Myth 4: Subcutaneous delivery requires extensive clinical trials when bridging device or from IV

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CONTROLLED RELEASE SOCIETY
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INTEGRATING Delivery Science ACROSS DISCIPLINES

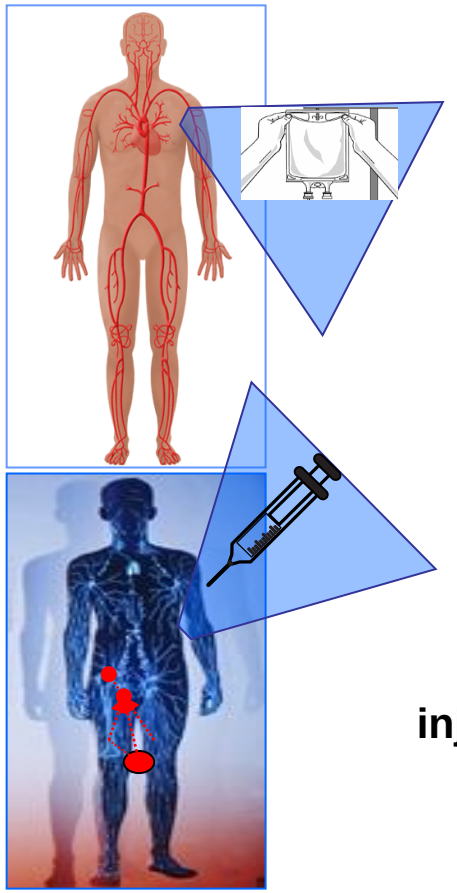
Content

- From IV to SC; how to arrive at the right SC dose regimen
- From SC to SC; how to bridge from one SC device to the next SC device
- From SC to IV; how to arrive at the right IV regimen

IV to SC

- From IV to SC; how to arrive at the right SC dose regimen

Impact of Subcutaneous vs. Intravenous Delivery on PK profile of Monoclonal Antibodies



Peripheral lymphatic system → **Central lymphatic ductus** (ductus thoracicus)

Lymph absorption pathway

SC injection site

Potentially some loss from SC injection site (e.g., catabolism by macrophages)

SC injection

IV infusion

1 Central compartment

k_{12}

k_{21}

2 Peripheral compartment

Ke * C

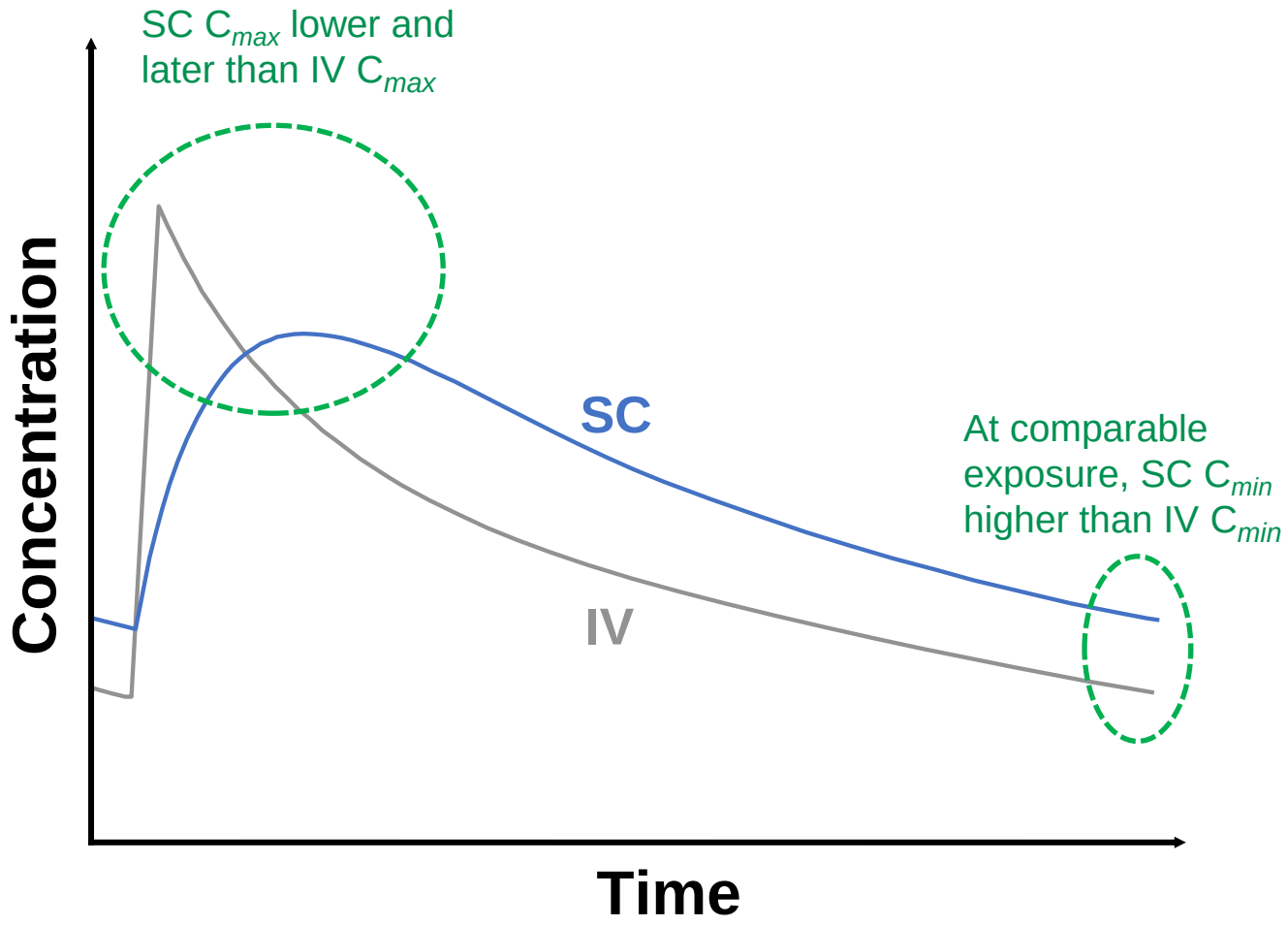
$\frac{Vmax * C}{Km + C}$

Linear clearance Target-independent elimination

Nonlinear clearance Target-specific elimination

Adapted from McLennan DN *et al*. Drug Discovery Today 2005.

