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**Clinical Trials: Phase 1**

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# Overview

## Phase 1 studies

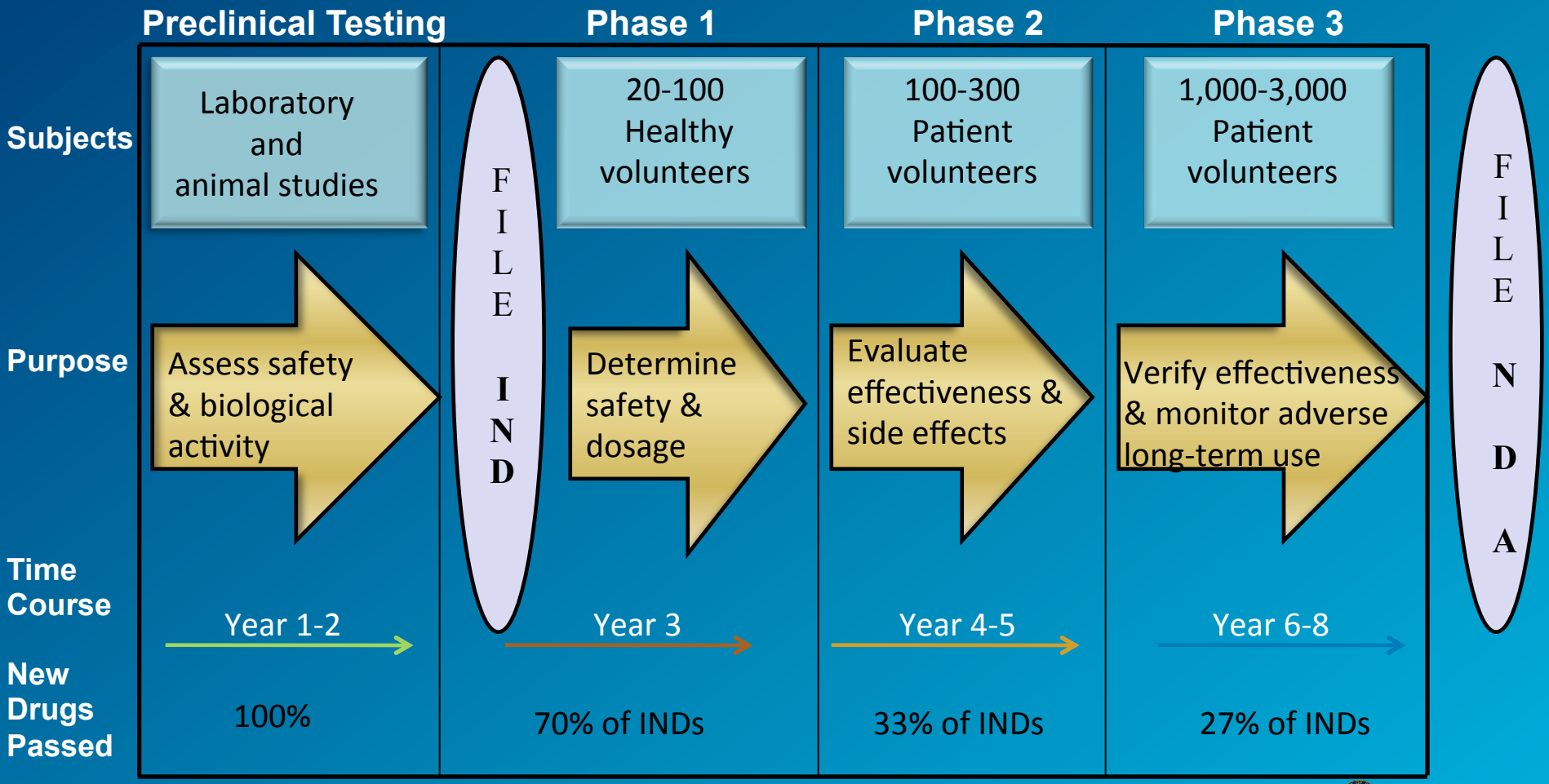
- Terminology
- Typical objectives
- Study Designs
  - population, entry criteria, use of placebo
  - dose escalation/stopping criteria
  - challenges in oncology
- Dose selection

# Introduction

Phase 1 studies characterized by competing objectives:

*getting maximal information from first clinical study vs. not compromising safety of subjects*

# Clinical Drug Development




*Redrawn from http://www.medscape.com*

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# Terminology

‘Phase 1’ is often used to mean different things, based on:

