

A stylized human silhouette is the central focus, filled with a dense array of colorful molecular and chemical structures. The background is a light blue network of interconnected nodes and lines, resembling a molecular or biological network. The overall aesthetic is scientific and data-driven.

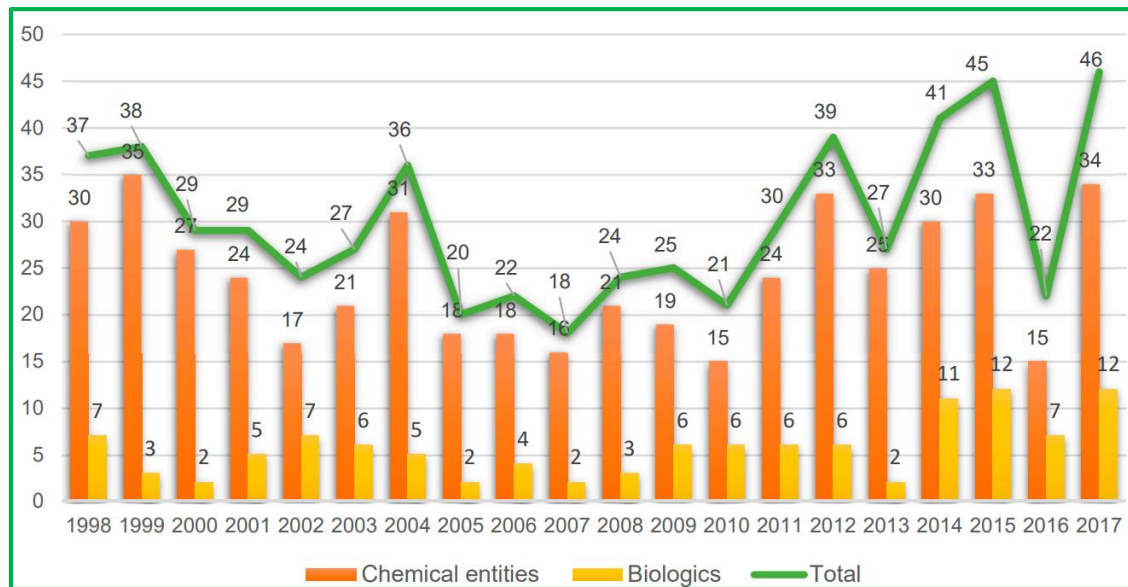
**The development of a quantitative systems pharmacology platform to predict and manage immunogenicity in clinical development**

Mario Giorgi, Piet van der Graaf & Andrzej Kierzek  
Certara QSP

*EIP, European Immunogenicity Platform, Lisbon,  
25<sup>th</sup>-27<sup>th</sup> February 2019*

# Introduction - Biologics

New Chemical Entities and Biologics approved by the FDA in the last two decades



Beatriz G. de la Torre and Fernando Albericio, *Molecules*, 2018

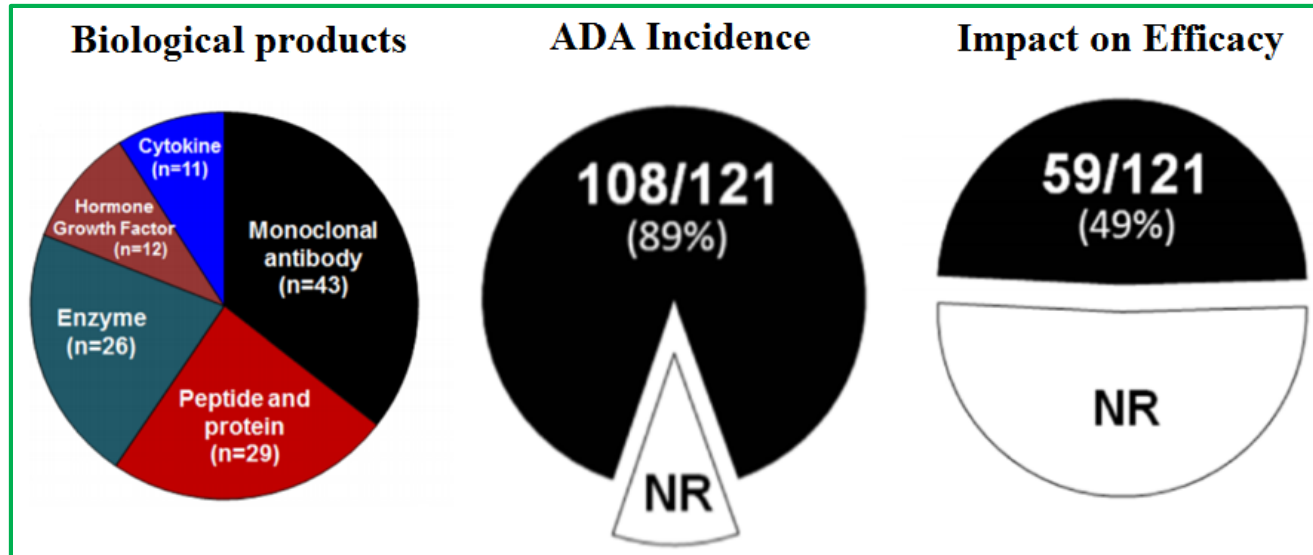
**Biologics:** ~30% of new drug approvals in 2017;

From Biopharma Dive, 2018:

*“Making up more than half of the drugs currently in development, the biologics market is forecast to reach **\$399.5 billions by 2025**”*

