Towards understanding anti-infliximab antibody development to predict Crohn's disease patients' underlying immunogenicity status

Alix Démaris

Dept. of Clinical Pharmacy and Biochemistry

Institute of Pharmacy, Freie Universität Berlin

Immunogenicity and Anti-Drug Antibodies

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Overview

Introduction

Anti-drug antibodies leveraged data

Modelling immunogenicity

Next steps & conclusion

CLINICAL PHARMACY

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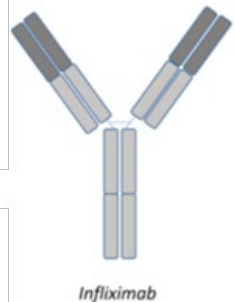
Infliximab in Crohn's Disease patients
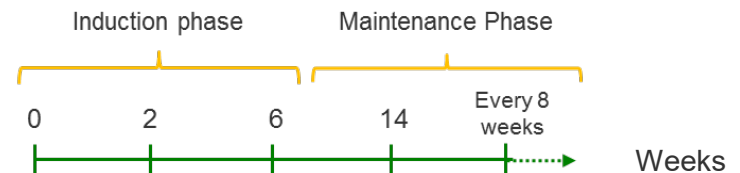
Crohn's Disease: Inflammatory bowel disease
- Chronic inflammation of the gut leading to mucosal impairment

Infliximab
- Anti-tumour necrosis factor α (TNFα)
- Immunosuppressive and anti-inflammatory effect
- Indications: **Crohn's disease** and other inflammatory diseases.

- Administration of infliximab:
5 mg/kg, i.v. infusion

Induction phase		Maintenance Phase	
0	2	6	14	Every 8 weeks

Weeks

- Challenge of infliximab therapy: Loss of response

How to predict/prevent?

Steenholdt C, et al. (2013)   Ordas I et al. (2012)   Vande Casteele N et al. (2015)
Keizer RJ et al. (2010)   Bendtzen K. (2015)

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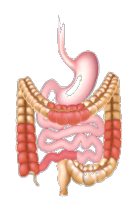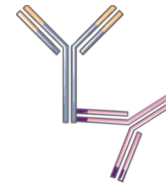
Loss of response (LOR)

- 50% patients fail to respond to treatment (LOR) in the first year

  → Dosing regimen intensification or change in therapy (different mAb)

- LOR related to sub-therapeutic drug concentrations

Increase CL
- High baseline TNFα
- High baseline C-reactive protein (CRP)
- Low serum albumin
- High body weight
- Sex (male)
- **Anti-drug antibodies (ADA)**

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Anti-Drug Antibodies (ADA)

- Monoclonal antibodies (mAb) therapy may provoke an immunogenic reaction:
  → Formation of anti-drug antibodies (ADA) against therapeutic mAb
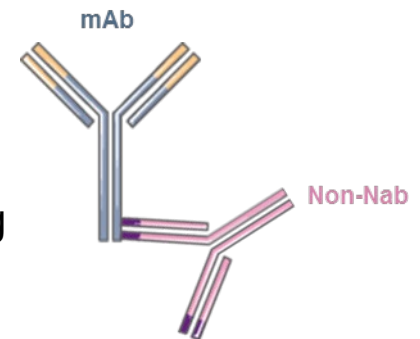
- Multiple species:

  - **Neutralising antibodies** (Nab):
    - Binding to complementarity determining regions
      → Prevents binding of IFX to target (TNFα)

    - Level of neutralisation dependent on titer of Nab
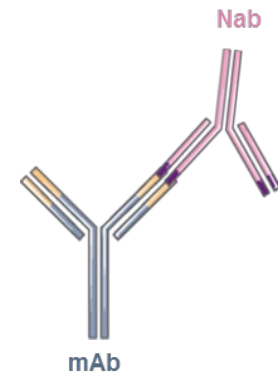
  - **Non-neutralising antibodies** (Non-Nab):
    - Do not interfere with antigen-binding capacity of mAb

    - Formation of circulating ADA-mAb immune complexes creating an additional elimination pathway
   → Increase elimination of mAb

Nab
mAb

mAb
Non-Nab

Ryman J.T. (2017).
Wang Y.M.C.(2016)

ADA: Anti-drug antibody
IFX: Infliximab
mAb: monoclonal antibody

Nab: Neutralising ADA
TNFα: Tumour necrosis factor α

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Motivation and objective

- Presence of ADA related to IFX low concentration.
    - → ADA increase risk of treatment failure (LOR)

Need to know early on which patients are at risk of ADA/Nab development

- Nab decrease efficacy by preventing IFX binding to its therapeutic target, TNFα.
    - → Nab impact PK and PD : higher risk of LOR

→ Prevent LOR

- ADA and Nab development depends on different patients-/disease-/drug-related factors

Why?

ADA/Nab

- ADA often looked at as status, covariate effect on CL
- Nab sub-entity rarely taken into account in modelling activities
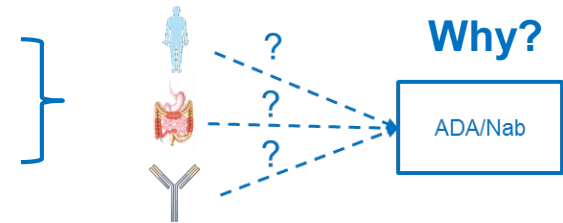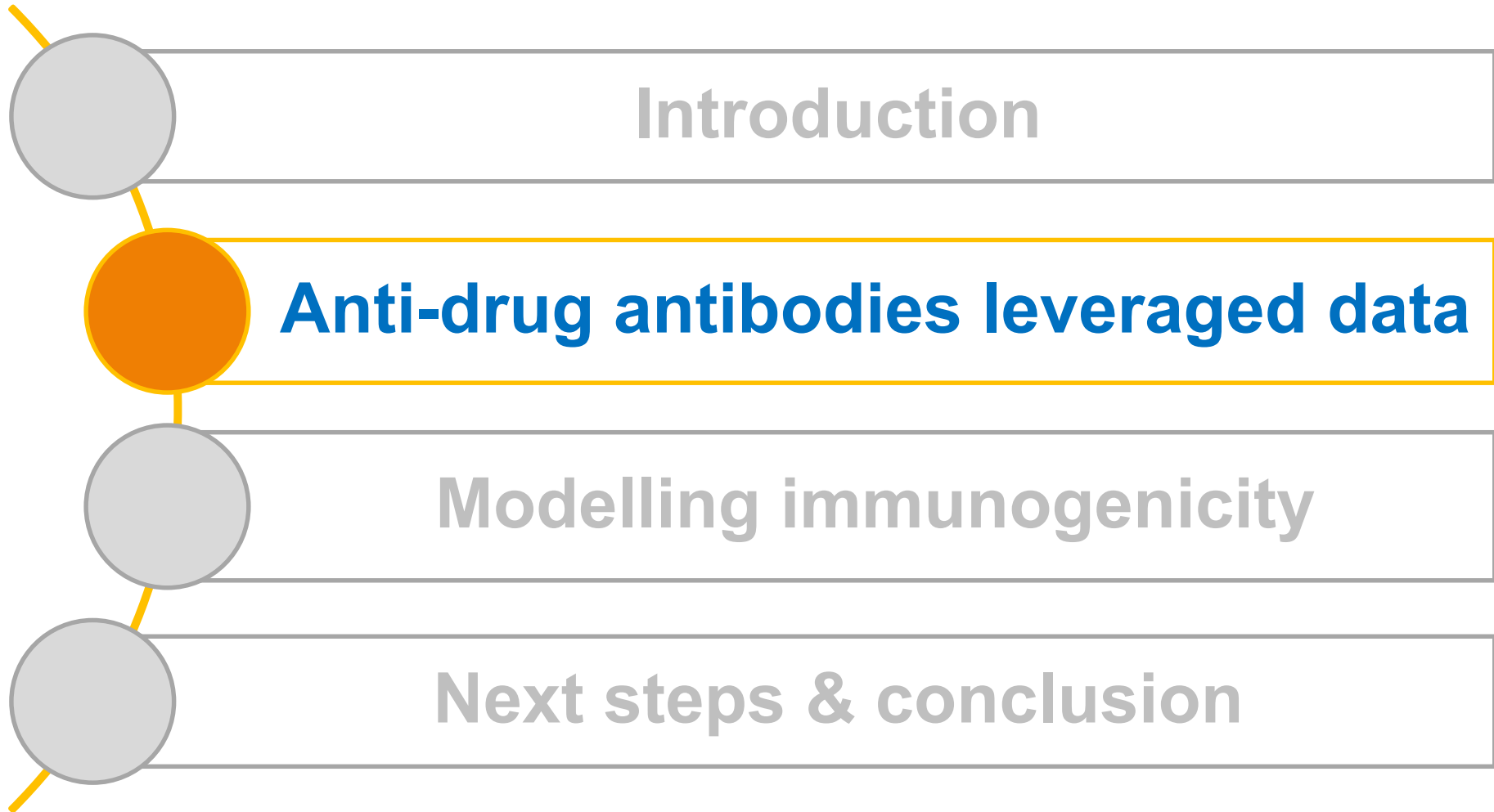
Need for a deeper understanding of ADA and Nab dynamics

