Registration of an IV secukinumab regimen not tested in clinical trial

Analyses used to support this MIDD approach

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- How we end up using MIDD to support the registration of an IV regimen for Cosentyx in Spondyloarthritis (SpA)
- Challenge
- Mitigation
- Conclusion, summary, and final thoughts

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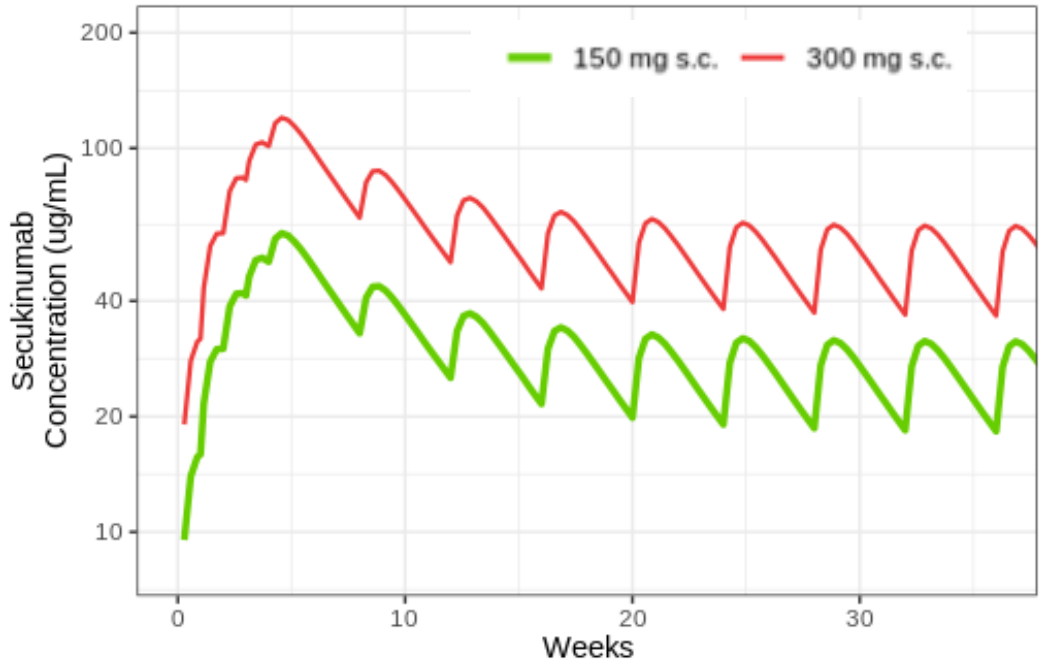
Background

Cosentyx is approved in SpA with two subcutaneous regimens

- Spondyloarthritis (SpA) is a group of inflammatory diseases that primarily affect the spine and other joints, causing inflammation and pain. It includes Psoriatic Arthritis (PsA) and axial SpA (axSpA)
- Secukinumab (brand name Cosentyx) is an anti-IL17 monoclonal antibody developed and marketed by Novartis
- Cosentyx is approved in SpA with subcutaneous (SC) maintenance doses of **150 mg Q4W*** and **300 mg Q4W****

Note: Cosentyx is also approved with SC regimens in Psoriasis and in Hidradenitis Suppurativa

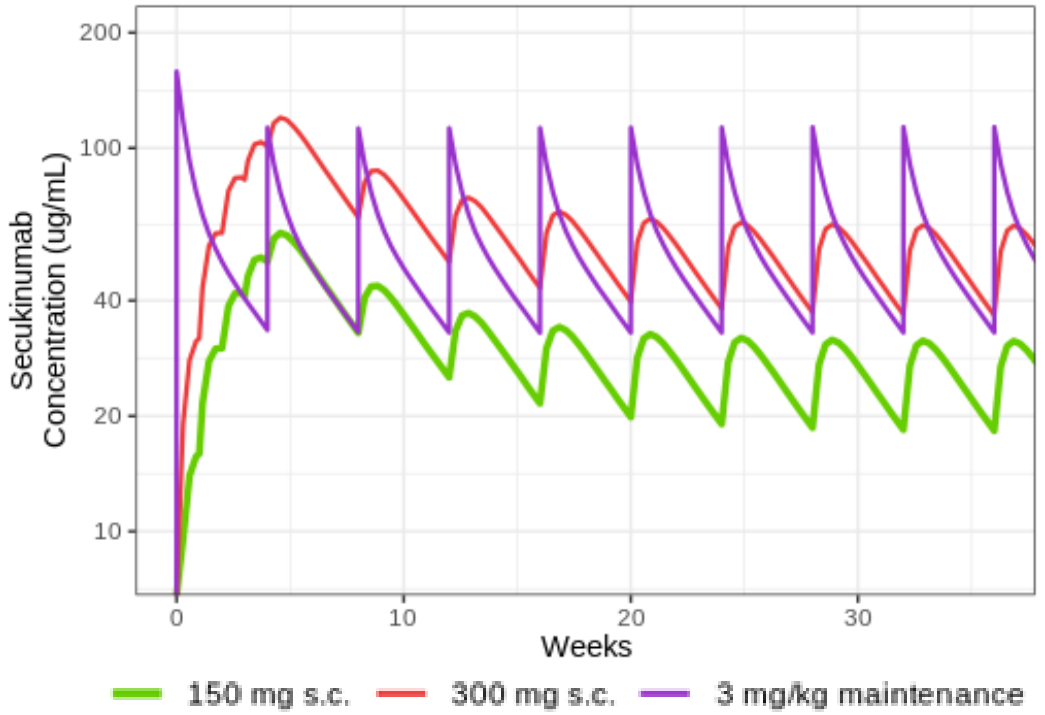


* 150 mg SC Q4W, either following 150 mg SC loading doses at Weeks 0, 1, 2, 3, 4, or with no loading

