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Clinical and statistical considerations of bridging approaches to alternative dosing regimen or formulations

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- D. Heinzmann is an employee of F. Hoffmann-La Roche Ltd.
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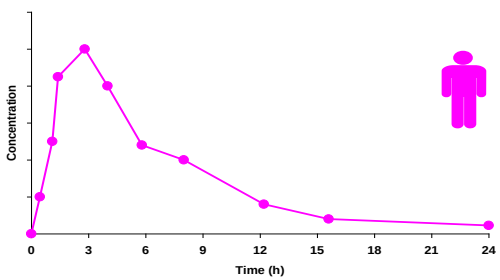
Change in dosing schedule

Situation

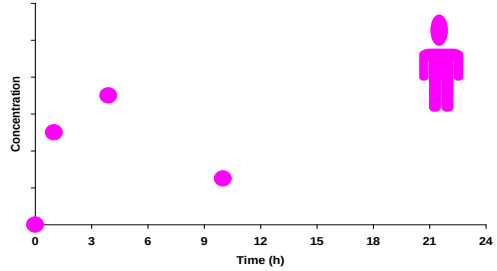
- Fixed dose 100mg for indications A and B every 4 weeks (Q4W) as infusion, monotherapy
- One wants to explore a Q2W and Q6W dosing schedule
- Available data
  - Dose finding study (DF) exploring various body weight adjusted and fixed dosing for Q4W in indication A
  - Other Phase Ib, II and III studies in both indications A and B

Part A: Population PK (popPK) model

- **Questions to address:**
  - Linear pharmacokinetics (within data available)?
  - Disposition (compartment models) and elimination (x-order)
  - Covariates that are statistically significantly related to drug's PK in popPK model (e.g. body weight, tumor burden, gender…)
    - Assess impact on exposure (relevant for interpolation / extrapolation to alternative schedules)
- **Model set-up (in short)**

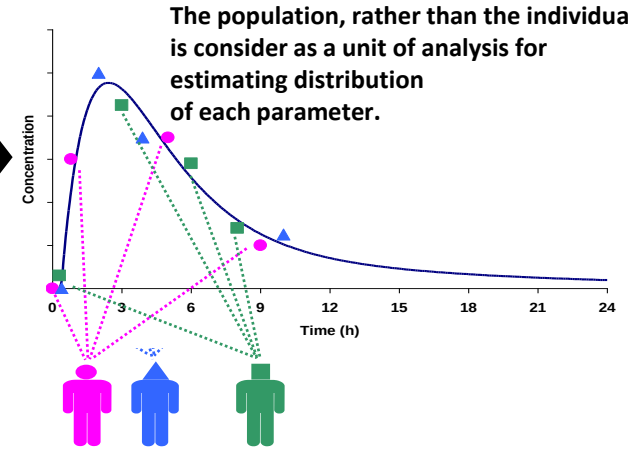


„Usual" PK Studies
Dense sampling, N small



Population PK Studies
Sparse data, N large

Model



Part A: Population PK (popPK) model

Example

- Use fitted popPK model to simulate / predict hypothetical doses / schedules
- Key benchmarks are Cycle 1 and steady state exposure
- For the example drug, assume Ctrough drives efficacy, Cmax safety