→ How to predict underlying immunogenicity in CD patients receiving IFX?

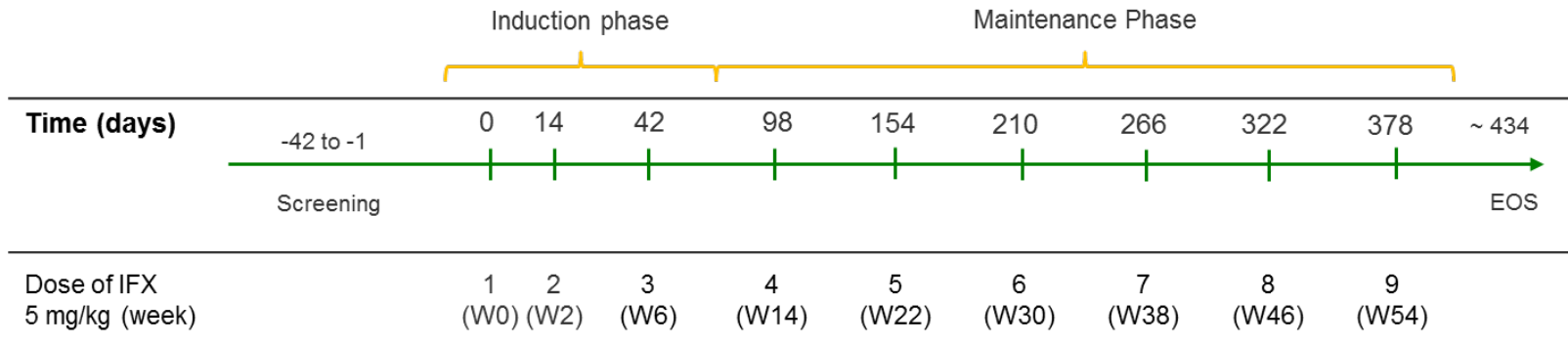ADA: Anti-drug antibodies
IFX: Infliximab
LOR: Loss of response

Nab: Neutralising ADA
PD: Pharmacodynamic
PK: Pharmacokinetic

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Study schedule

- 220 CD patients receiving IFX therapy, all naïve to mAbs

	Induction phase			Maintenance Phase					
Time (days)									
-42 to -1	0	14	42	98	154	210	266	322	378	~ 434
Screening										EOS

Dose of IFX 5 mg/kg (week)	1 (W0)	2 (W2)	3 (W6)	4 (W14)	5 (W22)	6 (W30)	7 (W38)	8 (W46)	9 (W54)

CD: Crohn's disease
EOS: End of study
IFX: Infliximab
mAbs: Monoclonal antibodies