** 300 mg SC Q4W, up-titrated from 150 mg based upon clinical response, except for PsA patients with moderate to severe psoriasis who use the recommended psoriasis dose

Background
Cosentyx intravenous (IV) development in SpA in U.S. region

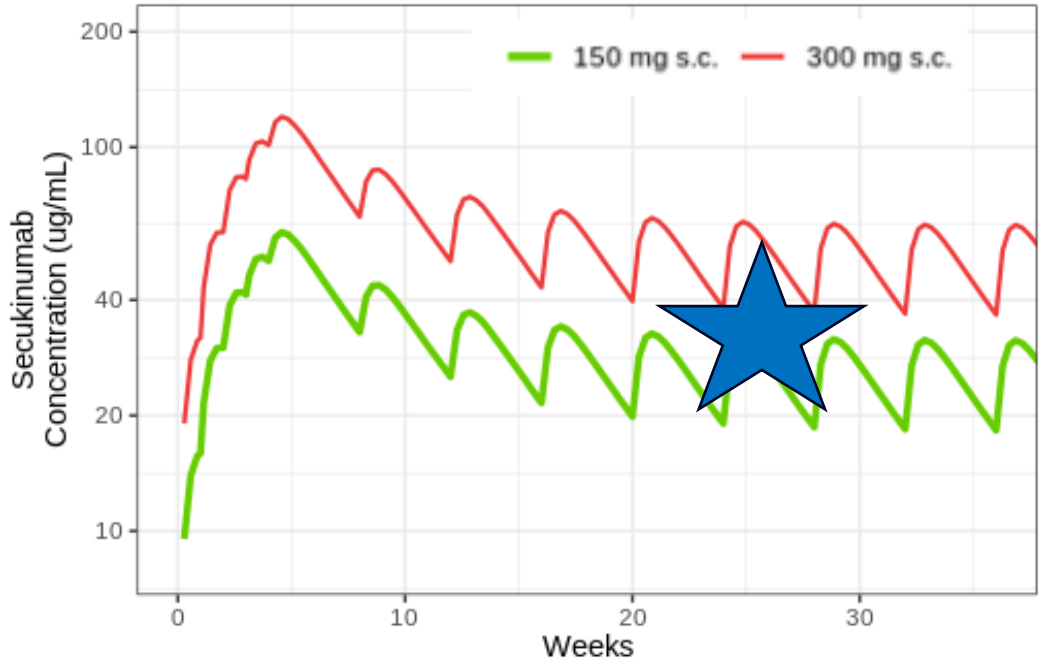
- 2019: initiation of Cosentyx IV program ("INVIGORATE") in SpA, for U.S. region:
  - Two lean Ph3 IV studies in PsA and axSpA
  - Maintenance dose (3 mg/kg IV Q4W*) with Cavg,ss similar to 300 mg SC Q4W
- In 2021, Interim Analysis results of the first study were positive
  - However, FDA: *"... IV regimen appears to result in higher Cmax ... and … may not have sufficient information to support the benefit-risk assessment ..., particularly for more rare and latent AEs"*



* 3 mg/kg IV Q4W following one 6 mg/kg loading dose at Week 0

Intravenous Cosentyx program in SpA
End 2021: Pre-submission meeting with FDA 2/2

- FDA:
  - Open to review a submission dossier for a modeled IV regimen, which “approximates” the PK parameters of the two approved SC regimens, and uses PK bridging for determining its efficacy and safety
  - Hint at the need of a PK study to check that this IV regimen achieves the predicted exposure levels



