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Simcyp

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

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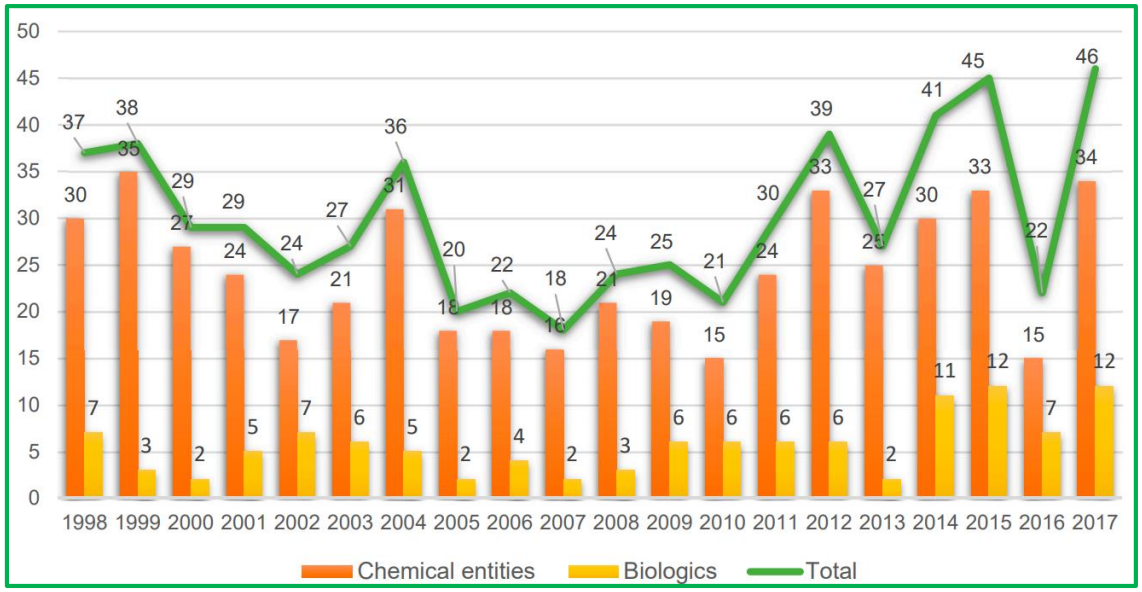
Certara QSP

EIP, European Immunogenicity Platform, Lisbon, 25th-27th February 2019

Introduction - Biologics

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



Beatriz G. de la Torre and Fernanado 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**"*

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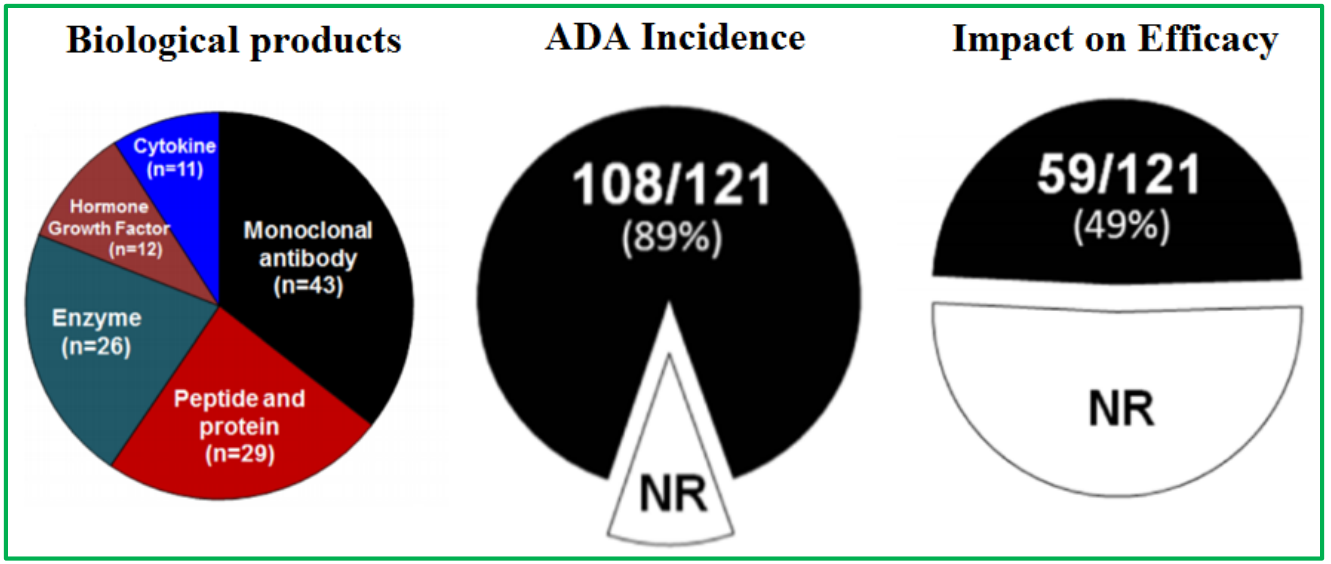
Introduction – Immunogenicity (IG)

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.

