Population pharmacokinetic/ pharmacodynamic modeling of a new antithrombotic drug, the Nanobody® ALX-0081/ALX-0681

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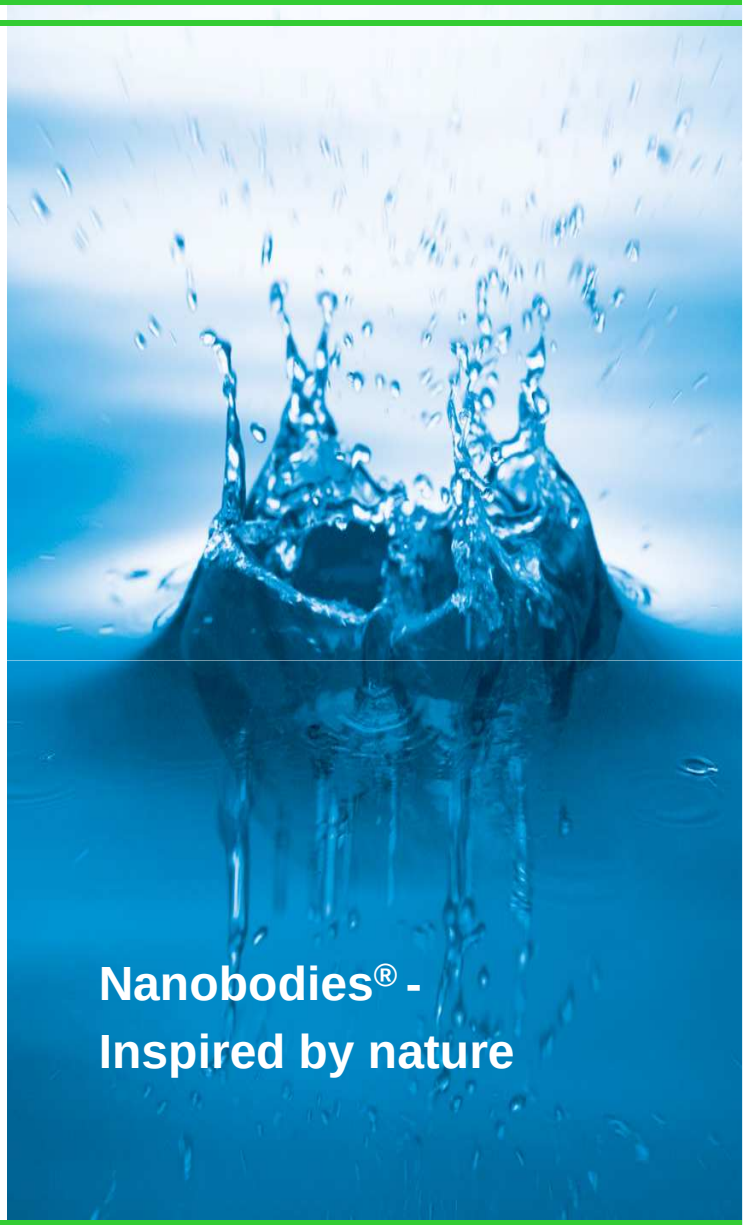
Athens, Greece