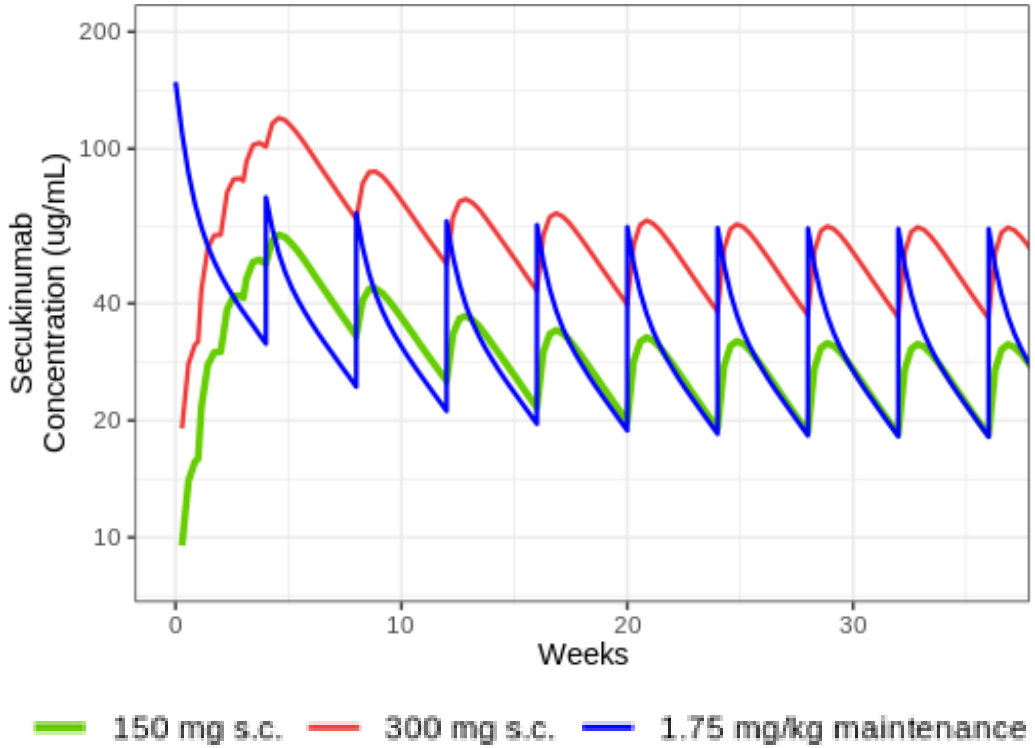
PK bridging = Leverage clinical efficacy and safety from an original regimen for a new regimen with “similar” exposure levels

popPK identified 1.75 mg/kg IV Q4W

Model predicts IV regimen matches 150 mg SC Q4W Cmin,ss and 300 mg SC Q4W Cmax,ss

popPK predictions

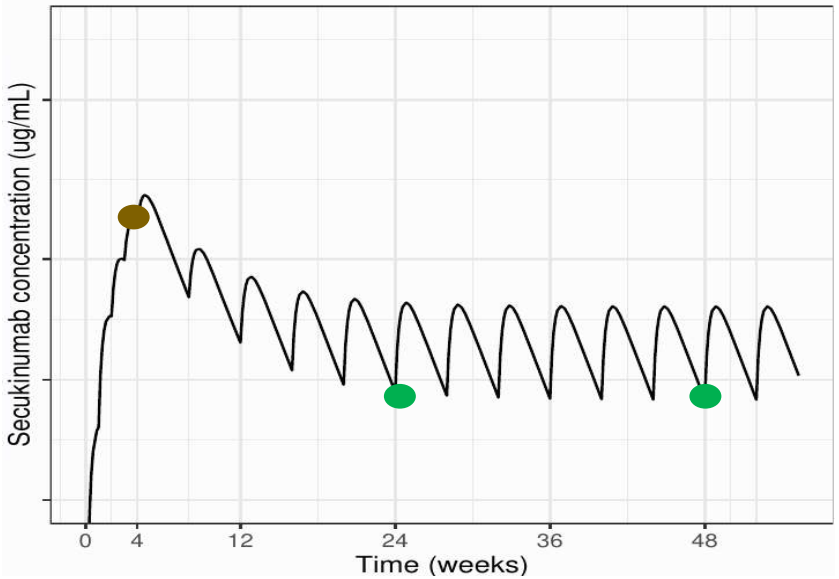
Maintenance dose	Median (90% PI), ug/mL	
	Cmin,ss	Cmax,ss
300 mg SC Q4W		63 (36, 109)
1.75 mg/kg IV Q4W	18 (9, 35)	62 (40, 97)
150 mg SC Q4W	18 (9, 37)	



1.75 mg/kg IV Q4W following one 6 mg/kg loading dose at Week 0

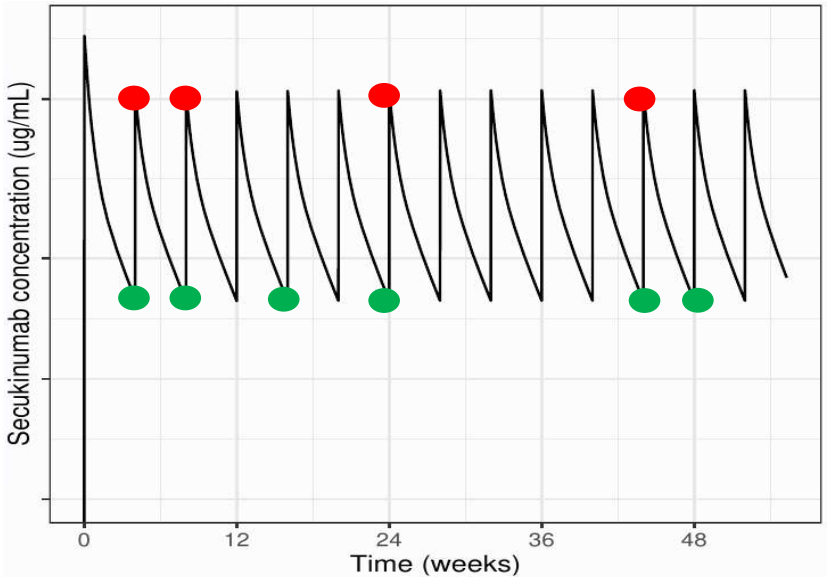
Specific validation plan to support the appropriateness of the identified IV regimen

