Integrated Study Protocols

The art of combining several questions into one well-designed clinical trial

28 Feb 2018

Dr. Christian Friedrich
Director Experimental Medicine

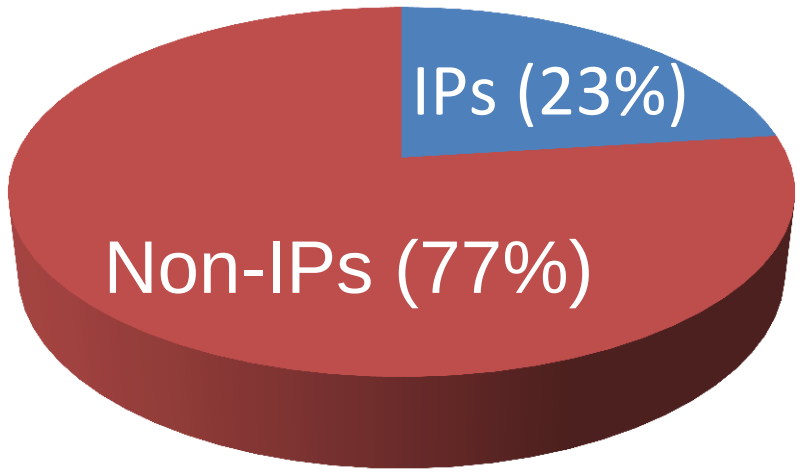
Agenda

- Background
- Integrated study protocols in the revised FiH guideline
- Types of integrated study protocols
- Recent examples from Bayer trials

Integrated Study Protocols - Background

The number of integrated protocols is steadily increasing

- **Broad definition:** Integration of several trial objectives into one exploratory clinical trial without statistical disadvantages.
- Number of integrated protocols in early development increased over the past decade.



- **Systematic analysis of 2969 clinical trials conducted between 2004-2014 in Germany**
- **From 2004 to 2014 the percentage of integrated early clinical trials increased from 17.9% to 28.2%**

Fruhner, Hartmann & Sudhop; Eur J Clin Pharmacol (2017) 73:1565–1577

Main motivation is

- **Why conducting integrated protocols? ➔ smart, time saving and cost-efficient integration of important key objectives of early clinical development (safety, PD, PK, rel or abs BA, food effect, crucial DDIs) to facilitate early decision making**

- **Time savings due to:**
  - **shorter overall approval times**
  - **earlier availability of data facilitating conduct of subsequent clinical studies**

- **Cost / resource efficiency:**
  - **synergies in combined studies, e.g. same control group can be used**
  - **Reduction of internal and external reporting steps (CSR, webposting etc.)**
  - **leaner CMC/Tox development for specific studies**

Integrated Study Protocols in the Revised FiH Guidance

Integrated study protocols in the revised 2017 FiH guideline

- Integrated protocols were not reflected in 2007 guidance

8.2.2. Integrated protocols

The practice of conducting FIH/early CTs with integrated protocols means that the information generated in previous parts needs to be analysed and integrated into an assessment in a limited timeframe prior to making a decision on proceeding to the next part (see section 8.3).

All parts, and the criteria to move from one part to another, should be predefined within an integrated protocol, as should possible modifications, based on the totality of available information and the related uncertainty. When definite doses cannot be predefined in all study parts, (dose selection) criteria should be established in the protocol. These criteria should integrate data from previous study parts. Feasibility to review and adapt the planned study design based on emerging clinical data should also be considered.

Any changes outside these predefined criteria should be implemented via a substantial amendment.

Regarding the time sequence for the conduct of different parts, the following recommendations apply:

- Overlap of SAD and MAD parts may be acceptable. However, any overlap should be scientifically justified and supported by decision points and a review of available data before starting the MAD part (see also section 7.6).
- Other single dose parts (e.g. food interaction) could be conducted in parallel to the SAD part provided the dose chosen and the expected exposure are equal to or lower than that which was reached in a concluded preceding SAD cohort where all relevant data has been reviewed and no dose escalation stopping criteria were met.
- Other study parts that involve multiple dosing (e.g. drug-drug interaction) should generally not overlap with earlier SAD or MAD cohorts. All relevant SAD and MAD data should be reviewed before starting these parts. Deviation from this should be justified in the protocol.

