From Preclinical Data to Proof of Concept – Strategies for First to Man Studies.

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Traditional Development Chaine

Process

- Exploratory Research
- Strategic Research
- Preclinical
- Phase I
- Phase IIa
- Phase IIb
- Phase III
- Registration
- Launch

Target identification
- Lead structure identification
- Lead structure optimization
- Lead structure evaluation
- FIM (Safety, Tolerability, PK)
- Effect, dose ranging, safety
- Dose finding, safety
- Efficacy, safety
Phase I Working Package

First in Man Package

- FIM studies: safety, tolerability and pharmacokinetics (sd and md)
- Food effect (pilot)
- Effect of age and sex
- Critical drug interactions
- Comparisons of formulations if required (relative bioequivalence)
Clinical Pharmacology is More Than “Phase I”

Clinical Pharmacology conducts about 80% of all clinical trials until NDA

**Process**

- **Extended phase I**
  - Drug interactions (pharmacokinetic, pharmacodynamic)
  - Special populations (women, hepatic/renal/target pop.)
  - Mass balance, Absorption site, Bioavailability
  - New/alternative formulation
  - Special studies
Clinical Pharmacology is Even More

Process

- Exploratory Research
- Strategic Research
- Preclinical
- Phase I
- Phase IIa
- Phase IIb
- Phase III
- Registration
- Launch

Phase I after launch
- Regulatory mandated studies
- Marketing support studies
- Studies supporting new indications
- Life cycle management
Contribution of Clinical Pharmacology to Drug Development

- Clinical Pharmacology conducts about 40 - 50 % of all clinical studies in a company

Number of Clinical Trials* Year 1999

- 56 % (n=77)
- 31 % (n=38)
- 12 % (n=22)

- Clinical Pharmacology contributes about 40 - 50 % of information to the package insert

= Clinical Pharmacology
= Clinical Pharmacology / Clinical

Bayer HealthCare
Economical Pressure in Drug Development

economical situation in drug industry requires from everybody working in drug development

„to do more, faster with less“

to bring new compounds earlier and more efficiently to the market
Problems in Drug Development

- increase in NCE´s released for development
- increase in development times
- increase in development costs
- failure in late clinical trials
- decrease in NME output
- reduced effective patent life
- increasing pricing regulations
- poor response rates/nonresponders after market authorization
- adverse events/withdrawal after market authorization

→ 2001-2003: 15
Challenge in Drug Development

• to avoid
  ➢ to develop drugs unlikely to be therapeutically effective
  ➢ to market new products with potential safety issues
  ➢ to market new products lacking superiority or a better safety margin over existing treatments

• to evaluate alternative ways
  ➢ to define the potential for a drugs safety and efficacy earlier
Cost and Probability of Success of NMEs in Clinical Development

Cost of drug development in clinical phases

mio Euros

Probability of success of NMEs in early clinical development

0.5 – 1.0 (2.0)
Economical pressure in drug development - how to deal with?

Phase I and II studies should be designed for decision making ......

Colburn, 1996

„Too often the thrust of change has been on process rather than scientific content“

Lesko et al, 2000
Reason for Failure during Clinical Development

- 10% fail because of unwanted PK/unfeasible galenics
- 20% fail because of toxicology
- 40% fail because of lack of efficacy
- Others (economical)
Exploratory Drug Development

→ goal
  → fast entry into human
  → rapid go/no-go decision
  → minimizing resource needs in early development phases
  → reducing attrition rates in late development

→ pre-requisite
  → no change in safety requirements for volunteers

→ cave: does not save development time
  may cause additional time
Clinical Pharmacology is contributing to the overall development process

- **Input for clinical development and development plan**
- **Support of marketing by lifecycle management and realising competitive advantage**
- **Increased probability for registration through specific expertise in registration activities (e.g. dossier writing, hearings)**
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- **Knowledge transfer for DP1 candidate selection**
- **First dose to man**
- **Fast decision through early confirmation of mechanism of action**

**Phases of Drug Development**

- Exploratory Research
- Strategic Research
- Preclinical
- Phase I
- Phase IIa
- Phase IIb
- Phase III
- Registration
- Launch
Exploratory and Confirmatory Phase I