# Introduction – Immunogenicity (IG)

Study on 121 approved biologicals products



*Adapted from Wang et al., AAPS J., 2016*

89% incidence of immunogenicity  
49% immunogenicity impact on efficacy

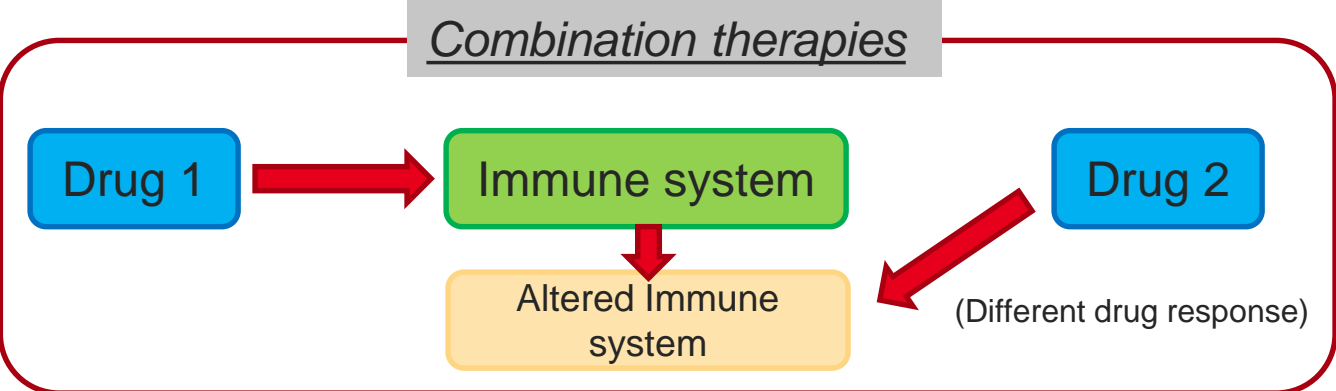
IG is mostly tackled preclinically:

- Predicts peptides that bind strongly to major histocompatibility (MHC) II receptors;
- Engineer protein sequences to avoid strong binding.

# Introduction – Limitation of bio-informatics

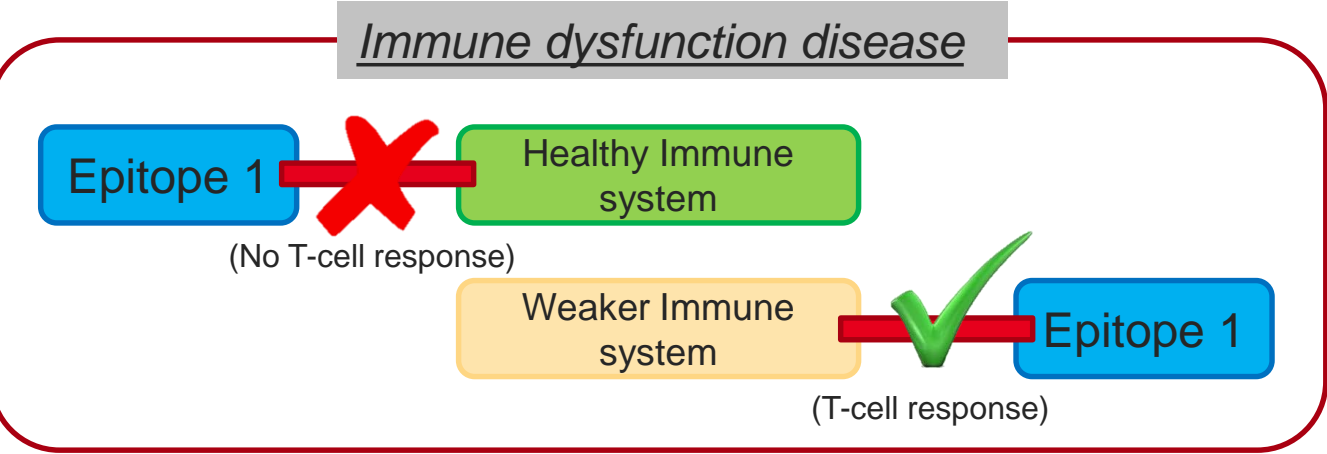
Examples of other important factors that could influence IG

## Combination therapies



- Limitation of bio-informatics:
- No PK time profiles;
  - Co-therapy
  - Disease state
  - Patient parameters (Age, gender, weight, etc...)

## Immune dysfunction disease



# Introduction – QSP

## Quantitative system pharmacology models (QSP) (Complement bio-informatics)

**Genentech**

A Member of the Roche Group

(Kapil Gadkar & Jennifer Rohrs)

Antibody Drug	# Binding peptides*	# MHC II alleles	% ADA+ Patients
<b>Bococizumab</b> (Pfizer)	2	12	68% ( <a href="#">Ridker, 2017</a> )
<b>Alirocumab</b> (Regeneron)	1	1	5.1% ( <a href="#">Roth, 2017</a> )
<b>Evolocumab</b> (Amgen)	0	0	0.1% ( <a href="#">Henry, 2016</a> )
<b>GNE anti-PCSK9</b> (Genentech)	2	8	4% (GENE data*)



\*Based on Phase II clinical study with ~200 subjects

# IG QSP Consortium

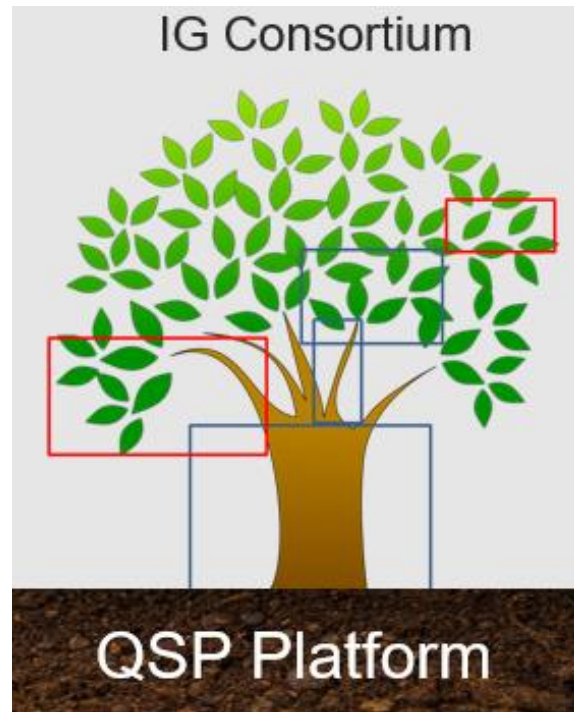
The Consortium aims to develop the industry-standard quantitative systems pharmacology (QSP) model, coupled to a robust IT platform, to predict and manage IG and guide decision making in drug development.