Key aspects on integrated protocols in the revised FiH guideline

Definition: Integrated protocols combine different studies *where data from a previous study part are analyzed and used to support & release a second study part*

- All parts (incl. modifications) need to be predefined
- Clear rules / decision criteria for transition from one part to the next needed (similarities with dose escalation)
- Doses need to be predefined or clear rules need to be specified how doses will be chosen
- Any other change ➔ substantial amendment

Key Aspects cont.

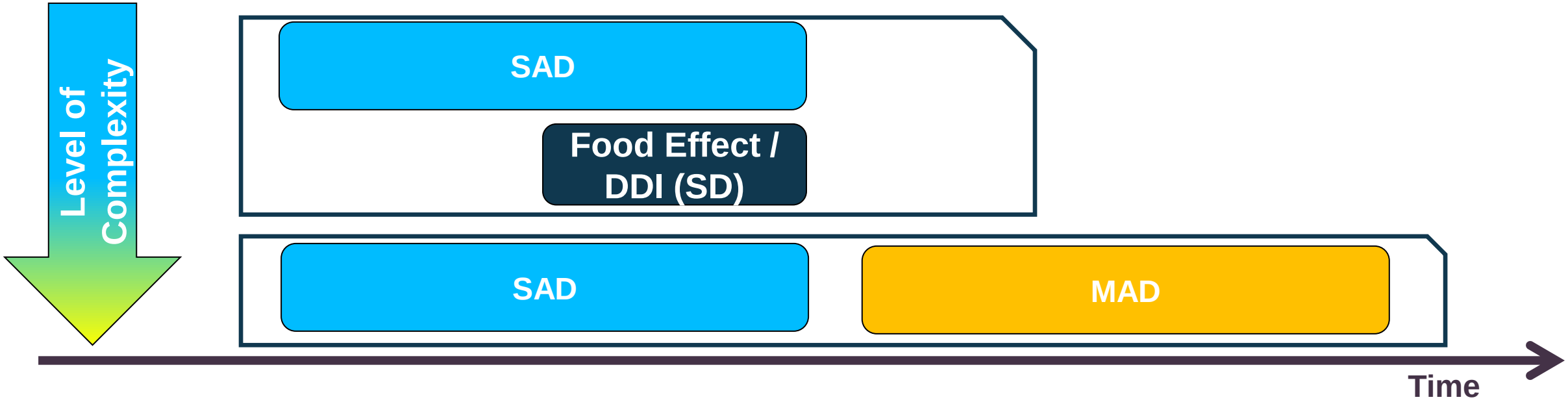
- SD questions like relative bioavailability investigations (e.g. LSF vs. tablet) or DDIs can be conducted in parallel to the SAD escalation if the expected exposure is equal/lower compared to the SAD parts already reviewed and found to be safe
- Other MD parts (e.g. MD DDI) should generally not overlap with earlier SAD/MAD parts; relevant SAD/MAD parts should be reviewed prior to starting those MD parts
- Overlap in SAD / MAD acceptable but needs to be scientifically justified
- *Deviations to be justified*

