PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Real-world clinical effectiveness and utility of ustekinumab in adults with psoriasis: ***statistical & pharmacometric perspectives***

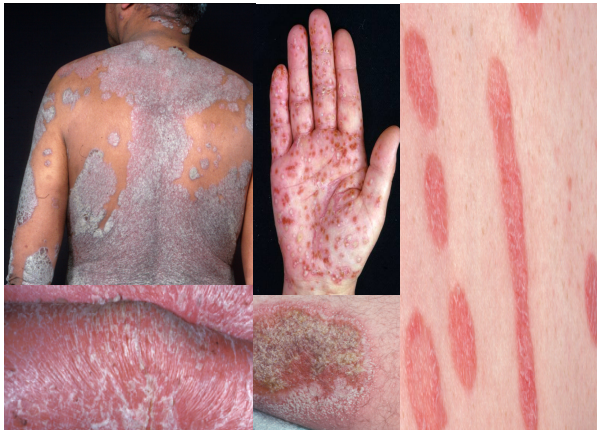
Shan Pan[1], Nina Wilkinson[2], Theo Rispens[3], Christopher EM Griffiths[4], Joseph F Standing[5], Catherine H Smith[1,6] on behalf of the PSORT consortium

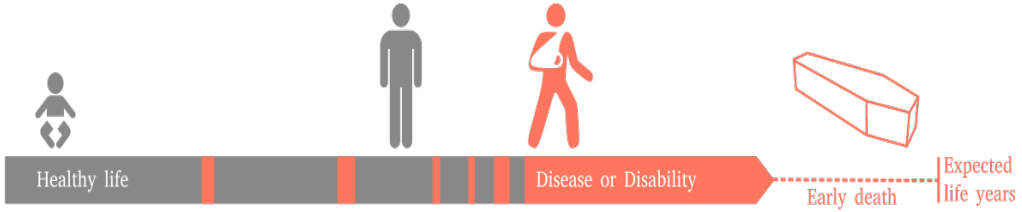
[1]St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[2]Faculty of Medical Sciences, Newcastle University, Newcastle-upon-Tyne, UK
[3]Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam, NL
[4]Centre for Dermatology Research, University of Manchester, Manchester, UK
[5]University College London Great Ormond Street Institute of Child Health, London, UK
[6]Faculty of Life Sciences & Medicine, King's College London, London, UK

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Psoriasis

- A chronic, autoimmune, inflammatory skin disease
  - affecting 2-3% of the worldwide population
  - clinical features: red plaques covered by silvery-white scales
  - pathogenesis: TNF-α, dendritic cells and T cells
  - impaired quality of life, disability, even early mortality