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Study schedule

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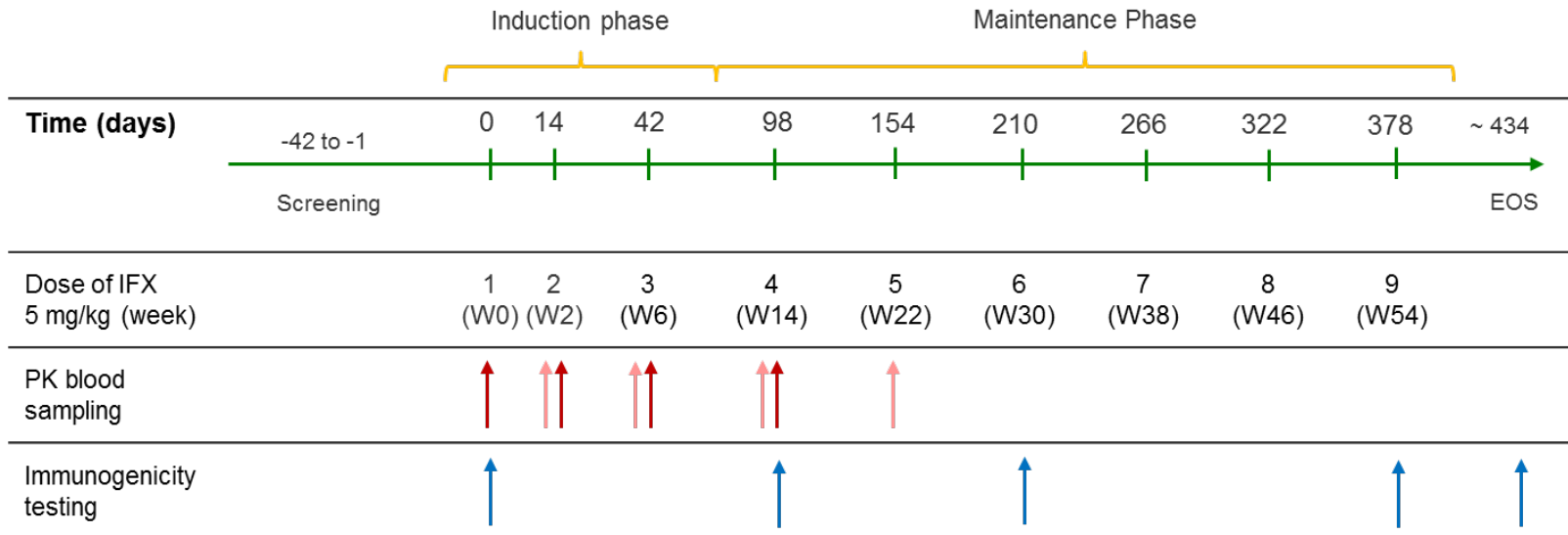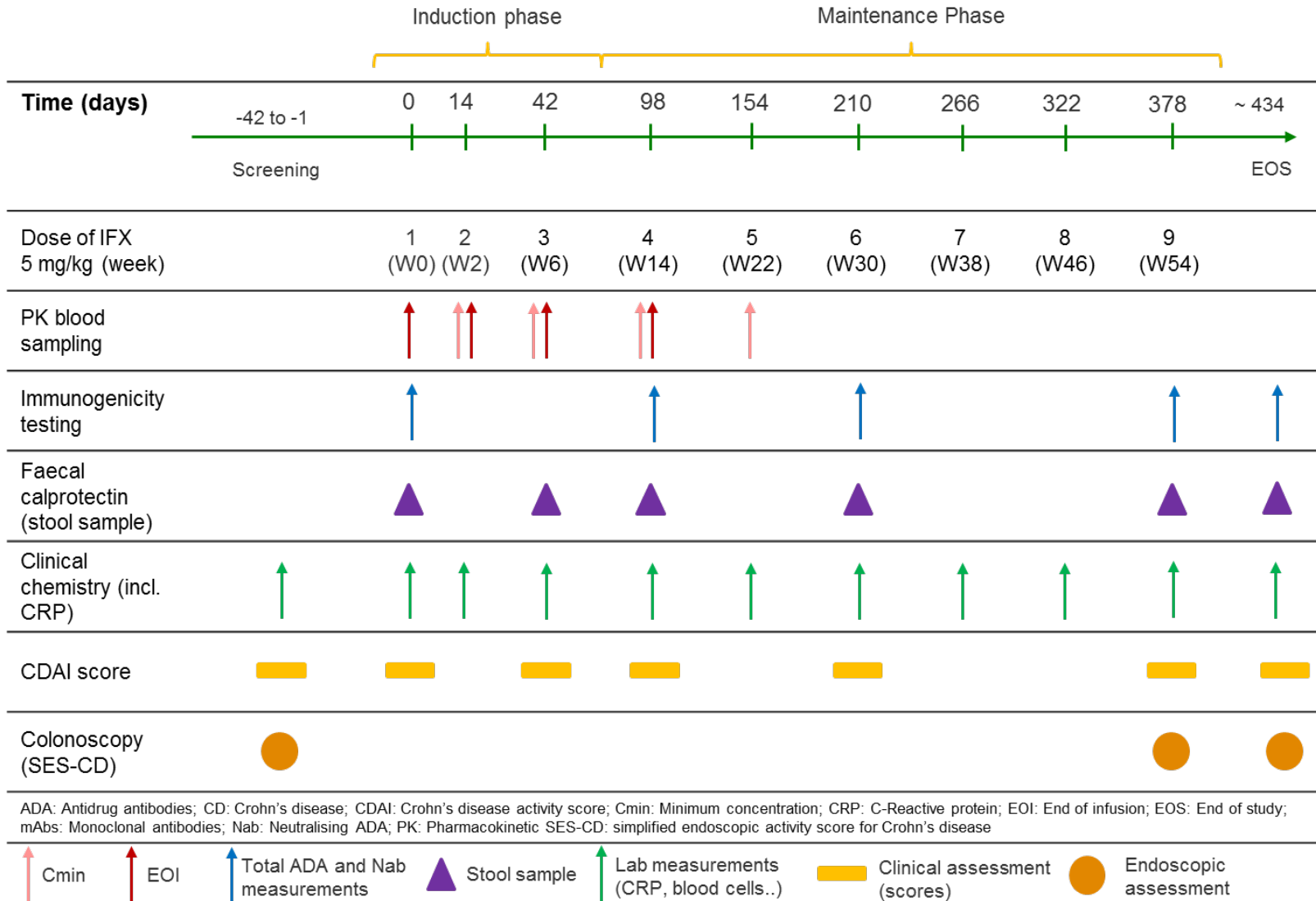

→ **Both ADA and Nab are reported as titers**

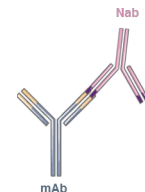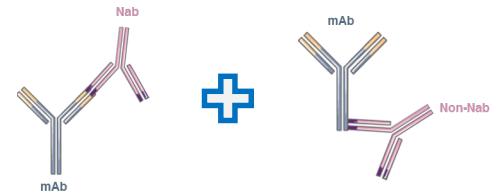|	
CD:	Crohn's disease
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Study schedule

- 220 CD patients receiving IFX therapy, all naïve to mAbs

ADA: Antidrug antibodies; CD: Crohn's disease; CDAI: Crohn's disease activity score; Cmin: Minimum concentration; CRP: C-Reactive protein; EOI: End of infusion; EOS: End of study; mAbs: Monoclonal antibodies; Nab: Neutralising ADA; PK: Pharmacokinetic SES-CD: simplified endoscopic activity score for Crohn's disease

Study schedule

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PK blood sampling											
Immunogenicity testing											
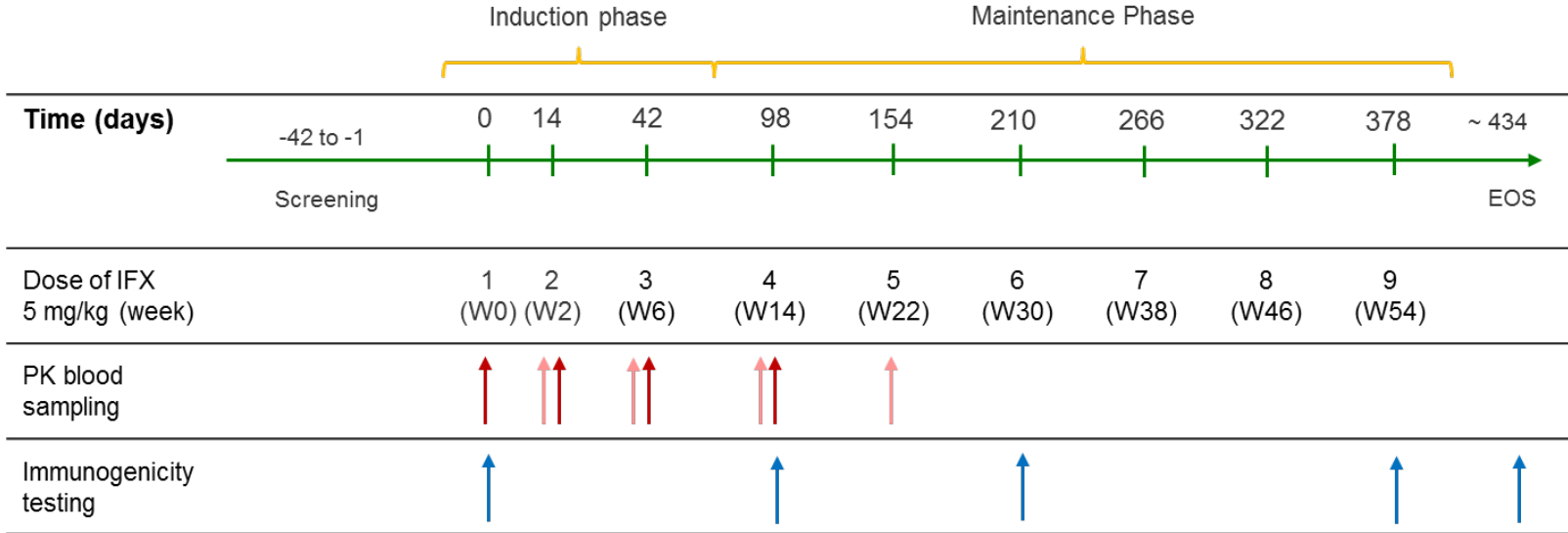
ADA testing strategy