PK samples in Ph3 SC studies



11 Ph3 SC studies,
~4000 patients
Maintenance dose: 75, 150, and 300 mg Q4W

PK samples in Ph3 IV studies

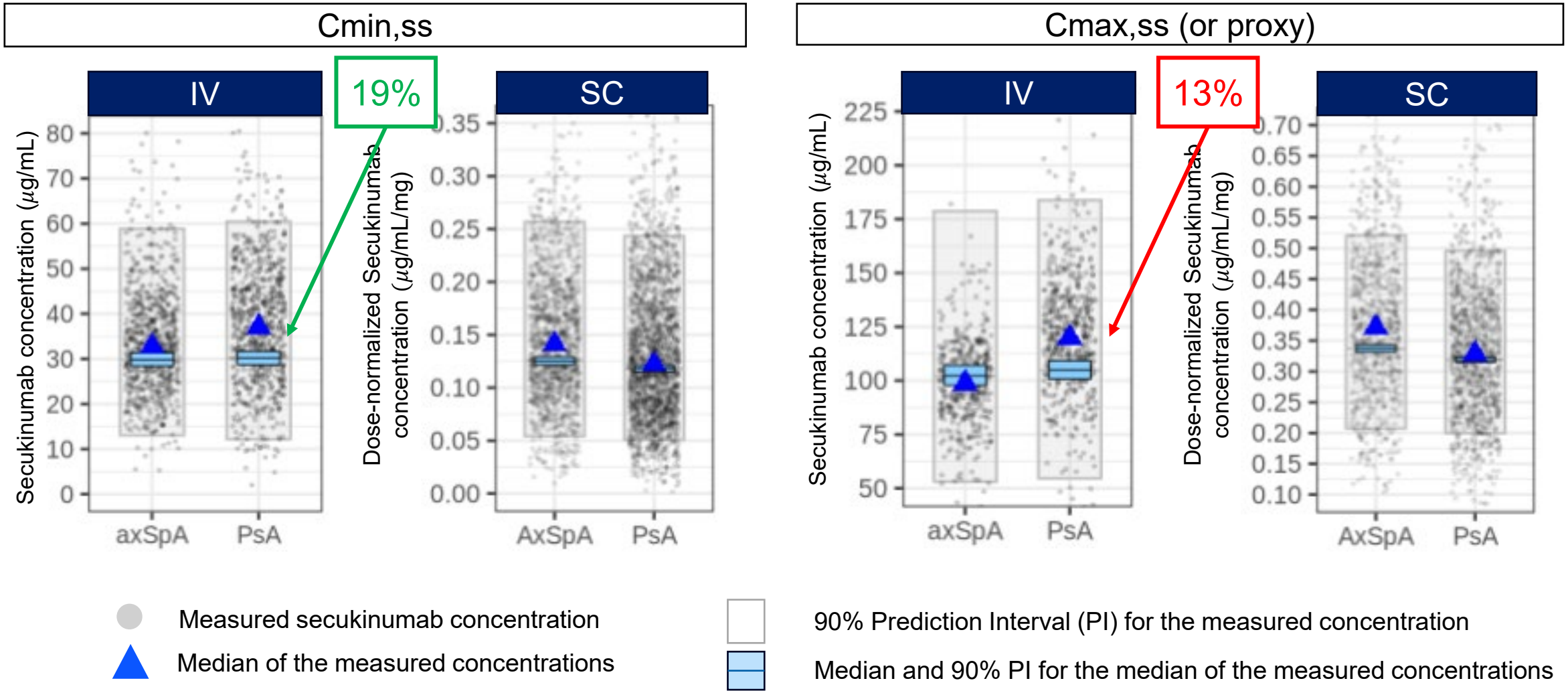


2 Ph3 IV studies (INVIGORATE),
~1000 patients
Maintenance dose: 3 mg/kg Q4W

PK samples at:
- Tmax,ss
- Tmax,ss proxy
- Pre-dose,ss

Summarized validation results

Some underpredictions, especially for IV in PsA, within BE limits*

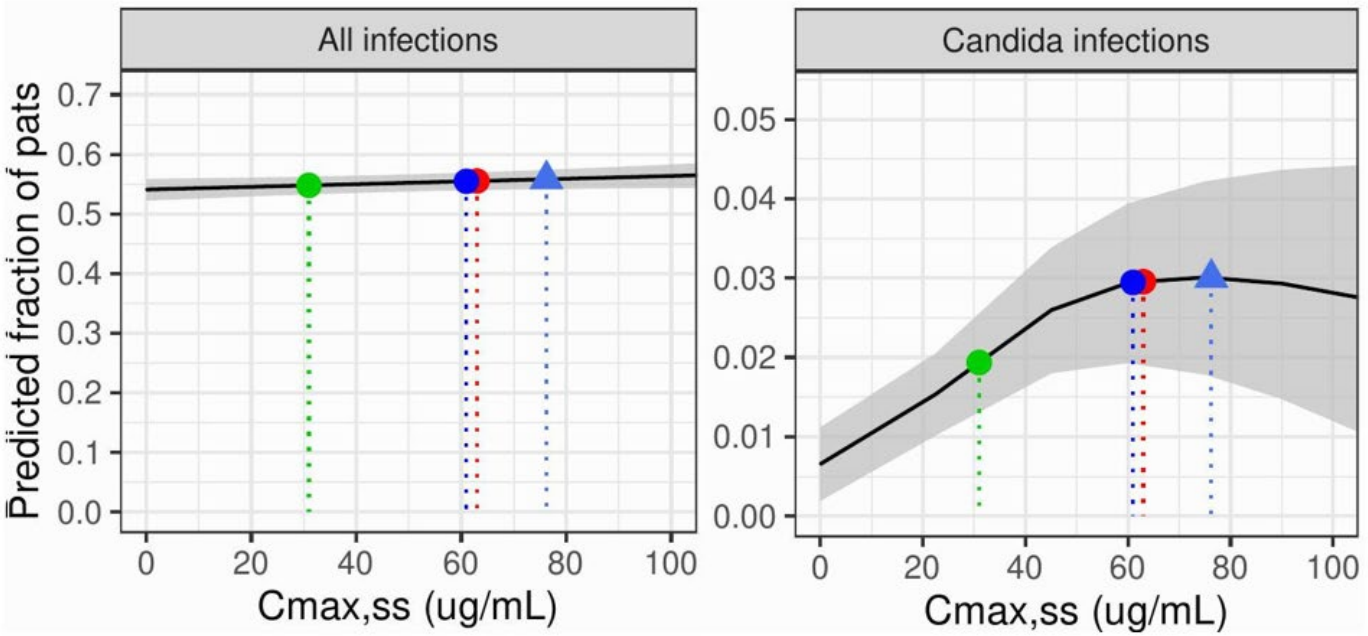


