Healthy Volunteers or Patients in Phase I Trials?

Hermann Fuder
AGAH – Club Phase I
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Agenda

• Definition of stages and type of clinical trials
• Regulatory environment of early clinical development
• Safety/tolerability and ethical aspects of trials in healthy subjects vs. patients
• Scenarios in early clinical drug development
• Conclusions
Drug Development in Phase I, II, and III

All we always want to know about an NCE to become a drug:

– Does NCE reach site of action?
– Has NCE the pharmacodynamic effect?
– Affects NCE the pathophysiology/disease?
– Therapeutic window of NCE?
– Variability in response to NCE in target patients?
**Definition Phase I Trial**

- Trial performed in the very early stage of clinical drug development in humans («first in human», e.g. single ascending dose study, subsequent studies). Phase I is research aimed at identifying the safety, toxicities, pharmacokinetics, and the appropriate dosing of a new drug for future efficacy studies (Phase II).

- What is not discussed here today: other human pharmacology trials (e.g. drug-drug interaction studies, formal relative bioavailability studies)
## Classification of Clinical Trials

ICH E8: «General Consideration for Clinical Trials»

### Table 1 — An Approach to Classifying Clinical Studies According to Objective

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Objective of Study</th>
<th>Study Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Pharmacology</td>
<td>• Assess tolerance</td>
<td>• Dose-tolerance studies</td>
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<tr>
<td></td>
<td>• Define/describe PK(^1) and PD(^2)</td>
<td>• Single and multiple dose PK and/or PD studies</td>
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<td></td>
<td>• Explore drug metabolism and drug interactions</td>
<td>• Drug interaction studies</td>
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<td></td>
<td>• Estimate activity</td>
<td></td>
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<tr>
<td>Therapeutic Exploratory</td>
<td>• Explore use for the targeted indication</td>
<td>• Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures</td>
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<tr>
<td></td>
<td>• Estimate dosage for subsequent studies</td>
<td>• Dose-response exploration studies</td>
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<tr>
<td></td>
<td>• Provide basis for confirmatory study design, endpoints, methodologies</td>
<td>• Adequate, and well controlled studies to establish efficacy</td>
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<tr>
<td>Therapeutic Confirmatory</td>
<td>• Demonstrate/confirm efficacy</td>
<td>• Randomized parallel dose-response studies</td>
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<td></td>
<td>• Establish safety profile</td>
<td>• Clinical safety studies</td>
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<tr>
<td></td>
<td>• Provide an adequate basis for assessing the benefit/risk relationship to support licensing</td>
<td>• Studies of mortality/morbidity outcomes</td>
</tr>
<tr>
<td></td>
<td>• Establish dose-response relationship</td>
<td>• Large simple trials</td>
</tr>
<tr>
<td>Therapeutic Use</td>
<td>• Refine understanding of benefit/risk relationship in general or special populations and/or environments</td>
<td>• Comparative studies</td>
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<td></td>
<td>• Identify less common adverse reactions</td>
<td>• Comparative effectiveness studies</td>
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<tr>
<td></td>
<td>• Refine dosing recommendation</td>
<td>• Studies of mortality/morbidity outcomes</td>
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<tr>
<td></td>
<td></td>
<td>• Studies of additional endpoints</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Large simple trials</td>
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<tr>
<td></td>
<td></td>
<td>• Pharmacoeconomic studies</td>
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</tbody>
</table>

\(^1\) Pharmacokinetics

\(^2\) Pharmacodynamics
3.1.3.1 Phase I (Most typical kind of study: Human Pharmacology)

Phase I starts with the initial administration of an investigational new drug into humans.

Although human pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients, e.g. patients with mild hypertension. Drugs with significant potential toxicity, e.g. cytotoxic drugs, are usually studied in patients. Studies in this phase can be open, baseline controlled or may use randomisation and blinding, to improve the validity of observations.
ICH E8 Guideline (2) «General Consideration for Clinical Trials»
Regulatory Environment for Phase I

- Traditionally Phase I is done in healthy volunteers (except for e.g. anti-cancer drugs), but, what we are actually interested in, are data from patients! We develop drugs for patients.