Types of Integrated Study Protocols

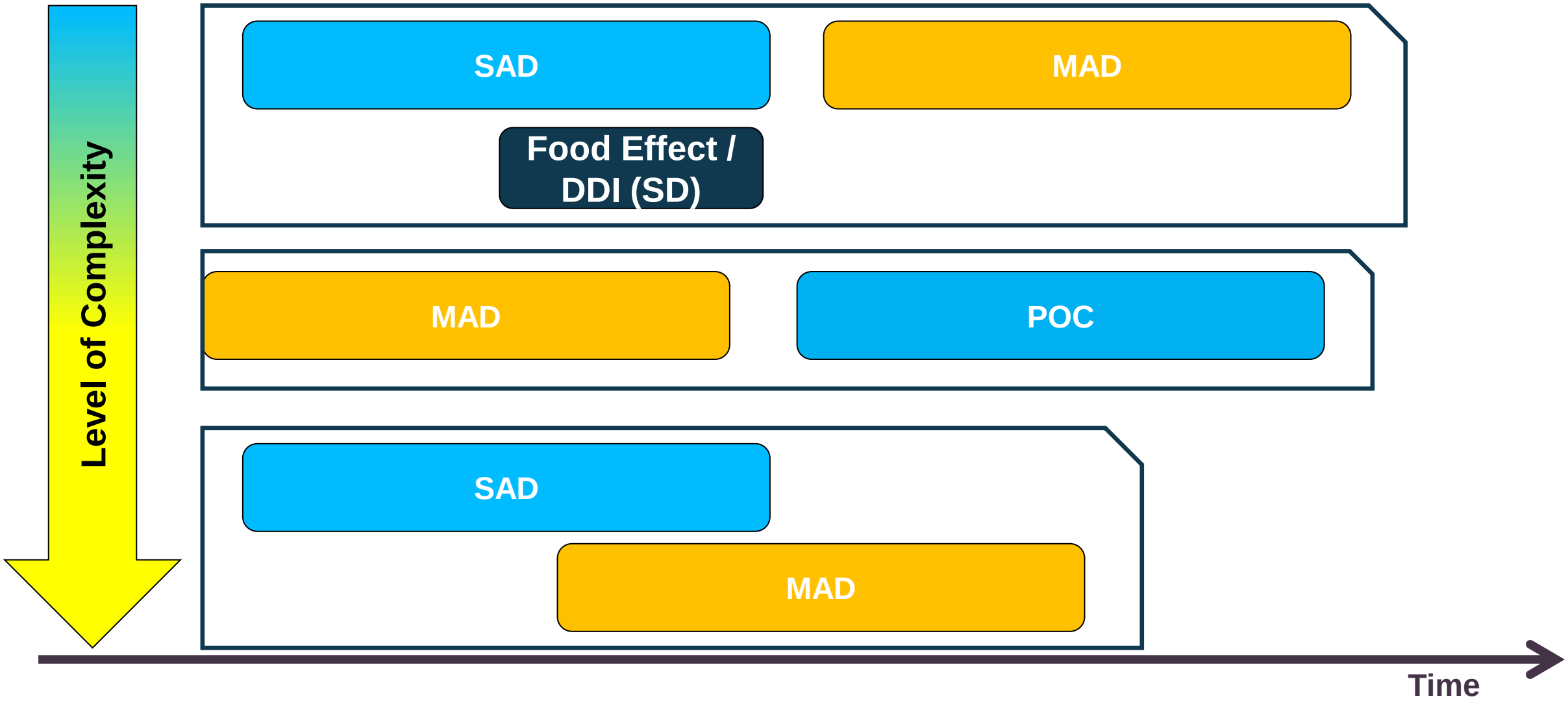
Different Levels of Integrated Protocols

Study parts / objectives don't influence each other , e.g. two SD objectives or two MD objectives integrated into one study protocol

- Not in scope of the 2017 FiM guidance
- Primarily used to limit the number of exposed HVs and to increase resource efficiency