abbvie

Lilly



Bristol-Myers Squibb

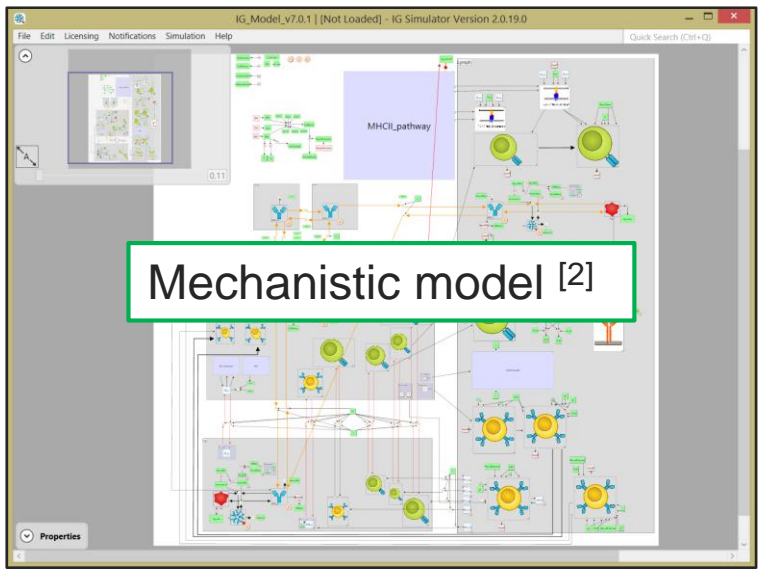


Genentech  
A Member of the Roche Group

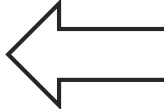
The QSP Consortium is a **tree**, where **trunk** represents biology common to all applications, while **branches** and **leaves** represent target specific mechanisms. The Consortium is rooted in **QSP Platform**.

# Overview of IG Simulator

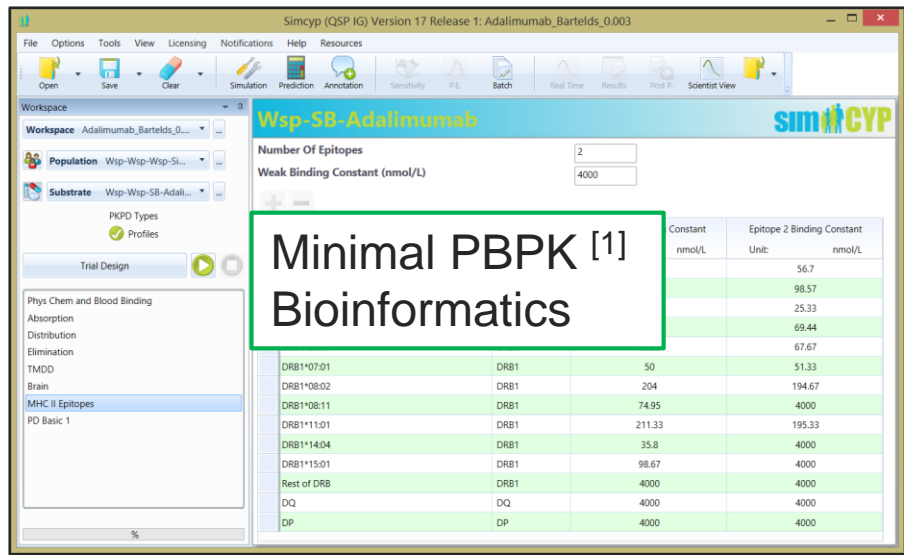
## Biological Process Map interface



Read workspace file.



## Simcyp simulator



Export IG Model code.



Write IG Model

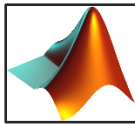


Read IG Model and augment ODEs




Simulate virtual trial and output results.







Matlab code



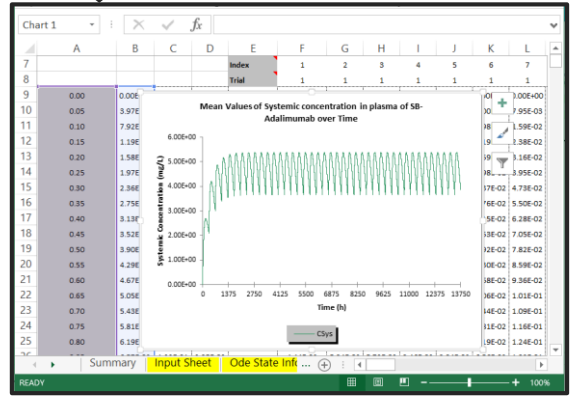
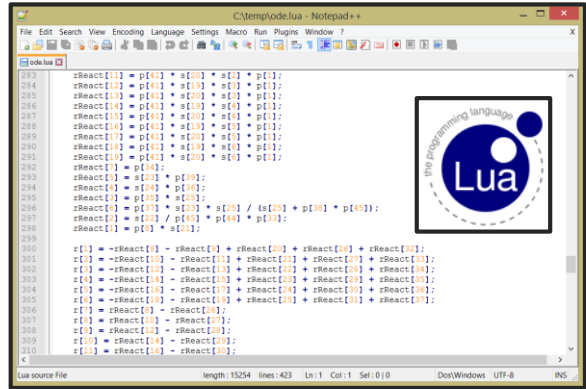
R code