Impact of Subcutaneous vs. Intravenous Delivery on PK profile of Monoclonal Antibodies



- Impact of C_{max} and C_{min} on **efficacy & safety profile**
- **For high-dose mAbs: Technical feasibility** of high-concentration formulations and **high-volume injection**

IV to SC Bridging: How to Leverage Preclinical Data During Development Pathway

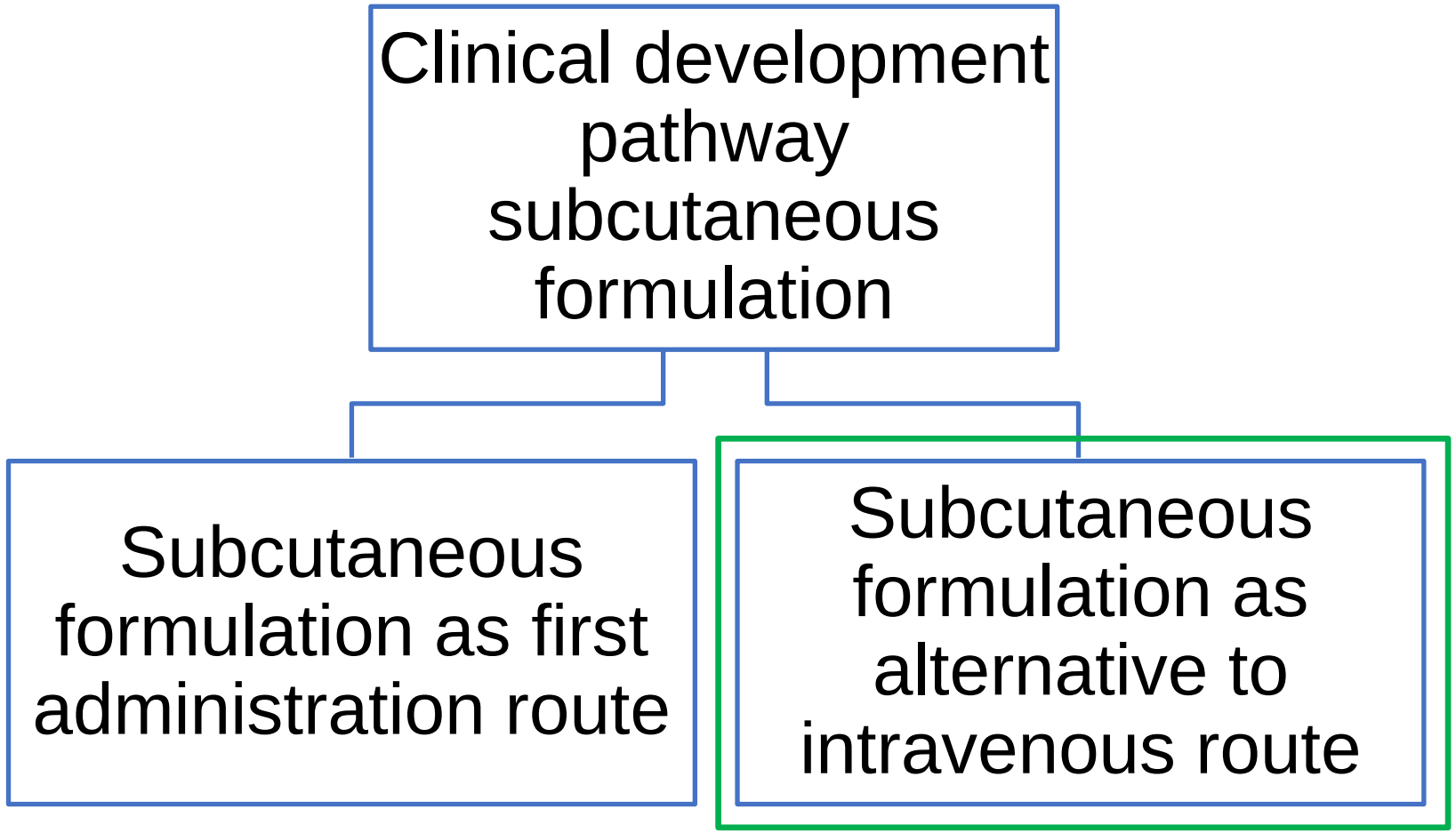
Supporting preclinical data

- Assess impact of administration route on PD parameters, incl. relevance of C_{max}
- Demonstrate SC toxicology and local tolerability
- Assess the impact of different formulations on the PK profile

Aims of the clinical development program

- Demonstrate PK non-inferiority between the IV and SC formulations to ensure comparable efficacy
- Show that the safety and immunogenicity profile of the SC formulation is consistent with that of the IV formulation
- Provide supportive efficacy data

SC Delivery of Monoclonal Antibodies - Development Pathway Depends on Prior Availability of an IV Formulation



Comparison of Trastuzumab IV and SC

	Trastuzumab IV[1]	Trastuzumab SC[1]

eBC, early breast cancer; IV, intravenous; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous; SID, single-use injection device; q1w, weekly dosing; q3w, 3-weekly dosing.

1. Herceptin® SC (Herceptin) Summary of Product Characteristics 2014
2. Jackisch C *et al*. Ann Oncol 2015
3. Goldhirsch A *et al*. Lancet 2013
4. Slamon D *et al*. N Engl J Med 2011
5. Perez EA *et al*. J Clin Oncol 2014
6. Perez EA *et al*. J Clin Oncol 2011.