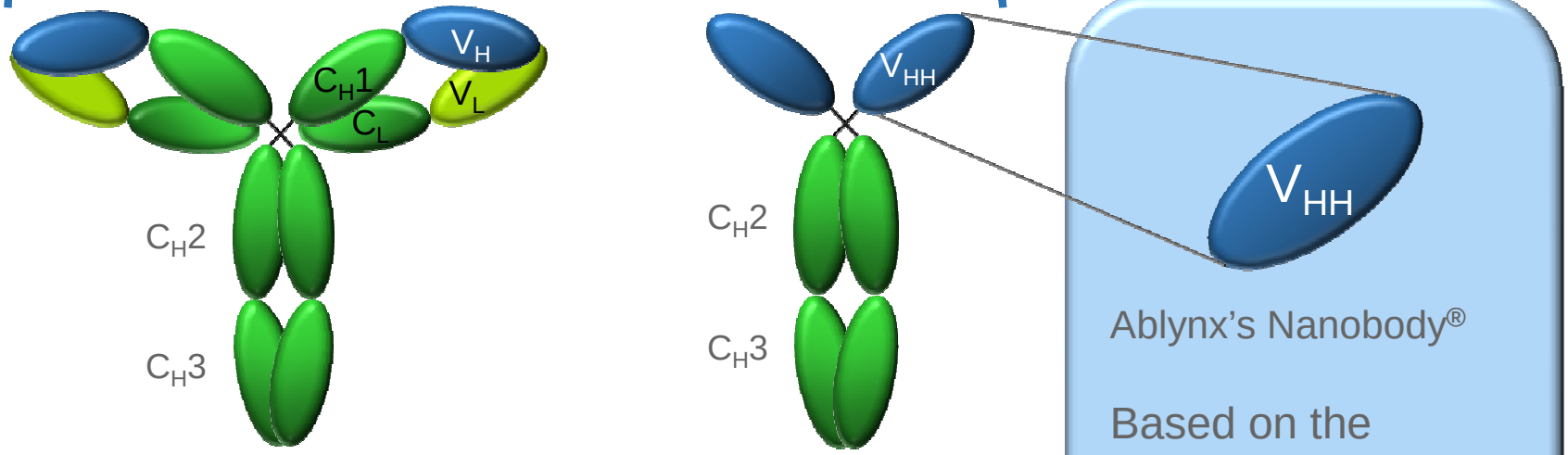
Agenda

- Introduction
  - anti-von Willebrand Factor (vWF) Nanobody (ALX-0081/ALX-0681)
    - product characteristics and mode of action
    - PK characteristics
- PK/PD modeling results
  - structural model
  - final model
  - VPC (PK and PD)
  - application of the model (special populations)
- Conclusions