- ***Chronology***: first set of clinical studies conducted during drug development (most common definition)
- ***Population***: studies conducted in healthy volunteers (regardless of timeframe)
- ***Intent***: studies conducted to evaluate safety of a *new* combination of drugs

# Typical **objectives** of Phase 1 studies

- Characterize safety
- Identify dose-limiting toxicities
- Identify recommended dose for further clinical development
- Characterize pharmacokinetics
- If tenable, measures of drug activity

# **Example** : TeGenero Phase 1 study (TGN1412)

- TGN1412
  - first clinical product by TeGenero Immune Therapeutics
  - humanized monoclonal antibody that binds to and is a strong agonist to CD28, the T-cell receptor

- First In Man Phase 1 initiated in London March 2006
  - starting dose 0.1 mg/kg (500-fold ↓ than safe dose from animal studies)
  - administered as 3-6 minute infusion concurrently to healthy volunteers; n=6 active and n=2 placebo

- Hospitalization of 6 volunteers; 4 with multiple organ dysfunction.

# Safety

- Safety is primary imperative of Phase 1 studies

- Safety assessments to minimally include
  - Physical examination
  - Laboratory tests (hematology, serum chemistry, urinalysis)
  - Vital signs
  - ECG assessments
  - Adverse event monitoring

- The timing of safety assessments (baseline and post-treatment) to be clearly outlined in study protocol.

# Safety

- Usually will include any ***additional*** safety assessments as necessary based on class of molecule, expected effects, observed findings in animals
  - e.g., troponin or MUGA scans
  - e.g., BP measurements for antiangiogenic drugs
- Should pay particular attention to any severe, irreversible, acute, or potentially clinically silent effects observed in animal toxicology studies
  - e.g. cardiac necrosis, Torsade de Pointes

# **Additional** measurements

- If there are pre-identified "No Go" criteria that would stop further clinical evaluation of the drug, it is beneficial to assess them upfront in FIH study

  - if QTc prolongation expected, include rigorous ECG assessments (e.g., placebo/baseline/time-matched ECGs with positive control)
  - if drug is expected to be time-dependent inhibitor of CYP3A4 include midazolam interaction
  - e.g., if plasma half-life is short & requires more frequent than once daily dosing
  - e.g., evaluation of effect of food will help guide dosing for future clinical studies

# **Markers** of drug activity

- Depending on intended effect the drug, may be feasible to include early markers of drug activity or mechanism of action.
  - e.g. FEV for asthma
  - Glucose levels for anti-diabetic
  - Changes in HIV viral load for AIDS

# **Enrollment** criteria: Phase 1 studies

Phase 1 studies typically conducted in a highly controlled study population

- Healthy male /female,18-55 years, within range for body mass index
- No clinically significant abnormalities/diseases
- Provided informed consent
- Willing to follow guidelines for meal and dietary restrictions: alcohol, tobacco and caffeine use
- No pregnant or nursing females; considerations for female subjects of child-bearing potential
- Use of most concomitant medications restricted
- No recent blood donation or participation in another study

# **Single-Dose** Phase 1 study

This is usually the FIH study

- Population: healthy volunteers, with some exceptions
- Number of subjects:
  - Depends on confidence in safety, nature of expected adverse events and expected PK variability.
  - Usually ~ 6 subjects active treatment + 2 subjects placebo
  - Can have more subjects depending on additional assessments included in study (e.g., QT assessments, biomarker assessments, metabolism via enzymes that demonstrate genetic polymorphisms)
  - Dropout considerations
- Site: Usually single site, in promixity of ICU/emergency medical facilities

# **Single-Dose** Phase 1 study

## STUDY DESIGN

Should provide required information without compromising safety of subjects.

- Usually *subject-* and *investigator-blinded*, *sponsor-open*
- Different designs have been used:
  - Crossover design favored (vs. parallel design)
    - uses fewer subjects
    - each subject acts as their own control for safety / drug activity.
    - carries potential for safety (and PK) carryover
    - drop-outs will impact results substantially
    - each subject will receive many doses

# **Single-Dose** Phase 1 study

– Crossover (placebo-substitution design)

| Cohort | Number of subjects | Treatment | | | |
|---|---|---|---|---|---|
| | | **Period I** | **Period II** | **Period III** | **Period IV** |
| **A** (n=8) | 2 | Placebo | Dose 2 | Dose 3 | Dose 4 |
| | 2 | Dose 1 | Placebo | Dose 3 | Dose 4 |
| | 2 | Dose 1 | Dose 2 | Placebo | Dose 4 |
| | 2 | Dose 1 | Dose 2 | Dose 3 | Placebo |
| **B** (n=8) | 2 | Placebo | Dose 6 | Dose 7 | Dose 8 |
| | 2 | Dose 5 | Placebo | Dose 7 | Dose 8 |
| | 2 | Dose 5 | Dose 6 | Placebo | Dose 8 |
| | 2 | Dose 5 | Dose 6 | Dose 7 | Placebo |

– In design above, 8 doses can be studied with two cohorts.