1. Patients tested for ADA: No differentiation between Nab and non-Nab
   - Assay: ELISA (enzyme-linked immunosorbent drug-tolerant assay)
   - If positive: patients labelled **"ADA positive"**
   - Total ADA (non-Nab and/or Nab) measured: "**Total ADA titers**"

2. Patient tested for Nab:
   - Assay: ECL (electrochemiluminescent) immunoassay
   - If positive: patient labelled **"Nab positive"**
   - Nab measured: "**Nab titers**"

ADA: Antidrug antibodies; CD: Crohn's disease; IFX: Infliximab; Nab: Neutralising ADA

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Occurrence of anti-drug antibodies

- Patients with **ADA** during the study: **125/220** (**57%**)

- Patients with **Nab** during the study: **78/220** (**34%**)

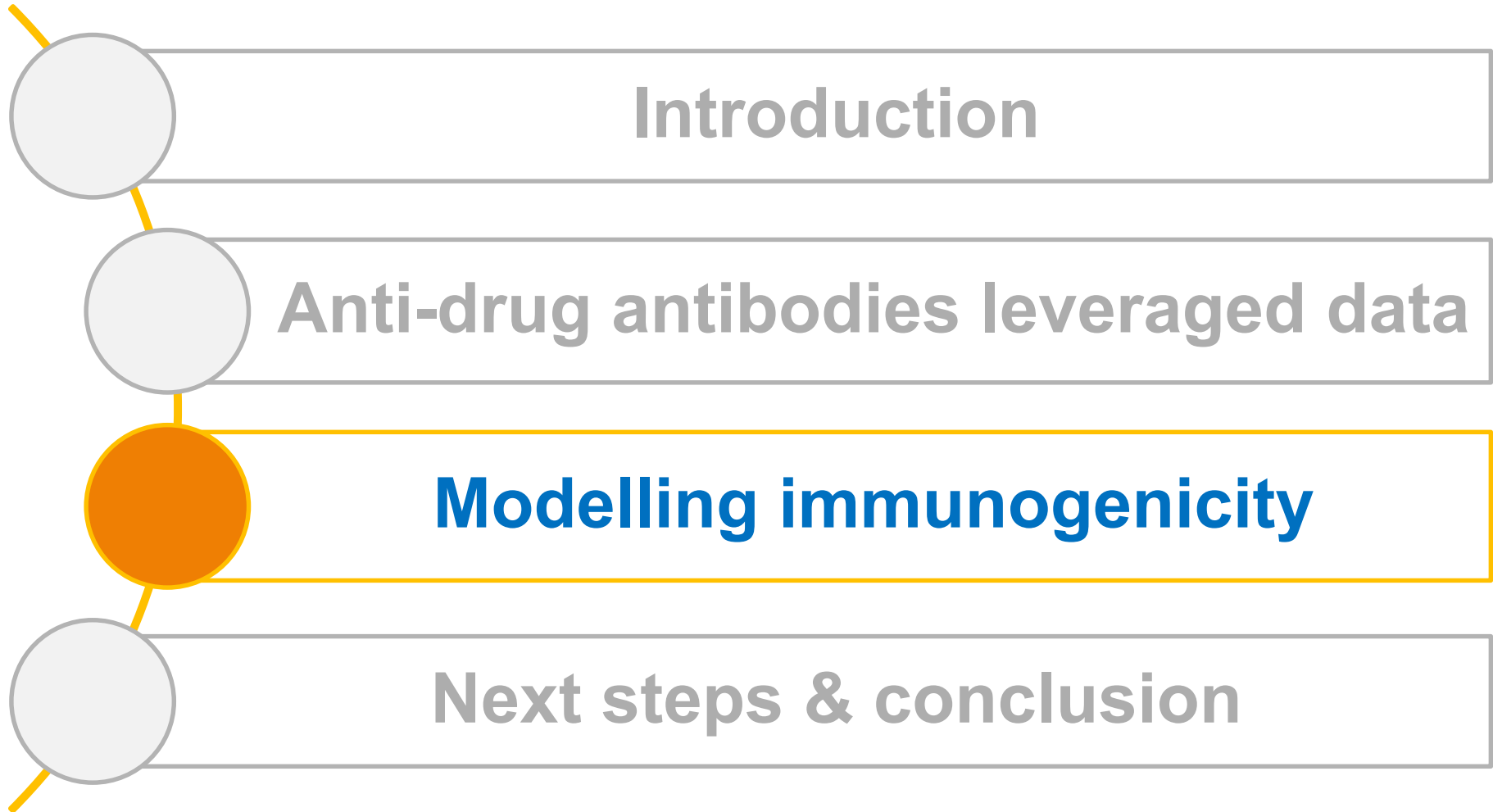%Nab+/ADA+: **50%**   **68%**   **48%**   **53% 61%**
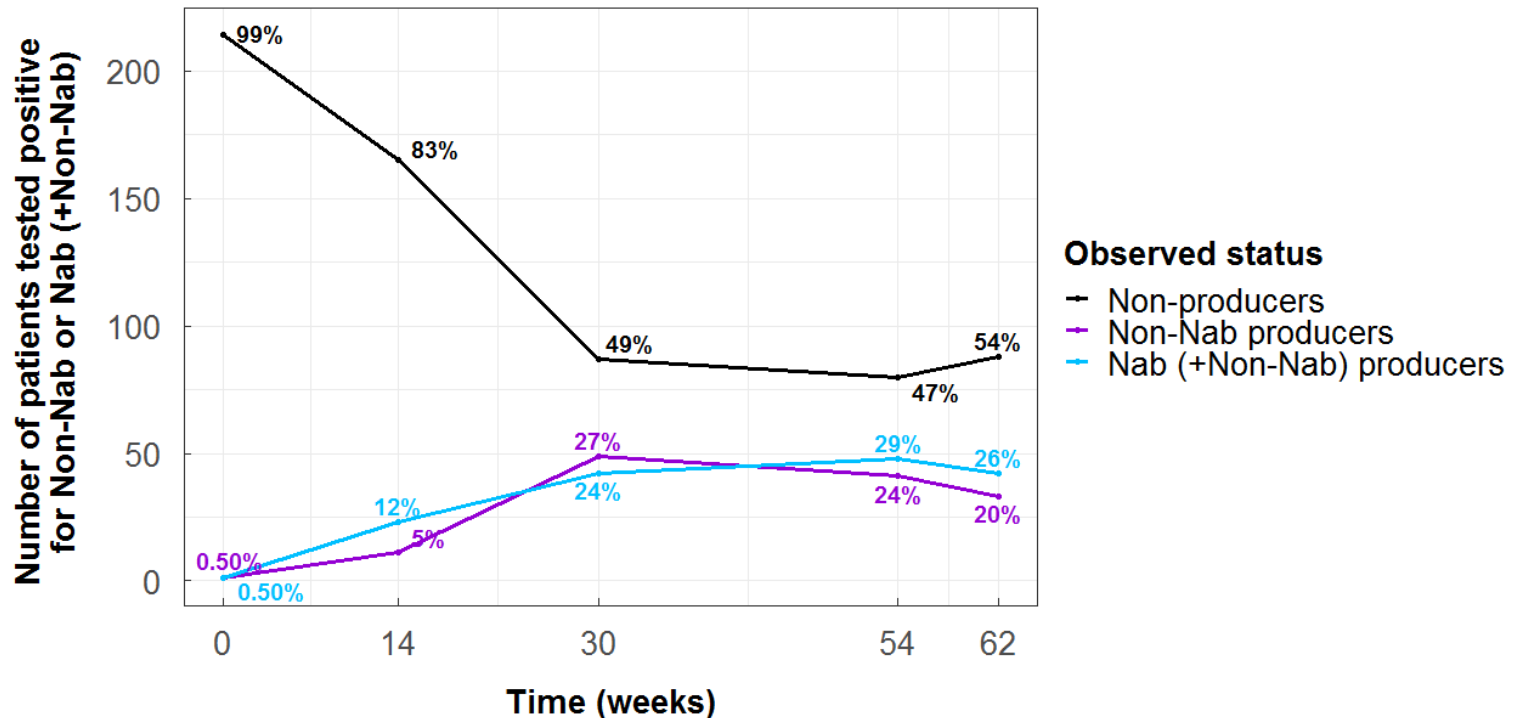
→ **%ADA+ and %Nab+ stabilised after week 30**