Exploratory phase I
Internal decision making
• go/no-go decisions based on
  – pharmacokinetics
  – pharmacodynamics
    • safety/tolerability
    • effect (PoM/PoP)
• candidate selection
• dose, dosing regimen
  – formulation, route
• critical interactions
• individualized plan for every compound before start of preclinics
• plan studies before FIM individually

Confirmatory Phase I
Labelling
• drug interactions
  – PK and PD
• special target populations
  – Women, hepatic/renal insuf.
  – Target population
• mass balance, bioavailability
• new/alternative formulations
special studies
• Concept for development before FIM
Before Exploratory Drug development

1. Preclinics
2. Standardized Programme
3. FIM Package
4. Phase Ila
Exploratory Drug development

Preclinics
Focused
Programme

Phase I
go/no-go
SD/MD/INT

PoM/PoP
„Phase I“
Setting

SD/MD/INT

PoM/PoP
„Phase IIa“
Setting

Preclinics
Focused
Programme

Phase I
SD

Preclinics
Focused
Programme

Phase I (vol. or pat.)
SD & MD

PoM/PoP
„Phase I“
Setting

Preclinics
Focused
Programme

SD/MD/INT

PoM/PoP
„Phase IIa“
Setting
Exploratory Phase I

- **Mandatory:**
  - First into man (SD): safety, tolerability, PK
    - but may only comprise limited number doses
  - Proof of Mechanism/Proof of Concept study
    - May be incorporated in FIM Study (PoM via lab. Biomarkers)

- **Optional:**
  - First into man (MD): safety, tolerability, PK
  - Food effect (pilot)
  - Effect of age and sex
  - Critical drug interactions
  - Comparisons of formulations if required
  - Absorption Site
  - **Integration of biomarkers whenever possible**
Exploratory Drug Development

→ goal
  → fast entry into human
  → rapid go/no-go decision
  → minimizing resource needs in early development phases
  → reducing attrition rates in late development

→ pre-requisite
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→ cave: does not save development time
  may cause additional time
Biomarker/surrogate/clinical endpoint - Definitions

• **Biomarker:** laboratory measurement or physiologic sign in association with physiologic process of putative therapeutic or diagnostic value

• **Surrogate endpoint:** laboratory measurement or physiological sign used as substitute for a meaningful clinical endpoint

• **Clinical endpoint:** clinical meaningful measure of how a patient feels, functions, survives

• used for safety and efficacy

Lesko et al. CPT, 2001
What is a Biomarker?

- Type 0: genotype/phenotype
- Type 1: plasma concentration
- Type 2: target occupancy
- Type 3: target activation
- Type 4: physiological measures
- Type 5: disease process
- Type 6: clinical scales

Dahnhof et al, Pharmaceutical Research 2005
First in Man Study

• Study design: Randomised non-controlled or placebo-controlled single- or double-blind cross-over or group-comparison usually monocentre studies

• Objectives: Safety, tolerability, pharmacokinetics, pharmacodynamics

• Subjects: Healthy (male) subjects, symptomatic subjects (mildly-diseased)

• Variables
  – Safety: Lab, vital signs, clinical measures (depending on compound and indication, subjective symptoms, questionnaire)
    • Nature of adverse events, maximum safe dose, reversibility countermeasures
First in Man Study

- **Pharmacokinetics** (drug and (active or major) metabolites): bioavailability, Cmax, tmax, t1/2, clearance, AUC, Vss
  - dose linearity/proportionality
  - bioavailability (absolute/relative)
  - interactions
  - age/gender
  - special populations

- **Pharmacodynamics**: variables depending on compound and indication, usually non-invasive
  - pharmacological profile
  - onset, duration, extent and variability of effects
  - interactions
  - age/gender
  - special populations

- **PK/PD relationship**
  - Dose/concentration effect relationship
  - Modelling and Simulation

- Formulation: service formulation possible
Adverse Events in Healthy Volunteers in Phase I Studies - Overall Results

