Session 1 *Choosing the most appropriate study population in early-phase studies (healthy subjects or patients)*

When are early-phase studies in patients not useful, or even not acceptable?

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What is meant by “early-phase studies”?

First-in-Man (FIM) studies

⇨ In some special indications, *e.g.*, oncology, phase-I studies should be conducted in the target patient population because the compound’s specific side effects or toxicity would put undue strain or risks to healthy subjects

Proof-of-Concept (PoC) studies

⇨ may be conducted at an early stage as soon as the results of the preceding clinical trials in healthy subjects are available

Special safety studies in patients

⇨ to be conducted, if the special pathophysiology of the disease may be associated with an increased risk that may not be present in healthy subjects

Pharmacokinetic (PK) studies in patients

⇨ to investigate whether the PK in patients is comparable to that in healthy subjects

What is meant by “early-phase studies”?

Pharmacokinetic (PK) studies in patients

⇨ **Bioequivalence (BE) studies** that are recommended to be conducted in the target patient population are not “early-phase” studies in the strict sense, but they are mentioned here in this context.

e.g., BE studies with

- biosimilars
- immunotherapeutics
- cytotoxic compounds
- inhaled compounds

In some cases, the conduct of the BE study in healthy subjects may be an alternative option.

Current situation (personal impression):

There is an increasing tendency, especially among venture-capital driven biotechnological companies, to initiate safety trials (even FIM trials) and PoC trials in the target patient population at a very early point in time to speed up the clinical development.

Moreover, more and more sponsors which to issue so-called “combined study protocols”, even for FIM studies, which comprise cohorts of healthy volunteers and patients or contain different study objectives or complex endpoints in one protocol.

PoC Studies in patients should not be initiated before …

- An adequate phase-I program has been completed in healthy subjects,
- All safety and exposure data in healthy subjects have been thoroughly reviewed,
- There is a clear understanding of the dose range to be investigated in patients.
- The need of a dedicated, highly-controlled safety study in patients has been evaluated,
- The need of a dedicated PK study in patients has been evaluated:

  e.g., Can the PK be changed by the pathophysiology of the disease?
  Can the metabolism or excretion be altered in some patients? (*e.g.,* renal impairment)
  Consider risk of DDIs with usual concomitant therapy !

Disadvantages of early studies in patients as compared to healthy subjects (I)

- Lower level of standardization in comparison to a highly-controlled trial in a phase-I unit:
  - Ward unit in a clinic is often not adequately staffed
  - Clinical routine activities running in parallel / site personnel has additional tasks
  - Exact times of measurements are often not met in a clinical setting
  - Incidence & prevalence of adverse events may be underestimated

- Data quality may be compromised in a clinical setting

- Possible recruitment problems
  - ⇨ may lead to multi-centre study, which, in turn, may increase variability of data

- Recruitment of patients takes longer which is also a matter of cost and time (especially, if study is on critical path)

Disadvantages of early studies in patients as compared to healthy subjects (II)

- Safety results of patient studies may be biased by the underlying disease:
  a) Symptoms of the disease may be regarded as side effects.
  b) In this context, SAEs or severe AEs that are, in fact, caused by the underlying disease may become a regulatory problem, if causality is not clear.
  c) In turn, side effects of the drug may be “masked“ by symptoms of the disease.

- Different systemic exposure because of the pathophysiology of the disease,

- Elimination may be influenced by hepatic or renal impairment,

- Possible drug-drug interactions with concomitant therapies,

- Similarly, the results of pharmacodynamic measurements may be directly influenced by concomitant therapies.

General comparison of studies in healthy subjects *vs.* patients

Strengths

- High level of standardisation
- Elimination of confounding factors (AEs resulting from the disease, CT)
- Healthy subjects are “less vulnerable“

Weaknesses

- Study population may differ from target population in some respect (*e.g.*, ADME)
- No personal benefit

Special value / focus on

- Highly controlled phase-I safety studies
- Pharmacokinetic studies
- Special safety studies, *e.g.*, TQT trials
- PoC trial, if suitable model exists

Strengths

- study population identical or close to target patient population
- patients may possibly benefit from treatment (However: Avoid therapeutic misconception!)