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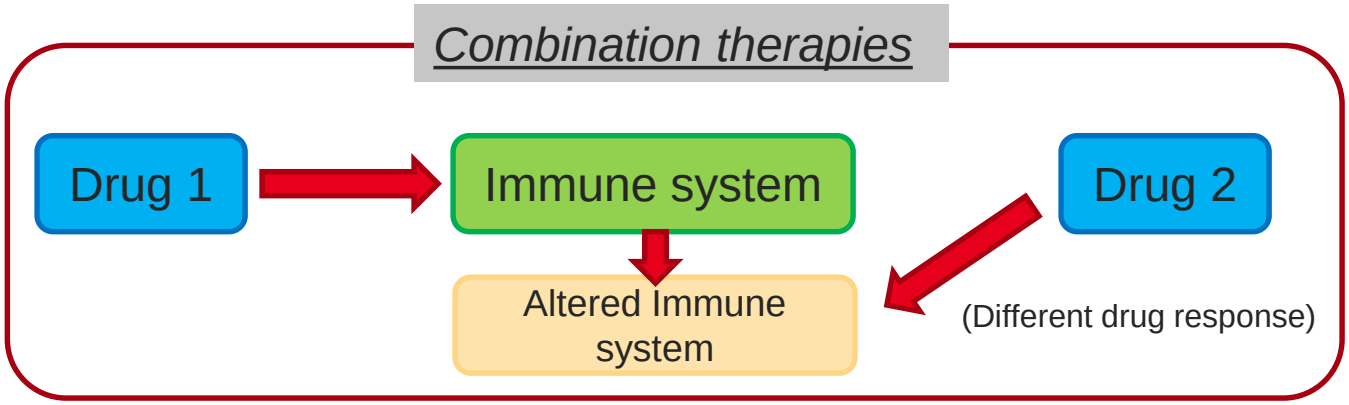
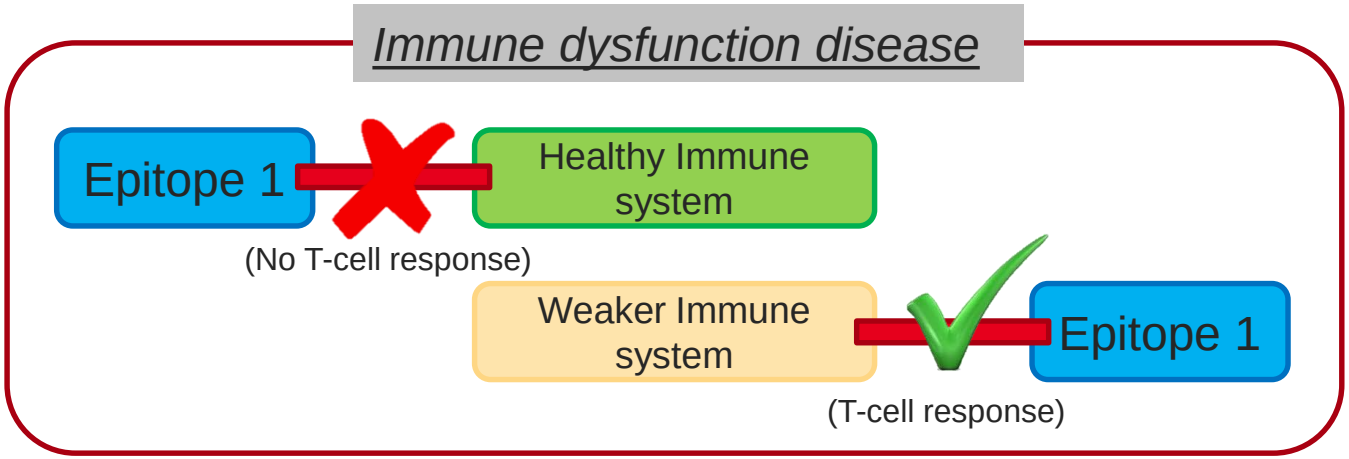
Introduction – Limitation of bio-informatics

Examples of other important factors that could influence IG





Limitation of bio-informatics:

- No PK time profiles;
- Co-therapy
- Disease state
- Patient parameters (Age, gender, weight, etc…)

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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
Bococizumab (Pfizer)	2	12	68% (Ridker, 2017)
Alirocumab (Regeneron)	1	1	5.1% (Roth, 2017)
Evolocumab (Amgen)	0	0	0.1% (Henry, 2016)
GNE anti-PCSK9 (Genentech)	2	8	4% (GENE data*)

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

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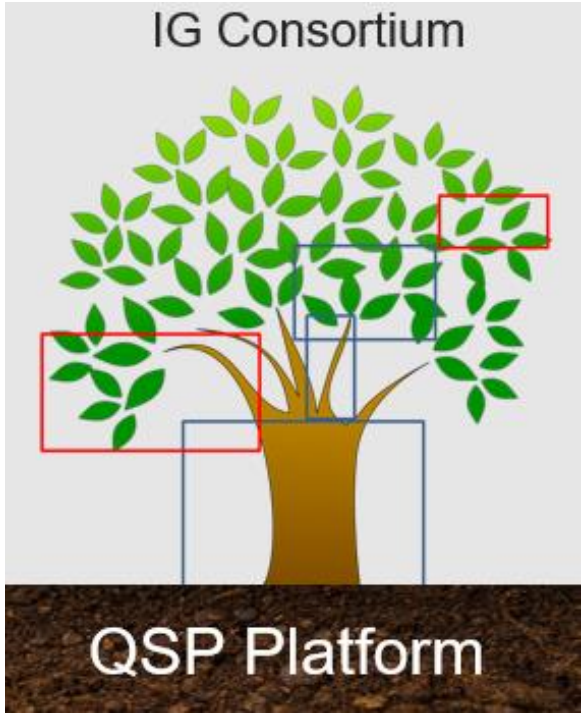
IG QSP Consortium

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



Pfizer

astellas
Leading Light for Life

Roche
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.

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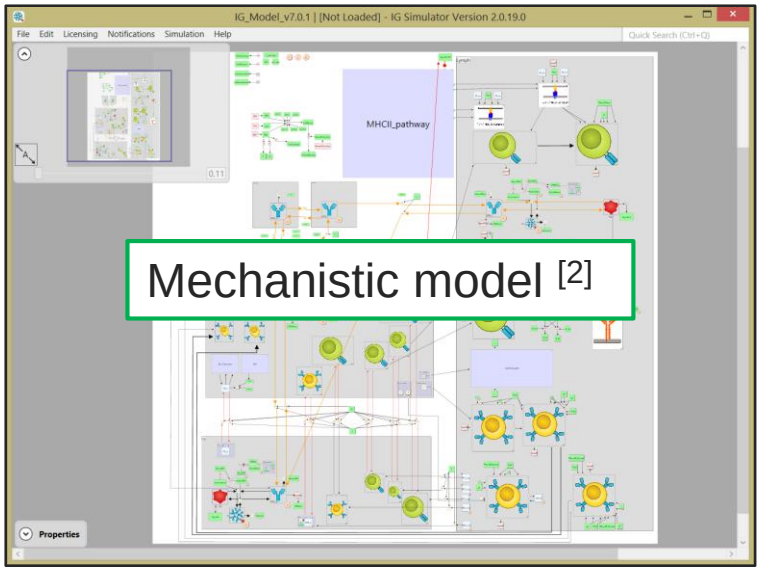
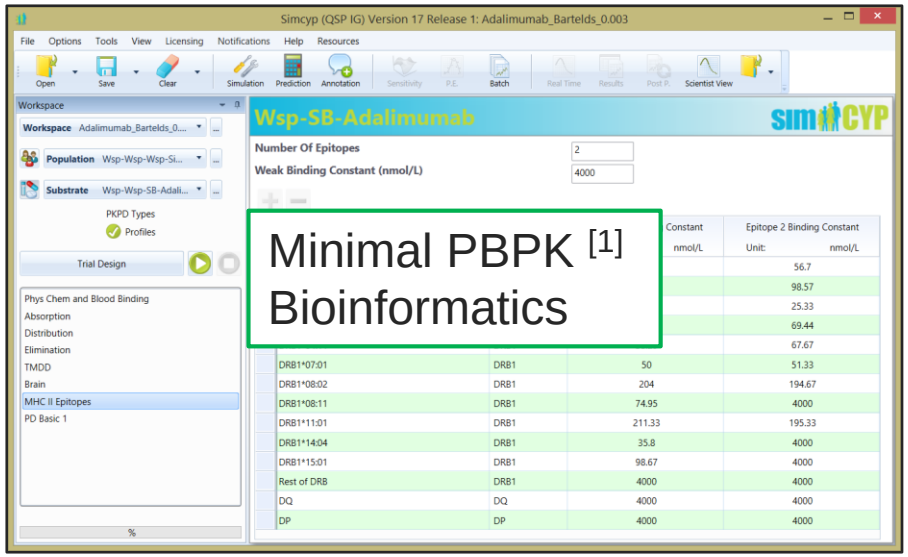
Overview of IG Simulator