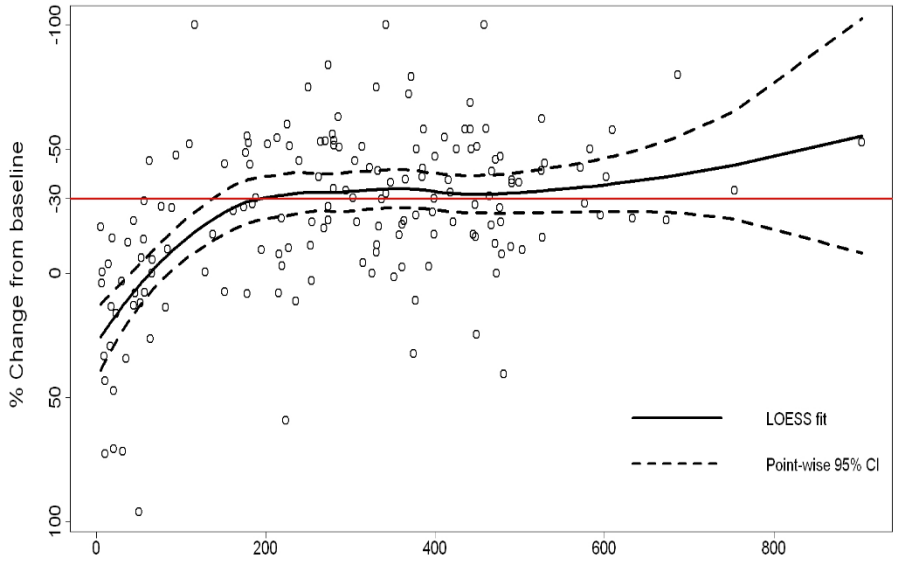
Regime	Cmax (ug/mL)		Ctrough (ug/mL)	
	Cycle 1	Steady state	Cycle 1	Steady State
100mg Q4W	33	50	9	17
55mg* Q2W	18	34	6	19
165mg* Q6W	55	62	14	15

* Dose determined using target exposure (often Ctrough) established based on non-clinical studies
To ensure "at least" target exposure

Part B: Exposure-response (ER) model

- **Questions to address**
  - Impact of exposure (AUC, Cmax, Cmin) on efficacy and safety
  - Assess patient characteristics with respect to prognostic & predictive impact on endpoints

- **Example**



Percent change from baseline in first RECIST measurement versus vemurafenib exposure **(Zhang, Heinzmann, Grippo, Clin Pharmacokinet 2017)**

How much evidence needed?

- Assume Package = PopPK model plus substantial evidence on approved dose plus some sparse data on other doses.

- Sufficient? – Efficacy considerations
  - Maybe if no exposure-response relationship found for efficacy and safety within range one wants to extend dosing
  - Exposure achieved by approved dosing regime is in the flat or plateau part of the exposure-response curve
  - No impact on efficacy outcome expected as long as new dosing regimen achieved exposure greater than target concentration and within range of approved dose regime

- Sufficient? – Safety considerations
  - Cmax (AUC) – safety relationship (ER): No trend? Can one exclude increase in safety risk by higher Cmax with Q6W?
  - “Sparse data”: Is highest Cmax observed in some Phase I / II / III data (although likely only limited N)?

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Rationale for considering subcutaneous instead of IV administration

Clinical activity

- Potential to provide comparable efficacy, pharmacokinetics and safety with subcutaneous administration, demonstrated in several clinical trials with other agents
  - Bortezomib subcutaneous[1,2]
  - Alemtuzumab subcutaneous[3,4]