Different Levels of Integrated Protocols



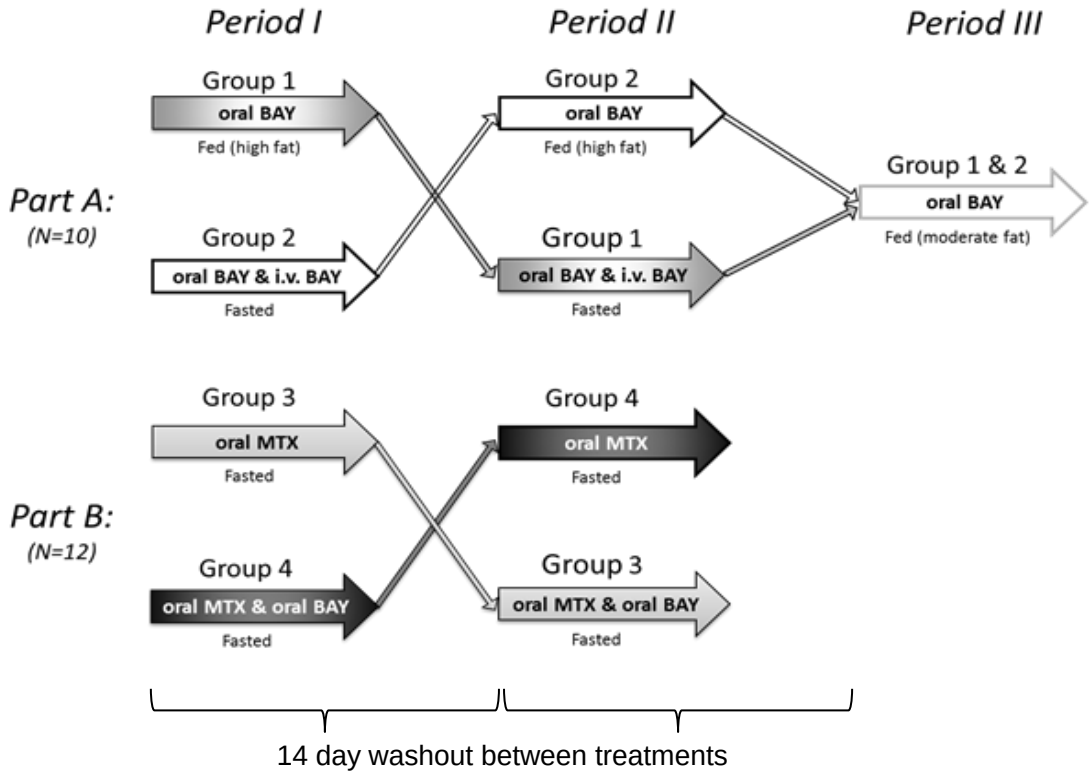
Recent Bayer Examples

Study parts do not influence each other – absolute BA (microtracer) integrated in food effect and DDI study

Design

Single center, open-label, randomized, cross-over study with two study parts

- Part A: simultaneous oral and i.v. administration of BAY XYZ and [$^{13}C_6$]-BAY XYZ) to investigate food effect and absolute BA (microtracer approach)
- Part B: DDI of BAY XYZ (perpetrator with light meal) with methotrexate (victim)

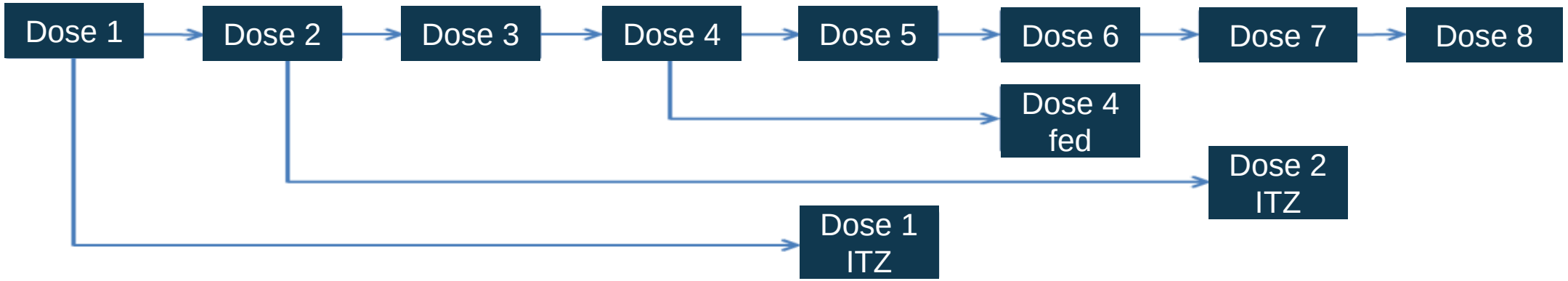


- **Study conducted in the Netherlands**
- **3 questions addressed in 1 study**
- **Key advantages: Budget saving due to avoidance of dedicated abs. BA study requiring iv Tox and a separate iv formulation development**