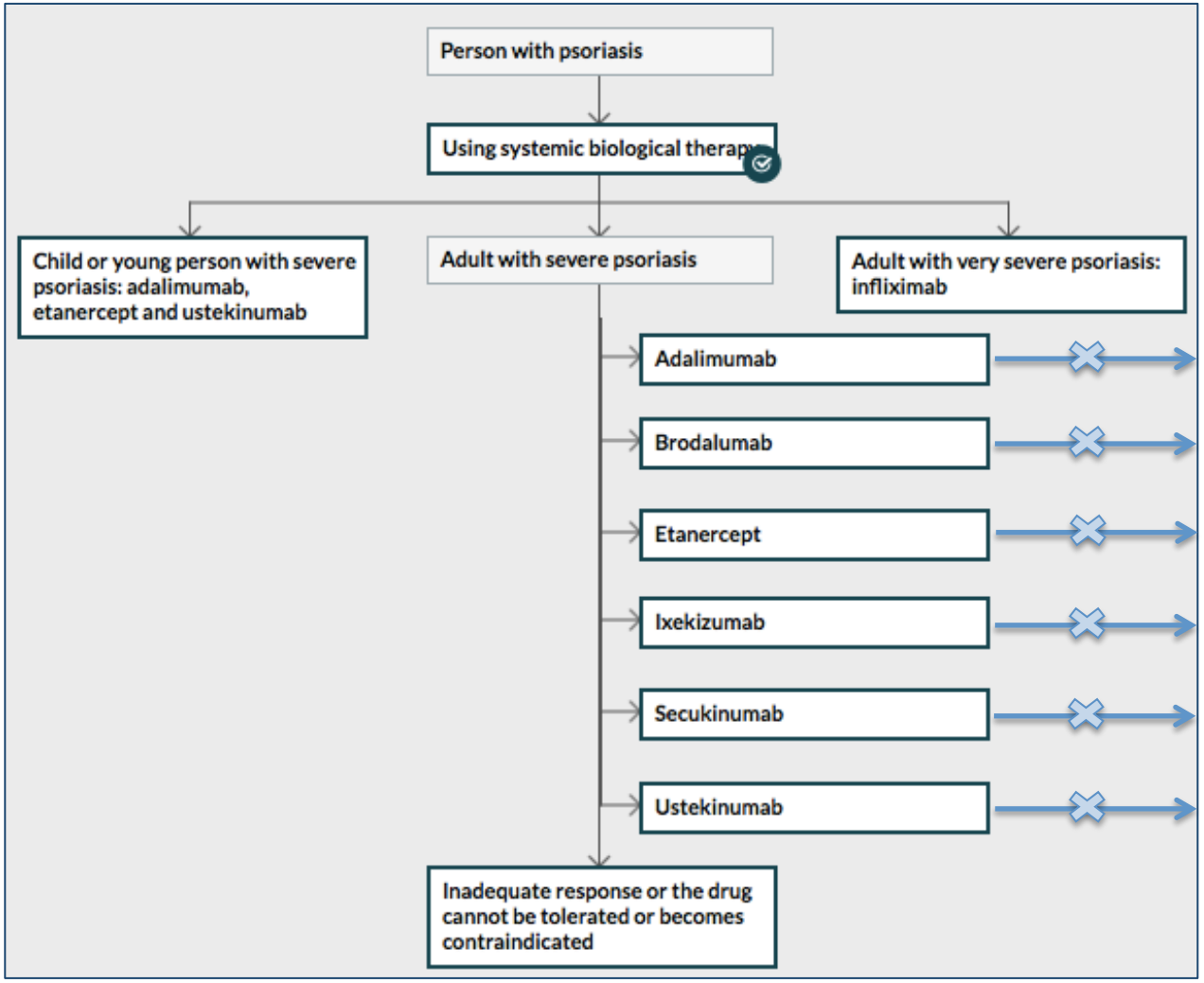




Griffiths and Barker. Lancet. 2007; 370:263-271
Springate et al. Br J Dermatol. 2017; 176:650-658

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Biologic agents for psoriasis



https://pathways.nice.org.uk/pathways/psoriasis

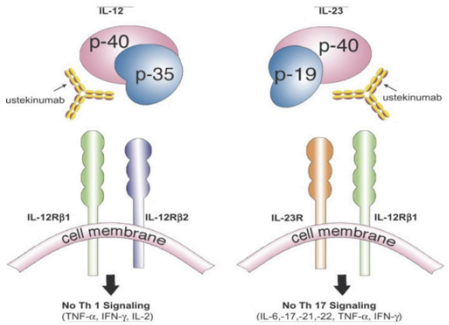
PSORT vision

- Personalise biologic therapies for psoriasis
  - "**trial and error**" prescription at very expensive cost (£10,000 per year per patient)
  - skin condition is easy to measure and monitor, well suited for **treatment stratification**
  - **investigate factors** that may influence individual treatment outcome (i.e. drug levels, change in skin and blood, genetic variation and etc)
  - **substantial resources**: MRC and industrial funding, consent from a large number of patients, clinical and scientific expertise, state-of-the-art investigative tools

Griffiths et al. J Investig Dermatol. 2015; 135:2903-2907

Ustekinumab (Stelara)

- A human IgG1 κ that neutralises the bioactivity of IL-12 & IL-23
  - by binding to the shared p40 subunit



- Clinical trials from Phase I to Phase III:
  - linear PK over wide dose range (0.1–5.0 mg/kg)
  - subcut BA: 57%, elimination $t_{1/2}$: ~3 wks
  - two subcut doses approved: 45 mg & 90 mg (<=100 kg & > 100 kg)
    - dosing at week 0, 4, then 12 weekly
- Heterogeneity in response to ustekinumab treatment
  - drug levels, demographics, adherence and etc
- Response assessment: Psoriasis Area Severity Index (PASI)
  - a composite, continuous score: 0 - 72
  - primary endpoint: PASI 75

Zhu et al. J Clin Pharmacol. 2009; 49:162-175
Benson et al. MAbs. 2011; 3:535-545
Edson-Heredia et al. J Investig Dermatol. 2014; 134:18-23

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Overall objectives

- To investigate the exposure-response relationship for ustekinumab in psoriasis using real-world data
  - through **statistical** analysis (step 1)
  - through population **PKPD** analysis (step 2)
- To guide ustekinumab dosing strategies for psoriasis
  - simulating variable dosing frequencies
  - establishing early target drug level

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Study design

- A multicenter (n=60) prospective observational cohort study within the UK

4847 patients in BSTOP cohort on adalimumab, secukinumab and ustekinumab (July 2017)

→

655 patients on ustekinumab monotherapy with serum samples

→

491 patients with ustekinumab serum samples and PASI within 12 mths

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Statistical analysis using real-world data

Statistical analysis

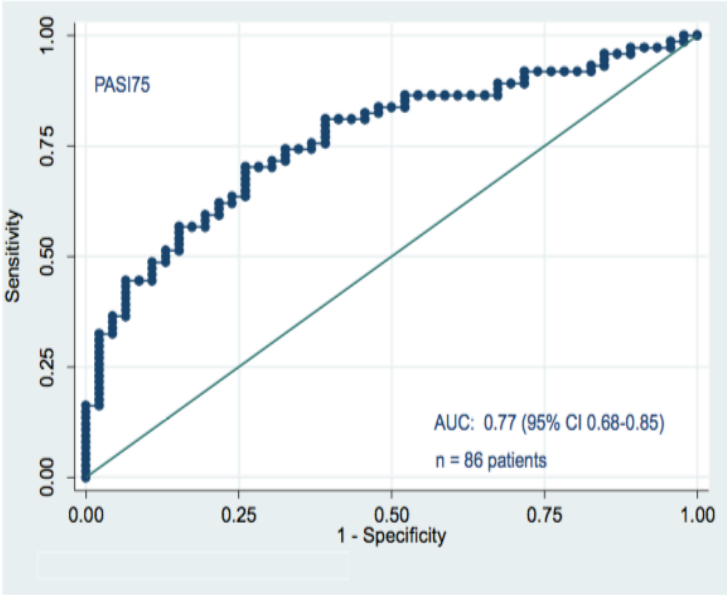
- Multivariable logistic regression
  - mismatched time points between PK and PASI 75
  - early dataset: PK at 1-12 weeks & PASI 75 at 6 mths
    - 119 samples from 85 patients
  - steady-state dataset: PK ≥ 16 weeks & PASI 75 on the same day
    - 175 samples from 148 patients