→ **%Nab+/ADA+ remains ~50% across the study**

ADA: Anti-drug antibody
Nab: Neutralising ADA

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Mixed hidden Markov model (MHMM)

Describe a relationship between two stochastic processes:

Hidden process → Underlying immunogenicity status

Observed process → ADA titers: most informative for prediction of immunogenicity status

Markov model
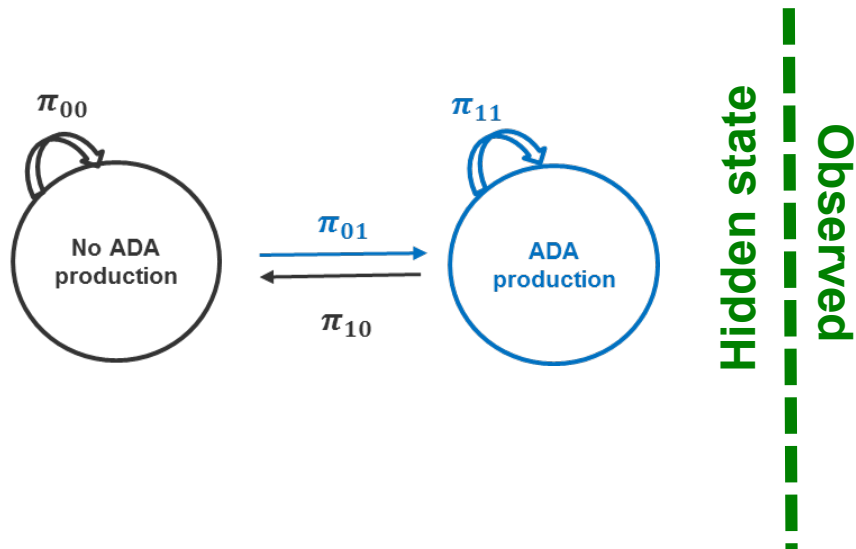

Characterised by its distribution

ADA: Antidrug antibodies
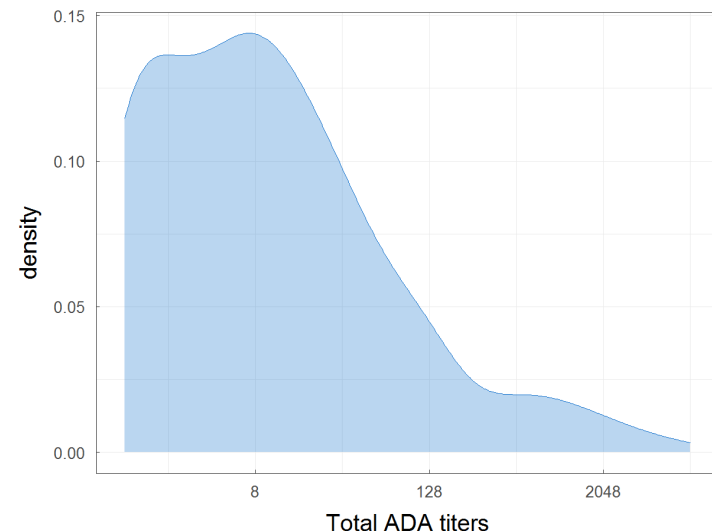
Model development strategy

1. Choice of hidden states
2. Choice of observed variables and the distribution to describe them

Hidden states			Observed variables	Distribution of the observed variables
3 states	-	No ADA production	- Total ADA titers	- ZTP distributions
	-	Non-Nab production	- Nab titers	
	-	Nab + Non-Nab production		$$P(X = k \mid X > 0) = \frac{\lambda^k}{(e^\lambda - 1)k!}$$

ADA: Anti-drug antibodies; Nab: Neutralising ADA; π: Transition probability; ZTP: Zero-truncated Poisson
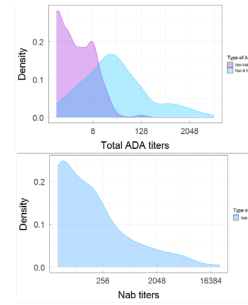
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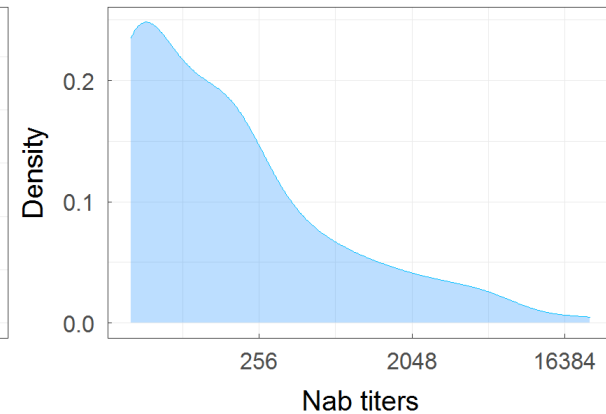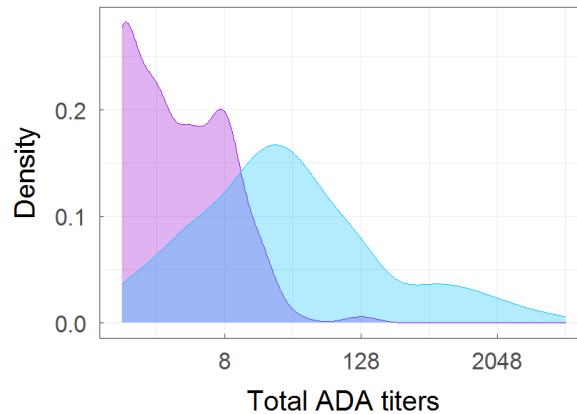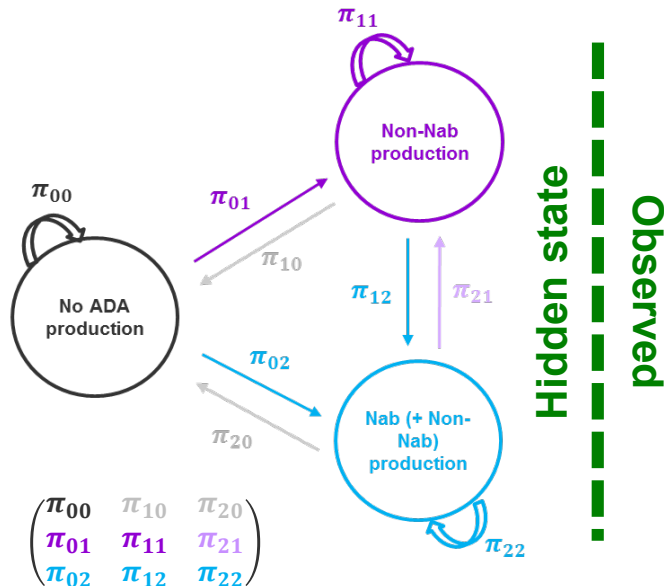
Model evaluation