Introducing Ablynx and Nanobodies®

Conventional antibodies *vs* Nanobodies

Camelidae family has both forms



Conventional antibody

Heavy and light chains
Both chains required for antigen binding and stability

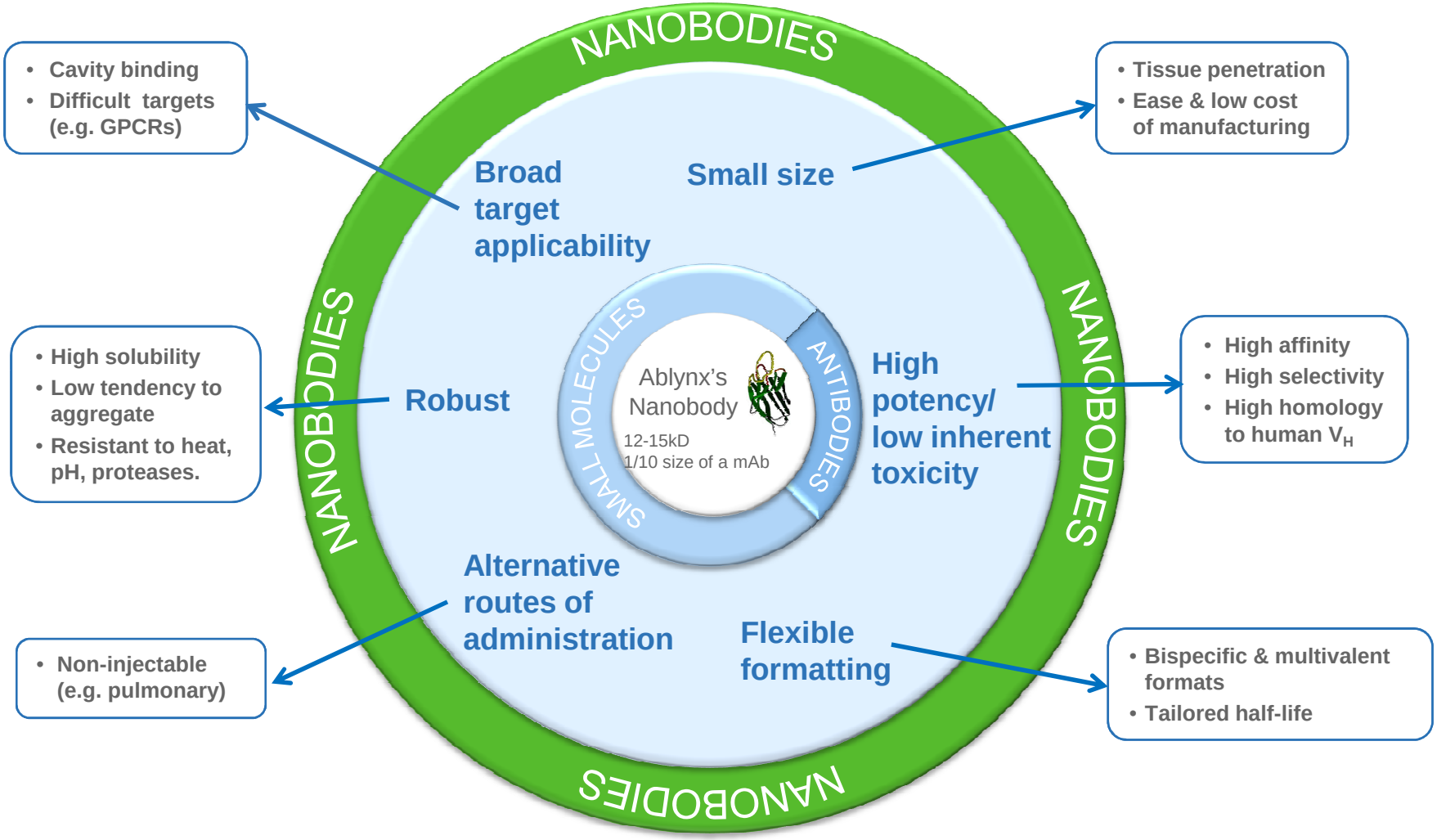
Heavy-chain antibody

Only heavy chains
Full antigen binding capacity and very stable

Ablynx's Nanobody®

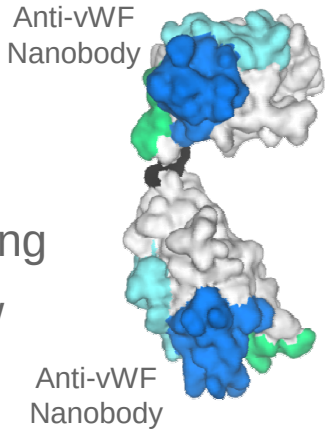
Based on the smallest functional fragment of a naturally occurring heavy-chain antibody

Nanobodies – beyond antibodies & small molecules



Anti-von Willebrand Factor (vWF) Nanobody

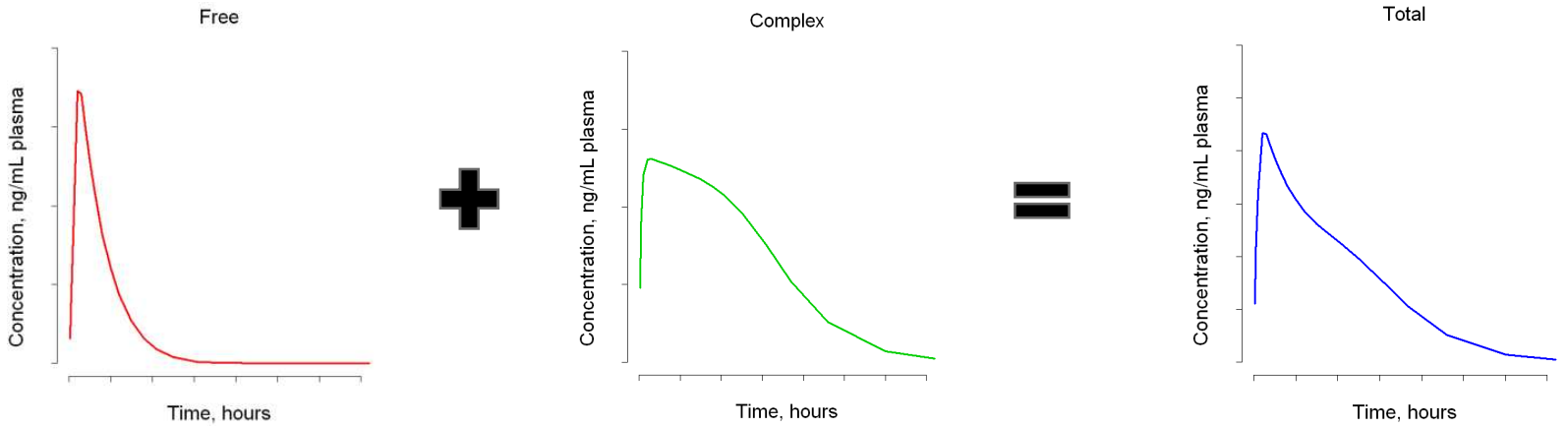
- Anti-vWF Nanobody product characteristics
  - bivalent construct - high potency through formatting
  - no half-life extension - “small molecule” pharmacology with mAb specificity
  - 2 forms of administration (ALX-0081 *iv* and ALX-0681 s*c*)