The Lack of Predictive Animal Data on SC Bioavailability of MAbs is Overcome with an Adaptive Phase 1/1b Dose Finding Approach

Example: Selection of trastuzumab SC dose in healthy male and eBC participants

Concept: Leverage existing PK model built based on prior IV PK data in HER2+ BC

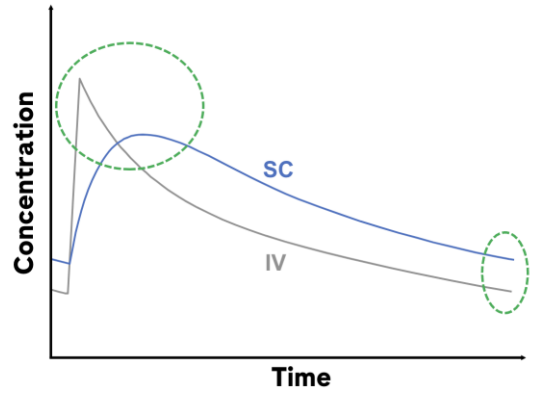
Part 1: Dose-finding

Dose-finding cohorts

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
6 mg/kg IV HMPs n = 6	6 mg/kg IV eBC participants n = 6	6 mg/kg SC HMPs n = 6	10 mg/kg SC HMPs n = 6	8 mg/kg SC HMPs n = 6

Part 2: Dose confirmation

Cohort A	Cohort B§
8 mg/kg SC eBC participants n = 20	12 mg/kg SC eBC participants n = 20

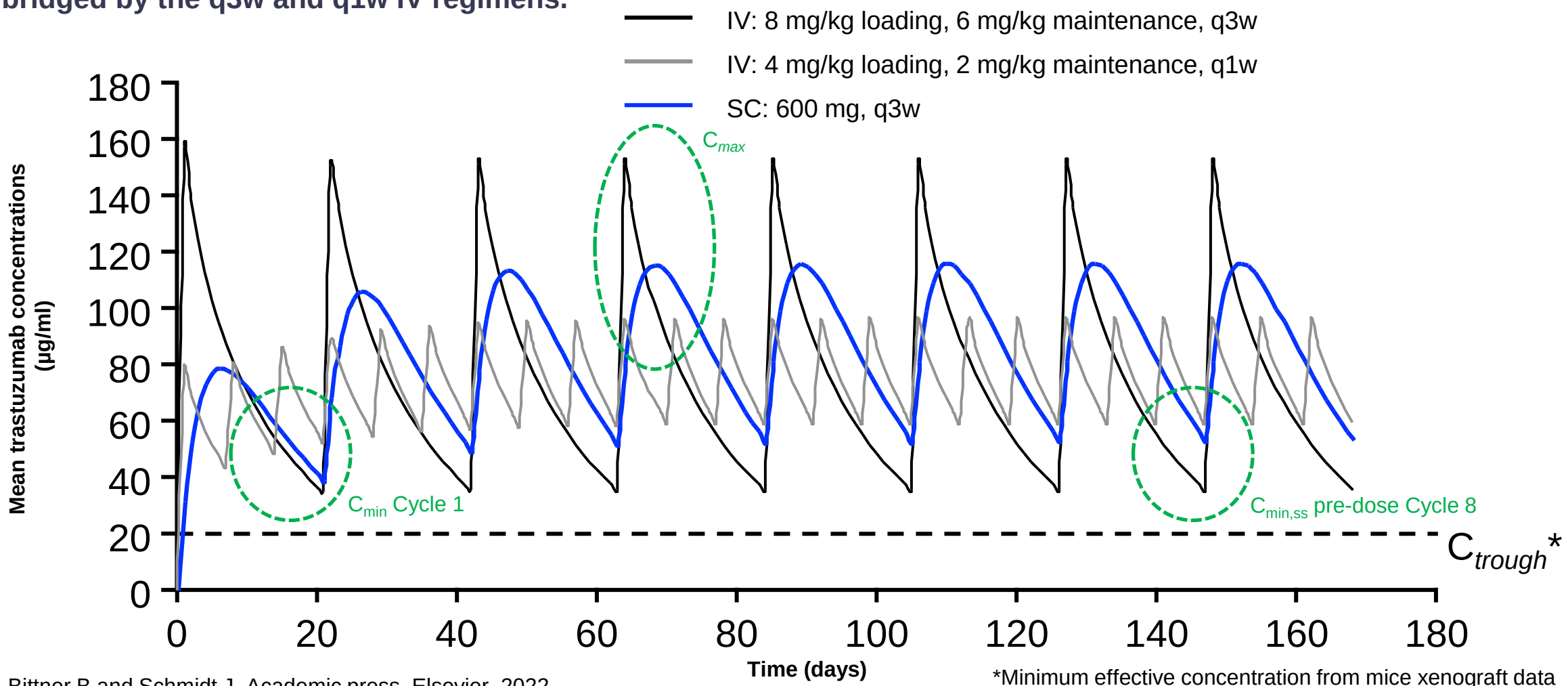


EBC, early breast cancer; HMPs, healthy male participants

Wynne C *et al*. J Clin Pharmacol 2012.

PK-based Clinical Bridging Approach

Hypothesis generation based on available trastuzumab PK data. The PK profile of the SC formulation was bridged by the q3w and q1w IV regimens.



Bittner B and Schmidt J. Academic press, Elsevier, 2022.

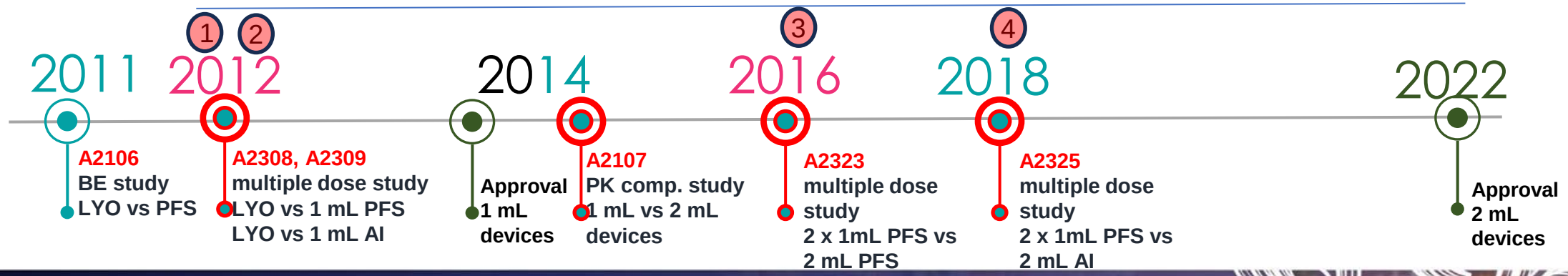
*Minimum effective concentration from mice xenograft data

SC to SC: How to include new Drug-Device-Combination-Products (DDCPs) in the Development Program?