Adverse events in 1559 volunteers with 2955 treatments

<table>
<thead>
<tr>
<th></th>
<th>active drug</th>
<th>placebo</th>
<th>total</th>
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<tbody>
<tr>
<td>follow-up (days)</td>
<td>25802</td>
<td>3862</td>
<td>29664</td>
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<tr>
<td>adverse events (n)</td>
<td>2192</td>
<td>153</td>
<td>2604</td>
</tr>
<tr>
<td>incidence (%)</td>
<td>9.1</td>
<td>8.5</td>
<td>8.8</td>
</tr>
<tr>
<td>incidence (%) placebo-contr.</td>
<td>14.1*</td>
<td>9.1</td>
<td>12.1</td>
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Lutfullin, Kuhlmann, Wensing IJCPT, 2005
Rates of occurrence of adverse events in healthy volunteers in phase I studies

<table>
<thead>
<tr>
<th></th>
<th>Sibille</th>
<th>Bayer</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>1558</td>
<td>2604</td>
</tr>
<tr>
<td>per subject</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>per treatm.</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>per study</td>
<td>29</td>
<td>18.3</td>
</tr>
<tr>
<td>mild/moderate %</td>
<td>97.2</td>
<td>99.2</td>
</tr>
</tbody>
</table>

Lutfullin, Kuhlmann, Wensing IJCPT, 2005
Considerations for Early PoM/PoC in Phase I/IIa

- **definition of study population**
  - healthy volunteers
  - patients with mild disease (symptomatic volunteers)
    - no disadvantage if no efficacy
    - no concomitant medication

- **validated biomarker**
  - feasibility in preclinical models
  - established PK/PD relationship
  - exploratory markers may be useful

- **safety first**

- **availability of adequate formulation**
  - usually service formulation (solution)/iv formulation
    - keep bioavailability problems low
    - feasibility in patients

- **focused preclinical program to support phase I up to PoP/PoM**
- **focused phase I program to support PoP/PoM study**
  - single/multiple dose escalation
  - special populations
Phase Ib/IIa: Proof of Concept

• Design: randomised placebo/competitor controlled, exploratory, double-blind single or multicentre trial (few centres only)

• Objective: Measurement of pharmacological activity

• Subjects: Healthy subjects or mildly diseased patients

• Variables: Biomarkers (surrogates) depending on indication

• Treatment: short term (up to 4 (-6) weeks), limited number of doses and subjects (50-100)

• Formulation: service formulation possible
Preclinical Pharmacokinetics

Rifa = Rifampicin
PB = Phenobarbital
Cp x = Compound x
Cp y = Compound y
Cp z = Compound z

CYP 3A4 activity
% of control

CYP 3 A4 enzyme induction in human hepatocytes

CYP3A3/4: 5 51%
CYP2E: 1%
CYP2D6: 24%
CYP2C8/9/19: 19%
CYP1A: 2.5%
CYP3A3/4/5: 51%

Fromm et al, Circulation 1999
Preclinical Pharmacokinetic Information

Information from basic pharmacokinetics in different species

- interspecies comparison
- absorption/elimination
- responsible enzymes
- most human like species
- polymorphic enzymes (2D6, 2C19)
- enzyme induction
- enzyme inhibition
- drug-drug interactions
- involvement of transporters
- absorption site

Information for phase I design
- go/no-go, up-scaling, interaction program, risk assessment
Exposure Predictions for Exploratory Phase I

• Estimation of likely human exposure (AUC and Cmax) for first dose in man

• Estimation of doses likely to be safe based on exposure in preclinical safety/toxicology studies

• Estimation of doses likely to be effective based on exposure in pharmacological studies
Determination of First to Man Dose

Safety Margin Considerations

Desired Effects

mouse in-vitro EC$_{50}$ 500 nM human in-vitro
EC$_{50}$ 48nM
rat in-vitro IC$_{50}$ 450 nM

mouse in-vivo C$_{max}$ 3.1 µM human (pred.) C$_{max}$ ~0.5 µM
(~1.5 mg/l @ 1.25 mg/kg bid) (0.2 mg/l @ 0.35 mg/kg)

f$_{u}$ 0.086 % $\Rightarrow$ C$_{\text{max},u}$ ~0.43 nM

Adverse Effects Safety Margin

HERG in-vitro EC$_{50}$ ~3 µM (EC$_{20}$ ~1 µM) 2
Purkinje fiber APD$_{90}$ shortening at ≥ 1 µM 2
consc. dog: no effects on ECG / heart rate