- Three hidden states
- Two observed variable
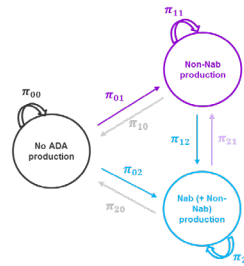
Observations
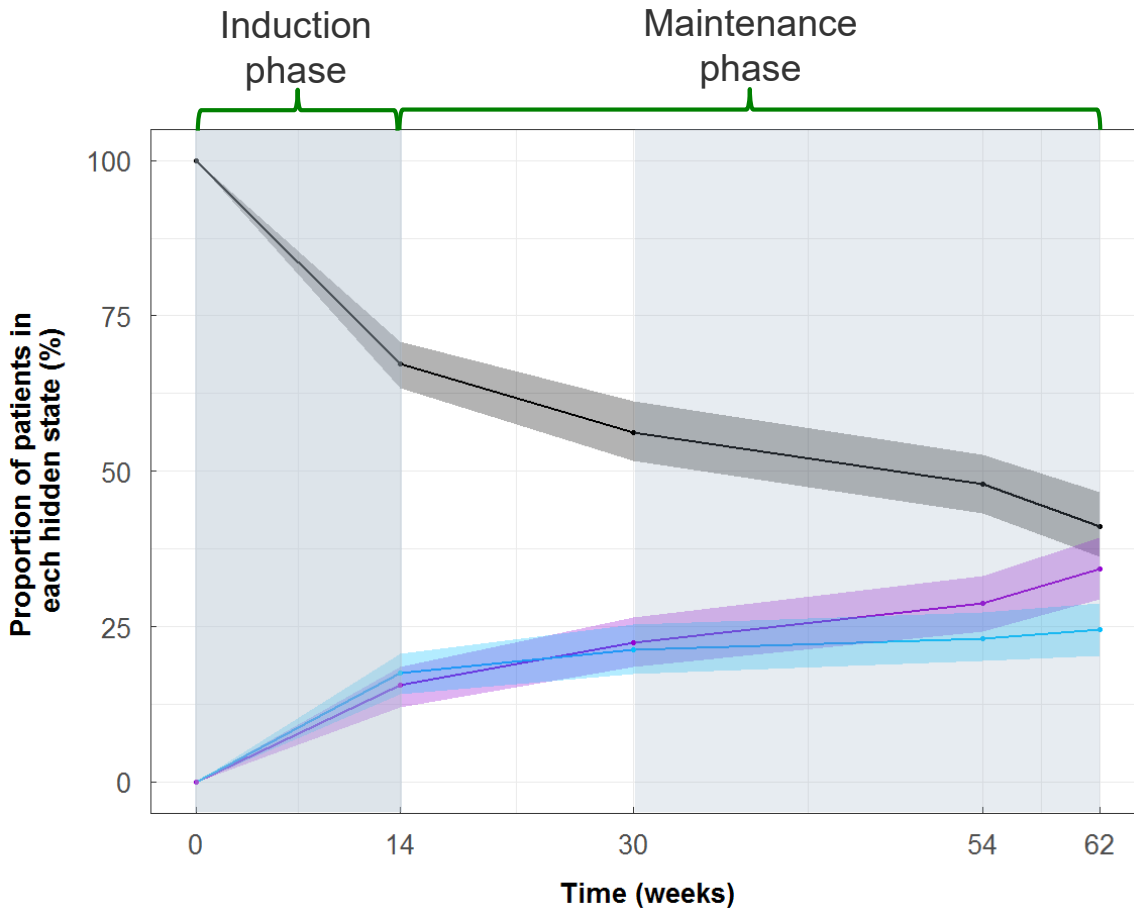
Median of the simulations, 95% CI

ADA: Anti-drug antibody
Nab: Neutralising ADA
π: Transition probability
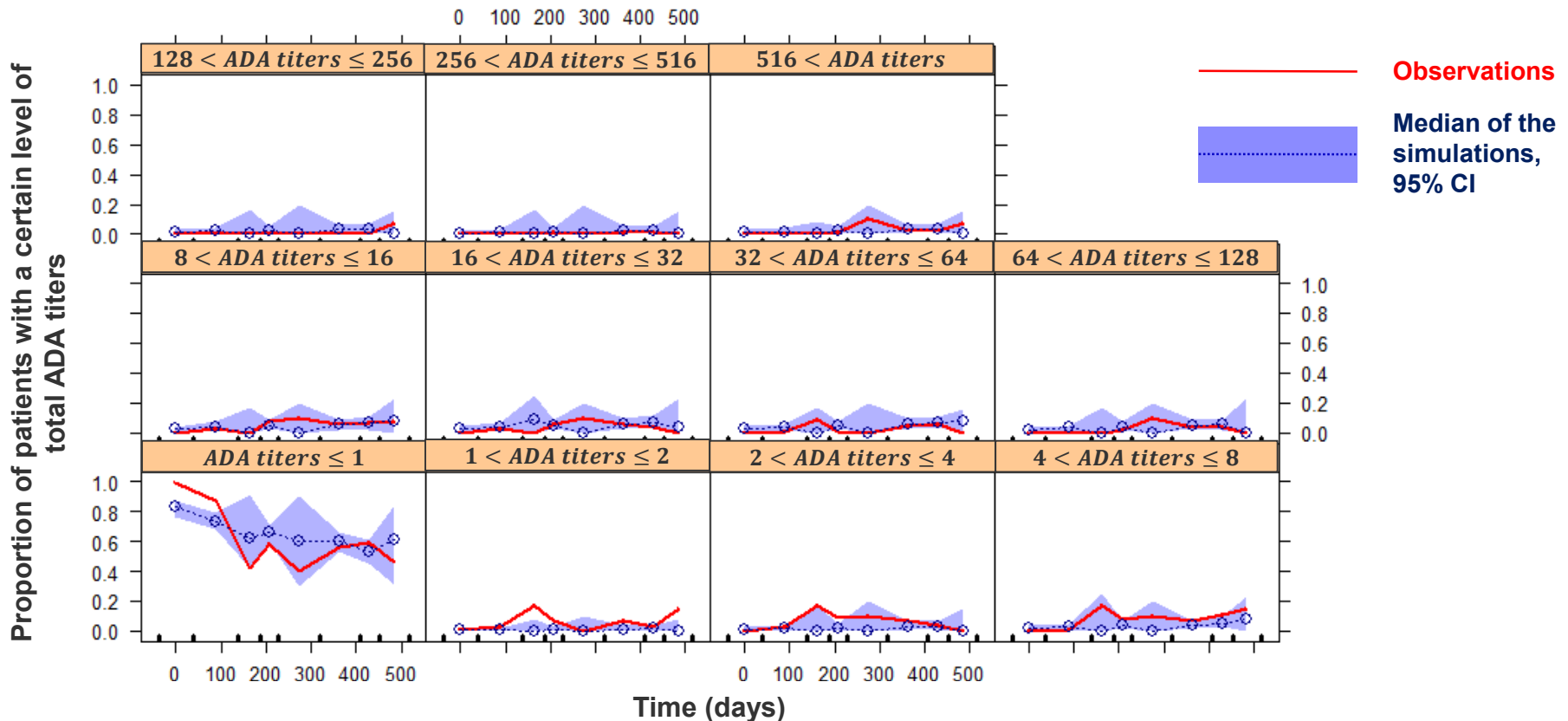
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Model results