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.

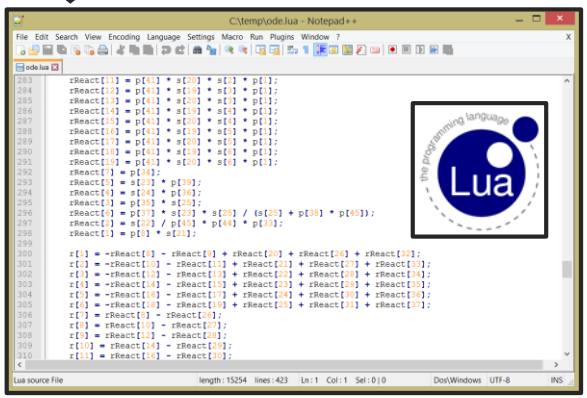
Matlab code

R code

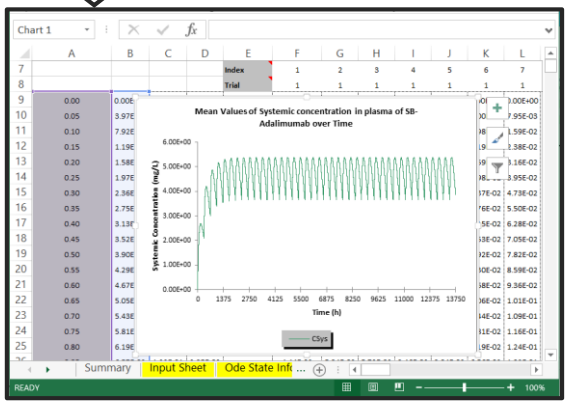
R code with equation in C

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

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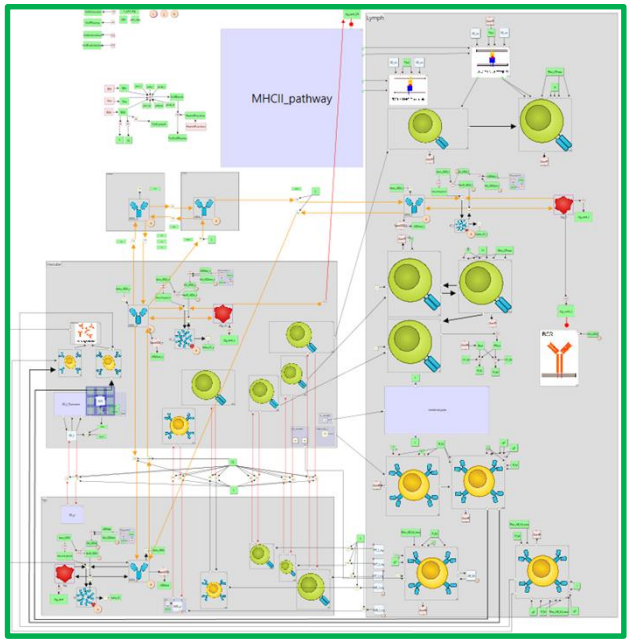
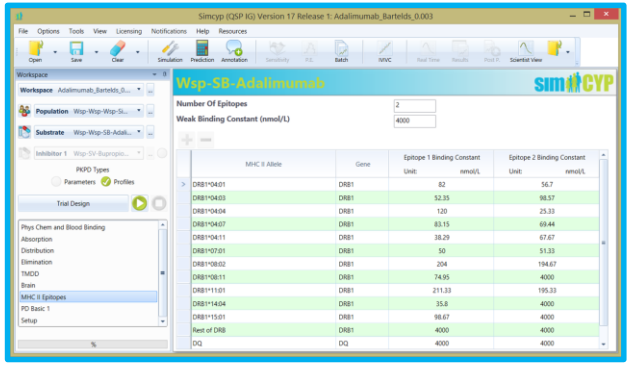
[1] Linzhong et al., AAPS J., 2014; [2] Chen et al., ASCPT, 2014

IG Simulator Application

IG Simulator



Simcyp



- 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.