– Time between consecutive periods must be defined (at least 7 days)

– Time between last period in Cohort A and first period in Cohort B should be long enough to allow safety and PK assessments

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# **Single-Dose** Phase 1 study

For very first dosing in humans, i.e., Period I of Cohort A (in any design), dosing should be staggered so safety initially evaluated in one subject at a time before dosing additional subjects.

# **Single-Dose** Phase 1 study

– Crossover (placebo-***insertion*** design)

| Cohort | Number of subjects | Treatment | | | |
|---|---|---|---|---|---|
| | | **Period I** | **Period II** | **Period III** | **Period IV** |
| A (n=8) | 2 | Placebo | Dose 1 | Dose 2 | Dose 3 |
| | 2 | Dose 1 | Placebo | Dose 2 | Dose 3 |
| | 2 | Dose 1 | Dose 2 | Placebo | Dose 3 |
| | 2 | Dose 1 | Dose 2 | Dose 3 | Placebo |
| B (n=8) | 2 | Placebo | Dose 4 | Dose 5 | Dose 6 |
| | 2 | Dose 4 | Placebo | Dose 5 | Dose 6 |
| | 2 | Dose 4 | Dose 5 | Placebo | Dose 6 |
| | 2 | Dose 4 | Dose 5 | Dose 6 | Placebo |

– In design above, 6 doses can be studied with two cohorts; increased study duration compared to placebo-substitution design

– **Each subject receives all 3 active doses and placebo**

– Two different active doses administered during some periods

# **Single-Dose** Phase 1 study

– Parallel design

| Cohort | Number of subjects | Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Period I** | **Period II** | **Period III** | **Period IV** | **Period V** | **Period VI** |
| A (n=8) | 6<br>2 | Dose 1<br>Placebo | | | | | |
| B (n=8) | 6<br>2 | | Dose 2<br>Placebo | | | | |
| C (n=8) | 6<br>2 | | | Dose 3<br>Placebo | | | |
| D (n=8) | 6<br>2 | | | | Dose 4<br>Placebo | | |
| E (n=8) | 6<br>2 | | | | | Dose 5<br>Placebo | |
| F (n=8) | 6<br>2 | | | | | | Dose 6<br>Placebo |

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# **Single-Dose** Phase 1 study

## Parallel design

- A subject will receive only 1 treatment: randomly assigned to active drug or placebo.
- requires substantially more subjects than crossover design
- Cannot evaluate intra-subject variability
- Typically employed when
  - (predicted) plasma half-life of parent/metabolite is so long that it is difficult to logistically implement washout and successive treatments in a crossover design.
  - there is concern about exposing participants to more than one dose of a drug (e.g., generation of neutralizing antibodies for biologics)

# **Multiple-Dose** Phase 1 study

- Usually performed immediately after the FIH single dose study
- Usually intended to determine the recommended Phase 2 dose for the drug.
- Objectives:
  - –Evaluate safety with continuous dosing
  - –Evaluate steady-state pharmacokinetics
  - –Assess, where tenable, measures of drug activity

# **Multiple-Dose** Phase 1 study

- Population: typically healthy volunteers
  - Unless safety considerations preclude use of volunteers (e.g., oncology drugs, high-risk biologics, drugs tolerated better in patients than volunteers)
- Number of subjects:
  - Depends on confidence in safety, expected PK variability.
  - Usually ~ 6-8 subjects active treatment + 2 subjects placebo
  - Can have more subjects depending on additional assessments
  - Dropout considerations (replacements assigned to same treatment)
- Site: Usually single site, in promixity of ICU/emergency medical facilities. Subjects confined from day prior to treatment through an appropriate time (e.g., at least 24-hours after last dose)