- Does the regulatory environment allow us to do Phase I for many other NCEs besides anti-cancer drugs, instead in healthy volunteers, (directly) in patients?
Phase I Trials In Seriously Ill Patients under IND

FDAMA 113: A clinical trial conducted under an IND is required to be submitted to ClinicalTrials.gov, if it is a drug to treat a serious or life-threatening disease or condition AND it is a trial to test effectiveness.

- **Life-threatening:**
  (1) diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and
  (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival.

- The **seriousness** of a disease is based on factors such as survival, day-to-day functioning, and the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.
ClinicalTrials.gov (1)

- Currently: >1000 trials in patients classified as Phase I and I/II
- Patient populations for Phase I trials such as
  - Cancers of various types and tissues, Glioma, Melanoma, Lymphoma, Sarcoma, and other tumours (total >500 trials in malignancies)
  - Severe acute respiratory syndrom (SARS), Pulmonary Emphysema
  - Acute Renal Failure, Incipient Diabetic Nephropathy
  - Sepsis, Meningitis, West Nile Fever
  - HIV/AIDS, Smallpox, Hepatitis B and C
  - Graft Versus Host Disease
  - Rheumatoide Arthritis
  - Crohn’s Disease, Ulcerative Colitis
  - Lupus Erythematosus, Scleroderma, Varicose ulcer
  - Alzheimer Disease, Multiple Sclerosis, Spinal Cord Injury, Muscular Dystr.
  - Congestive Heart Failure, Myocardial Infarction, Coron. Heart Disease
  - Diabetes mellitus Type 1
  - Traumatic Brain Injury, Epilepsy, ….
Types of NCEs/Drugs Used in Phase I Trials in Patients:

– Cytotoxics/Cytostatics/Immunosuppressants
– Biotech products such as Antibodies, Vaccines, Gene products, Growth Factors, Autologous Cell Therapy
– Anti-infectives/Anti-virals
– Small molecule type new drugs
Case Study wetAMD

• GenVec Reports Encouraging Findings From Phase 1 Trial of AdPEDF in Patients With Wet Age-Related Macular Degeneration
• ... presented findings from a Phase 1 safety trial evaluating adenovector carrying the transgene encoding for human pigment epithelium-derived factor AdPEDF in patients with severe wet age-related macular degeneration (wet AMD).... Summarizing the study findings, Dr. Holz said, "We have seen an excellent safety profile, feasible delivery, and in some patients improvement in the appearance of the retina and stabilization of vision loss after administration of AdPEDF. We believe these findings are encouraging and that further testing in patients with less severe disease is the logical next step."

• The Phase 1, multi-center, open-label, dose-escalation study involved 28 patients with advanced disease at 8 dose levels. Seven patients were included at the top dose level, 1 x 10(9.5) pu. No dose limiting toxicities, drug-related serious adverse events, or cases of infection in the eye (endophthalmitis) were seen. The few adverse events observed during the study were minor and not dose-related. Improvements in retinal appearance and stabilization of visual acuity in patients with very advanced disease were seen. Analysis of findings from the study is continuing so that plans for additional clinical testing of AdPEDF can be made.

• The study was conducted at six sites nationwide including the Wilmer Eye Institute at Johns Hopkins University, Jules Stein Eye Institute at UCLA, the Kresge Eye Institute at Wayne State University, the Casey Eye Institute at Oregon Health & Science University, the University of Washington School of Medicine, and the Cullen Eye Institute/McPherson Retina Center at Baylor College of Medicine.