Weaknesses

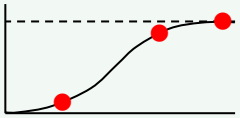
- Lower level of standardisation
- several confounding factors exist
- possible risks exist, if side effects of the drug interfere with pathophysiology of diseases
- burden for patients (should be minimized)

Special value / focus on

- Clinical efficacy trials under the patients‘ usual living conditions
- Controlled phase-Ib safety trial or ADME study in patients, if needed
- PoC trial (clinical setting)

Switching from healthy subjects to patients during clinical development

– on the way from a highly controlled environment to a clinical setting

Ph-I program	PoC trial	DRF study	Ph-II	Ph-III
exploratory	exploratory	exploratory	exploratory	confirmatory
healthy subjects	(healthy subjects) **patient subpopulation** (or target population)	**patients** (target population) 	**patients** (target population)	**patients** (target population)
ascending doses MTD not yet clear	one or three doses	investigate three doses to identify dose-response curve	usually two doses	one or two doses
Highly controlled	controlled	clinical setting	clinical setting	clinical setting
Monocentre study	Monocentre study or few qualifed sites	few qualified sites or multicentre study	multicentre study (*e.g.*, mono-national)	multicentre study (*e.g.*, multinational)

may be combined

may be combined

Possible medical or ethical problems of early studies in patients

Medical or ethical problems may result from the fact that the patient is actually in need of a treatment which must be washed out.

This may, *for example*, be the situation when the conduct of bioequivalence studies is recommended in patients.

⇨ **Possible way out**: Consider study conduct in healthy subjects

- The approach should be discussed with regulatory authorities
- Consider measures to reduce the toxicity of the compound

Measures to enable study conduct of a PK study in healthy subjects as an alternative to patients (Example 1)

Concomitant administration of a receptor antagonist, *e.g.*, naltrexone in case of a BE study with an opiate

	Day -1	Day 1													Day 2		Day 3		Day 4
Relative time in h	-10	-2	0	0.5	1	1.5	2	3	4	5	6	8	10	12	16	24	36	48	60	72
Naltrexone administration	**X**	**X**											**X**							
Opiate administration			**X**																	
PK sample collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Reproduction of study flow chart is not complete.
Only one treatment period is depicted here.
Adequate and serial safety measurements were done during the study, *e.g.*, pulse oxymetry, vital signs, ECG, clin. lab.
Medical screening and follow-up examinations were perfomed.

Measures to enable study conduct of a PK study in healthy subjects as an alternative to patients (Example 2)

Antagonisation of the pharmacodynamic effect,
e.g., folinic acid in case of a BE study with low-dose methotrexate

	Day -1	Day 1														Day 2	Day 3
Relative time in h	-12	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	10	12	16	24	48
Folinic acid administration																**X**	**X**
Low-dose methotrexate administration		**X**															
PK sample collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administration of K-Na-hydrogencitrate (Uralyt U®)	**X**	**X**										**X**		**X**			

Reproduction of study flow chart is not complete.
Only one treatment period is depicted here.
Adequate and serial safety measurements were done during the study, *e.g.*, vital signs, ECG, clin. lab., creatinine clearance
Medical screening and follow-up examinations were perfomed.

Measures to enable study conduct of a PD (or PK) study in healthy subjects as an alternative to patients (Example 3)