C$_{\text{max}}$ ≤ 8.0 mg/l (≤ 16.7 µM) > 33
f$_{u}$ 0.138% $\Rightarrow$ C$_{\text{max},u}$ ≤ 23 nM > 53

Proposed human starting dose: 0.1 mg/kg or 10
Determination of First to Man Dose - Species Scaling

AUC \( n=24 \)

- 67% within a factor of 2
- 79% within a factor of 3

C\(_{\text{max}}\) \( n=24 \)

- 55% within a factor of 2
- 77% within a factor of 3
Preclinical Pharmacodynamics

Experimental Pharmacology
Toxicology
Safety Pharmacology

formally well standardized (ICH-Guidelines; standard models)

but

often uncertainty about physiological relevance of target in man
Safety Pharmacology

- investigation of the effect on important physiological systems
  - mandatory (ICH)
    - cardiovascular, respiratory, central-nervous
  - additional (dependent on drug class, indication)
    - gastro-intestinal, excretory, endocrine, blood, metabolism etc.
    - dose-response relationship
- special investigations
  - pyrogenicity, immunotoxicity, hypersensitivity
### Duration of Toxicology Studies

Duration of toxicology studies required before starting studies in humans

<table>
<thead>
<tr>
<th>Clinical treatment</th>
<th>EU</th>
<th>USA</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>single dose</td>
<td>2 weeks</td>
<td>2 weeks*</td>
<td>2 weeks (non-rodent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 weeks (rodent)</td>
</tr>
<tr>
<td>multiple dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 2 weeks</td>
<td>2 weeks</td>
<td>2 weeks</td>
<td>2 weeks (non-rodent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 months (rodent)</td>
</tr>
<tr>
<td>up to 1 month</td>
<td>1 month</td>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>up to 3 months</td>
<td>3 months</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>up to 6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>6 months (rodents)</td>
<td>6-9 months (non-rodents)</td>
<td>* alternative: single dose with extended examinations</td>
</tr>
</tbody>
</table>
Preclinical Pharmacodynamics

• predictions for use in man
  – „therapeutic effect“ in relevant animal model
    • target concentration, minimum/maximum effective dose
    • dose-effect relationship
    • type of pharmacological measures to be used in man
  – toxicological/safety pharmacological targets
    • NOAEL
    • safety margin
    • type of precautions to taken in phase I
    • availability of decision making data (QTc)
  – effect of sex, age, disease

• need of biomarkers validated in preclinical studies
  – availability and use feasible in man
Preclinical Evaluation

- compound characteristics
  - high lipophilicity, low solubility
- meaning of target
- meaning of pharmacological model
- adequate description of dose/concentration-effect relationship
  - same species for all preclinical disciplines
  - relevant doses and time course, adequate number of animals
  - consistency of formulations in human and preclinical studies
- availability and use of biomarkers also feasible in humans
- availability and interpretation of required toxicological and safety pharmacological data
  - toxicokinetics
- description of metabolic pathways
  - most human like species, responsible and polymorphic enzymes, enzyme induction and inhibition QTc (HERG Channels), polymorphisms
Screening IND - I

- question: are single dose toxicology studies adequate to support s.d. phase I studies?
  

  
  guidance for s.d. animal tox to support s.d. phase I studies
  - 2 mammalian species
  - 2 routes of administration
  - wide range of doses incl. doses to cause life-threatening toxicity
  - male and female gender
  - observation for 14 days after dosing
  - histopathologic evaluation of all major organs and tissues (early and late - reversibility?)
  - toxicokinetics with validated assays
  - complete preclinical pharmacology efficacy program
Own single dose approach