# **Multiple-Dose** Phase 1 study

- Dosing Interval:
  - usually predicated by half-life (and duration of effect, if available) from single-dose FIH study
- Duration of treatment:
  - Typically 7-14 days.
  - Typically dose at least to steady-state (3-5 half lives)
  - Longer duration can be considered provided there is toxicological coverage from animal studies.
  - At least 1-week between successive periods (for safety & pharmacokinetic evaluation); may be longer
- Design: Usually, randomized, placebo-controlled, double-blind (investigator and subject blinded), parallel group study.
- Dosing:
  - Usually escalated from a low dose, to ensure safety from prior dose before exposing subjects to higher dose

# **Multiple-Dose** Phase 1 study

– Parallel design, representative example:

| Cohort | Number of subjects | Treatment | | | |
|---|---|---|---|---|---|
| | | **Period 1** *Week 1-2* | **Period 2** *Week 4-5* | **Period III** *Week 7-8* | **Period IV** *Week 10-11* |
| A (n=10) | 8<br>2 | Dose 1<br>Placebo | | | |
| B (n=10) | 6<br>2 | | Dose 2<br>Placebo | | |
| C (n=10) | 6<br>2 | | | Dose 3<br>Placebo | |
| D (n=10) | 6<br>2 | | | | Dose 4<br>Placebo |

– ***For very first dosing, i.e., Period I of Cohort A, dosing should be staggered so safety evaluated in single subjects at a time***

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# **Multiple-Dose** Phase 1 study

In addition to usual safety and pharmacokinetic assessments, should also consider:

- Evaluation of human metabolites with multiple dosing
- Dose-linearity with multiple dosing
- Assessment of protein binding with multiple dosing
- Differences in safety/pharmacokinetics based on demographics (e.g., gender, ethnicity, age)

Pharmacodynamic measures of drug effect more relevant with multiple dosing, since will drive design of Phase II study

# **Stopping Rules** for Phase 1 studies

- Safety from ongoing-study reviewed in real time.
- Safety % pharmacokinetic data reviewed prior to escalation to next dose group.
- Dose-escalation halted if pre-determined safety threshold exceeded:
  - observed adverse events, laboratory findings, vital signs (including ECGs), or other criteria.
  - escalation may be halted for other reasons, e.g., observed drug-interaction/half-life makes it commercially untenable.
- Stopping rules should be clearly identified in study protocol and approved by IRB.

# **Dose Selection** for Phase 1 studies

- Dose selection for a FIH study is often a combination of art & science. Relevant doses that need to be projected include
  1. maximum tolerated dose
  2. pharmacologically effective dose
  3. starting dose

- Dose selection typically based on presumption that same (unbound) drug plasma concentration produces same effect **in all species**.

- Dose selection typically driven by a multitude of data sources:
  - toxicology studies
  - animal pharmacology studies (intended effect)
  - animal pharmacokinetic studies
  - *in vitro* metabolism studies
  - dosing/formulation options

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# **Dose Escalation** Considerations

**Starting dose → pharmacologically active dose → MTD**

- Ideally want to avoid excessive steps in getting to MTD
- May employ large dose increase steps initially (e.g., up to 3-fold) until clinical signs are observed, and then less aggressive dosing.
- Unless the drug is expected to have a steep dose-response, very small dose increases (e.g., < 2-fold) may not be useful, because these doses may not be pharmacokinetically distinguishable.
- May have wording built into protocol that escalation will proceed less aggressively after observation of specific signs (exposures>NOAEL, expected safety signals)

# Challenges with **Phase I studies in oncology**

- In most instances, FIH study conducted in patients with cancer
  - patients who have exhausted other therapeutic options
  - desire to get to 'therapeutic dose' during escalation soon, so subjects have greater chance of benefit
  - Need to expose as few subjects in earlier cohorts as possible

- Evaluation of safety may be confounded because
  - patients could have compromised end-organ (renal, hepatic) function
  - patients could be taking variety of concomitant medications that may interact with investigational drug

- Desire to characterize long-term safety to be weighed against permitting intra-cohort dose-escalation in lower dosing cohorts

# "Phase 0" study

- Study conducted with a dose of drug that is so small as to not be considered pharmacologically active
  - Typically done to decide if the drug is worth further clinical development (e.g., determine half-life of drug)
  - Can be accomplished by administration of a micro-dose of radiolabeled compound

# Example : TeGenero Phase 1 study (TGN1412)

- Could anything have been done differently to avoid the outcome from the TGN1412 Phase 1 (FIH) study ?