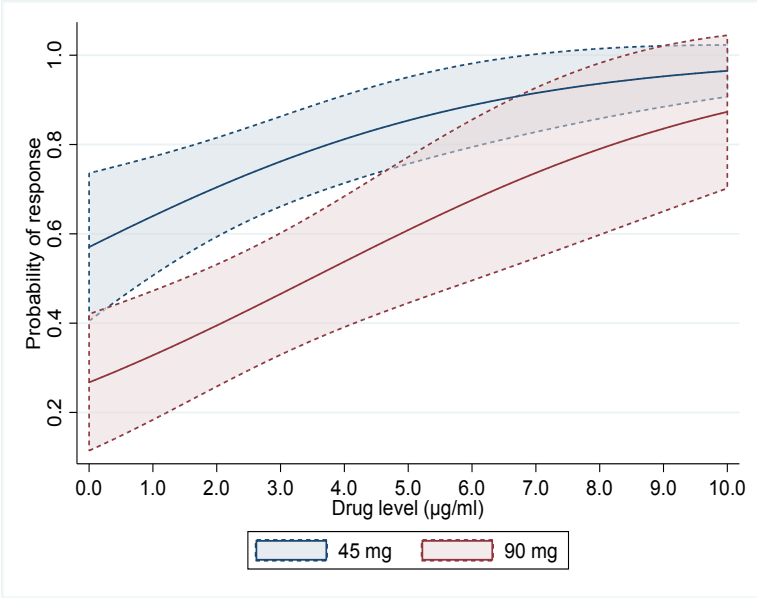
Variable	OR (95% CI)	P value
Drug level	1.38 (1.11, 1.71)	0.004
Baseline PASI	1.10 (1.01, 1.20)	0.03
Age	1.04 (1.00, 1.07)	0.03
Dose (90 mg)	0.24 (0.10, 0.56)	0.001

Tsakok T et al. JAMA Dermatol. 2019 Apr (in press)

Statistical analysis

- ROC curve
  - ↑ early drug level → ↑ probability of PASI 75 response
- Model prediction
  - ↑ USK dose → ↓ probability of PASI 75 response





Tsakok T et al. JAMA Dermatol. 2019 Apr (in press)

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Pharmacometric analysis using real-world data

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Data preparation challenges

- STATA dataset to NONMEM dataset
  - convert from wide to long format
  - extract additional covariates (comedications, comorbidities)

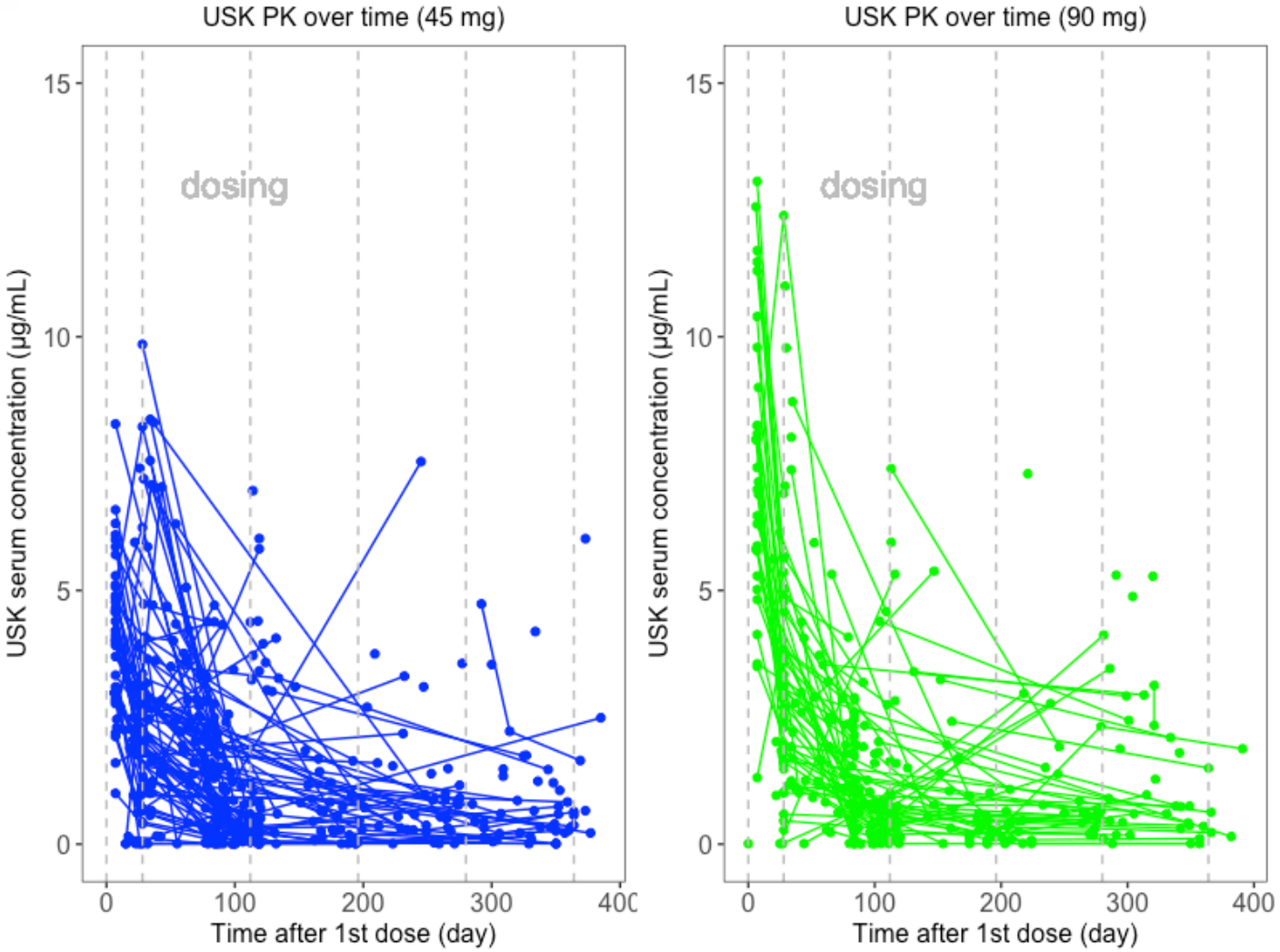
- "Missing" injection dates
  - impute standard doses until date of last dose or date of last serum sample or PASI
  - assume 100% medication adherence (no clinical documents to disprove so)