* BE limits: Bioequivalence limits (-20% + 25%)

What if actual IV exposure 25% higher than predicted?

Our interpretation: Small changes in AE incidence, likely irrelevant

Fraction of patient with AE by Year 1 versus PK metric



E-R relationship (90% CI)

Warning: Figures adapted for educational purpose

1.75 mg/kg i.v.

150 mg s.c.

1.75 mg/kg i.v. (increased)

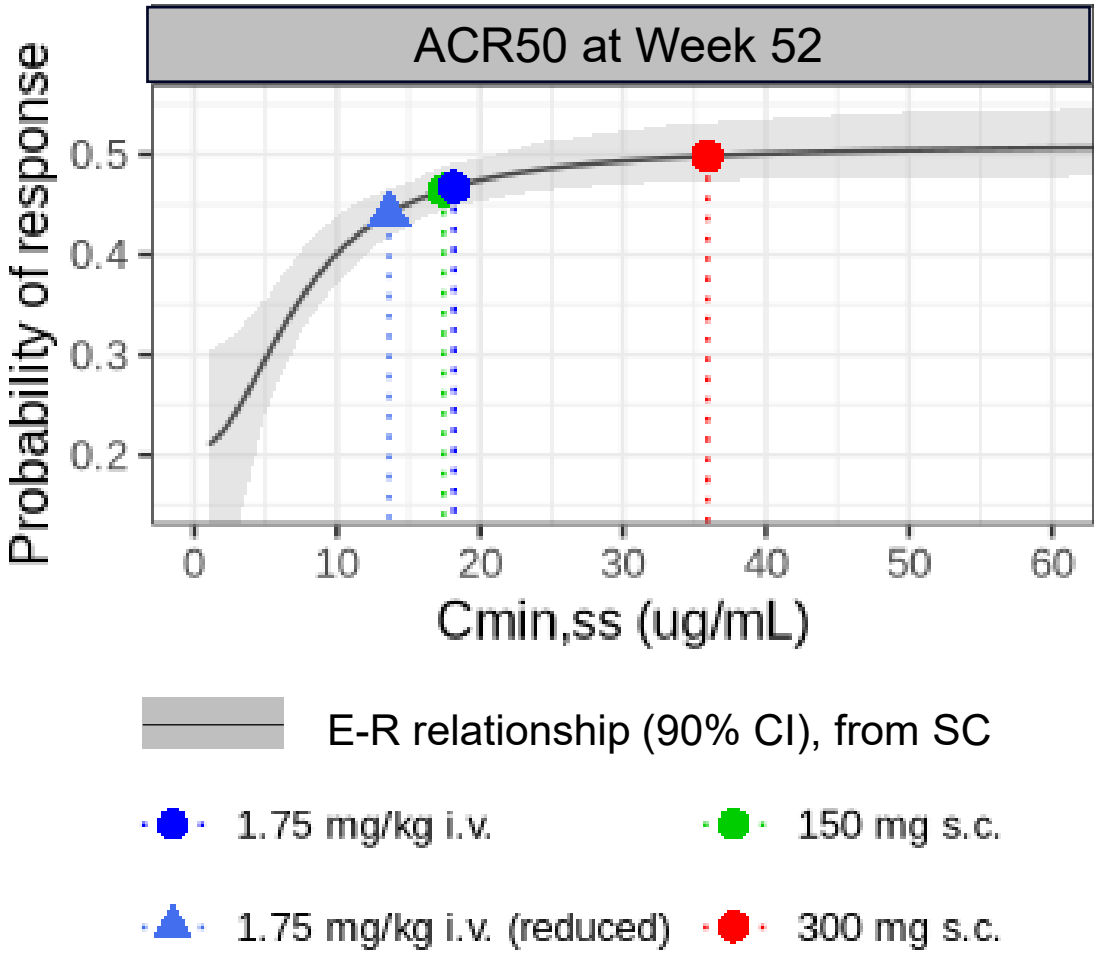
300 mg s.c.