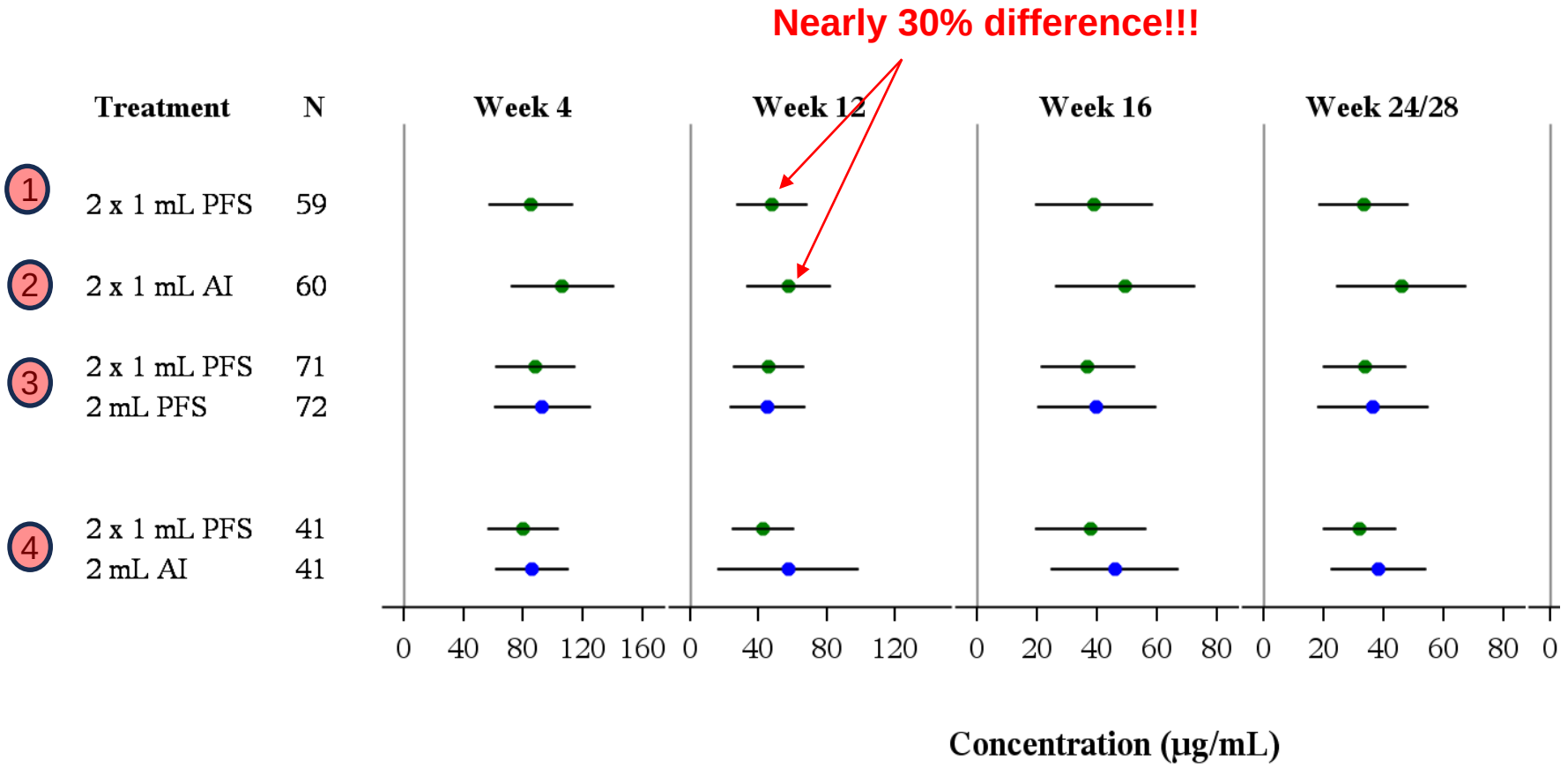
Are really so many studies and so much time needed?

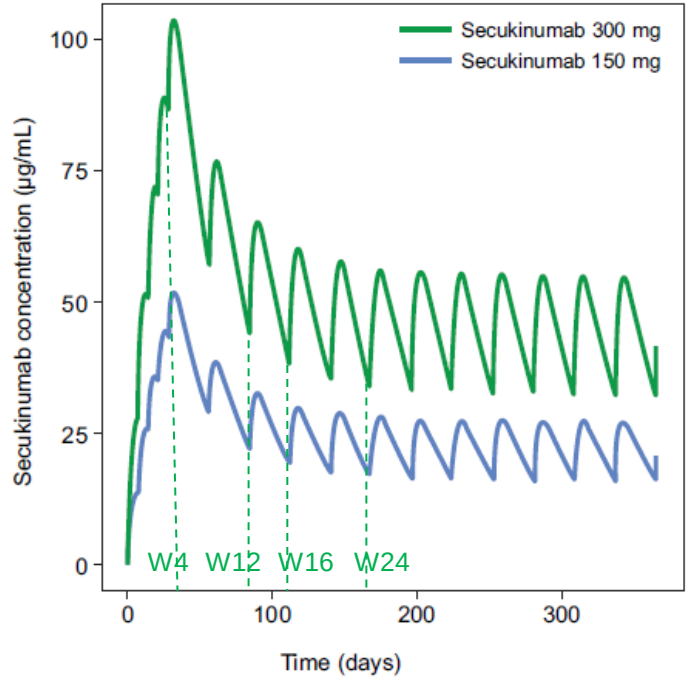
Drug	From	To	Clinical study	HV/Patients	Number of subjects / arms	HA request	Comment
secukinumab	300 mg, 2 x 1 mL LYO,	300 mg, 2 x 1 mL PFS	AIN457A2106 single dose BE	HV	141 / 2	N	with excipients change from LYO to PFS
	1 150, 300 mg 1 or 2 x 1 mL LYO	150, 300 mg 1 or 2 x 1 mL PFS	AIN457A2308 multiple dose Phase 3	Pso	174 / 3	Y	
	2 150, 300 mg 1 or 2 x 1 mL LYO	150, 300 mg 2 x 1 mL AI Delta	AIN457A2309 multiple dose Phase 3	Pso	177 / 3	Y (FDA only)	
	300 mg, 2 x 1 mL PFS or 2 x 1 mL AI Delta	300 mg, device prototypes	AIN457A2107 single dose – PK comparability	HV	122 / 6	N	Abdomen/thigh, injection time comparison
	3 300 mg, 2 x 1 mL PFS	300 mg, 2 mL PFS	AIN457A2323 multiple dose Phase 3	Pso	214 / 3	Y	Abdomen/thigh comparison
	4 300 mg, 2 x 1 mL PFS	300 mg, 2 mL AI YpsoMate	AIN457A2325 multiple dose Phase 3	Pso	122 / 3	Y (FDA only)	Abdomen/thigh comparison

Cosentyx® (secukinumab)



Things can go wrong in Cross-Study Comparisons with Sparse PK!