R code with equation in C



Excel file with documentation of variables, equations and parameters



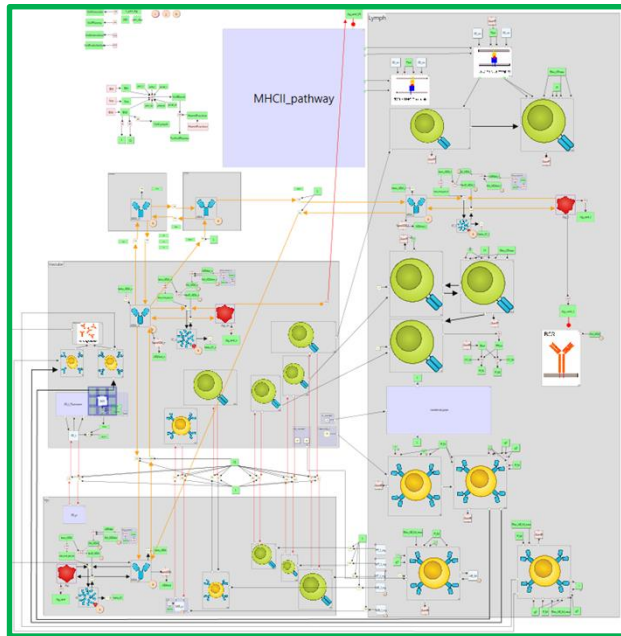
IG Model code and documentation

IG Model code and PBPK variable connections in Lua

Virtual trial results in Simcyp formatted Excel file

# IG Simulator Application

## IG Simulator



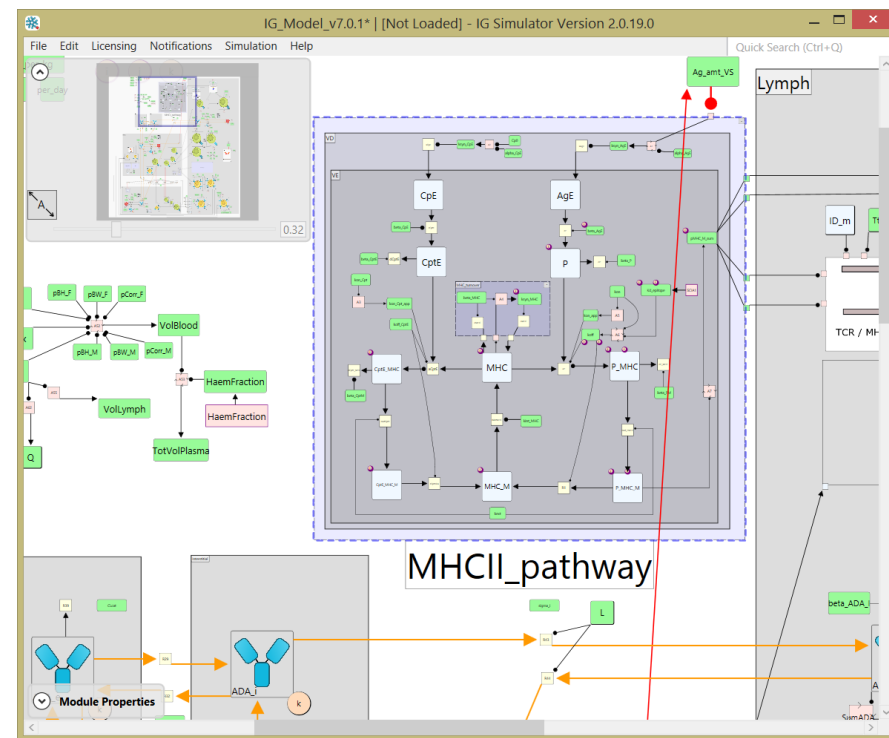
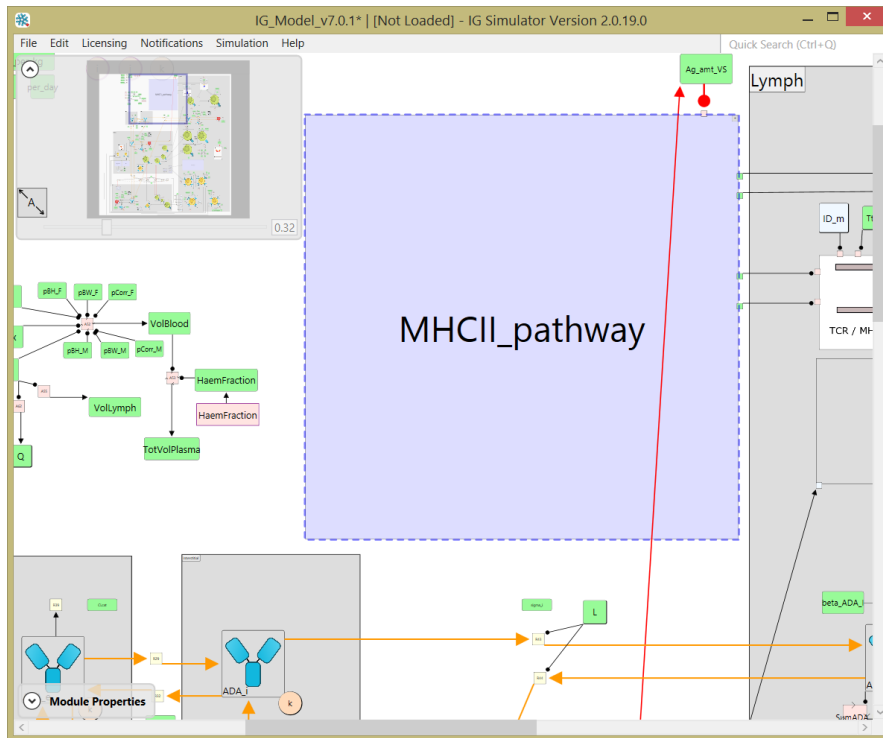
## Simcyp

MHC II Allele	Gene	Epitope 1 Binding Constant Unit: nmol/L	Epitope 2 Binding Constant Unit: nmol/L
DRB1*0401	DRB1	82	56.7
DRB1*0403	DRB1	52.35	98.37
DRB1*0404	DRB1	120	25.33
DRB1*0407	DRB1	83.15	69.44
DRB1*0411	DRB1	38.29	67.67
DRB1*0701	DRB1	50	51.33
DRB1*0802	DRB1	204	154.67
DRB1*0811	DRB1	74.95	4000
DRB1*1101	DRB1	211.33	195.33
DRB1*1404	DRB1	35.4	4000
DRB1*1501	DRB1	98.67	4000
Rest of DRB	DRB1	4000	4000
DQ	DQ	4000	4000

- Extrapolation to population with different HLA allele frequencies;
- Personalised & Precision medicine: Prediction of PK and IG for genotyped individual;
- Extrapolation to larger populations. (Phase III, IV);
- IG Management: Extrapolation to different dosing regimes;
- Extrapolation to paediatric population or individual children;
- Extrapolation to disease population;
- Extrapolation to age group;
- Prediction of the effect of co-therapy.