Patient needs

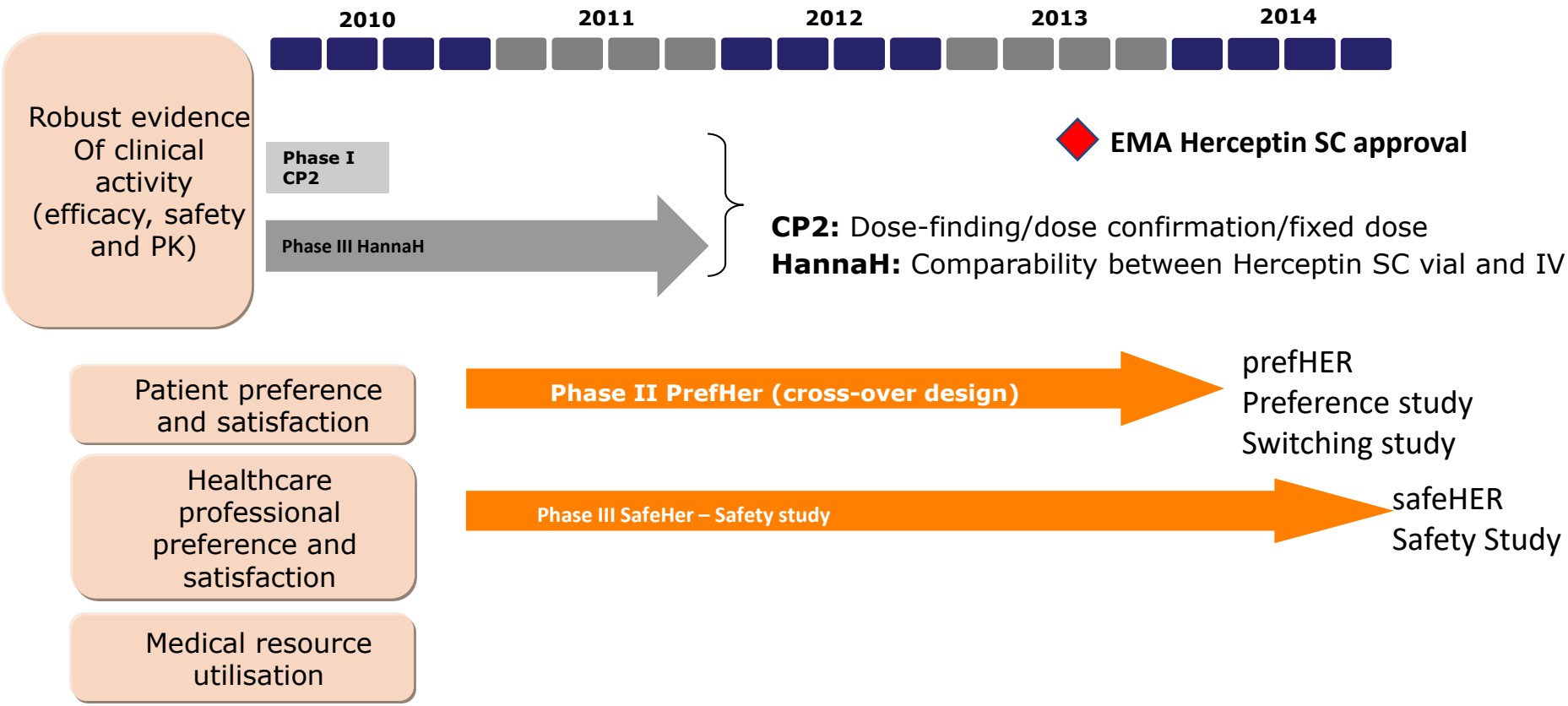
- Potential for greater patient preference and satisfaction, and reduced treatment burden with subcutaneous administration
  - Denosumab subcutaneous[5,6]

Healthcare professional needs

- Potential to optimise medical resource utilisation
  - Reduced administration time
  - No requirement for dedicated infusion suites/staff
  - No need for infusion bag preparation

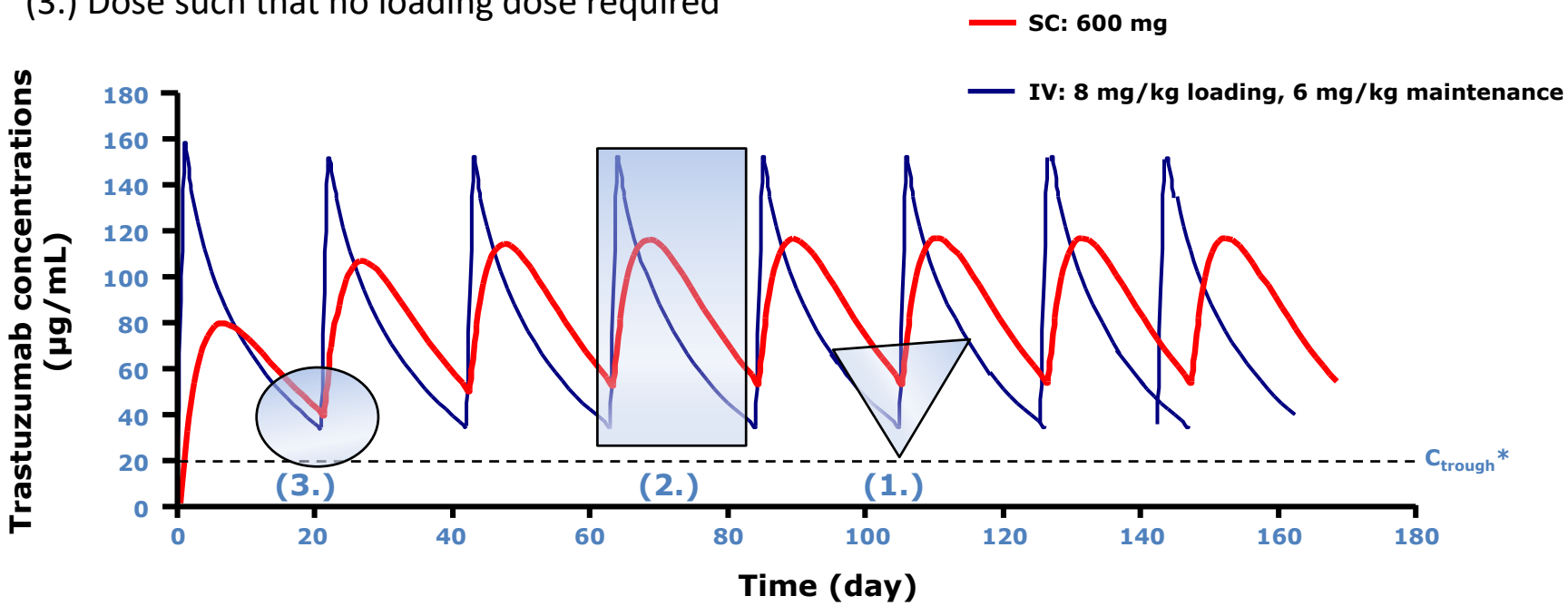
1. Moreau P, et al. 2011; 2. Moreau P, et al. 2008; 3. Faderl S, et al. 2010; 4. Hale G, et al. 2004
5. Freemantle N, et al. 2012; 6. Kendler DL, et al. 2010