The glucose clamp technique

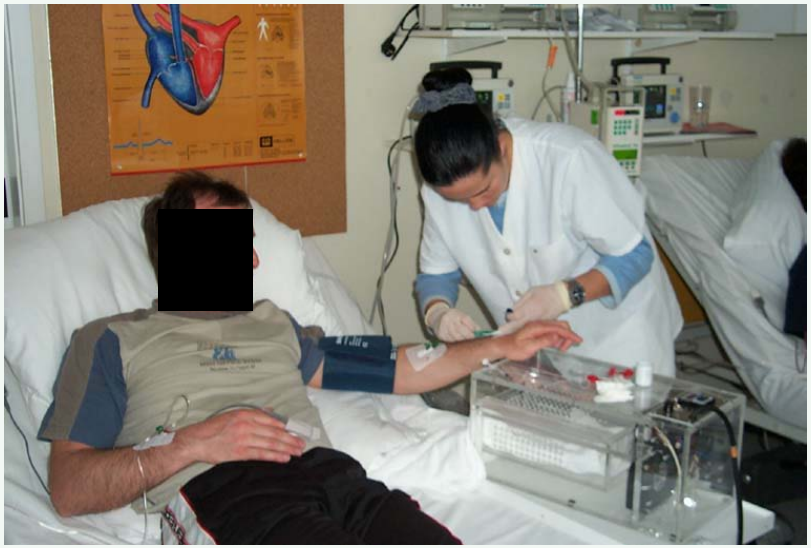
Basic principle:

Repeated blood samples will be obtained at bedside for immediate determination of whole blood glucose concentrations.

The rate of a glucose infusion will be adjusted to maintain a pre-determined target blood glucose concentration.

The varying glucose infusion rate will reflect any activity of an exogenous blood sugar lowering agent (primary endpoint: baseline-corrected glucose infusion rate).

The method can be automatized.



Special topic:

Shall BE studies with inhaled formulations be conducted in patients (COPD, asthma) or healthy subjects?

The applicable EMA Guideline focusses on therapeutic equivalence

GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS INCLUDING THE REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE BETWEEN TWO INHALED PRODUCTS FOR USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

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Special topic:

Shall BE studies with inhaled formulations be conducted in patients (COPD, asthma) or healthy subjects?

"In some cases, the use of only ***in vitro* data** … may be considered acceptable"

"if any of the … mentioned criteria are not fulfilled … ***in vivo* studies** should be performed"

"Equivalent **pulmonary deposition** in combination with safety data … **might** be considered as sufficient demonstration of therapeutic equivalence.
Otherwise, therapeutic equivalence must be demonstrated by means of appropriate clinical studies." ?

I. **Pharmacodynamic studies:**
(in patients)

"will almost always be required" ?

II. **Pharmacokinetic studies:**
(in healthy subjects or patients) ?

a) <u>with charcoal</u>:
to assess pulmonary deposition

b) <u>without charcoal</u>:
to investigate systemic safety

When are early-phase studies in patients not useful, or even not acceptable?

FIM Studies	Early PoC trials	BE Studies
When - the compound's specific side effects or toxicity would ***not*** put undue strain or risks to healthy subjects Because - Skipping Phase I in healthy subjects would put unacceptable risks to patients - Results of patient studies may be biased - EC / Reg. Authorities may not accept the trial application	When - no adequate Ph-I program was done in HS - no safety study in patients, though needed Because - unacceptable risk for the patients When - ADME in patients is not clear - the dose range is not understood Because - study design would not be appropriate - Results may be biased (e.g., insufficient exposure)	When - not requested by Reg. Authorities Tip: - Always try to negotiate study conduct in healthy subjects When - CT cannot easily be withdrawn Because - Ethical dilemma - Results may be biased (e.g., DDI) When - patient population difficult to recruit Because - lack of standardisation - time and cost issues

Some conclusions

- Patient studies should only be initiated after an adequate phase-I program (SAD, MAD) was completed in healthy subjects (apart from the well-known exceptions).
- Basic principles of reasonable project development should always be considered.
- More specifically, “wishful thinking“ should be avoided, and the critical path in the clinical development plan should always be identified.
- Combined study protocols do generally reduce transparency and clarity, and do often lead to the need of protocol amendments with subsequent delay (!)
- PoC trials in patients which are initiated too early may imply unnecessary risks.
- In particular, the design of a PoC study may not be appropriate, if the IMP‘s pharmacokinetic behaviour or safety margin is not fully understood.
- For standard PK studies, the use of healthy subjects should generally be preferred.