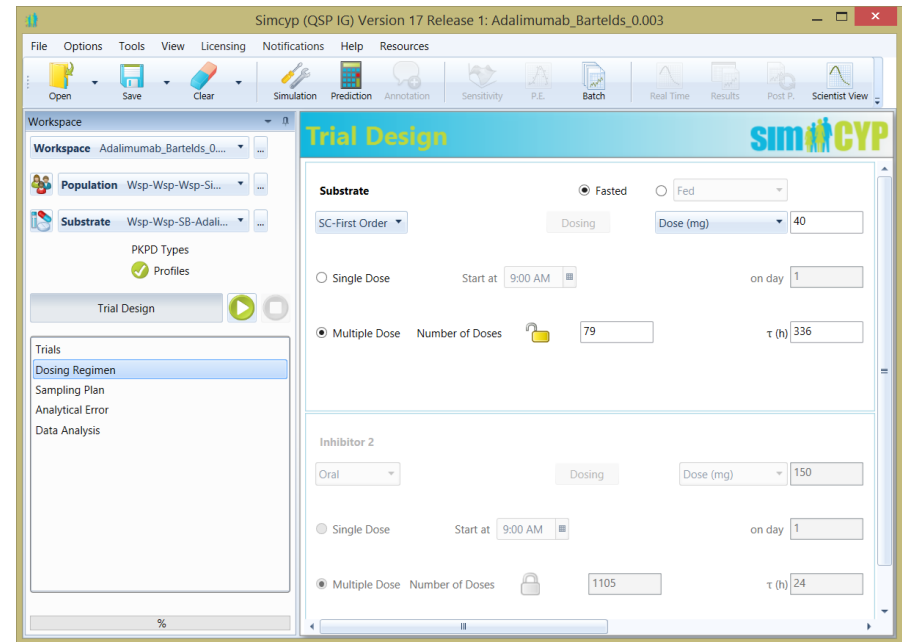
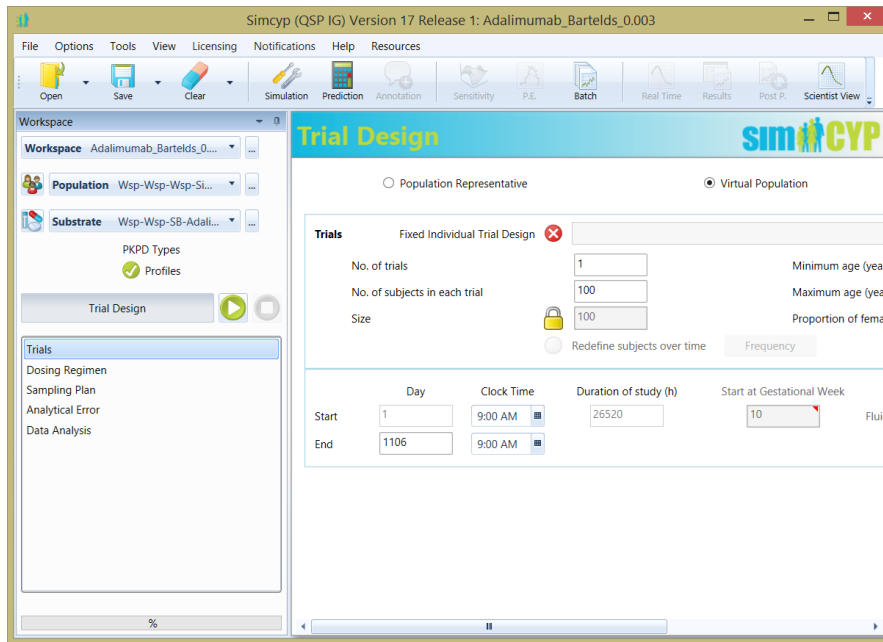
# Modular Biological Process Map interface



Modules encapsulate complex mechanisms which are connected to the model through well defined interfaces. This facilitates both visualisation and consortium team development of multiscale mechanistic models.



# Trial design



- Simcyp simulator is modularised into System, Compound, Population and Trial design.
- Trial screens specify number of subjects from target Population and dosing regime of the Compound.

# Simcyp simulator with Immunogenicity screens

Simcyp (QSP IG) Version 17 Release 1: Adalimumab\_Bartelds\_0.003

Workspace: Adalimumab\_Bartel...

Population: Wsp-Wsp-Ws...

Substrate: Wsp-Wsp-SB-...

PKPD Types: Profiles

Trial Design

Phys Chem and Blood Binding

Absorption

Distribution

Elimination

TMDD

Brain

MHC II Epitopes

PD Basic 1

Number Of Epitopes: 2

Weak Binding Constant (nmol/L): 4000

MHC II Allele	Gene	Epitope 1 Binding Constant Unit: nmol/L	Epitope 2 Binding Constant Unit: nmol/L
> DRB1*04:01	DRB1	82	56.7
DRB1*04:03	DRB1	52.35	98.57
DRB1*04:04	DRB1	120	25.33
DRB1*04:07	DRB1	83.15	69.44
DRB1*04:11	DRB1	38.29	67.67
DRB1*07:01	DRB1	50	51.33
DRB1*08:02	DRB1	204	194.67
DRB1*08:11	DRB1	74.95	4000
DRB1*11:01	DRB1	211.33	195.33
DRB1*14:04	DRB1	35.8	4000
DRB1*15:01	DRB1	98.67	4000
Rest of DRB	DRB1	4000	4000
DQ	DQ	4000	4000
DP	DP	4000	4000

Simcyp (QSP IG) Version 17 Release 1: Adalimumab\_Bartelds\_0.003

Workspace: Adalimumab\_Bartel...

Population: Wsp-Wsp-Ws...

Substrate: Wsp-Wsp-SB-...