- Targets first mover in cascade of thrombosis
  - could prevent unwanted blood clot formation
  - in animal models, demonstrated highly potent inhibition of clotting without increased bleeding – possible large therapeutic window
- Targets pathophysiological mediator in Thrombotic Thrombocytopenic Purpura (TTP)
- Potentially first-in-class
- Manufactured in *E. coli* – relatively low cost of goods
- Phase II trials in progress in two indications – ACS/PCI and TTP

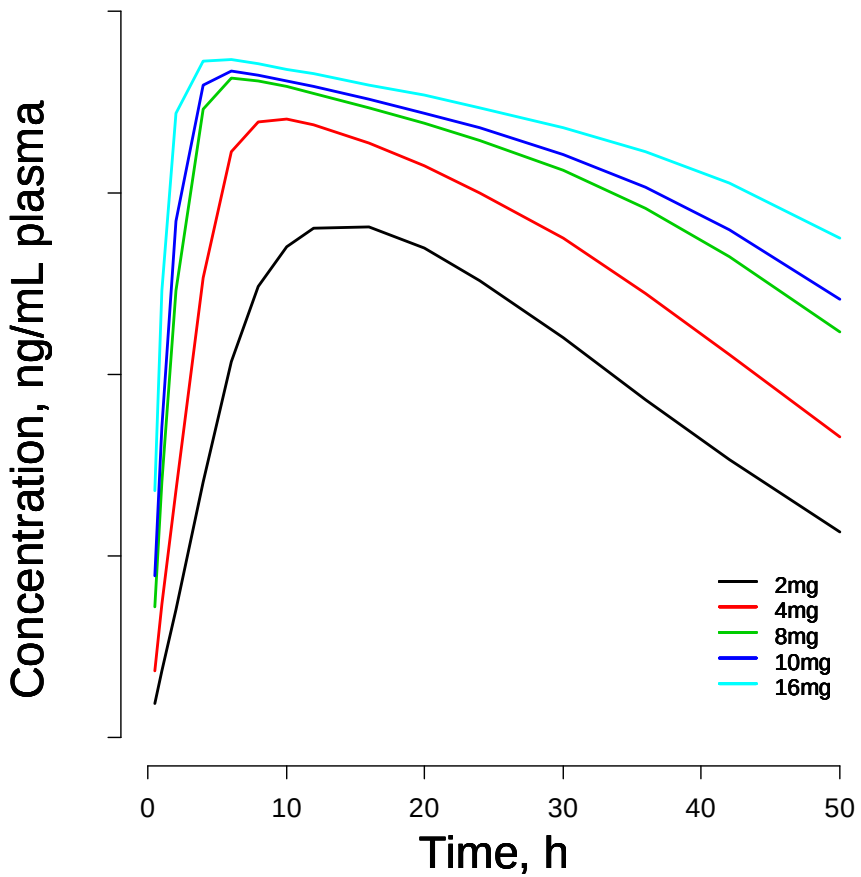
ALX-0081/ALX-0681 pharmacokinetics
What do we see?

