Exploratory IND

The Problem

- Less than 10% of INDs for new molecular entities progress beyond the investigational agent stage to NDA
- 90% of INDs FAIL.
- FDA Critical Path report (2004)
  - reduce time and resources expended on candidate products that are unlikely to succeed.
- New tools needed to distinguish promising candidates from those that have a low probability of success.

FDA Guidance –April 06

- Existing regulations (21CFR 312) allow flexibility in the amount of data required for an IND depending on the:
  - Goal of the investigation
  - Specific human testing proposed
  - Expected risks
- Sponsors have not taken full advantage of this flexibility and often provide more information than required
- Purpose of the April 06 guidance is to clarify approaches for consideration in planning limited, early exploratory IND studies in humans:
  - Preclinical
  - Clinical
  - Chemistry, manufacturing and controls information
  - Previous human experience with the investigational drug or related compounds

Exploratory IND Study

Limited subjects, limited dose, for limited time

An exploratory IND study is:

- Conducted early in Phase 1, prior to traditional dose escalation/safety studies
- Intended to assess feasibility for further development
- Involves very limited human exposure
- No therapeutic/diagnostic intent/no MTD
  - (eg. Screening studies, microdose studies)
- Involves limited duration of dosing (e.g. < 7 days)

Objectives of Exploratory IND Studies

- Determine whether MOA defined in nonclinical studies is also observed in humans (e.g. binding property or inhibition of an enzyme)
- Provide PK information
- Select the most promising lead product from a group of candidates
- Explore biodistribution characteristics using various imaging techniques

Traditional vs Exploratory Approach

Traditional

- Broad objectives
- Only 1 compound
- Extended duration of dosing
- Toxicology is extensive-rodents/nonrodents
- Allows selection of a safe starting dose (1/10 HED based on NOAEL)
  - Target organ toxicity-estimate margin of safety between clinical and toxic dose
- Resource intensive – more subjects, more API needed

Exploratory

- Exploratory objective
- Multiple compounds
- Limited duration of dosing (<7 days)
- Smaller tox program
- Limited exposure/dose range (1/50 – ¼ NOAEL)
- Less resource intensive – less API, less subjects
- Earlier into humans
- *Does not replace traditional IND*
  - *Exploratory IND to be withdrawn upon completion of planned studies*
  - *Exploratory IND can be referenced*

Types of Clinical Studies

- Single-dose: sub-pharmacologic or pharmacologic dose given to a limited number of subjects (HV or patients)
  - e.g. microdose study involving single small dose
  - Collect PK data and/or perform imaging studies
  - Not designed to induce pharmacologic effects

- Multiple-dose: PD endpoints
  - <7 days
  - Dose escalate to evaluate PD endpoints not tolerability

Content of traditional vs exploratory

IND

- Clinical development plan
- MTD
- CMC (graded information)
- Batch to batch information
- Extensive toxicology
- Certified GLP

Exploratory

- Rationale only
- <7 days, no MTD
- CMC Summary report-not all impurities need to be characterized
- Limited toxicology-fewer animals 4 non-rodent/group,
- Limit species/single sex if no gender differences
- Consistent with GLP-exemptions allowed

Exploratory IND - CMC Information

- General information – similar to traditional IND
  - Description of product, method of manufacture, excipients, dosage form, test methods, stability
- Analytical characterization – 2 scenarios
    - Same batch used in toxicology studies and clinical trial(s)
      - Impurities are “qualified” in tox studies
      - Establish impurity profile to extent possible but not all impurities must be characterized at this stage.
    - Clinical batch different from tox batch
      - By analytical testing, show that clinical batch is representative of tox batch – identity, structure, purity, impurities, potency, physical and microbiological characteristics as appropriate.

Exploratory IND - Safety Program Examples Microdose studies

- Single dose study designed to evaluate PK or imaging of specific targets
- Not intended to induce pharmacologic effects
- Microdose is
  - <1/100 of dose calculated (based on animal data) to yield a pharmacologic effect
  - maximum dose ≤100 µg or ≤ 30 nanomoles for a biologic
- Single dose toxicity study by clinical route with 14 day observation period
  - Establish a dose causing minimal toxic effect or establish large safety margin (eg 100 X)
- Single mammalian species OK if justified by in vitro metabolism data and data on in vitro PD effects
- Additional studies in nonrodents (dogs) to confirm the rat as the sensitive species
- Genetic toxicity and safety pharmacology studies not needed.

Exploratory IND - Safety Program Examples Studies at Pharmacologically Relevant Doses

- Study of pharmacologic effects, no MTD, dosing up to 7 days
- Starting clinical dose <1/50 NOAEL
- Maximum dose – lowest of (1) ¼ NOAEL, or (2) ½ AUC in rat or AUC in dog or (3) dose with pharmacological effect
- Further dose escalation after consulting FDA
- 2 week at toxicity study by clinical route in sensitive species + TK
  - Goal of study is to select safe starting and maximum doses for clinical trial
  - Single dose level approximating the NOAEL
- Additional studies in nonrodent (dog) can confirm that rat is the sensitive species
  - Dose escalation culminating in repeated doses equivalent to rat NOAEL
  - If rodent not more sensitive species, 2-wk study in nonrodent is needed
- Safety pharmacology and genetic toxicity studies needed

Exploratory IND - Safety Program Examples Studies of MOA Related to Efficacy

- Alternative pharm/tox studies can establish clinical starting dose and escalation scheme
- Short term studies in 2 species with dosing strategy to achieve clinical PD endpoint can serve as basis for selecting safe starting dose
- Animal studies would incorporate endpoints based on the pharmacology of the drug that are believed to be important to effectiveness
- Single species can be used if established as the more relevant species
- Safety endpoints considered important to evaluate in clinical study should also be assessed in the toxicity studies

Advantages

- Test multiple compounds under 1 IND
- Toxicology program is abbreviated
- Smaller quantity of drug
- Shorter timelines (~8 months to FIM)
- Eliminates non-promising drug candidates early

Disadvantages

- Study objectives must be exploratoy
- No MTD
- Dose range tested is limited, esp. with low NOAEL
- Dosing duration limited (< 7 days)
- After completion of exploratory IND objectives, it should be closed and a traditional IND should be opened to further develop the drug
- Start of Phase 2 may be delayed