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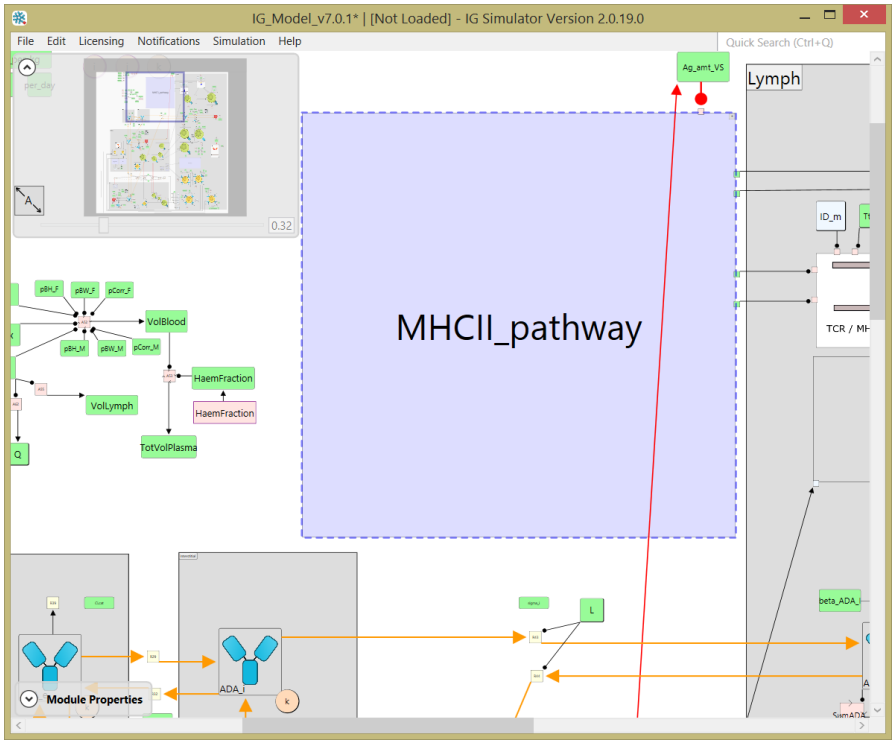
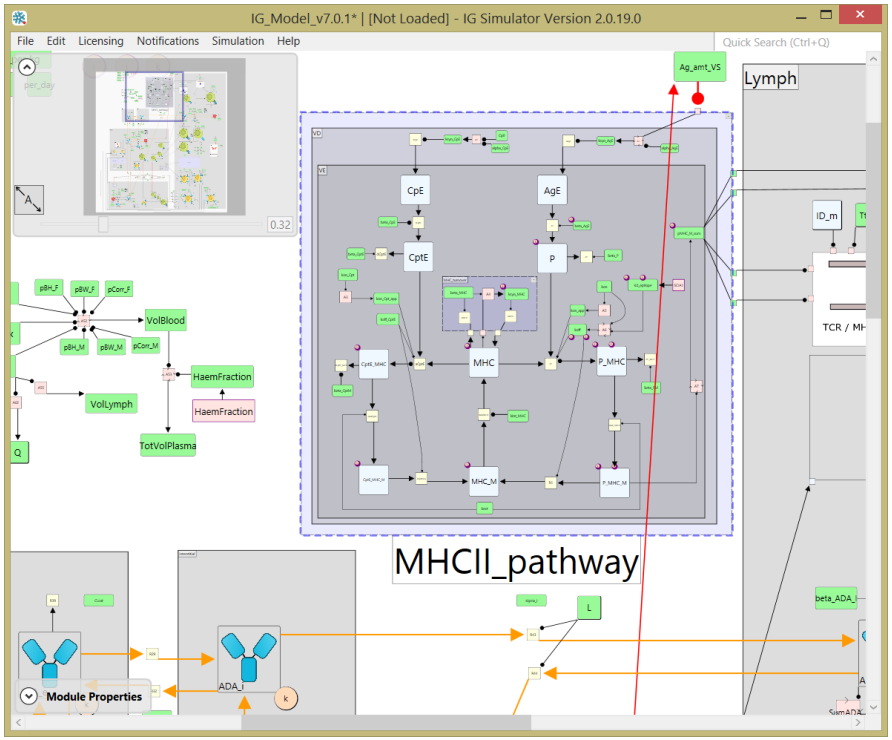
Modular Biological Process Map interface





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.

