteria

• Criteria for diagnosis of PD

• Disease status
  – Patients with a prospect of direct benefit
  – Not well-controlled; disabled
  – Ability to provide informed consent
  – Informative with regard to safety (and possibly efficacy)
  – Concomitant medications stable
FIH Trials – Dose / Administration

• Dose
  – Starting dose based on pre-clinical experience with study agent, and on any clinical experience with related products

• Dose-escalation
  – Sequential cohorts

• Unilateral intra-cerebral administration
FIH Trials – Dose / Administration

• Specify administration procedure, e.g., volume of administration; rate of administration; devices / catheters (whether FDA-cleared or investigational)

• Training in administration procedure
• Immunosuppression
  – Necessary or not?
  – If necessary, for what duration?

• Concomitant medications
  – Maintain constant dosing for study duration, if feasible
  – Document dose and regimen
FIH Trials - monitoring

- Long-term Follow-up
- Endpoints
  - Biochemical markers
  - Brain Imaging
  - Clinical outcomes (safety and efficacy)
Cell Therapies for Parkinson’s Disease (PD)

- First-in-Human (FIH) Clinical Trials
  - Trial Design
  - Example: Product is a cell, or genetically-modified cell, for intracerebral administration

- Expedited Programs for Serious Conditions
  - Breakthrough Designation
Expedited Programs

• Fast Track
• Accelerated Approval
• Priority Review
• Expanded Access ("compassionate use")
• Breakthrough Designation
Fast Track, Accelerated Approval, and Priority Review

• These terms apply to licensure or to the licensure process for drugs and biologics

• Fast Track: process designed to facilitate the development, and expedite the review of drugs to treat serious diseases and fill an unmet medical need; available at any stage of development prior to submission of license application
Fast Track, Accelerated Approval, and Priority Review

- **Accelerated Approval**: allows earlier approval of drugs or biologics that treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint. A confirmatory trial is needed.

- **Priority Review**: Two-tiered system of review times
  - **Standard Review**: ten-month time frame
  - **Priority Review**: six-month time frame. Designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists.
Expedited Programs

A serious disease or condition is defined … as:

“a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. … the morbidity need not be irreversible if it is persistent or recurrent.
Expedited Programs

Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

from FDA Draft Guidance for Industry: Expedited Programs for Serious Conditions
Expanding Access to Investigational Drugs

• Use of an investigational drug outside of a clinical trial, for the sole purpose of treating a patient or patients with a serious or life-threatening disease who have no acceptable medical options.

• Levels of expanded access are based on the number of patients to be treated and how much is already known about the drug:
  – Individual or intermediate size group access
  – Treatment IND
Food and Drug Administration Safety and Innovation Act (FDASIA)

- Signed into law July 9, 2012
- Fourth reauthorization of the Prescription Drug User Fee Act (PDUFA)
- Sec 902- Breakthrough Therapies
Breakthrough Therapy

A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement** on a clinically significant endpoint(s) over available therapies.
Breakthrough Therapy

• All Fast Track designation features, plus
  – Intensive guidance on efficient drug development, beginning as early as Phase 1
  – Organizational commitment involving senior managers
Draft Guidances

• Expedited Programs for Serious Conditions – Drugs and Biologics (June 2013)
• Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2012)
• Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (July 2013)
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Regulatory Questions:
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### Acknowledgements – Division of Clinical Evaluation and Pharmacology / Toxicology

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