Hidden states
- Non-producers
- Non-Nab producers
- Nab (+Non-Nab) producers

— Median of simulations

▬ 10th and 90th percentiles of simulations

Induction phase

Maintenance phase

Proportion of patients in each hidden state (%)

Time (weeks)

ADA: Anti-drug antibody
Nab: Neutralising ADA
π: Transition probability

No ADA production 85%

Non-Nab production 84%

Nab (+ Non-Nab) production 98%

10%
1%
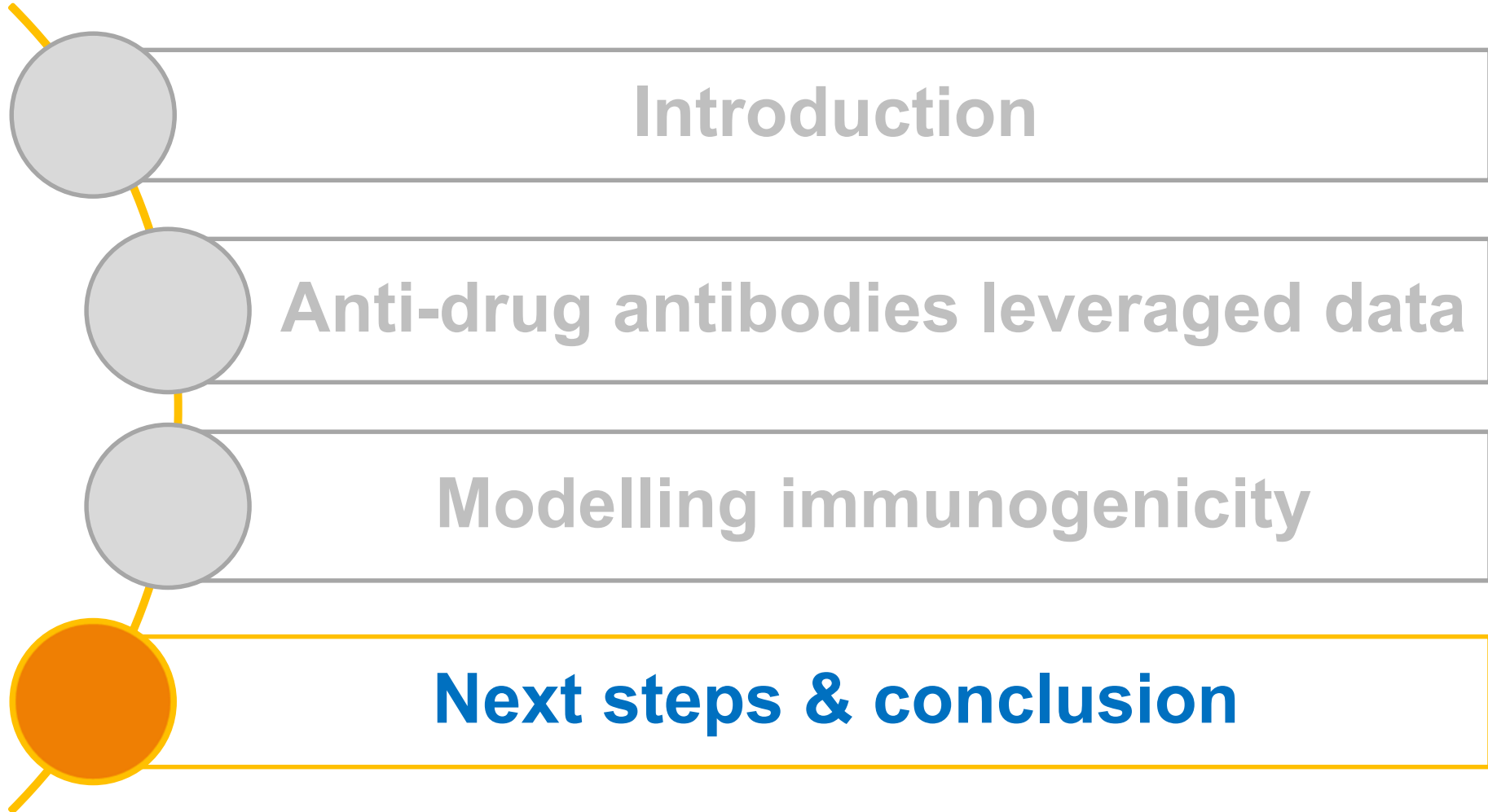15%
1%
5%
1%
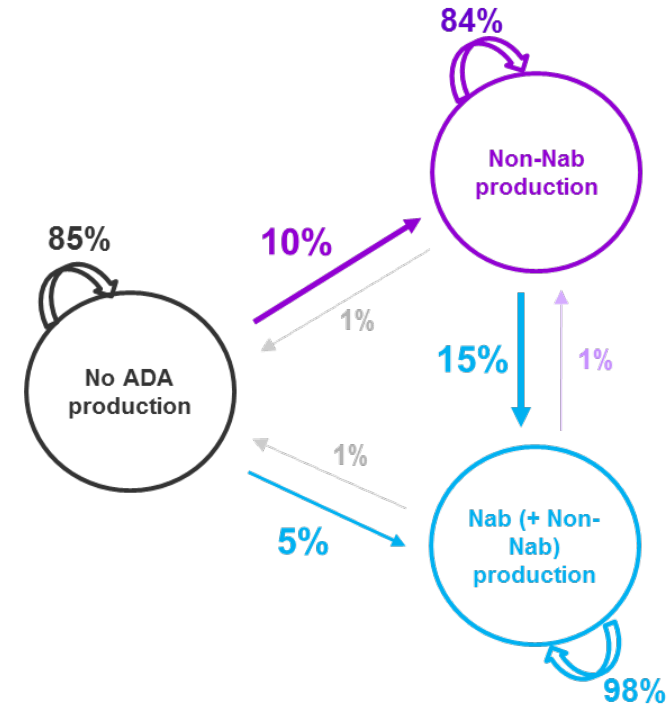
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Model results