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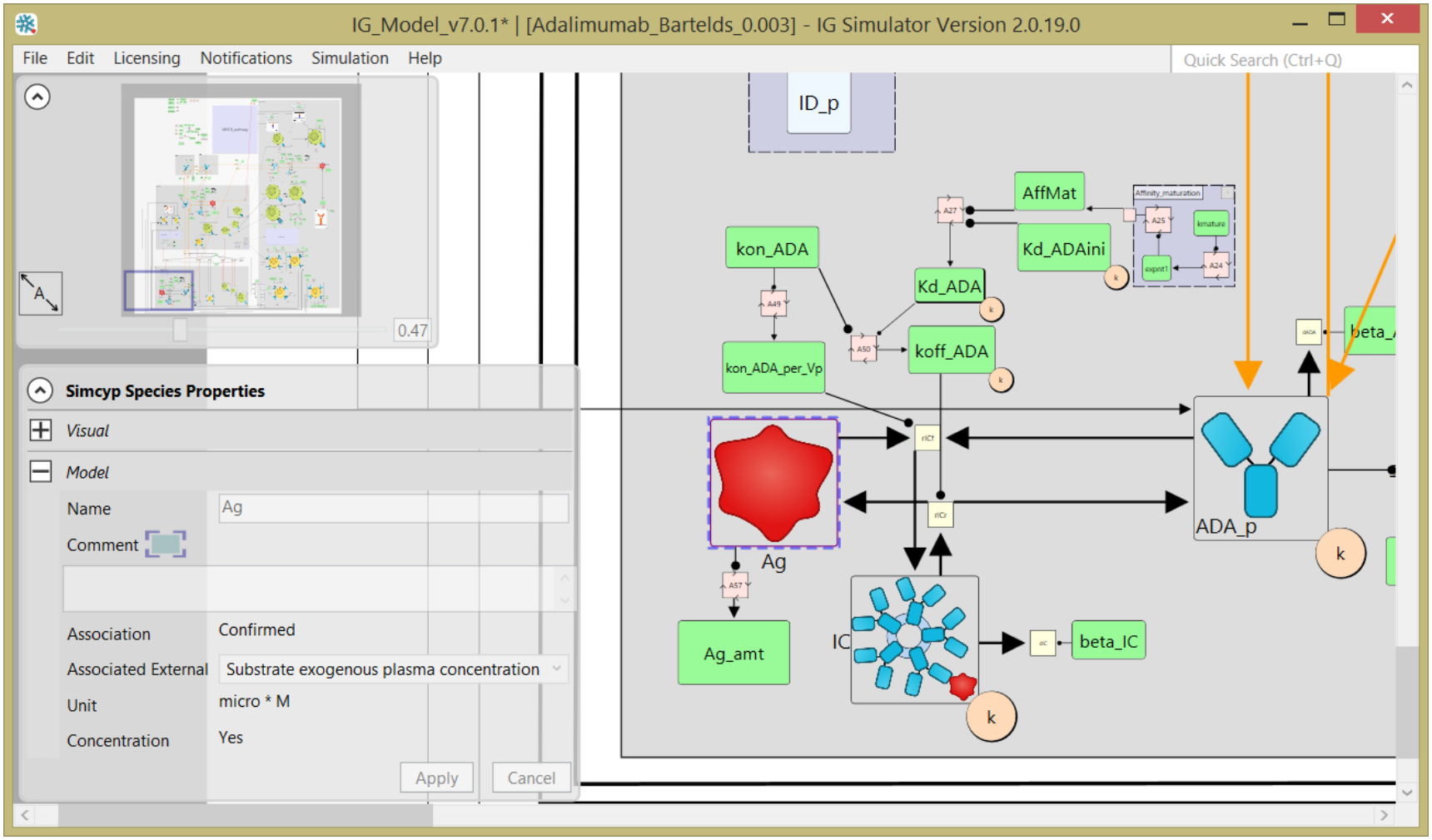
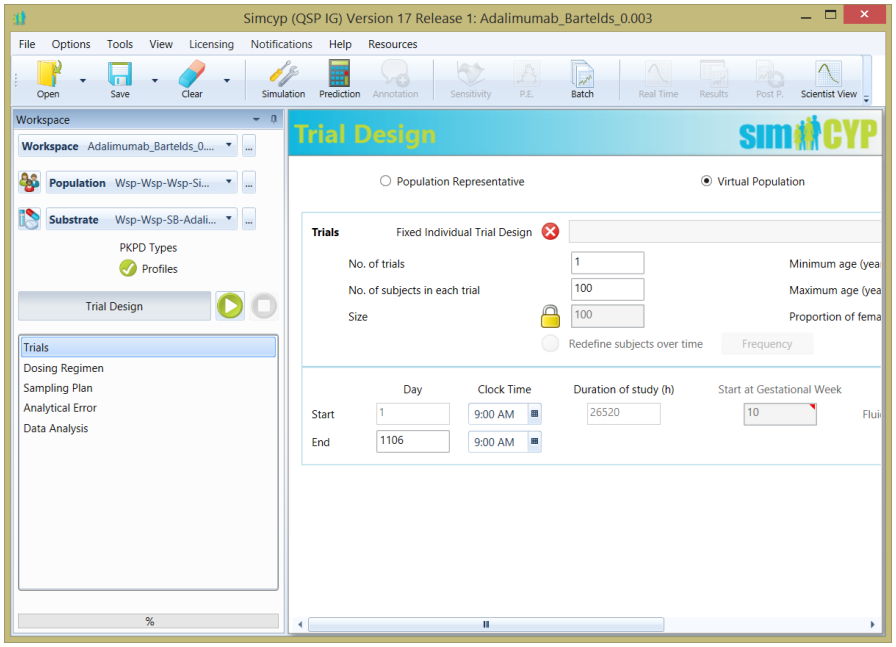
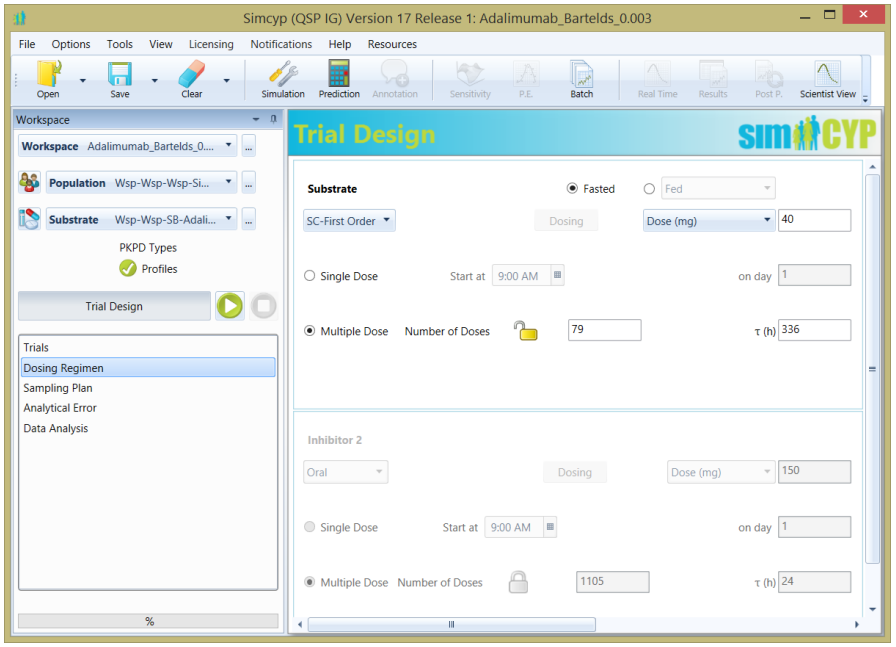
Connection to Simcyp PBPK model



Specie “Ag” in biological process map is merged with variable “Substrate exogenous plasma concentration” in Simcyp PBPK. The ODE for Simcyp variable is augmented by rate laws of ADA binding and Immune Complex dissociation.