- Survival framework (semi parametric Cox) for time-to-AE
- 6 AE endpoints
- Several time-varying PK metrics (running average last day, last 7 days, …)
- Several functional relationships between log-hazard and PK metrics (linear, splines, …)
- Include ~ 5000 axSpA and PsA patients from the Phase 2 and 3 studies

AE endpoints: Infections and infestations, candida infection, lower respiratory tract infections, hypersensitivity reactions, serious infections and infestations, and all serious or severe events.

What if actual IV exposure 25% lower than predicted?

Our interpretation: Small efficacy decrease, likely clinically irrelevant



- Sigmoid cross-sectional ER model
- 7 axSpA and 9 PsA efficacy endpoints
- Include ~ 1000 axSpA patients and ~1600 SpA patients under SC regimens from the Phase 3 studies
- Weeks 16 and 52, separately
- Several PK metrics (Cmin,ss, Cavg,ss, Cavg0-16wk, …)

- axSpA endpoints : ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, ASDAS-CRP major improvement, ASDAS-CRP inactive disease, BASDAI50
- PsA endpoints: ACR20,ACR50, ACR70, MDA, PASDAS-LDA including remission, HAQ-DI response, PASI90, Resolution of Dactylitis and Resolution of Enthesitis

Approval of the IV formulation in SpA

- May 2022: BB with preliminary modeling results and validation plan
  → FDA's preliminary comments very encouraging → MIDD meeting cancelled
- Dec 2022: Submission dossier (SCE, SCS, SCP, and Modeling report including full popPK model diagnostic and ER analyses) sent to FDA
- Aug 2023: FDA questions about loading dose, addressed by PK simulations
- Oct 2023: Agree on a pediatric plan for the IV formulation in Juvenile PsA patients 2 to 18 years of age
- Nov 2023: Approval of the untested **1.75 mg/kg IV Q4W regimen** with and without a 6 mg/kg IV loading dose at Week 0 using PK bridging and without the need to conduct any PK studies

Summary and final thoughts

- Option to register a modeled Cosentyx IV regimen by PK bridging in PsA and axSpA
- The popPK model showed some underprediction for IV PsA data (within the bioequivalence limits)
- Using ER relationship, those possible PK mispredictions were projected on the efficacy and safety response scales, which facilitates a clinical assessment of their consequence, considered by us likely irrelevant
- Sensitivity analyses is one useful tool mentioned in ICH M15 to assess the credibility of MIDD approaches

Acknowledgment ...

... to the Analytics project team members and close associates:

Xiaofei Zhou, Tingting Zhuang, Xuan Zhu, Jennifer Ng, Ruvie Martin, Rainer Mertes, Ivan Demin, Larissa Lachi Silva, and many others ....

BACK-UP SLIDES

Large secukinumab PK dataset in SpA, a priori adequate

- ~ 5500 patients
- ~ 30000 PK samples
- 15 studies
  - 2 Phase 2 studies (with IV administration) with rich PK sampling, allowing determination of the “standard” Cosentyx structural model a 2-compartment model with linear elimination
  - 11 Phase 3 studies with SC administration
  - 2 Phase 3 studies with IV administration (INVIGORATE)

Number of patients with PK data

Route	Phase	Maintenance regimen	N patients
SC	3	75 mg Q4W	679
		150 mg Q4W	3310
		300 mg Q4W	837
IV	3	3 mg/kg Q4W	400 + 580*
	2	0.1 mg/kg (Wks 0 and 2)	12
		1 mg/kg (Wks 0 and 2)	12
		10 mg/kg (Wks 0 and 2)	50