STATA

NONMEM7™
The program for Nonlinear Mixed Effects Modeling

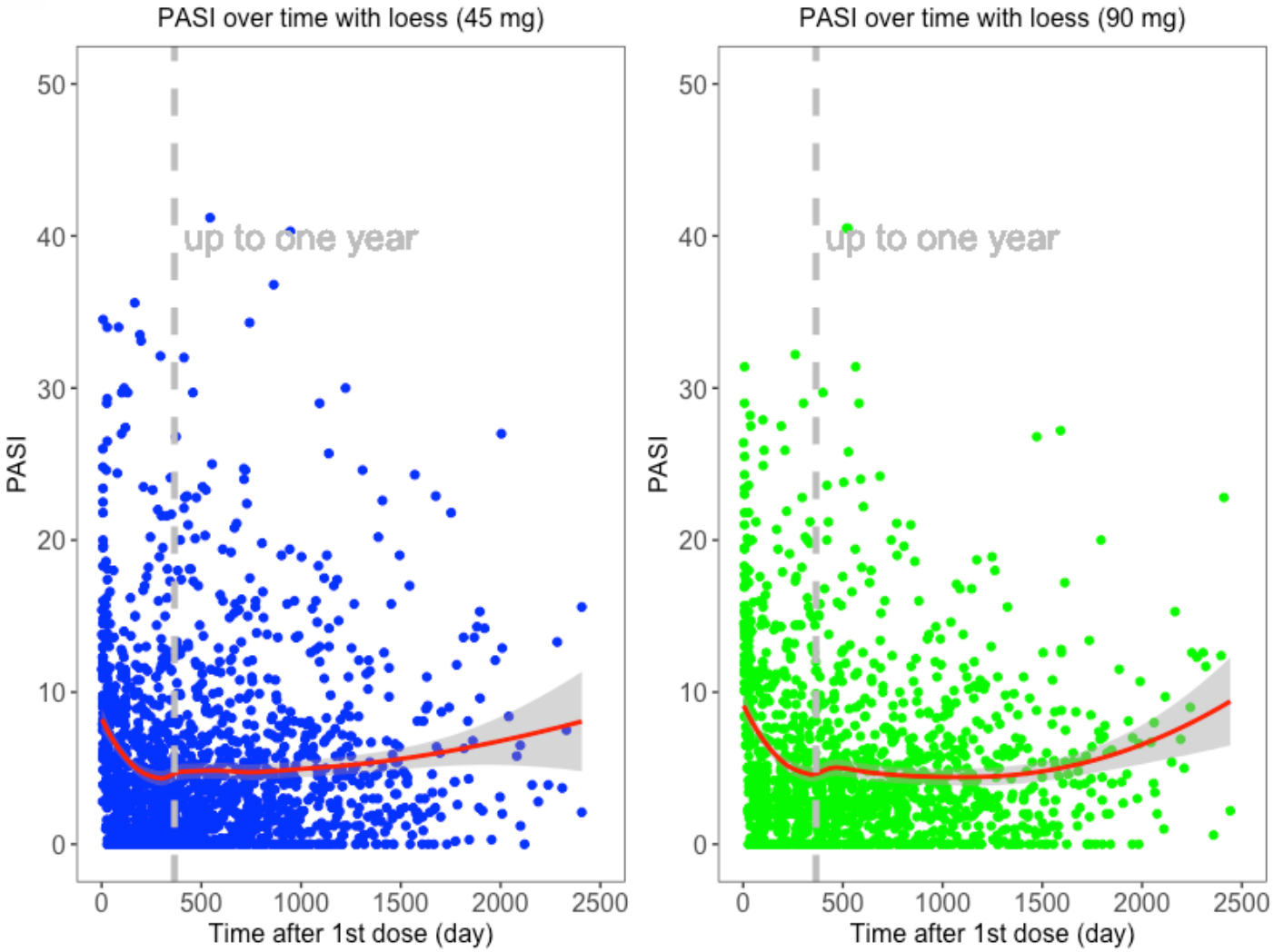
PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Exploratory PK analysis