Study parts influence each other – SD objective integrated in SAD

Design: Randomized, placebo-controlled, double-blind, parallel group study in healthy men to investigate:

- Safety, tolerability and pharmacokinetics of increasing single oral doses of BAY ABC
- The effect of food and itraconazole on the relative bioavailability of BAY ABC



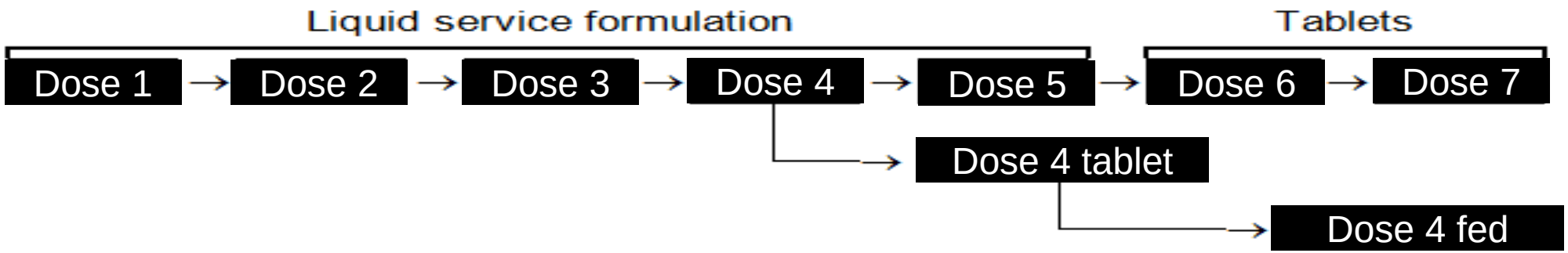
Prerequisites for conduct of food and ITZ interaction:

- No food effect expected based on in-vitro data ➔ re-dosing justified once dose 4 was found to be safe
- Up to 10-fold DDI predicted based on *in vitro* data ➔ DDI re-dosing in dose group 1 to be conducted once a 10 fold exposure (not dose) was found to be safe
- Re-dosing in dose group 2 to be conducted once the expected exposure based on dose group 1 DDI data was found to be safe
- *Indirect time saving due to enhanced recruitment in subsequent trial (allowance of 3A4 inh. as comeds)*

Study parts influence each other – SD objective integrated in SAD

Design: Randomized, placebo-controlled, double-blind, parallel group study in healthy men to investigate:

- Safety, tolerability and pharmacokinetics of increasing single oral doses of BAY BCD
- The effect of food and the relative bioavailability between an LSF and a tablet



Prerequisites for conduct of food and rel. BA comparison:

- Equal or lower exposure expected with a tablet in comparison to a liquid formulation ➔ re-dosing justified once the dose 4 was found to be safe (equal or lower exposure expected for tablet)
- No food effect expected based on in-vitro data ➔ re-dosing justified once dose 5 was found to be safe
- *Indirect time saving due to enhanced recruitment in subsequent trial (intake w/wo food allowed)*

Study parts influence each other – combined SAD & MAD (well-established MoA)

Design:

- Double blind, vehicle controlled, single center, dose escalating study starting with SAD part followed by MAD part, including a positive control group in healthy adult male volunteers
- Escalation by BSA and formulation type

Prerequisites for conduct of MAD part:

- MD part started with 15% BSA of the 0.1% ointment formulation, which has to be demonstrated to be safe and without meeting the stop criteria for the corresponding 60% BSA dose within the SD part
- Time savings due to overall shorter preparation times
- Submission of interim data to competent authority after SAD part