Herceptin SC development program



Phase I: popPK model to determine Herceptin SC dose

(1.) C_{min} at least as high
(2.) Comparable AUC
(3.) Dose such that no loading dose required



Quartino et al, 2015, Cancer Chemother Pharmacol

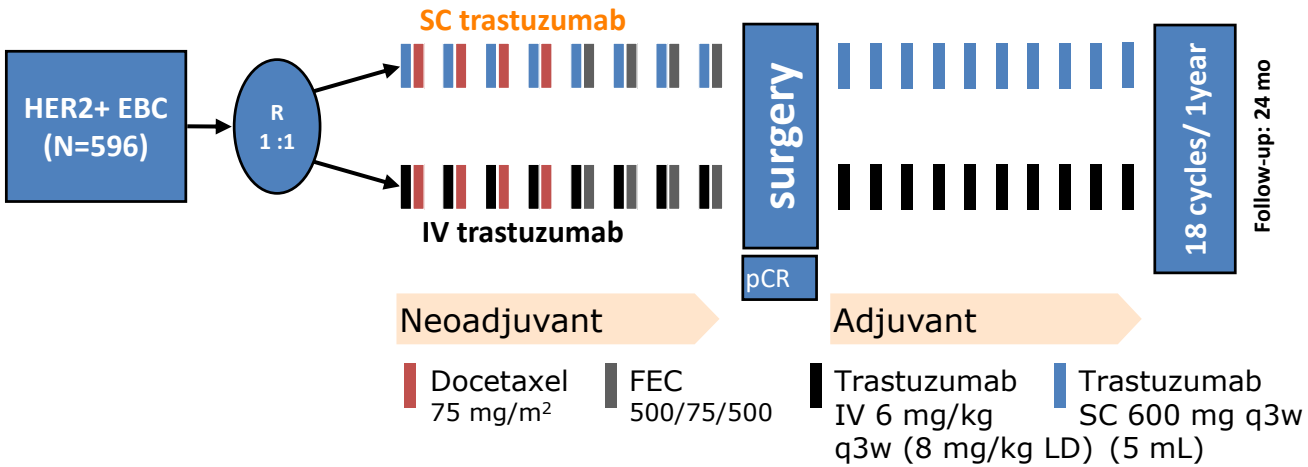
Phase III: Optimal population and endpoint

- **Guiding principle: Sensitivity**
  - The idea is to study Herceptin SC in the population of patients with an endpoint such that – *if there is a difference between Herceptin SC and Herceptin IV* – that difference will most likely be detected

- Extensive analyses show that this is satisfied by:
  - **Population:** Neoadjuvant
  - **Endpoint:** pathologic Complete Response (pCR)

  - **REF: Jackisch, Scappaticci, Heinzmann** et al 2015, Future Oncol. *« Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation»*