PKPD Types: Profiles

Trial Design

skin

GI Tract

Tissue Composition

Tissue Flow Rates

Brain

Lung

Additional Organ

FcRn IgG

Lymph & Subcutaneous

Target

Blood

HLA Genotype

Immune Cell Baselines

HLA-DRB1

MHC II Allele	Allele Frequency
> DRB1*04:01	0.014302281
DRB1*04:03	0.000386548
DRB1*04:04	0.042520294
DRB1*04:07	0.014302281
DRB1*04:11	0
DRB1*07:01	0.022419791
DRB1*08:02	0.001159644
DRB1*08:11	0
DRB1*11:01	0.029377658
DRB1*14:04	0
DRB1*15:01	0
Rest of DRB	0.875531503

HLA-DQ

MHC II Allele	Allele Frequency
> DQ	1

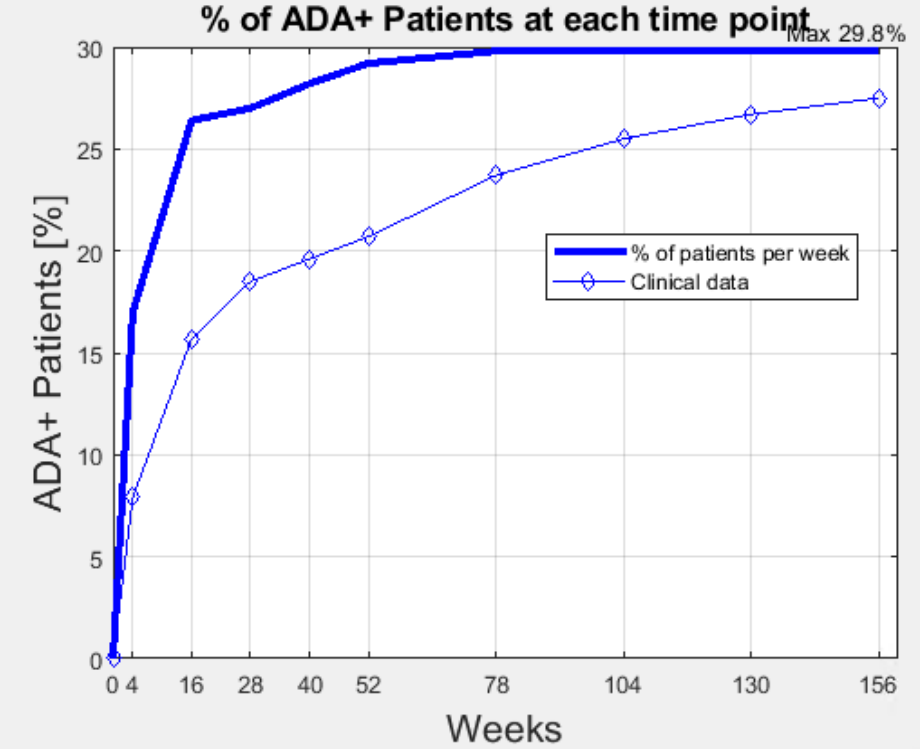
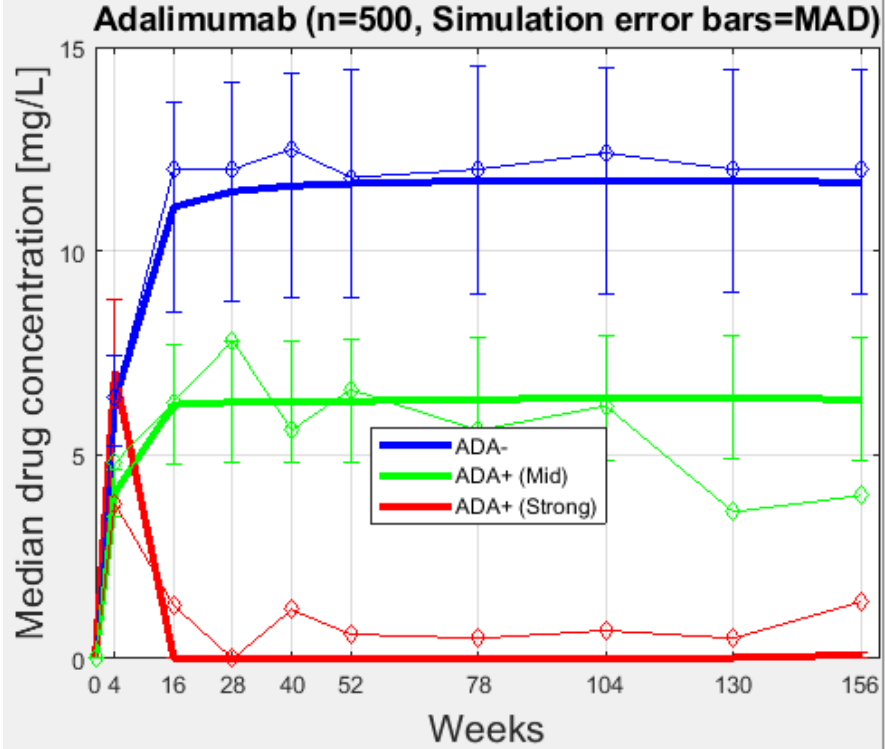
HLA-DP

MHC II Allele	Allele
> DP	1

- The compound section of Simcyp biologics model has been expanded to allow input of antigenic peptide binding constants.
- Population section of Simcyp has been expanded to allow input of allele frequencies used to generate MHC II binding constants.