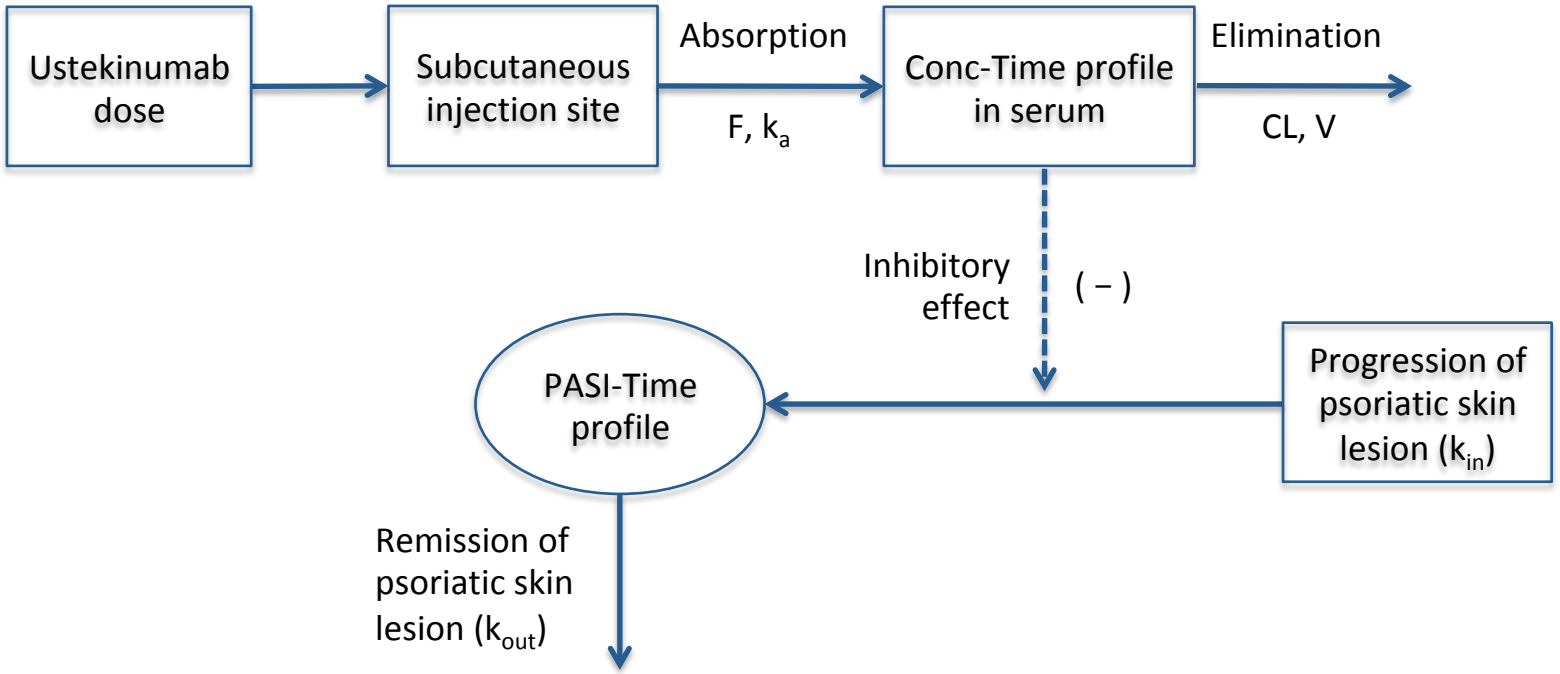
PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Exploratory PKPD analysis



PSORT
Psoriasis Stratification to Optimise Relevant Therapy

USK PKPD model diagram



Assumption: all patients respond to IL-12 & 23 pathway

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

USK PK parameter estimation

Parameter	Estimate	RSE (%)	Literature value
k_a (/day)	0.23	16.1	0.35
CL/F (L/day)	0.44	6.7	0.47
V/F (L)	10.2	8.2	15.7
BSV_CL (%)	44.7	20.7	
BSV_V (%)	36.5	57.7	
corr(CL,V) (%)	24.5	-	