HannaH: Phase III, non-inferiority trial



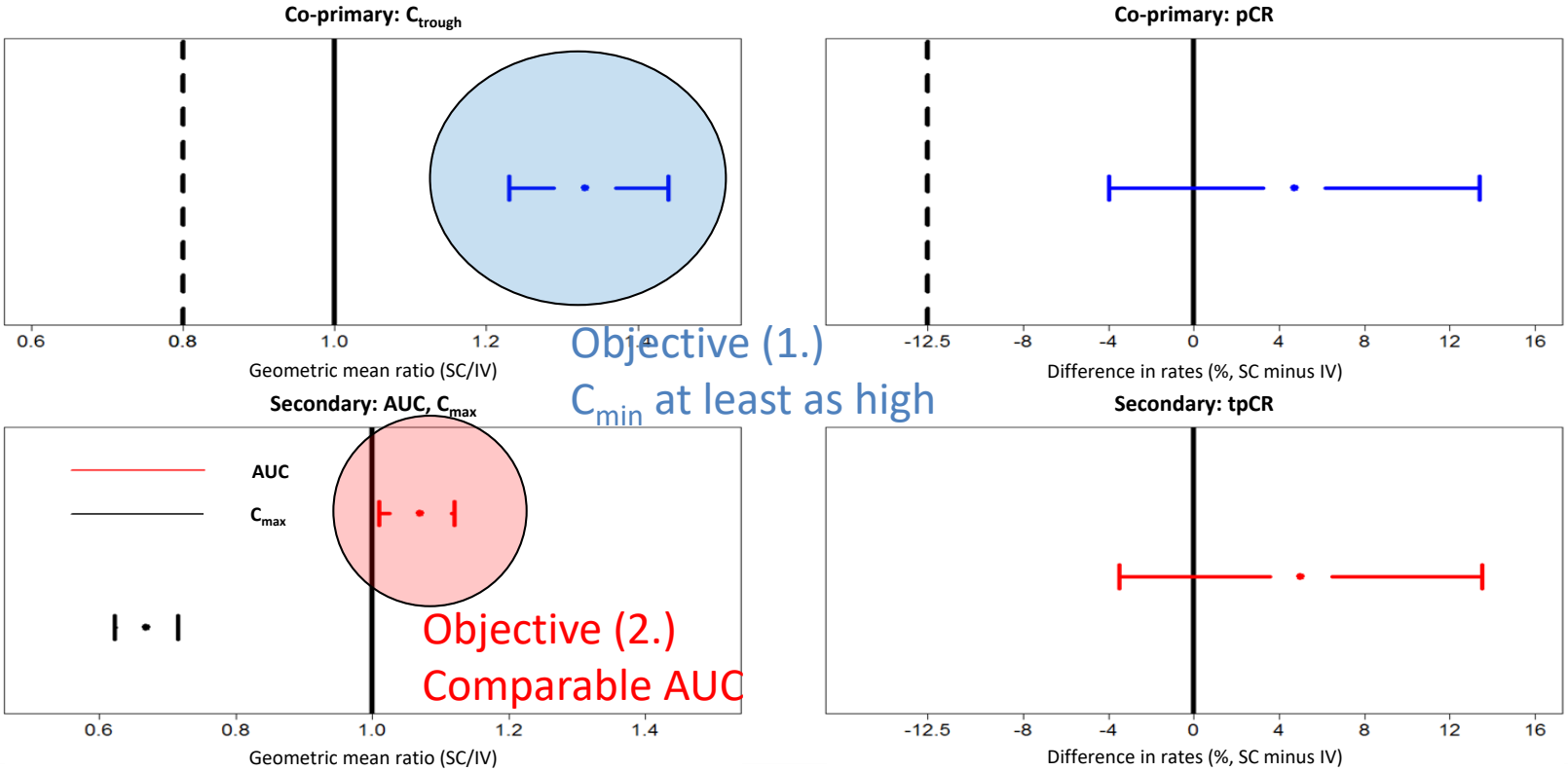
Co-primary endpoints

PK: Observed C_{trough} at pre-dose cycle 8 (non-inferiority)