- **toxicology**
  - s.d. tox. study rodent (clinical route)
  - 14-day study in rats (formulation maximising exposure)
  - 14-day study in non-rodent (formulation maximising exposure)
  - genotoxicity tests covering two different endpoints
    - e.g. Ames and micronucleus
    - reversibility should be built in the 14-day studies
- inclusion of 14-day studies offers more flexibility
  - e.g. start of up to two week studies in man
- **safety pharmacology**
  - traditional program
    - some parameters substituted by toxicology
    - if only s.d. toxicology available: full program needed
SD FIM and PoM - Laboratory Biomarker
Concentration-Effect Relationship for a Direct Factor Xa Inhibitor
Prediction of Plasma Concentrations and Pharmacodynamic Effects

observe and model
Prediction of Plasma Concentrations and Pharmacodynamic Effects

predict and verify
Prediction of Plasma Concentrations and Pharmacodynamic Effects

Mechanistic Parameter

Time [h]

#75 to be excluded

individual subject data
observations subject #75
model & prediction subj. #75
Sd FIM - PK and Exploratory Biomarker

The graph shows the plasma concentration over time and pharmacodynamic effect. The x-axis represents time in hours (0 to 25) and the y-axis represents plasma concentration ranging from -4 to 12. The graph also shows the pharmacodynamic effect ranging from -2 to 2.
Pupilloplophography as Exploratory Biomarker
Concentration-Effect Relationship

Healthy Volunteers

Patients

Sd phase I data (200-2000 µg, p.o.)
SD PoP - Clinical Biomarker in Healthy Volunteers

Animal experiment

Levitra effects after oral administration

Study 10010

Study 10011

Healthy volunteers

BAY 38-9456 induces much stronger erections than Sildenafil
The maximal Sildenafil effect can be achieved with 10× lower doses
SD PoP - Clinical Biomarker in Healthy Volunteers

LTD$_4$ induced bronchoconstriction

Study 1
- Placebo
- 250mg 2h

Study 2
- Placebo
- 100mg 2h
- 500mg 2h

Study 2
- Placebo
- 100mg 8h
- 500mg 8h
MD PoC in Patients - Laboratory and Clinical Marker

Plasma Renin Activity [µU/ml]

Time [h]

20 mg
50 mg
100 mg
200 mg
300 mg
400 mg

RR Patients

Plasma Renin Activity [µU/ml]

Time [h]

20 mg
50 mg
100 mg
200 mg
300 mg
400 mg

Renin Patients 7d

RR Diastolic Decrease in mmHg

Time [h]

2h (day 1) 2h (day 7) 12h (day 1) 12h (day 7)

20 mg
50 mg
100 mg
200 mg
300 mg
400 mg

RR Patients
SD PoM Healthy Volunteers vs Patients - Laboratory Marker

Renin Patients

Renin Volunteers

Plasma Renin Activity [µg/L/h]

Time [h]

Placebo
20 mg
50 mg
100 mg
200 mg
300 mg
400 mg

Plasma Renin Activity [µU/ml]

Time [h]

Placebo
10 mg
20 mg
40 mg
80 mg
200 mg
300 mg
400 mg
What has changed?
Technology and Knowledge and Degree of Certainty
Other approaches in Early Drug Development

• Screening IND
  – on the basis of existing guidelines
  – SD approach already mentioned

• Microdosing
  – guideline available
  – No own experience

• Exploratory IND
  – exploratory IND (US guideline)
  – just released, so far no experience
Exploratory IND

• FIM Limited toxicological programme to support
• Questions
  – Kinetics
  – Dynamics
  – Candidate selection
  – Not to replace MTD
• Sd Tox
• MD Tox: one species: three doses
  second species: one dose
• Starting doses: 1/50 AUC NOAEL rat
Conclusion

• FIM studies
  – should be individualized for every compound and focused on early go/no-go decisions

• FIM planning should consider
  – early evaluation of new compounds in preclinical phase
  – preclinical pharmacokinetic data
  – inclusion of biomarkers in FIM studies
    • clinical biomarkers/laboratory biomarkers
      ☑ pharmacogenetics/genomics
    • modelling and simulation
  – early realisation of PoM/ PoC
Basis of Medicine

Primum non nocere