* N=580 from INVIGORATE-axSpA not available at time of popPK estimation

Summarized validation results, in %

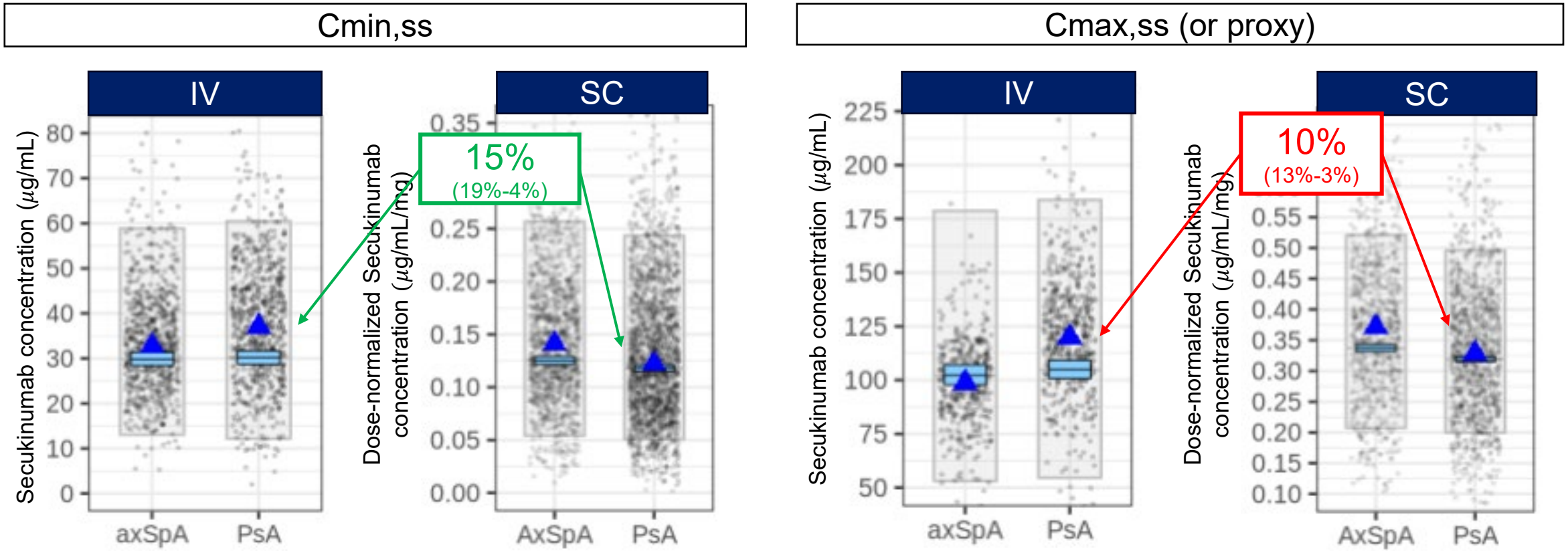
Our interpretation: Deviations of small magnitude, within the standard bioequivalence limits

Population	Underprediction for Cmin,ss			Underprediction for Cmax,ss		
	s.c.	i.v.	Difference (i.v. – s.c.)	s.c.	i.v.	Difference (i.v. – s.c.)
PsA	4%	19%	15%	3%	13%	10%
axSpA	11%	9%	-2%	7%	-2%	-9%
Overall	5%	14%	9%	4%	6%	2%

% underprediction = Median of the measured secukinumab concentrations relative to the median of their model predictions, averaged across time points (and doses)

Summarized validation results

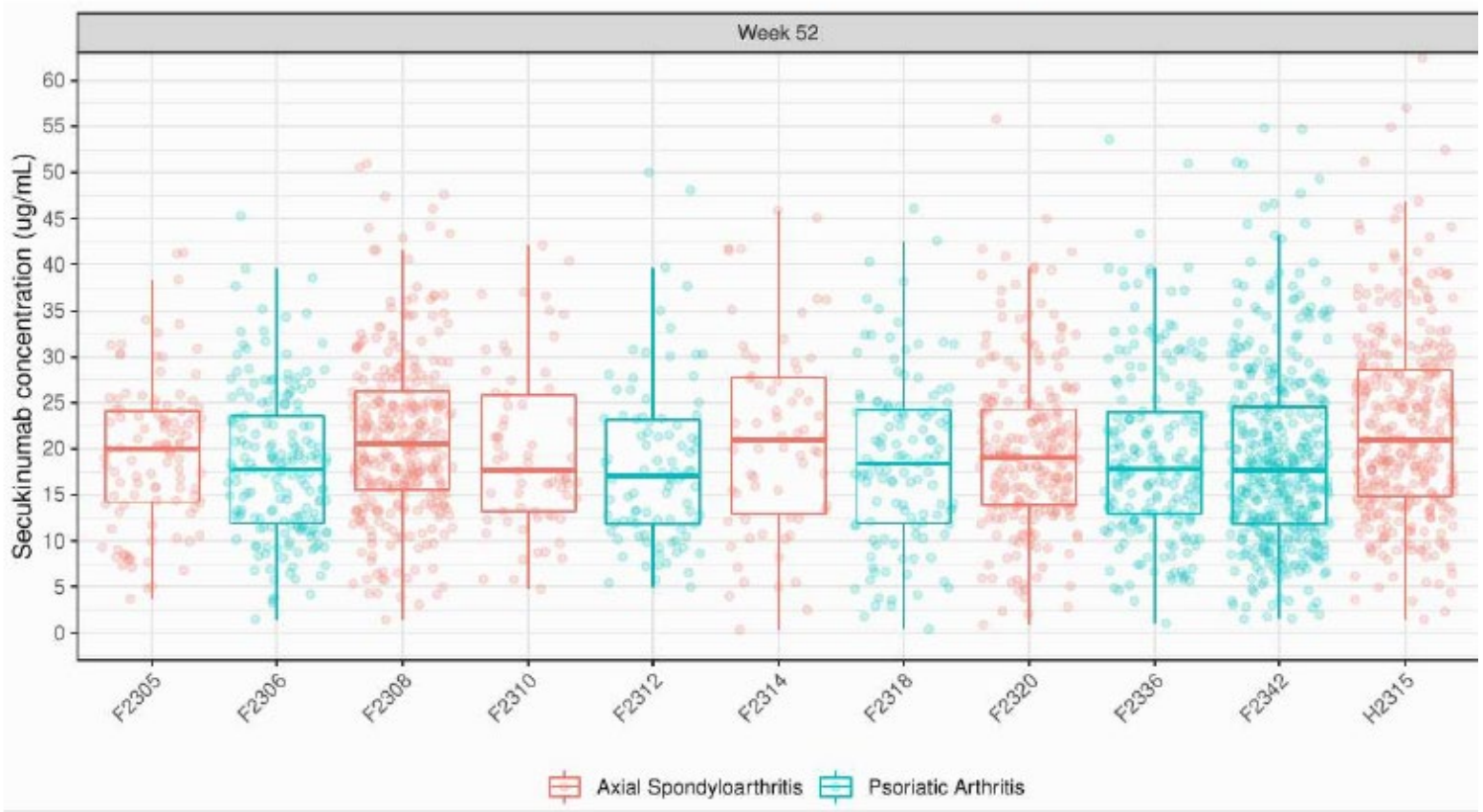
Our interpretation: Deviations of small magnitude, within BE* limits