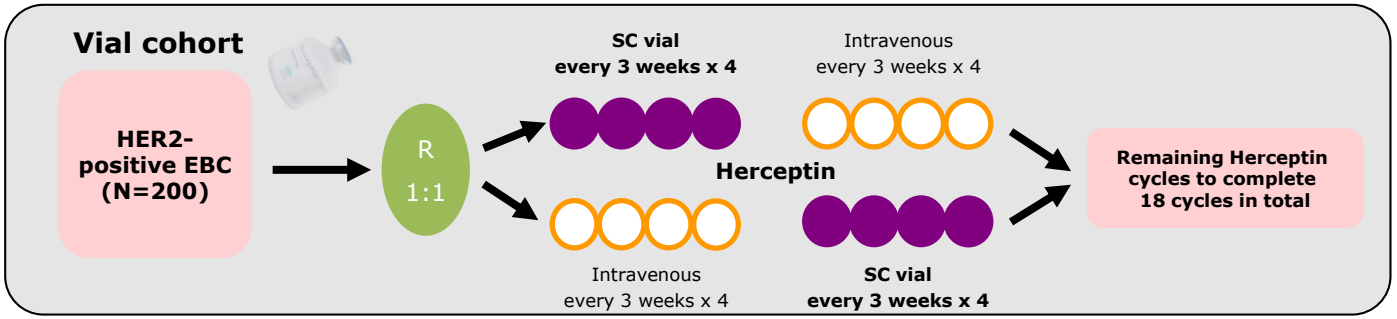
pCR: Pathological complete response in the breast (non-inferiority)

HannaH: Phase III, non-inferiority trial

PK hypotheses confirmed by non-inferior efficacy



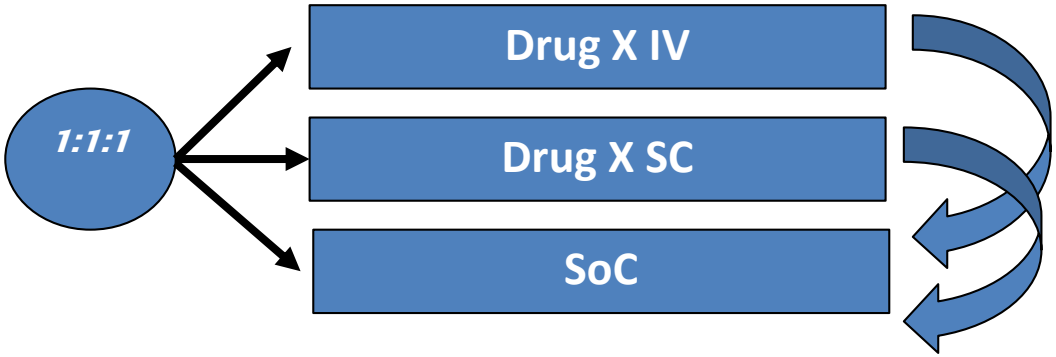
prefHER study: Patient preference, Time and motion



- **Primary objective: Assess patients' preference for Herceptin subcutaneous vs intravenous administration in patients with HER2-positive early breast cancer**
- **Secondary objectives: HCP satisfaction, safety, efficacy and immunogenicity**

Alternative designs?

- Done: Comparative trial IV vs SC (non-inferiority)
- Alternative: 3 arm design with testing superiority of IV and SC versus SoC



Two tests of superiority vs SoC

Scenario*	Alpha	Sample size (events/pts)
Non-inferiority	2.5% one-sides	~631 / 814
Superiority	2.5% two-sided for both tests	~338 / 446 (three arms)

***Assuming TTE endpoint, median TTE in SoC arm 8 mo, target median in experimental 12 mo with 80% power, non-inferiority margin HR=1.25, target HR for superiority 0.67, accrual 22 mo, similar event/patient ratio and trial duration**

Summary

- **Dose schedule changes**
  - M&S sufficient?
  - If data on alternative dosing schedules needed, how much data?
- **Changes of administration route**
  - Same active substance, similar efficacy and safety
  - What type of Phase III needed (non-inferiority, or alternative a three arm superiority trial)?
- **Open item: Switching**
  - What data needed to support switch between dose schedules & formulations?
  - If switching study is needed, what endpoints to look at?

Doing now what patients need next