# Clinical trial simulation: IG affects PK

Simulation of Adalimumab clinical trial of Bartelds et al., JAMA 2011



Simulation

Number of ADA+ Mid = 70%  
 Number of ADA+ Strong = 30%

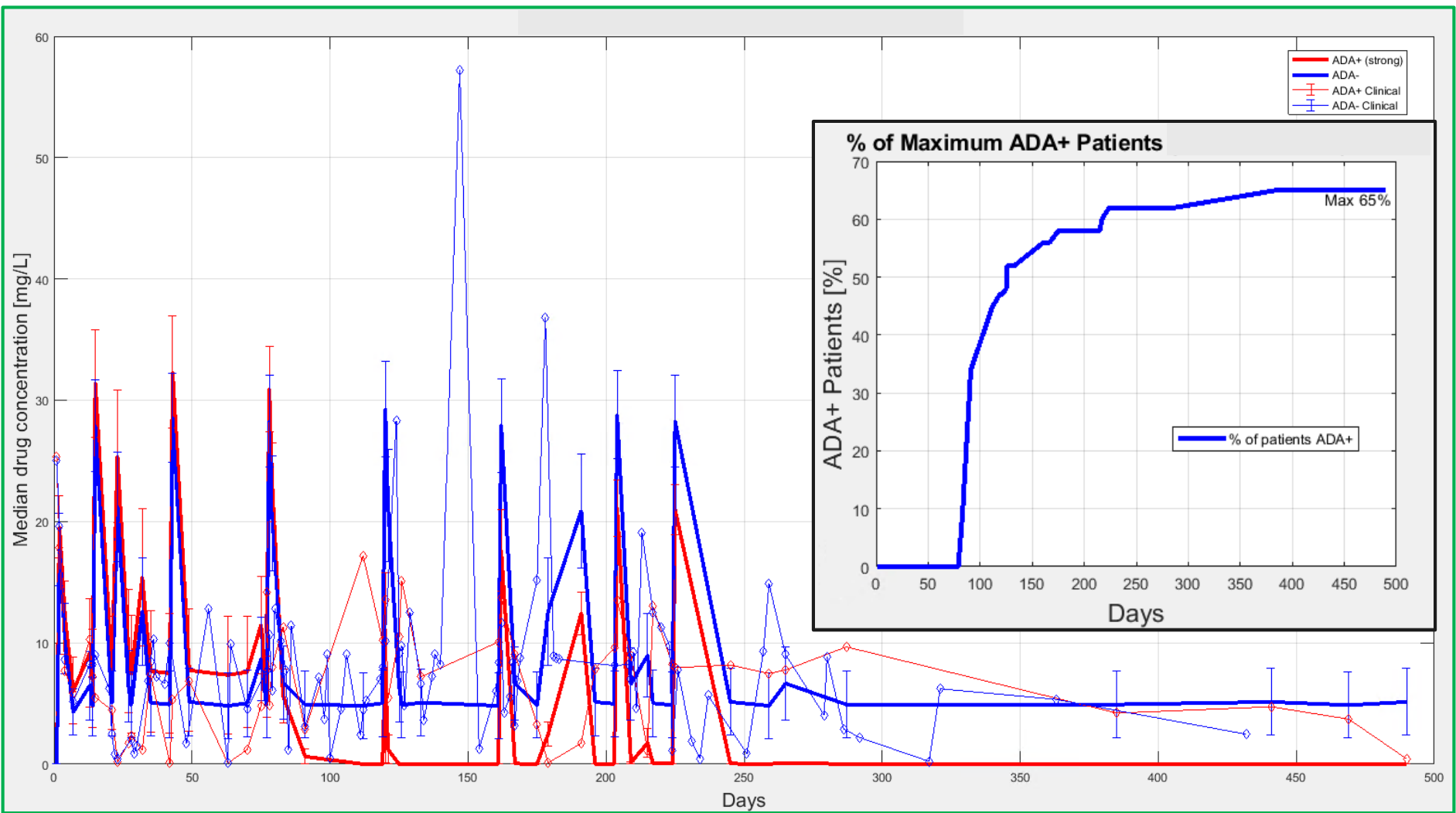


Clinical Data

Number of ADA+ Mid = 60%  
 Number of ADA+ Strong = 40%

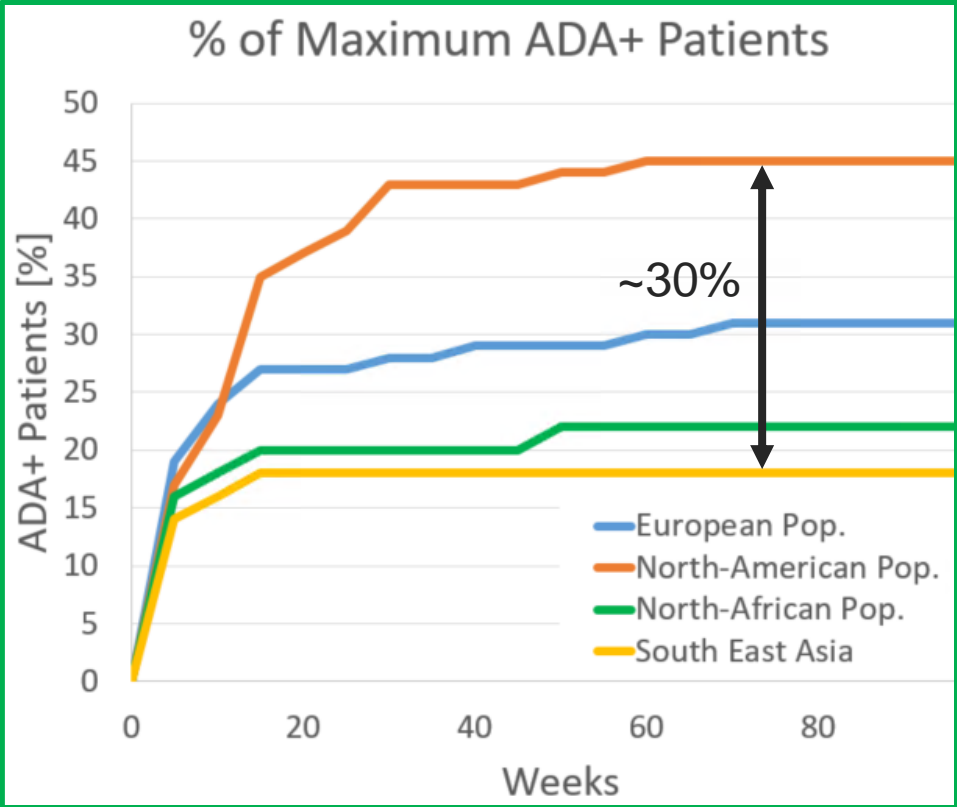
By using Bartelds classification criterion