Table 1: Sequence of treatment cohorts and %BSA treated per treatment cohort

Formulation	%BSA									
	SD, Part 1 (occlusive administration)						MD, Part 2			
Treatment cohort No	1	2	3	4	5	6	7	8	9	10**
0.01% Lipophilic cream	6.25	30								
0.1% Lipophilic cream			13							
0.01% Ointment							15 on Day 1		60 on Day 1	
0.1% Ointment				13	30	60	15 on Days 2-6	30*	60 on Days 2-6	
Clobetasol 0.05% ointment**										15 on day 1 followed by 30 on Days 2-5

* Non-occlusive treatment on first treatment day followed by 5 days of occlusive treatment
** The clobetasol group is timely independent

Table 2: Corresponding predicted AUC (ng/ml *h) per day based on *in vitro* data

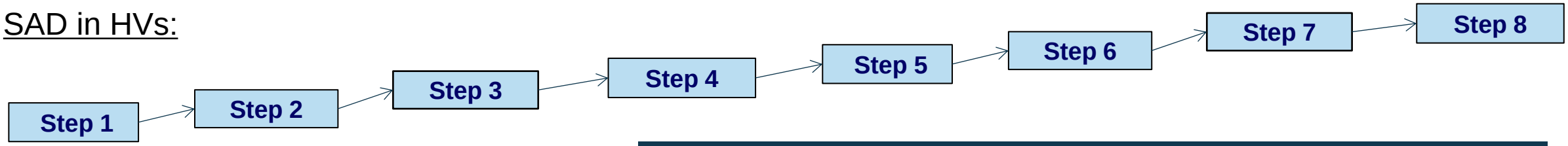
Formulation	SD, Part 1						MD, Part 2		
Group No	1	2	3	4	5	6	7	8	9
0.01% Lipophilic cream	0.099	0.48							
0.1% Lipophilic cream			2.06						
0.01% Ointment							(SD: 0.7)		(SD: 2.6)
0.1% Ointment				5.68	13.1	26.3	> 6.6	>13.1	>26.3

Theoretic factor between SD cohorts: 4.7x - 4.29x - 2.76x - 2.3x - 2.0x

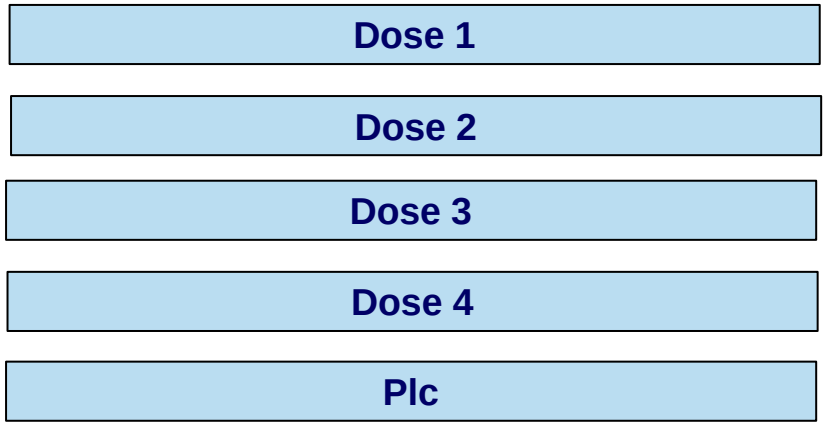
Study parts influence each other – SAD & MD combined

Design: Multi-center, randomized, double-blind, placebo controlled, first-in-man study to investigate the safety, tolerability and pharmacokinetics of the monoclonal antibody BAY following single (SAD - part 1) and repeated (MD – part 2) subcutaneous administration to healthy postmenopausal women

SAD in HVs:



MD in HVs (parallel start of different doses):



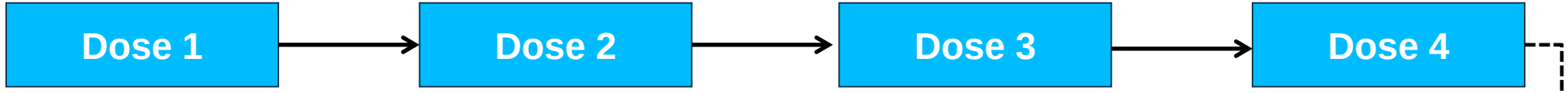
Prerequisites for conduct of MD part:

- Only started after respective SAD part (with drug exposures over up to 15 weeks) was completed and found to be safe
- Submission of interim data to competent authority (here: Paul Ehrlich Institut) between part 1 and 2

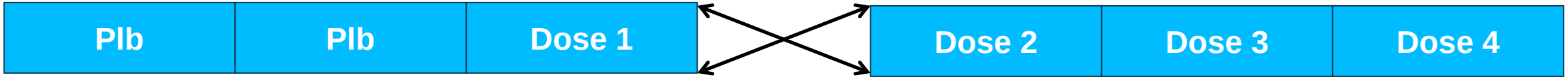
Study parts influence each other – MAD & PoC combined

Design: Two-part, double-blind, placebo-controlled, randomized, study – single center MAD in part 1 in healthy male volunteers followed by multi-center PoC in part 2 in a cross-over design in patients with refractory chronic cough

MAD (Healthy volunteers):



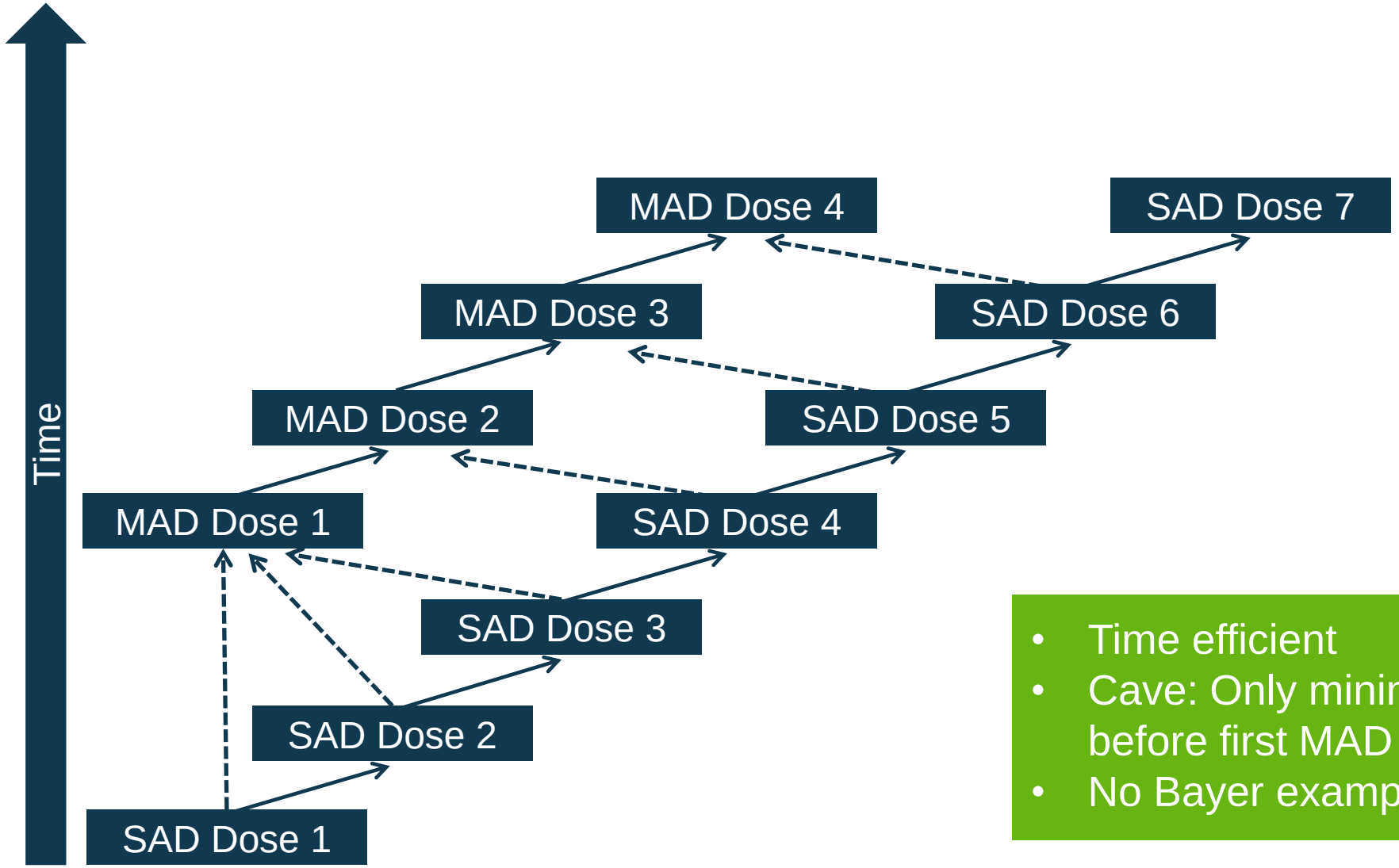
POC (Patients with Refractory Chronic Cough):