Zhu et al. J Clin Pharmacol. 2009; 49:162-175

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

USK PK parameter estimation

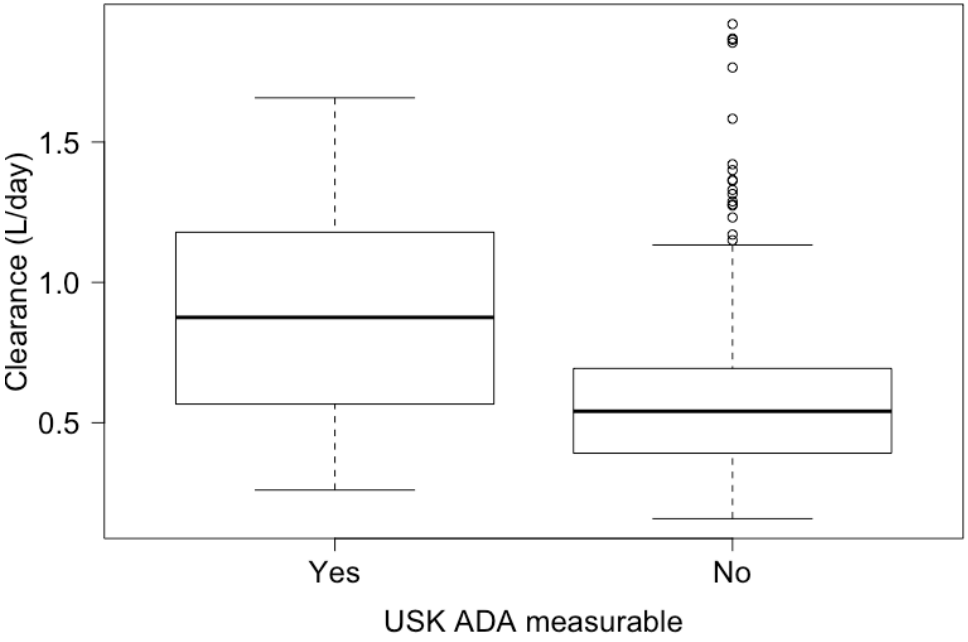
Parameter	Estimate	RSE (%)
k_a (/day)	0.23	16.1
CL/F (L/day)	0.44	6.7
V/F (L)	10.2	8.2
BSV_CL (%)	44.7	20.7
BSV_V (%)	36.5	57.7
corr(CL,V) (%)	24.5	-
Weight_CL	0.75 [FIX]	-
Weight_V	1 [FIX]	-
BioNaive_CL	-0.13	34.1
Creatine_CL	-0.36	35.5
Waist_CL	0.84	18.0
Alcohol_CL	0.15	42.7

Covariates

1) Diabetic status had ~30% increase on CL perhaps due to deceased lymphatic function and increased antibody glycation, *NOT* statistically significant after two-way selection.
2) Diabetic status had *NO* effect on V, although with increased interstitial volume and capillary permeability.

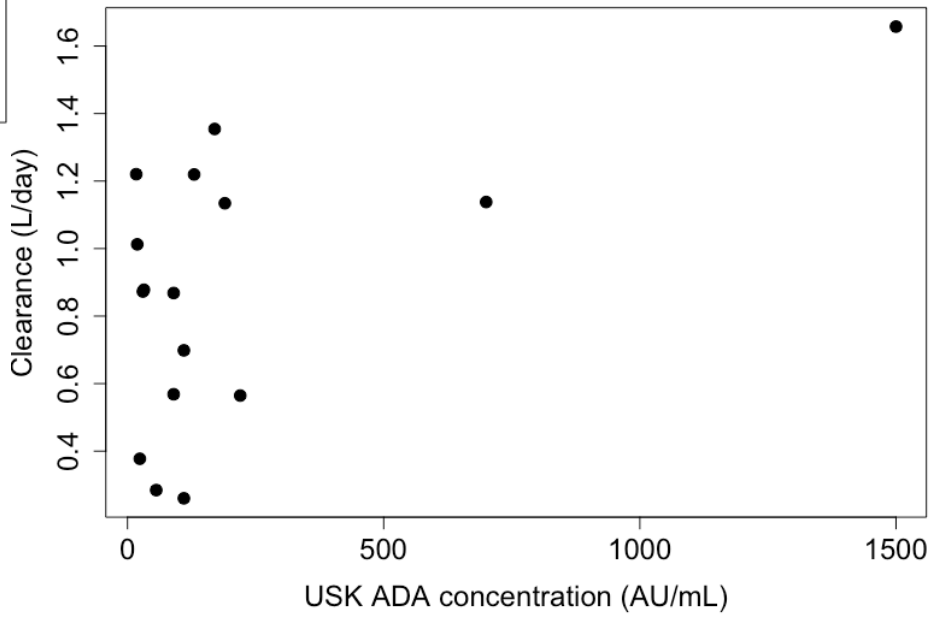
PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Anti-drug antibody & clearance



- 16 patients with measurable ADA
- higher CL in measurable group
- not statistically different

- CL appeared to increase with higher ADA concentration
- ADA developed over time & higher USK exposure?



PSORT
Psoriasis Stratification to Optimise Relevant Therapy

USK PD parameter estimation

Parameter (unit)	**Estimate** (single population)
Baseline PASI	15.5
k_{out} (per day)[1]	0.022
Emax	1 [FIX]
IC50[2] (µg/mL)	0.14
BSV_BSL (%)	43.6
BSV_k_{out} (%)	66.4
BSV_IC50 (%)	148.3

[1]k_{out} = 0.031 from *Zhou et al.* 2010
[2]estimate for single population

Zhou et al. J Clin Pharmacol. 2010; 50:257-267

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

USK PD parameter estimation

Parameter (unit)	Estimate (single population)	Estimate ($MIXTURE two subgroups)
Baseline PASI	15.5	15.8
k_{out} (per day)[1]	0.022	0.024
Emax	1 [FIX]	1 [FIX]
IC50[2] (µg/mL)	0.14	0.07
IC50[3] (µg/mL)	-	1.21
BSV_BSL (%)	43.6	41.4
BSV_k_{out} (%)	66.4	66.9
BSV_IC50 (%)	148.3	42.7

[1]k_{out} = 0.031 from *Zhou et al.* 2010
[2]estimate for single population **OR** 76% responders in $MIXTURE
[3]estimate for 24% non-responders in $MIXTURE