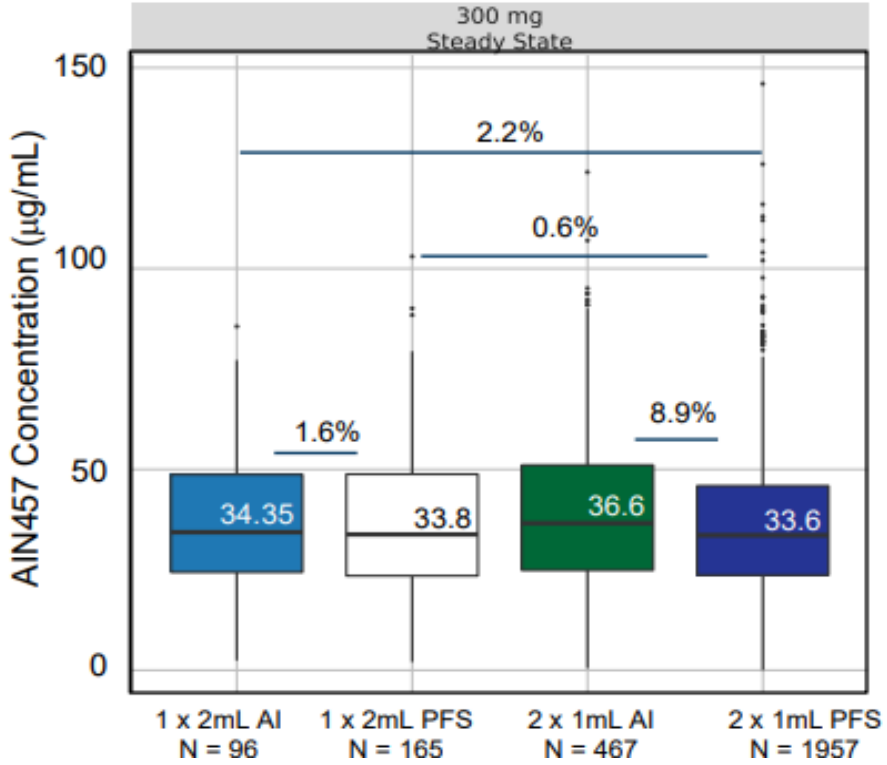




Simulated concentration profiles of secukinumab 300 and 150 mg with subcutaneous dosing regimens derived from phase 3 trials. Patients were simulated to receive secukinumab at baseline; weeks 1, 2, and 3; and then every 4 weeks from week 4 to week 48.

Combined Ph 3 studies with Psoriasis (PsO) and Psoriatic arthritis (PsA) Patients

No impact of Drug-Device-Combination-Product on PK, clinical efficacy, and safety of Cosentyx/secukinumab!



Studies	N	2x1mL PFS	2x1mL AI	1x2mL PFS	1x2mL AI
A2308	135	X			
A2309	147		X		
A2323	323	X		X	
A2325	181	X			X
F2312	236	X			
F2318	320		X		
F2342	570	X			
F2366	773	X			

4 PsO Phase 3 studies

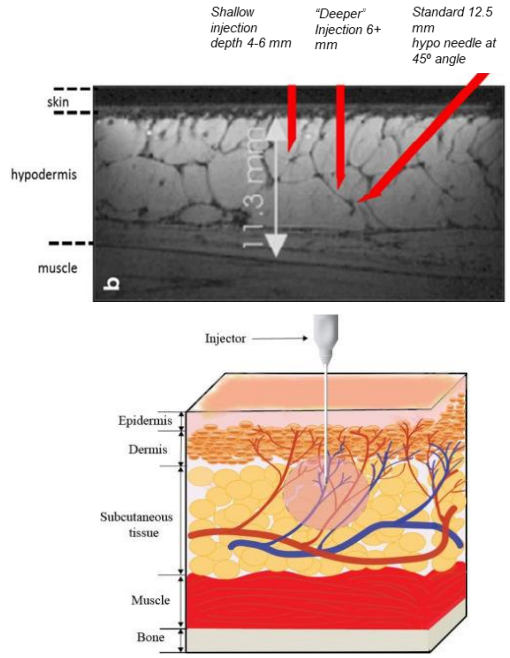
4 PsA Phase 3 studies

Are Injection Depth Differences between PFS and AI Significant Factors for PK?

Position: Comparability between PFS vs. AI injection depth in SC administration (e.g., 1.0 - 2.0 mL) for SC administration of mAb's may not raise significant PK questions and could be justified without a PK study measuring bioequivalence.

Supporting Information:

- Standard 12.5 mm PFS needle inserted at a 45° angle reaches the same depth as a typical AI needle insertion depth (5-7.5 mm). Geometrical comparability is supportive.
- Delivery to SC tissue with either delivery device typically reaches the same SC biospace. Potential factors affecting PK (catabolism, intercellular diffusion and lymphatic drainage) for short delivery times will not meaningfully impact C_{max} (typically occurring after 5-7 days) or AUC.
- CDRH allows a wide acceptance criterion for AI injection depth in upper and lower specification limit (e.g., ± 2mm) based on potential tolerances of component parts suppliers. Minor differences in manual and AI injection depth should not be a critical factor.



Dingding et al, Transport and Lymphatic Uptake of Biotherapeutics Through Subcutaneous Injection, Journal of Pharmaceutical Sciences, Volume 111, Issue 3, 2022

[1] Hu P, Wang J, Florian J, Shatzer K, Stevens AM, Gertz J, Ji P, Huang SM, Zineh I, Wang YC. Systematic Review of Device Parameters and Design of Studies Bridging Biologic-Device Combination Products Using Prefilled Syringes and Autoinjectors. AAPS J. 2020 Feb 27;22(2):52. doi: 10.1208/s12248-020-0433-8. PMID: 32107671. https://pubmed.ncbi.nlm.nih.gov/32107671/

Are Injection Time Differences between PFS and AI Significant Factors for PK?