Prerequisites for conduct of PoC part:

- PoC part started once highest MAD dose has been demonstrated to be safe and without meeting a stop criterion
- *Significant time gain due to time consuming patient study approval process in UK*

Study parts influence each other – SAD overlaps with MAD



- Time efficient
- Cave: Only minimum of clinical data before first MAD dose available
- No Bayer example available

Summary

- Integrated protocols are of increasing importance
- Integrated protocols offer opportunities to address key objectives of early clinical development in a smart, time saving and cost-efficient way. However, time gain needs to be balanced against resource needs/frontloaded investment and complexity in each case
- Less healthy subjects may be exposed to experimental drug
- New FiM guideline gives guidance on integrated studies with interdependent study parts
- SD (food effect / DDI) objectives integrated into SAD or MAD trials are the combinations most often used within Bayer
  - Direct and indirect time gain due to recruitment facilitation in subsequent studies
  - No separate control arm is needed
- Other combinations (MAD / POC or SAD / MAD combination) are used based on a case by case decision

Thank you!

Bye-Bye

Acknowledgment

- Beate Rohde
- Herbert Wiesinger
- Joern Kraetzschmar
- Kristin Kowal
- Stefan Jodl
- …..

Backup

Treatment Cohort	Formulation BAY	Conc.	BSA %	pred. AUC (ng*h/mL)	Formulation	Conc.	BSA %	predicted AUC (ng*h/mL)	Treatment Cohort
1	**Lipophilic Cream**	**0,01%**	**6,25**	0,099					
2	**Lipophilic Cream**	**0,01%**	**30**	0,48					
3	**Lipophilic Cream**	**0,10%**	**13**	2,06	**Lipophilic Cream**	**0,01%**	**60**	0,95	A
4	**Ointment**	**0,10%**	**13**	5,68	**Lipophilic Cream**	**0,10%**	**30**	4,75	B
5	**Ointment** (occlusive)	**0,10%**	**30**	13,1	**Ointment** (occlusive)	**0,01%**	**60**	2,62	C
	Ointment (non occlusive)	**0,10%**	**30**	<13,1	**Ointment** (non occlusive)	**0,01%**	**60**	<2,62	
6	**Ointment**	**0,10%**	**60**	26,3					

Backup

Treatment Cohort	Day	Formulation BAY ·	Conc.	BSA %	administration	pred. AUC(0-24h) (ng*h/mL)
7	Day 1-6	**Ointment**	**0,10%**	**15**	occlusive	> 6.6
8	Day 1-6	**Ointment**	**0,10%**	**30**	occlusive	>13.1
9	Day 1-6	**Ointment**	**0,10%**	**60**	occlusive	>26.3
D	Day 1-6	**Ointment**	**0,01%**	**60**	non-occlusive	≥ 2.62
10 (timely independent)	Day 1-6	**Clobetasol**	**0,05%**	**30**	occlusive	n.a.

planned path

considered, if stop criterion met