Zhou et al. J Clin Pharmacol. 2010; 50:257-267

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

USK PD parameter estimation

Parameter (unit)	**Estimate** (single population)	**Estimate** ($MIXTURE two subgroups)	**Estimate** (manually stratified three subgroups)
Baseline PASI	15.5	15.8	15.4
k_{out} (per day)[1]	0.022	0.024	0.023
Emax	1 [FIX]	1 [FIX]	1 [FIX]
IC50[2] (µg/mL)	0.14	0.07	0.03
IC50[3] (µg/mL)	-	1.21	0.37
IC50[4] (µg/mL)	-	-	1.96
BSV_BSL (%)	43.6	41.4	42.4
BSV_k_{out} (%)	66.4	66.9	67.6
BSV_IC50 (%)	148.3	42.7	39.6

[1]k_{out} = 0.031 from *Zhou et al.* 2010
[2]estimate for single population **OR** 76% responders in $MIXTURE **OR** 63% full-responders (>= 75% reduction from baseline)
[3]estimate for 24% non-responders in $MIXTURE **OR** 23% partial-responders (>= 50% & < 75% reduction from baseline)
[4]estimate for 14% non-responders (< 50% reduction from baseline)

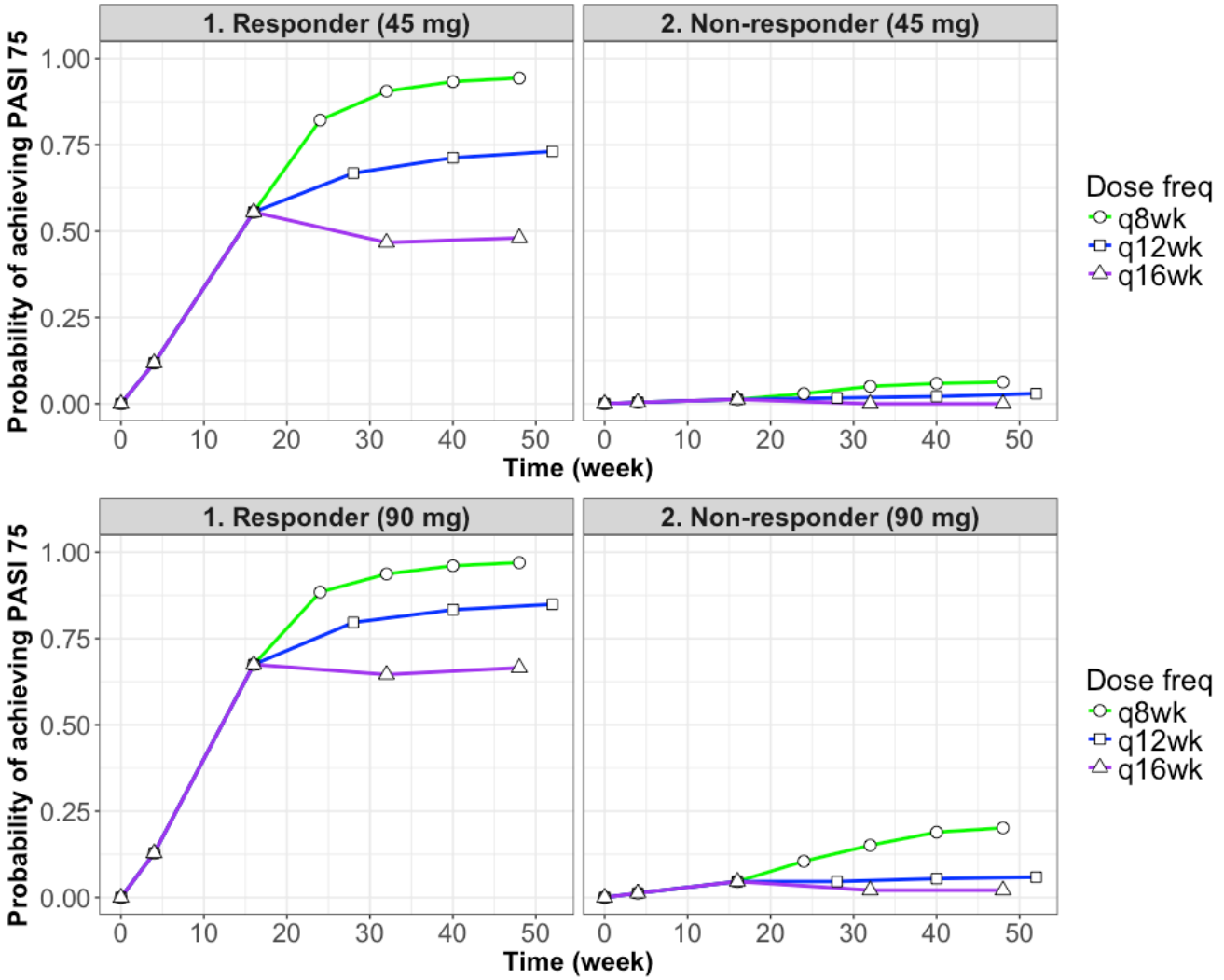
Zhou et al. J Clin Pharmacol. 2010; 50:257-267

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Dosing simulation for PASI 75