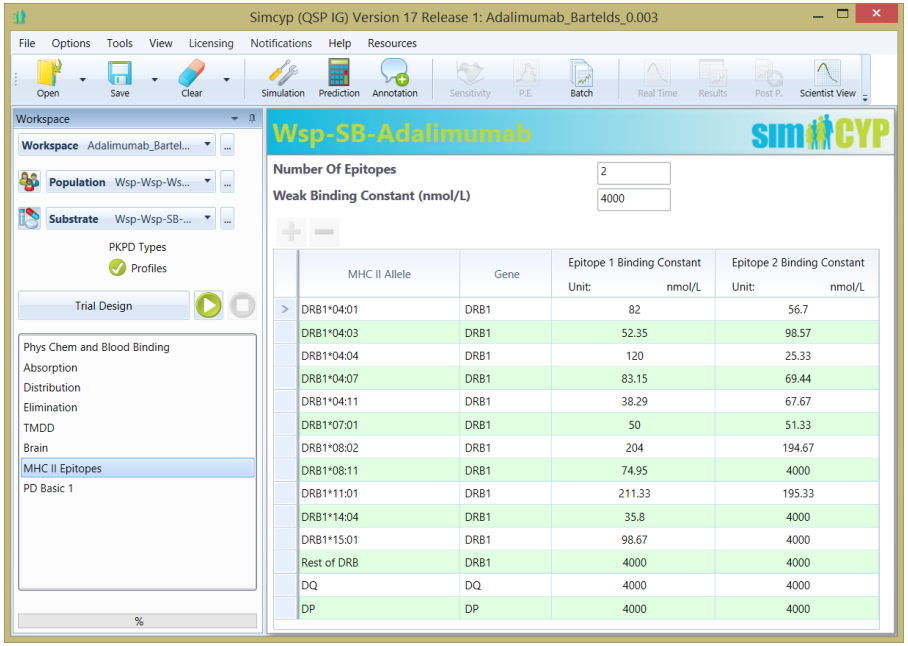
Trial design

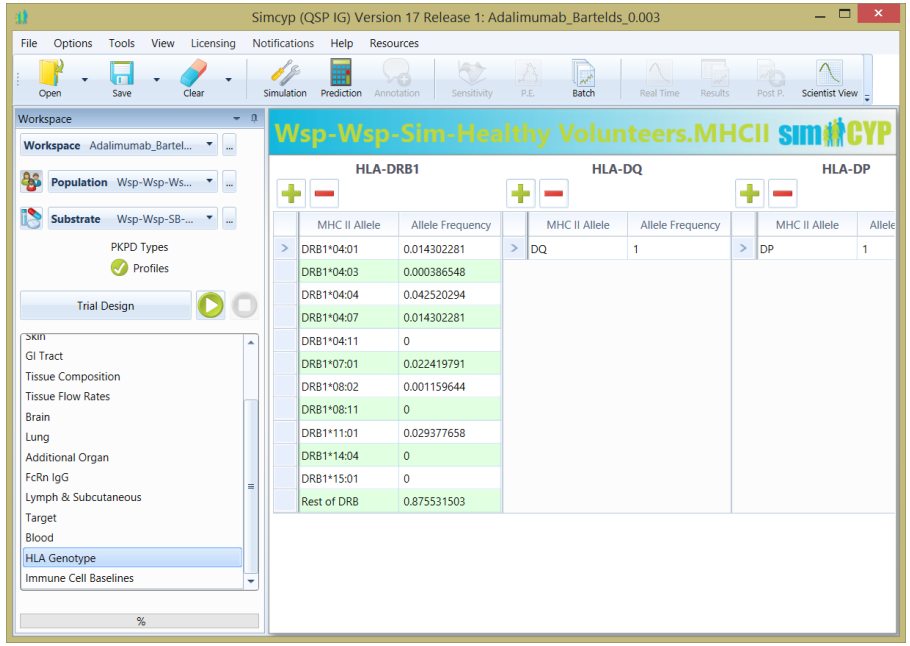




- Simcyp simulator is modularised into System, Compound, Population and Trial design.
- Trial screens specify number of subjects from target Population and dosing regime of the Compound.

Simcyp simulator with Immunogenicity screens





- 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.

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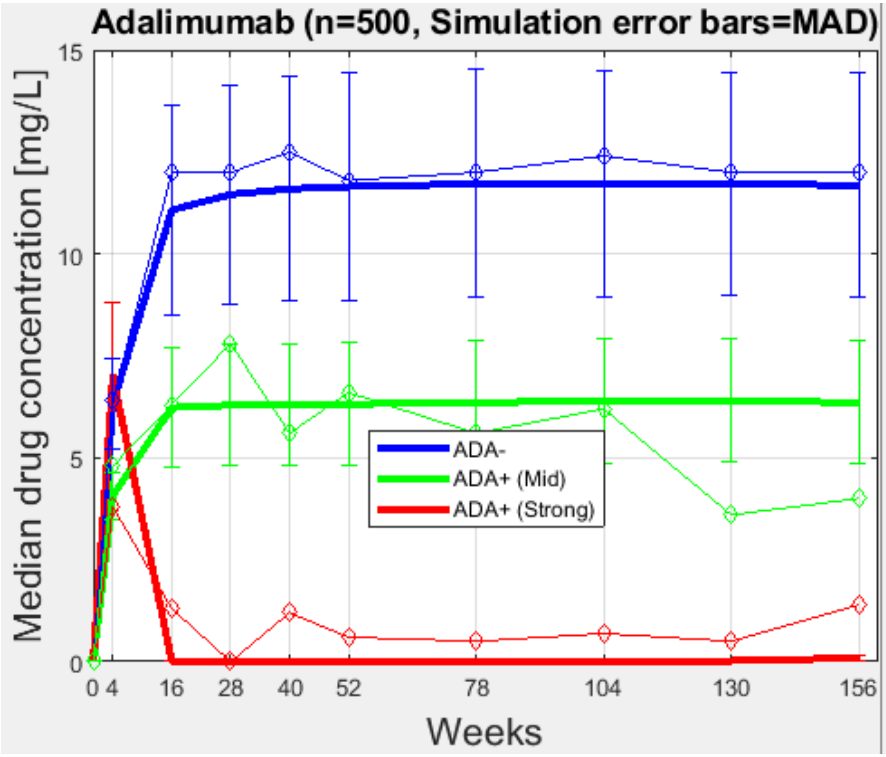
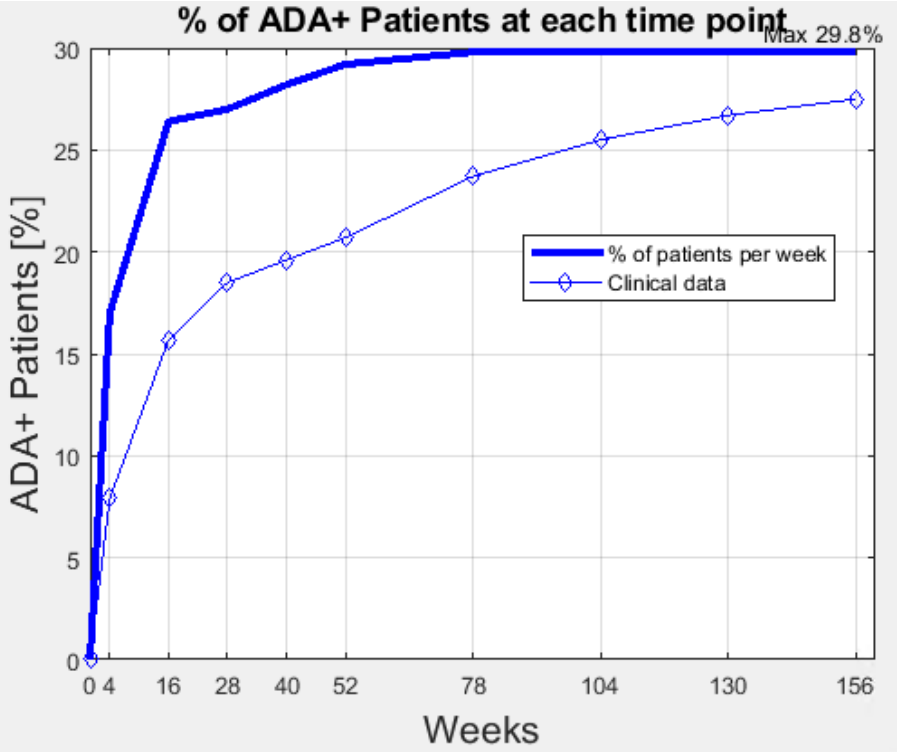
Clinical trial simulation: IG affects PK