• Pigment Epithelium-Derived Factor (PEDF) is a protein normally produced in the eye that serves as a key regulator of retinal blood vasculature and also as a protective agent for photoreceptors (the eye cells that sense light and darkness). Levels of PEDF in the eye are low in patients with wet AMD. AdPEDF produces PEDF locally in the eye in order to raise the levels of this key protein.
Case Study: Type 2 Diabetes Mellitus (T2DM)

Novel principle of action NCE

Phase I/II program:

• First in human study in 32 T2DM patients:
  – Single ascending dose, safety/tolerability, PK, PD

• Multiple dose study in T2DM patients: 4 weeks
  – safety/tolerability, PK, pharmacodynamics (biomarker and surrogate)

• Planned: range finding study in T2DM patients with different co-medications to prepare Phase III
Benefit/Risk Ratio in Patients and Healthy Subjects

• Traditional development assumes that the benefit/risk ratio is in favour of performing Phase I trials in healthy volunteers and not in patients, except in cases where predictable unacceptable toxicity may cause AEs converting healthy subjects into patients.

• Why should a moderately hyperlipidemic, or hyperglycemic, or hypertensive, or ... patient, but otherwise healthy subject have a less positive benefit/risk ratio than the majority of healthy subjects?

• Group or individual benefit affects ratio positively in patients, not in healthy subjects

• Conversely, risk of a trial is more acceptable to a non-healthy patient volunteer who has a chance to benefit from a treatment; potentially increased risk can be balanced by Data Safety Monitoring Board (DSMB)
<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
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<tbody>
<tr>
<td>Vor Beginn der erstmaligen Anwendung am Menschen müssen die im Prüfpräparat enthaltenen arzneilich wirksamen Bestandteile in präklinischen Untersuchungen hinsichtlich ihrer Pharmakodynamik, Pharmakokinetik, Toxizität soweit untersucht sein, dass der im Prüfplan vorgesehene Dosisbereich, die Art und Dauer der Anwendung am Menschen sowie die Ein- und Ausschlusskriterien für die Probanden/Patienten und ggf. erforderliche medizinische Sicherheitsmaßnahmen begründet werden können.</td>
<td>Vor Beginn klinischer Prüfungen in Phase II sollte der für das Prüfpräparat im Prüfplan vorgesehene Dosisbereich, das Dosierungsschema sowie die Art und Dauer der Anwendung am Menschen in klinischen Prüfungen der Phase I hinsichtlich: Pharmakodynamik, Pharmakokinetik, Verträglichkeit so weit untersucht werden sein und in der vorzulegenden Dokumentation durch Daten belegt werden können, dass das mit dessen Anwendung verbundene Risiko eingeschätzt werden kann.</td>
<td>Der zu prüfende Dosisbereich sowie das vorgesehene Dosierungsschema sollten in klinischen Prüfungen der Phasen I und Phase II in dem bei Antragstellung entsprechendem Umfang hinsichtlich: Pharmakodynamik, Pharmakokinetik, Wirksamkeit, Verträglichkeit, so weit untersucht werden sein und in der Dokumentation durch Daten belegt werden, dass das mit dessen Anwendung verbundene Risiko eingeschätzt werden kann.</td>
<td>In der Regel ist für die klinische Prüfung eines in einem Mitgliedstaat der EU zugelassenen Arzneimittels die Vorlage der vom Sponsor ausgewählten Fachinformation bzw. der &quot;Summary of product characteristics&quot; (SmPC) ausreichend, solange die im Prüfplan vorgesehene Indikation, Darreichungsform, Anwendungsart und der vorgesehene Dosisbereich den Bedingungen der vorgelegten Fachinformation bzw. SmPC entspricht.</td>
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Toxicological Requirements for Phase I/II

<table>
<thead>
<tr>
<th>Dauer der Klinischen Prüfung</th>
<th>Minimale Dauer der Toxizitätsstudien mit mehrmaliger Verabreichung</th>
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<tr>
<td></td>
<td>Klinische Prüfungen</td>
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<tr>
<td></td>
<td>Phase I und II</td>
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<tr>
<td></td>
<td>Nagetier</td>
</tr>
<tr>
<td>Einmalige Verabreichung</td>
<td>2 Wochen</td>
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<tr>
<td>Bis zu 2 Wochen</td>
<td>2 Wochen</td>
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<td>Bis zu 1 Monat</td>
<td>1 Monat</td>
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<tr>
<td>Bis zu 3 Monaten</td>
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<td>Bis zu 6 Monaten</td>
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<td>&gt; 3 Monate</td>
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<td>&gt; 6 Monate</td>
<td>6 Monate</td>
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<table>
<thead>
<tr>
<th>Klinische Prüfungen</th>
<th>Phase III</th>
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<tr>
<td></td>
<td>Nagetier</td>
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<td></td>
<td>1 Monat</td>
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<td>3 Monate</td>
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<td>6 Monate</td>
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<td>6 Monate</td>
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Conclusion (1)

• The regulatory environment generally allows or even requests in many cases to start the Phase I clinical development in patients.