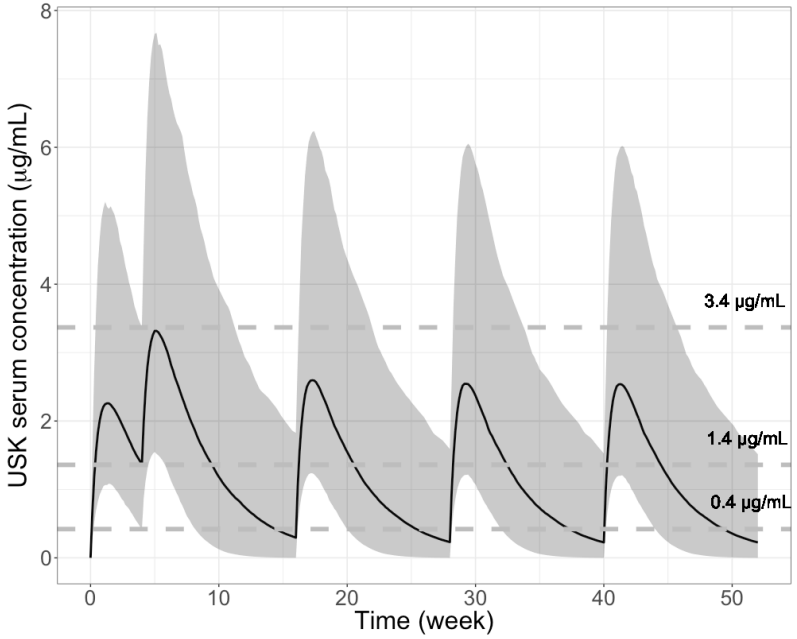
Simulation—45 mg vs. 90 mg:

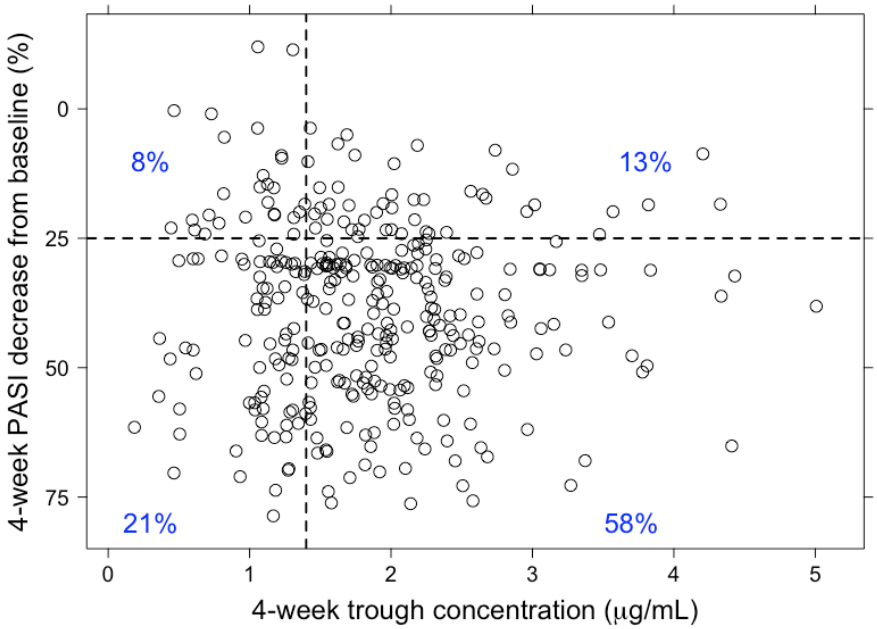
- 1000 subjects (76% & 24% for responders and non-responders)
- random sampling for significant PK covariates within realistic ranges (runif() vs. rbinom())
- PK covariates significantly different between 45 mg and 90 mg: weight & waist
- consider variability in IC50 for each subpopulation
- calculate % achieving PASI 75 for each subpopulation



Therapeutic drug monitoring

- Trough level at week 4: targeted to be predictive of 80% PASI 75 probability at 6 months
  - **9.3** µg/mL (95% PI: 3.1 – 24.3 µg/mL) for all patients
  - **1.4** µg/mL (95% PI: 0.4 – 3.4 µg/mL) for responders only





PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Discussion – Overall

- Statistical vs. PKPD analysis for ustekinumab in psoriasis
  - no obvious linear conc-PASI relationship using reduced dataset (insufficient power? alternative assumptions?)
  - nonlinear PKPD relationship using pooled data (comparable estimates between real-world and clinical trial data)
- Real-world data: less optimal data quality
  - no placebo group for disease trajectory
    - average placebo response rate ~4% from psoriasis trials
  - pragmatic sampling strategy (scattered / random time points)
  - less strict recruitment criteria wrt disease baseline
    - similar disease-specific estimate between high and low baseline groups (data not shown)

Lamel et al. Arch Dermatol Res. 2012; 304:707-717

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Discussion – PKPD

- Linear PK + turnover PD assuming perfect adherence
  - similar PK estimates & covariates (except diabetes on CL)
  - similar PD estimates (except unpublished IC50 in literature)
- Individual variation in response to USK
  - large difference in IC50 values & large BSV
  - no obvious covariate-response correlation (causal information from immune biomarker studies?)
  - stratification into responder subgroups
- PASI 75 simulation of alternative dosing scenarios
  - + dose or - interval beneficial for responders
  - overall no improvement for non-responders

Thorneloe et al. J Invest Dermatol. 2018; 138:785-794

PSORT
Psoriasis Stratification to Optimise Relevant Therapy

Discussion – Application

- Future application
  - incorporated into a Bayesian TDM tool for clinical use
    - e.g. Dashboard as a single integrated interface
  - clinical decision-making for individual patients
    - dose escalation for improved response
    - dose reduction with lower cost
    - treatment switching as early as possible

Mould et al. AAPS J. 2014; 16:925-937

Acknowledgement