# Clinical trial simulation: IG does not affects PK

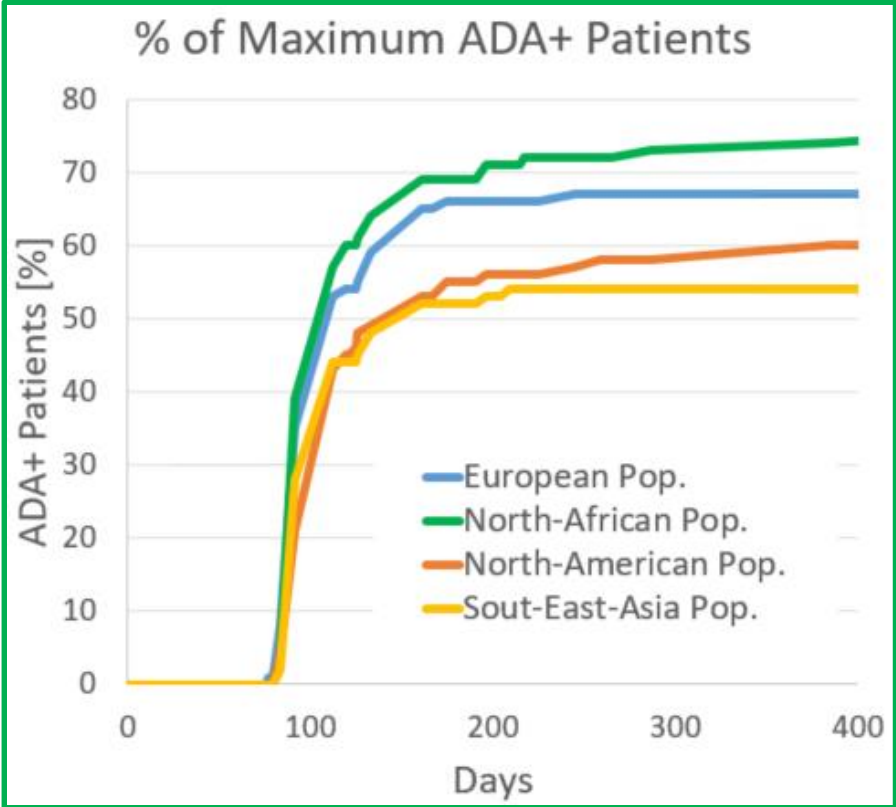


# Predictions across population groups

Compound X



Compound Y

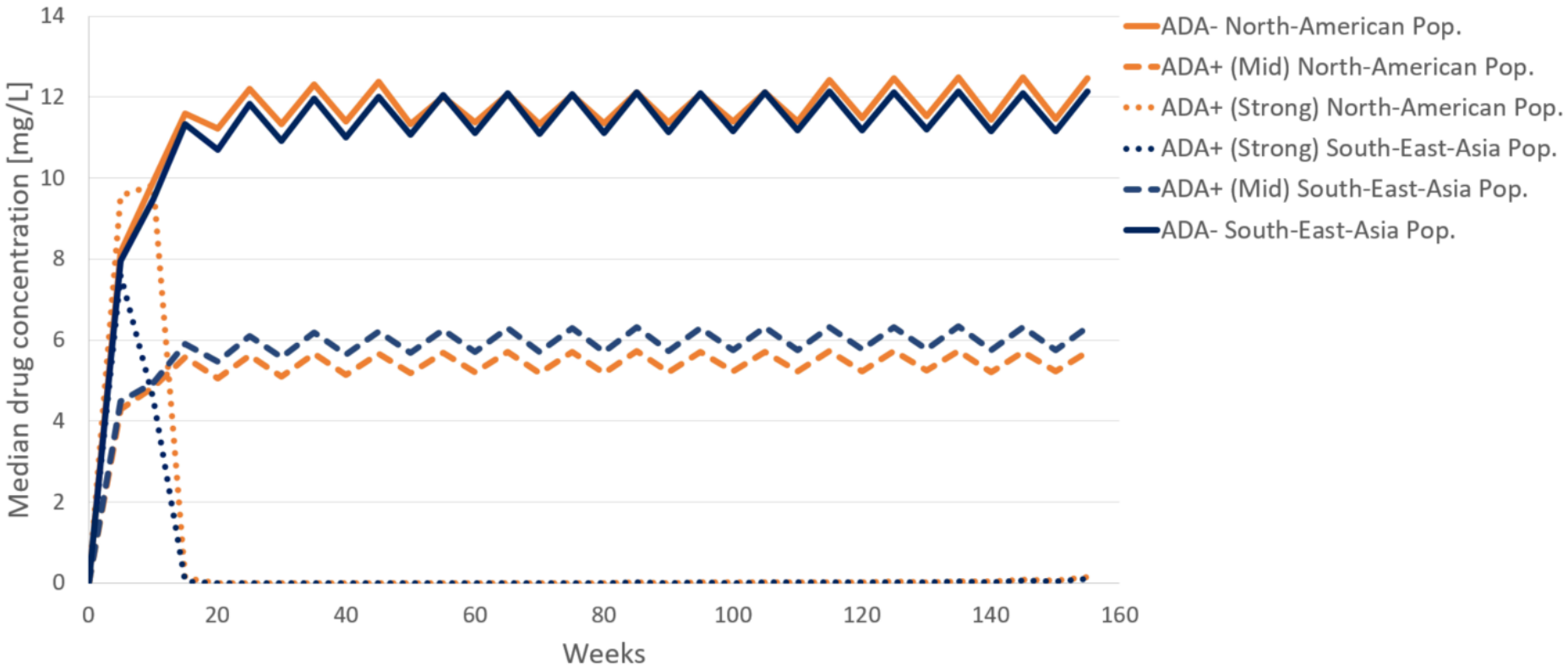


Any changes in the PK between North American Pop. and South East Asia pop.?

# Predictions across population groups

PK differences between North American pop. and South East Asia pop.

Generic compound (n=100, Comparison between populations)



- No differences in ADA- profiles;
- Higher drug concentration (ADA+ strong) at early time points for the North American pop.
- Lower drug concentration (ADA+ mid) for the North American pop.



# Acknowledgements

- Abbvie
- Astellas
- BMS
- Genentech/Roche
- Lilly
- Pfizer

## Certara QSP IG Consortium Team

### Leadership



Andrzej Kierzek



Neil Benson



Piet van der Graaf

### Science: IG Model development



Mario Giorgi



Maciej Swat



Ben Small

### IT: IG Simulator development



Richard Matthews



David Hollinshead



Adrian Barnett

**Questions?**