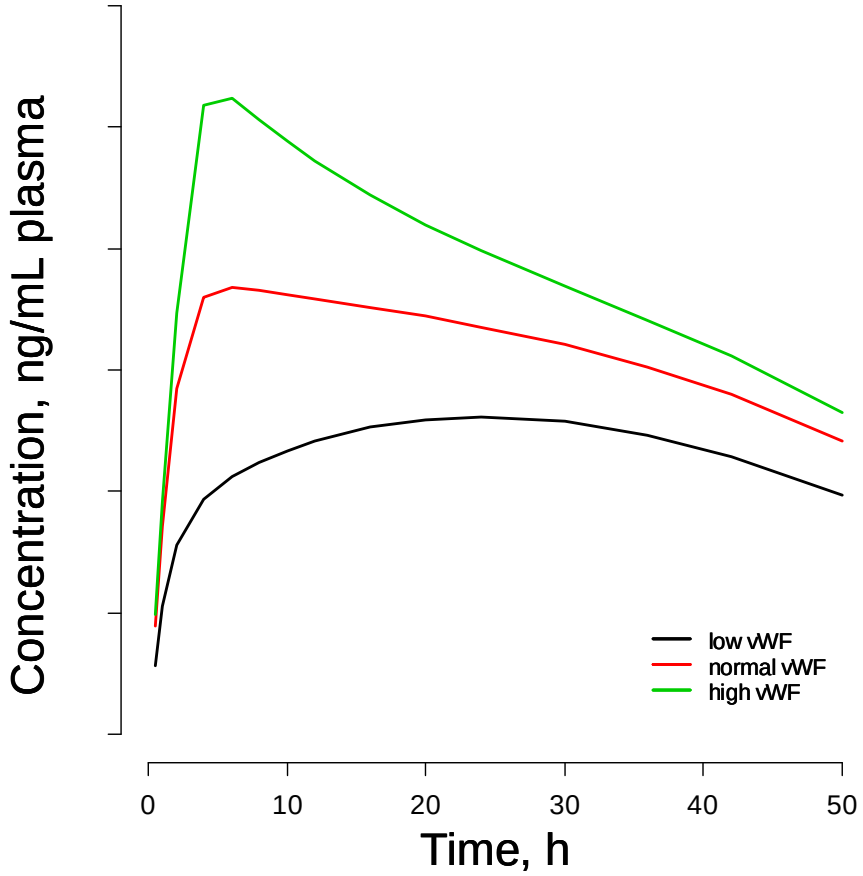
- What are we measuring?
  - total ALX-0081/ALX-0681 (free + complex)
  - total vWF (free + complex)
- Hypothesis
  - the free drug will be cleared by the kidney
  - the drug in complex will be cleared via their receptor
  - PK profile total ALX-0081/ALX0681 is the superposition of the PK profiles of free drug and drug in complex



ALX-0081/ALX-0681 pharmacokinetics
Drug in complex

- Target mediated drug disposition (TMDD)
  - clearance pathway can be saturated
  - depending on the vWF levels in circulation





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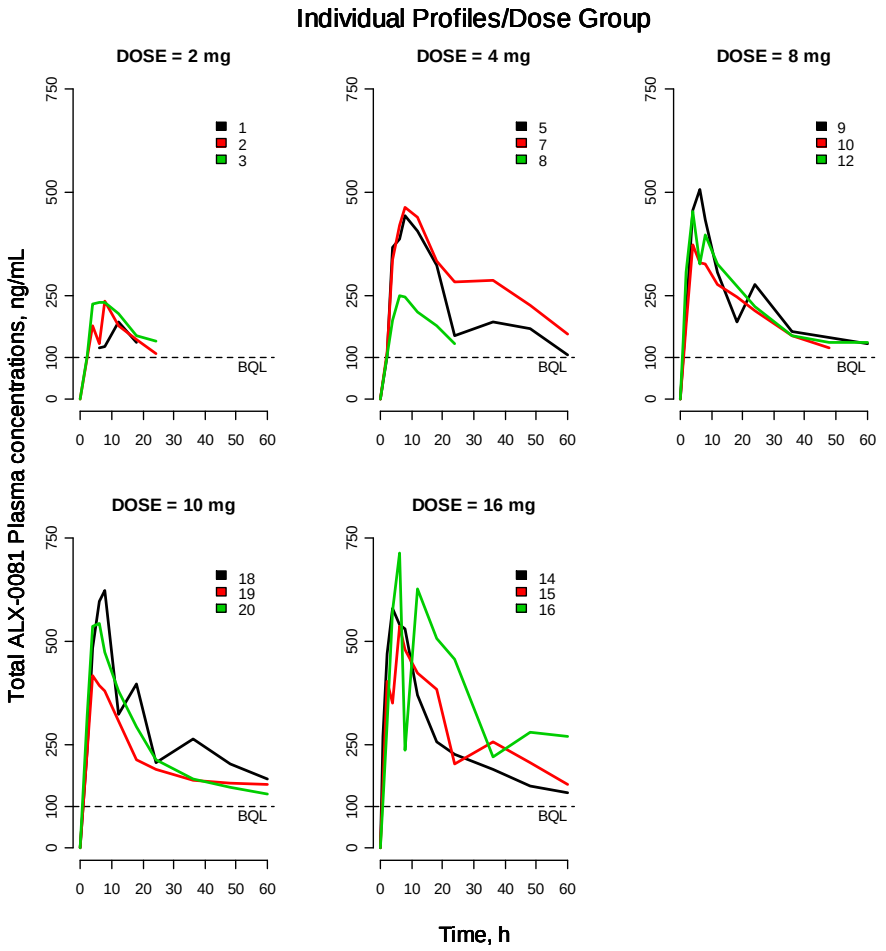
ALX-0081/ALX-0681 Pop PK/PD
Included studies