* BE limits: Bioequivalence limits (-20% + 25%)

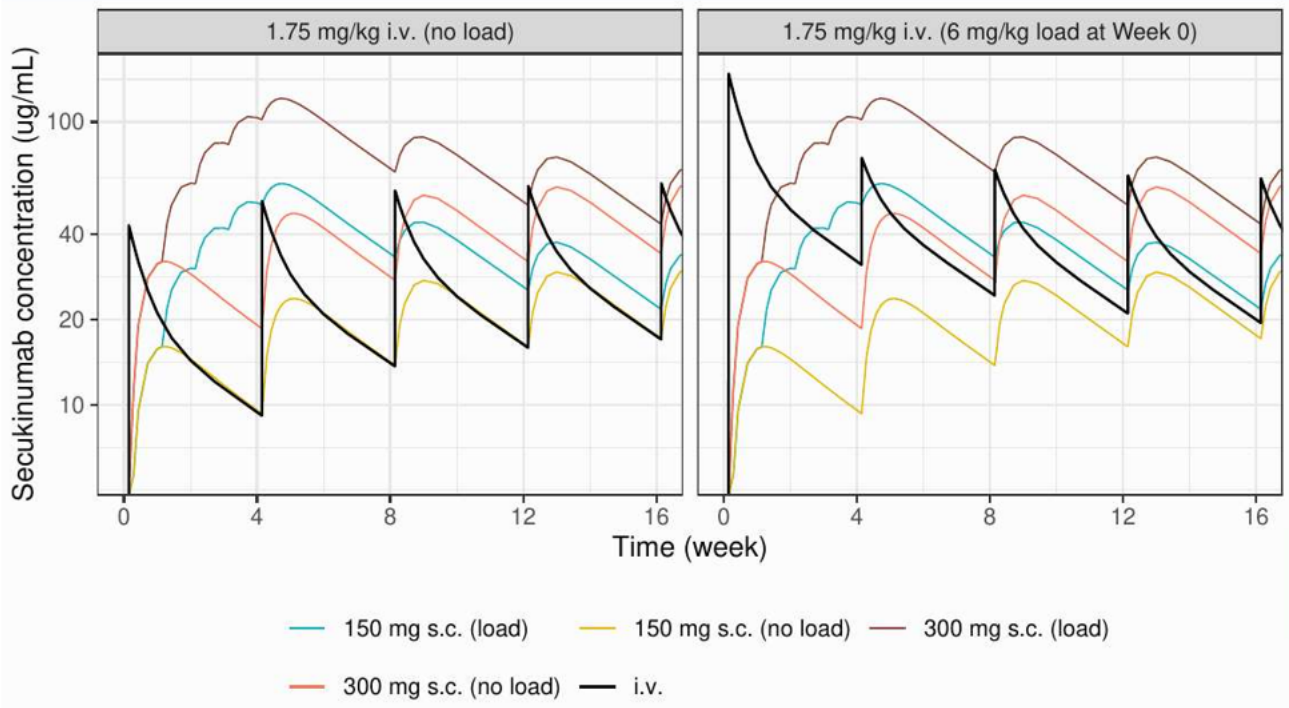
Between studies variability

Figure 5-23 Distribution of secukinumab Cmin concentration at Week 52 in subjects treated with the 150 mg s.c. q4w regimen, by study



Simulations conducted to support approval of the IV regime with and without one loading dose

Figure 1-1 **Median predicted concentration time-profiles (Week 0 to 16) for the 1.75 mg/kg i.v. maintenance regimen with and without loading, along with the 150 and 300 mg s.c. regimens with and without loading**



The lines represent the median of the secukinumab concentration time-profiles for two i.v. and four s.c. treatments, as predicted from the final popPK model included in SN 0000 for patients with same characteristics (body weight and race) as patients from studies P12301 and P12302.