Position: Comparability of injection time for manually administered mAb (1.0-2.0 mL) PFS vs. AI for SC administration may not raise significant PK questions and an *in vitro* assessment without a PK study might be justified.

Supporting Information:

- Manual administration time depends on a user-specific "comfortable" application of force on the syringe plunger and can vary from 5-10 seconds for a 1 mL PFS.
- AI injection time is more consistent and typically varies (<10 seconds) for 1 mL volume depending on the AI technology.
- There are no studies or data to suggest that different injection times of this duration are a significant factor for BA/BE for typical mAbs where Cmax occurs 5-7 days post-dose. Studies support the case that injection times are insignificant for BE.[1,2]

[1] Portron A, et al. Study to Assess the Effect of Speed of Injection on Pain, Tolerability, and Pharmacokinetics After High-volume Subcutaneous Administration of Gantenerumab in Healthy Volunteers. Clin Ther. 2020;42(1):108-120.e1. doi: 10.1016/j.clinthera.2019.11.015.

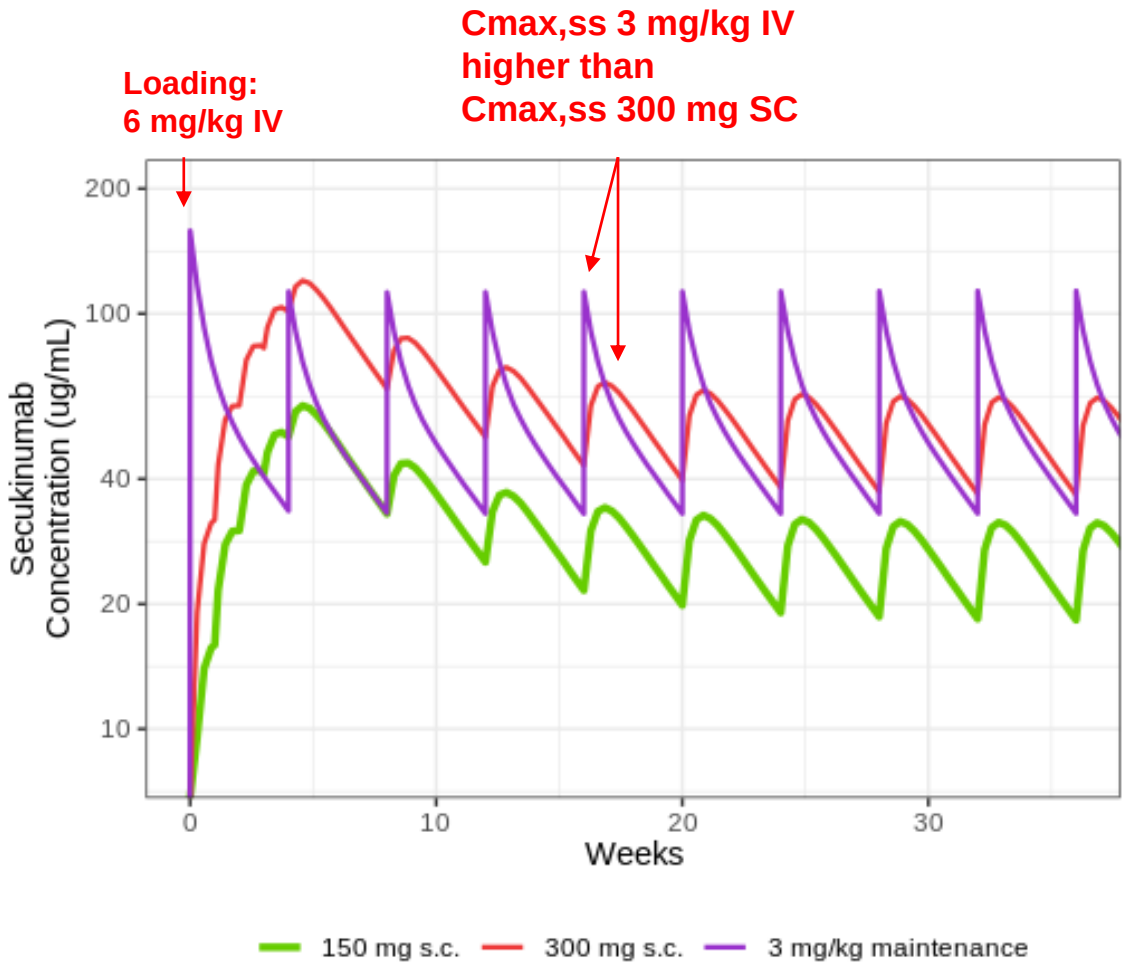
[2] Bruin G, et al. Comparison of pharmacokinetics, safety and tolerability of secukinumab administered subcutaneously using different delivery systems in healthy volunteers and in psoriasis patients. Br J Clin Pharmacol. 2020;86(2):338-351. doi: 10.1111/bcp.14155..

From SC to IV: How to arive at the Right IV Regimen?

Cosentyx, an IL-17A mAb

Brief development history (2019)