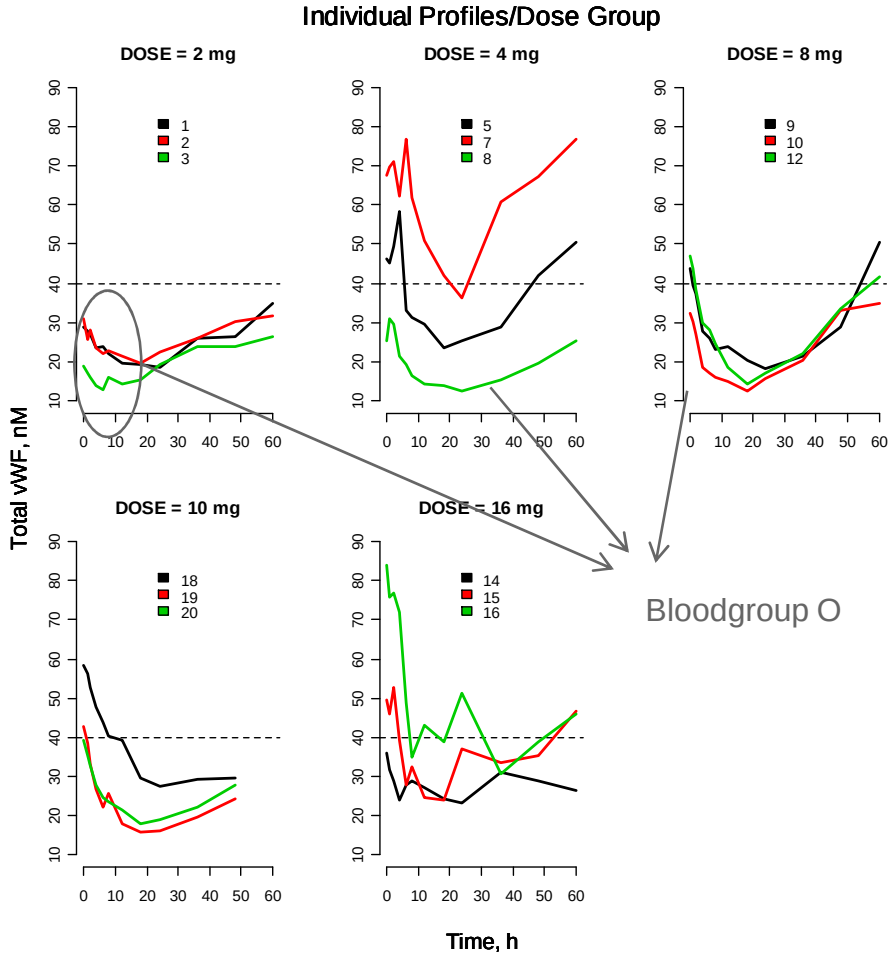
Ablynx

- Summary of included studies

Study number	Type	Subject N° active Population	Route, dose regimen and formulation	PK PD sampling scheme	Number of samples
ALX-0081-1.2/08a	Phase I	Patients n=12	SD iv 60 min, 2, 4, 6, 9 mg	**rich**	PK=97 PD=120
ALX-0081-1.2/08b	Phase I	Patients N=6	MD iv 60 min, 6 mg+(3x4mg)	**sparse**	PK=41 PD=48
ALX-0081-1.2/08c OLE	Phase I	Patients N=20	MD iv bolus, 6 mg+(3x4 mg)	**sparse**	PK=119 PD=151
ALX-0081 sc a	Phase I	Healthy N=15	SD sc 2, 4, 8, 10, 16 mg	**rich**	PK=135 PD=177
ALX-0081 sc b	Phase I	Healthy N=12	MD sc 10 mg od	**rich**	PK=456 PD=234
Total		**65**			**PK=848 PD=730**