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

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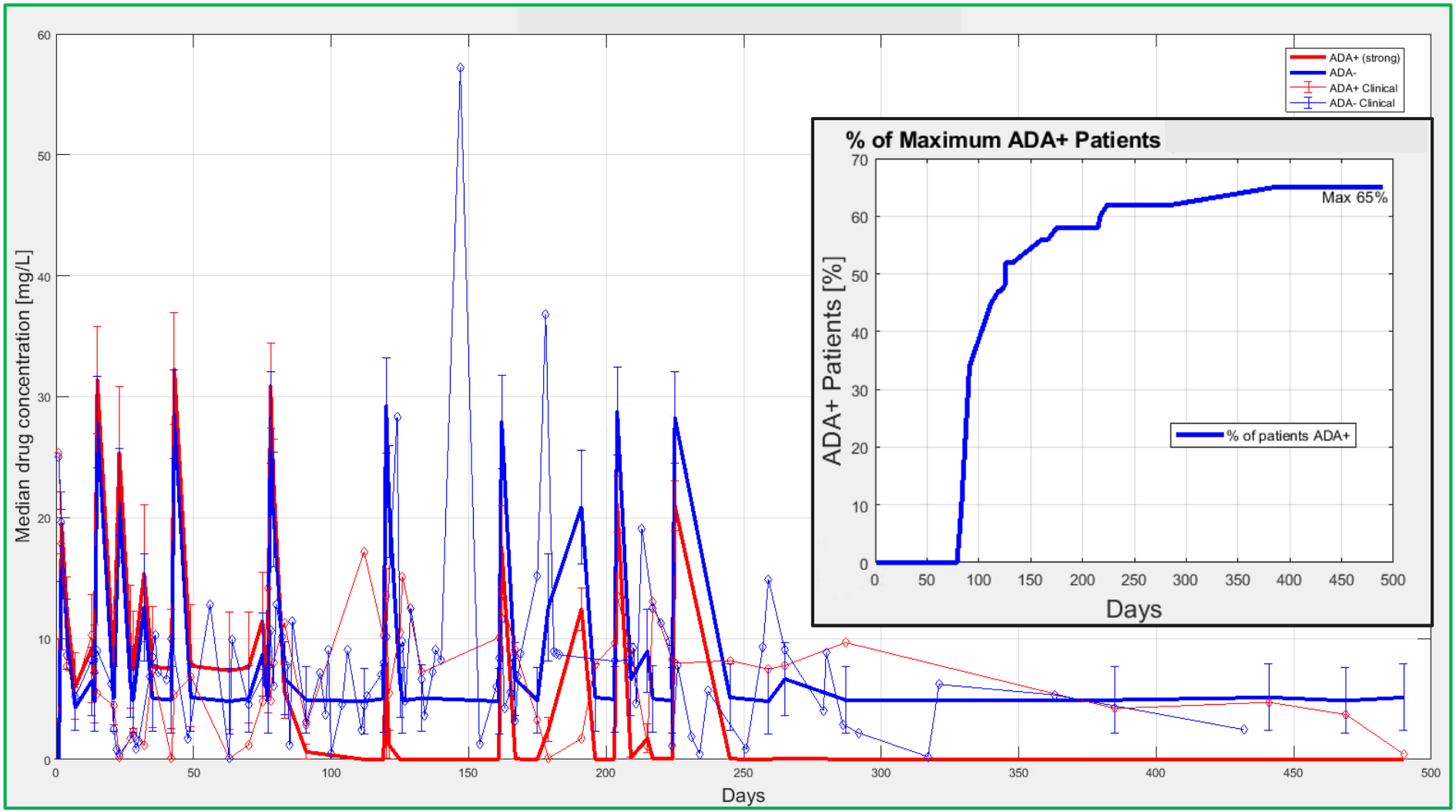
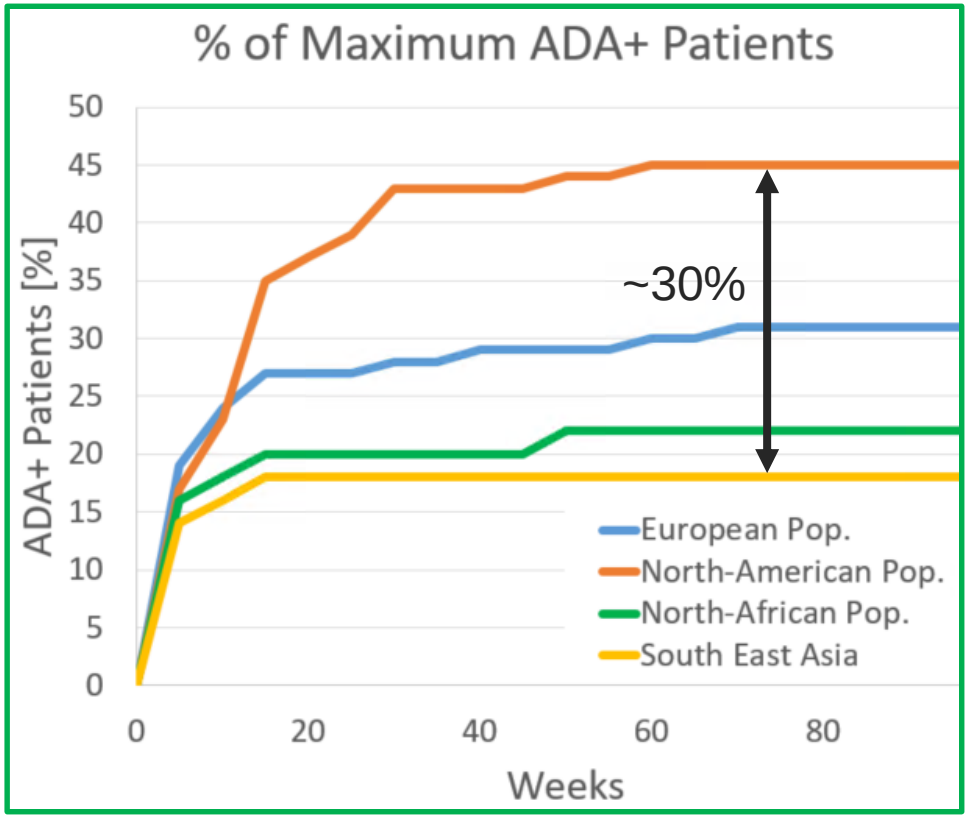
Clinical trial simulation: IG does not affects PK