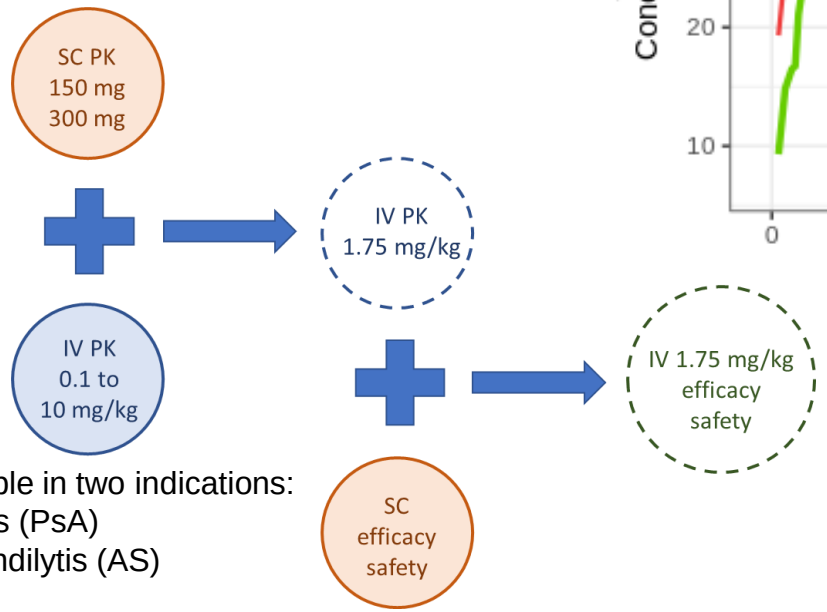
- Cosentyx was approved for doses of 150 mg SC and 300 mg SC in Spondyloarthritis (SpA) (2015)
- Two Phase III studies were conducted to test a new IV regimen (6 mg/kg IV loading, then 3 mg/kg IV, q4w) in SpA
- This regimen was discussed (and we thought agreed!) with FDA
- 2021: The IV studies were positive and confirmed the expected efficacy and safety profile like SC
- But FDA's Pre-BLA feedback:
  "... IV regimen appears to result in higher Cmax ..." and "We are concerned that your IV regimen may not have sufficient information to support the benefit-risk assessment ..., particularly for more rare and latent AEs"
- FDA also hinted at a potential next step using MIDD (Model-Informed Drug Development)



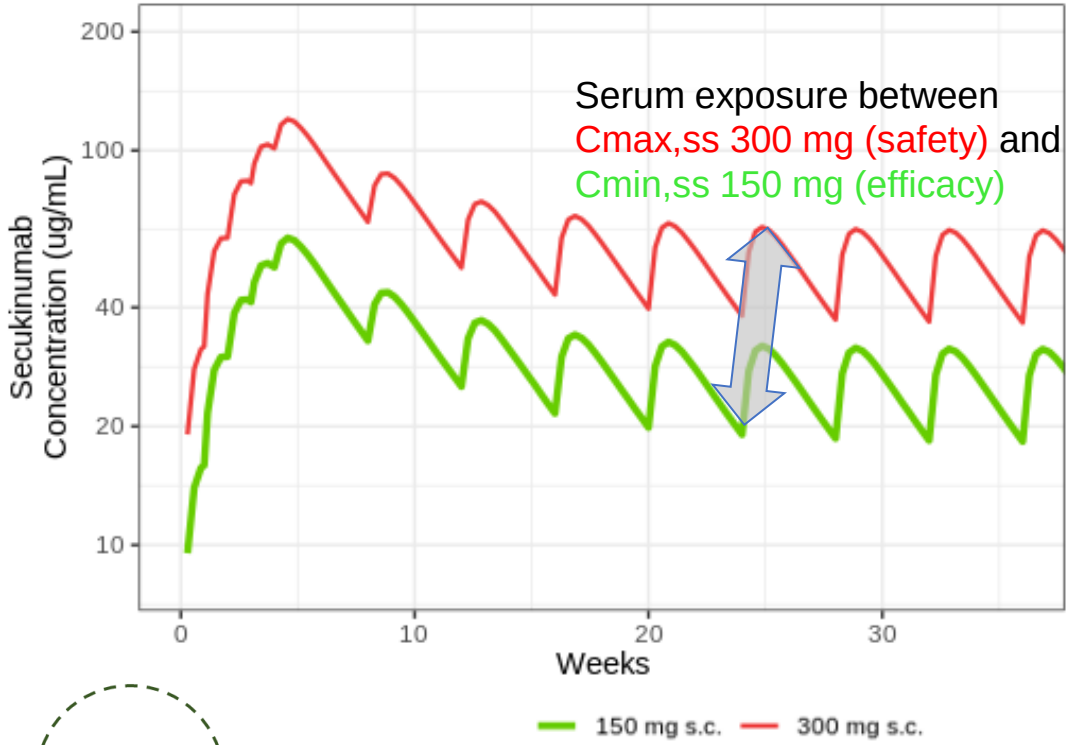
2022 - How can Model Informed Drug Development (MIDD) help our Case?

1. <u>Identification</u> of a new, lower IV regimen that approximates the exposure of the s.c. regimens
2. Extrapolation of the efficacy and safety from the SC regimens to a lower IV regimen on the basis of: Same exposure with IV and SC will lead to same efficacy/safety