• Phase I and II are frequently one seemless entity.

• Phase I/II in patients provides early relevant clinical data in the target population.
Phase I Always in Patients for Any NCE?

• Is a Phase I/II development in patients able to provide a fast, adequate safety/tolerability profile of NCEs similar to the one obtained in carefully screened healthy volunteers?
Caveats for Phase I in Patients

• Single Dose: as a rule, no benefit to patients
• Requires frequently washout of preceding medication or adds complexity (potential drug-drug interaction)
• Recruitment rate low for patients: long duration of Phase I, multi-centre approach adds complexity
• Underlying disease affects biological parameter profile: risk of seemingly «dirty» drug safety/tolerability profile
Ethical Pros and Cons Phase I in Healthy Subjects/Patients

• Exposure to NCE of healthy subjects:
  – High scientific data quality, clean safety profile
  – Reliable PK data in very short time (PK as discontinuation criterion)
  – No benefit, only risk
  – Study conditions unlike real world

• Exposure of patient population:
  – No benefit on single dose, only group benefit
  – Potential benefit on multiple dose, but
  – Discontinuation of treatment pre-programmed, even in case of benefit at early stage of drug development
Drug Development Aspects of Phase I, II, and III

• What do we want to know about NCE?
  – Does NCE reach site of action?
  – Has NCE the pharmacodynamic effect?
  – Affects NCE the pathophysiology/disease?
  – Therapeutic window of NCE?
  – Variability in response to NCE in target patients?

• Studies in which population to get answers?
  – Healthy subjects and target patients Phase I
  – (Healthy subjects and) Patients Phase I/II
  – Patients of target population Phase I/II
  – Patients Phase I/II/III
  – Patients Phase II/III
Drug Development Phase I in Patients

- Critical success factors in drug development:
  - Time
  - Clear, relevant decision points
  - Costs
  - Quality

- Benefit/Risks for Phase I in patients:
  - Recruitment delayed?
  - Safe time in Phase II?
  - Relevance of patient data
  - Contamination of safety profile by influence of disease
  - See time, potentially lower
  - «Realistic» assessment in patients with large variation
  - Patient data quality frequently questionable (e.g. compliance)
Current Frequent Practice

- Single ascending dose: Healthy volunteers
- Multiple dose: Mild-moderate Patients
  - If meaningful positive PD outcome (biomarker): go into large Phase II trial
- Proof of Principle: Healthy subjects (with «disease» provocation) in parallel with MD study or, if feasible, in patients
- Phase IIa: only if MD not done in patients
Planing Scenarios  
Phase I/II

• Antipsychotic drug development in healthy volunteers/patients
  – First in healthy humans (not well tolerated, MTD low)
  – PET study to investigate target receptor occupancy (additional time and costs)
  – Multiple dose study in healthy volunteers (PK, metabolism at too low doses) and 1 patients group
  – Phase II in patients, dosing based on PET results

• Antipsychotic drug development in psychotic patients
  – First in patients (long duration, no improvement)
  – PET study
  – Multiple dose in patients (long recruitment; no efficacy, if less than 6 weeks duration)
  – Exploratory study in patients based on clinical outcome, 6-8 weeks, 2 doses (risk of failure: dose)
Conclusion (2)

• The answer to the question in the title: yes, volunteers and/or patients, depending on therapeutic area
• No single process to a fast and solid success
• Design the early development program to meet the specific needs of the NCE and of the therapeutic area
• Avoid the «one size fits all» concept and find the way to provide
  – maximum safety to volunteer (healthy subjects and patients),
  – optimum quality, costs and speed relationship