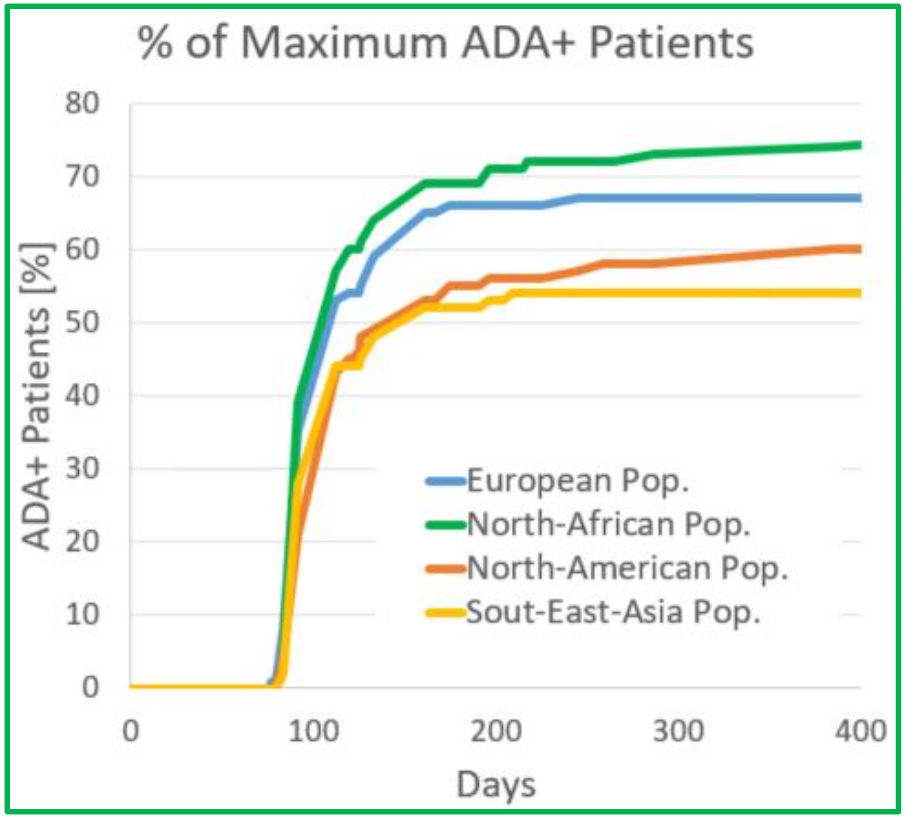


Predictions across population groups

Compound X



Compound Y



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

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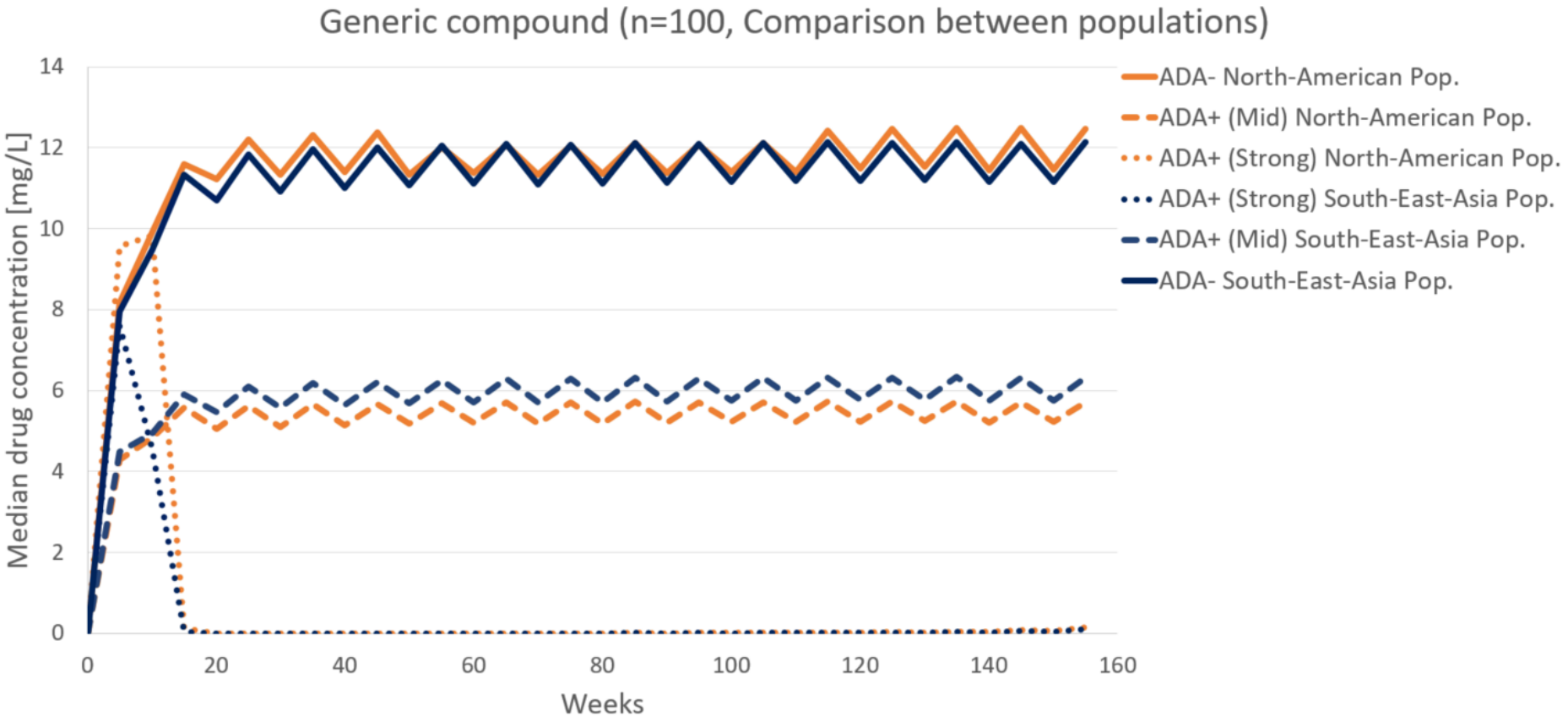
Predictions across population groups

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



- 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.

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Acknowledgements

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

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Questions?