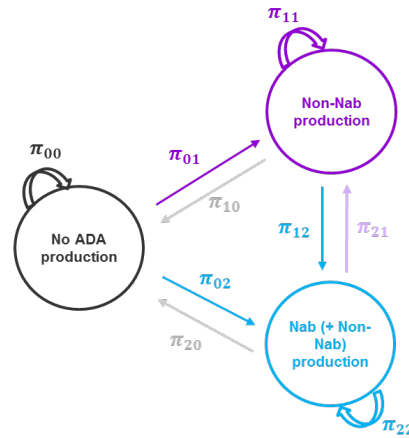- Three hidden states
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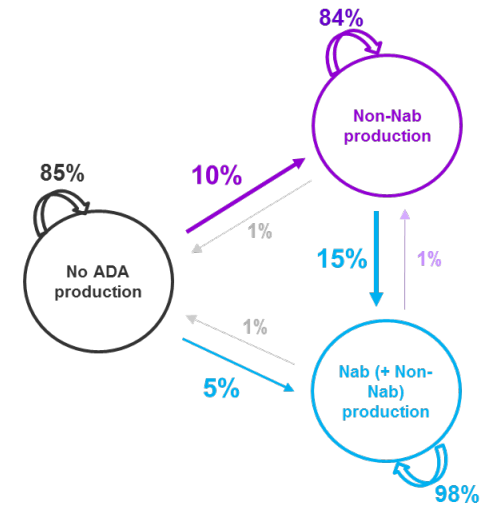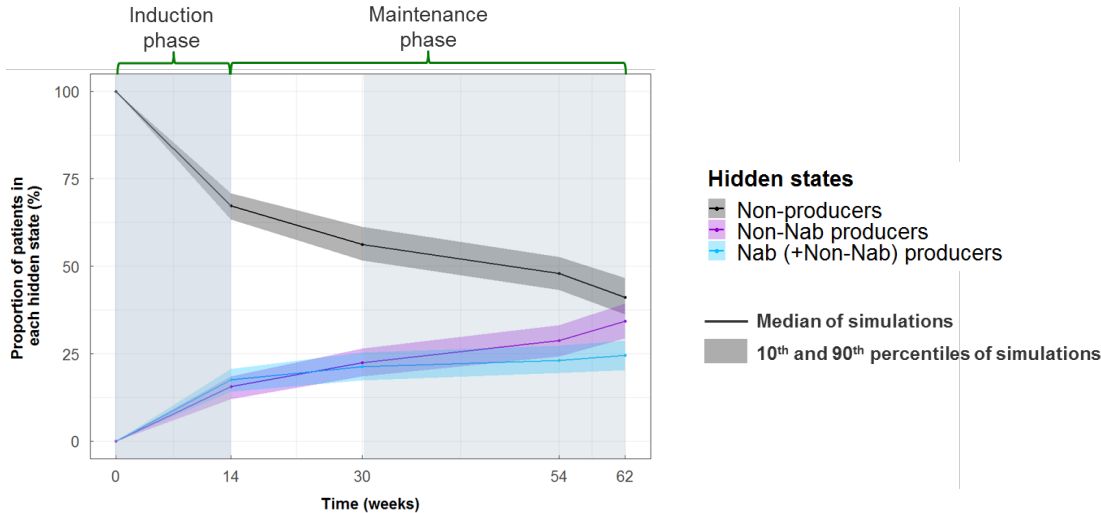
- 1/3 patients develop ADA during induction phase

- Stabilisation of ADA development at week 30 → Decreased risk of developing ADA

- ~ 50% patients present an immunogenic response
  - ➢ ~ 25% Non-Nab: ↑ risk of LOR due to PK
  - ➢ ~ 25% Nab: ↑ risk of LOR due to PK and PD

ADA: Anti-drug antibody
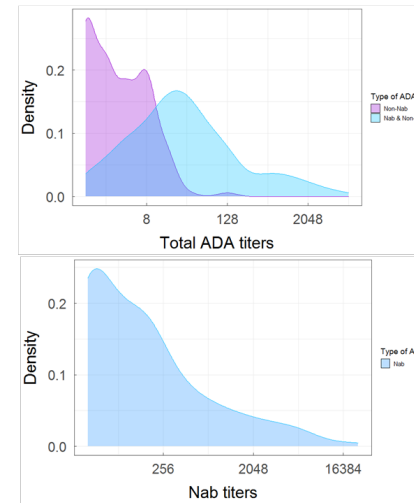Nab: Neutralising ADA
π: Transition probability

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Next steps

- ❖ **ADA-Nab BV MHMM:**

  - ➢ Correlated bivariate ZTP

    - → Need to describe the **correlation** between the two observed variables

  - ➢ Inclusion **time dependency** on transition probabilities:

    - → Hypothesis: After a while, risk of developing ADA/Nab decreases

  - ➢ **Covariate** analysis :

    - → Impacting factor on Non-Nab and Nab development?

ADA: Anti-drug antibody   Nab: Neutralising ADA
BV: Bivariate π: Transition probability
MHMM: Mixed hidden Markov model   ZTP: Zero-truncated Poisson

Conclusion

- **Underlying immunogenicity in CD patients receiving IFX:**
  - ➢ Successfully described with **3 states**, comprising **Nab** development

- **MHMM**: comprehensive framework for predicting underlying immunogenicity
  - ➢ Predict sequence of unobservable states on an individual level: ADA and Nab development
  - ➢ Simulations of further studies possible: sampling of Nab

- **Final objective:** Assess impact of Non-Nab and/or Nab development on PK and PD
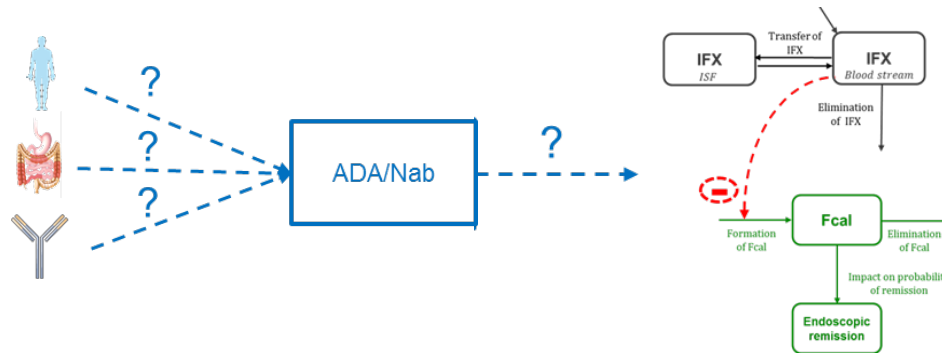
→ **Impact of immunogenicity on treatment outcome: LOR**

ADA:	Antidrug-antibodies
CD:	Crohn's disease
IFX:	Infliximab

Nab:	Neutralising ADA
PD:	Pharmacodynamics
PK	Pharmacokinetics

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Acknowledgements

Universität Potsdam   Universität Navarra   Humboldt Research Fellow   Universität Hamburg

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