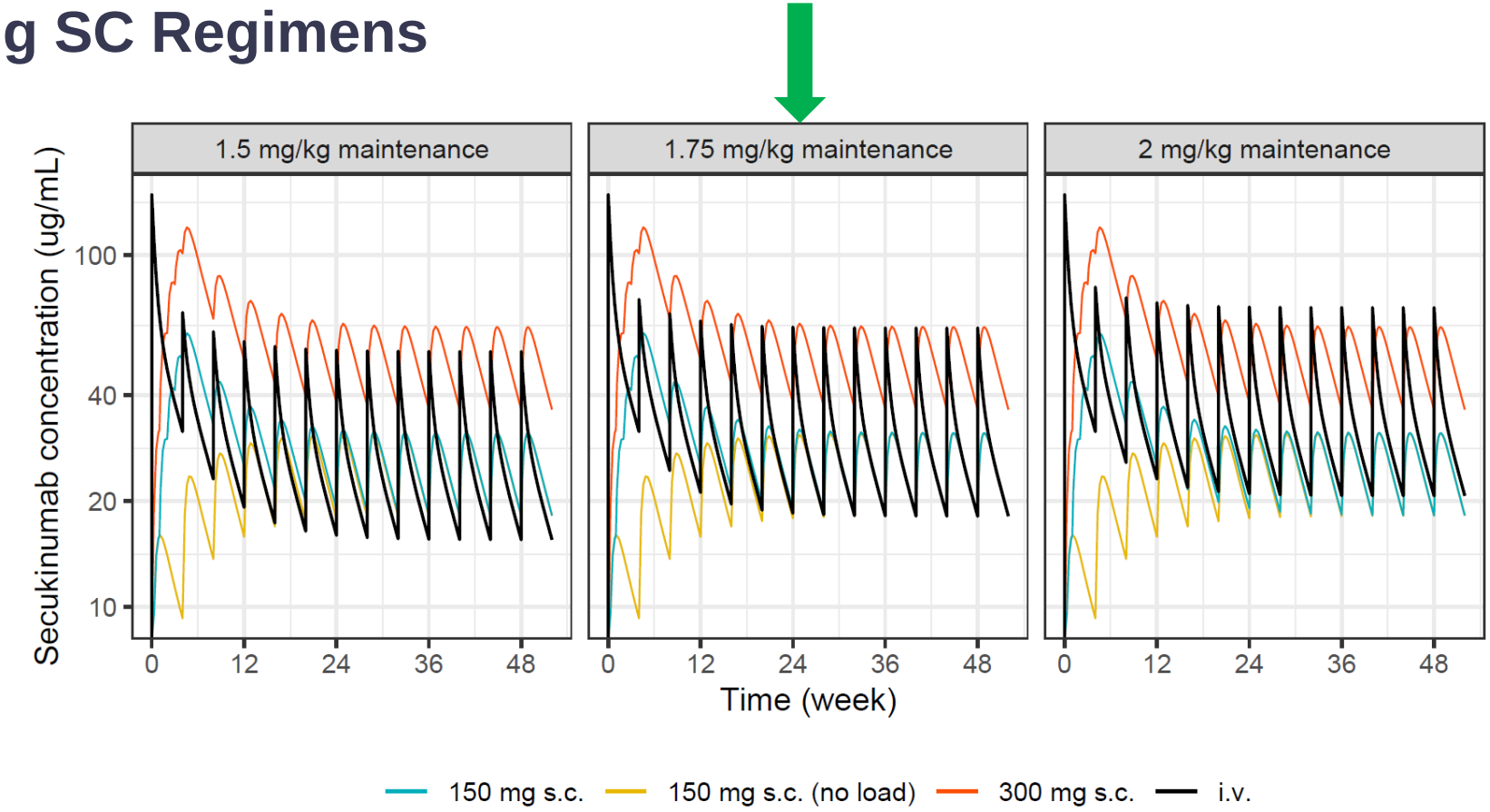
SC PK data available in three indications:
- Psoriatic Arthritis (PsA)
- Ankylosing Spondilytis (AS)
- nonradiographic-axial Spondyloarthritis (nr-axSpA)



IV PK data available in two indications:
- Psoriatic Arthritis (PsA)
- Ankylosing Spondilytis (AS)



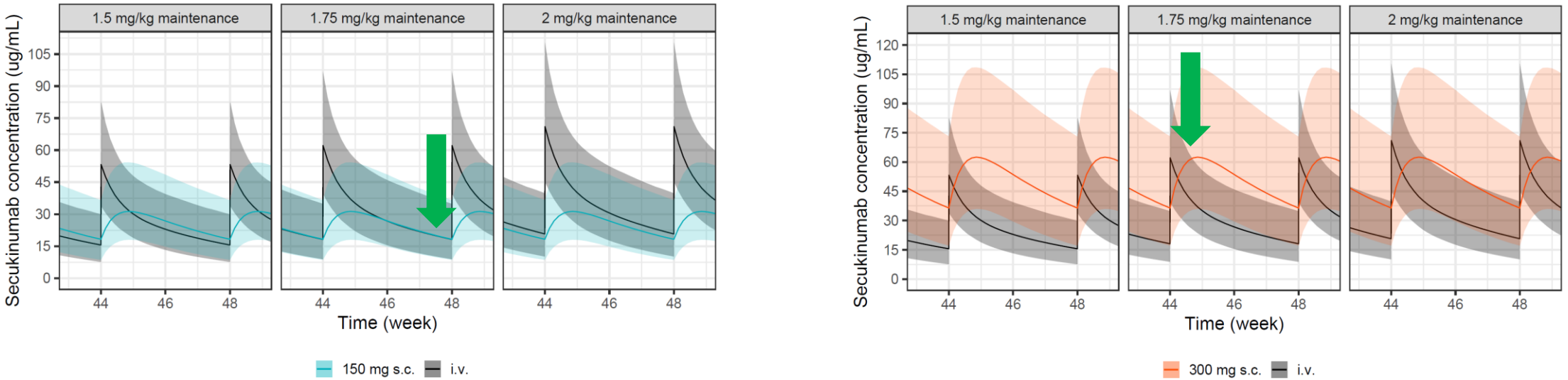
Predicted PK Profiles of three IV Regimens that Approximate the 150 mg and the 300 mg SC Regimens



The three IV regimens comprise a 6 mg/kg loading dose at Week 0 followed by a maintenance with 1.5, 1.75, or 2 mg/kg administered q4w starting on Week 4.

The lines represent the median of the secukinumab concentration-time profiles predicted for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, as obtained from the final popPK model.

Distribution of PK Profiles at Steady-State for three IV regimens and the 150 and 300 mg SC q4w Regimen



The lines represent the median of the secukinumab concentration-time profiles simulated for 3000 PsA and 3000 axSpA subjects for each secukinumab regimen, obtained from the final popPK model. The ribbons correspond to the 90% PI.

Maintenance regimen	Median (90% PI)		
	Cmin,ss (µg/mL)	Cavg,ss (µg/mL)	Cmax,ss (µg/mL)
1.5 mg/kg i.v. q4w	15.6 (7.6, 29.9)	25.1 (13.7, 45.7)	53.3 (34.0, 83.0)
1.75 mg/kg i.v. q4w	**18.1 (8.9, 34.8)**	**29.2 (16, 53.4)**	**62.1 (39.6, 96.9)**
2 mg/kg i.v. q4w	20.7 (10.2, 39.7)	33.4 (18.2, 61.0)	71.0 (45.3, 110.7)
150 mg s.c. q4w	18.2 (8.6, 36.5)	25.1 (12.3, 50.6)	31.3 (18.0, 54.3)
300 mg s.c. q4w	36.4 (17.2, 73.2)	50.1 (24.6, 101.2)	62.6 (36.1, 108.7)

Conclusions

- Bridging from IV to SC currently involves PK-based dose finding plus assessment of immunogenicity and supporting efficacy in target population in comparatively small Phase 3 studies)
- Bridging to to-be-marketed Drug-Device-Combination-Products might be possible by leveraging historical (PK) data and/or by using platform device technology
- Bridging from SC to IV can be achieved by Phase 1 PK studies or by MIDD approaches
- It can be expected that clinical bridging trials will be smaller and increasingly complemented by MIDD approaches in the future

Round Table Discussions