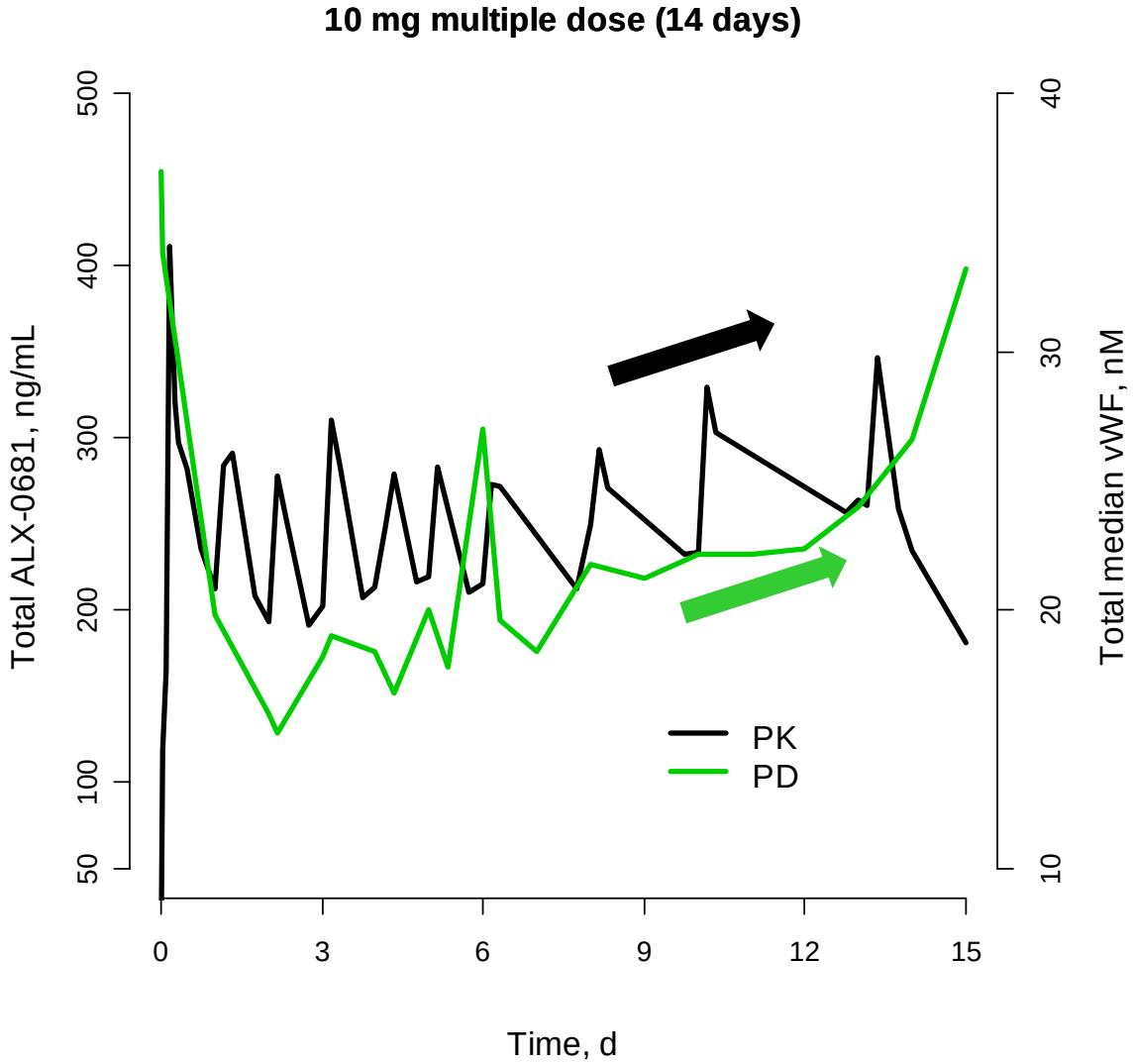
ALX-0081/ALX-0681 Pop PK/PD
Raw data



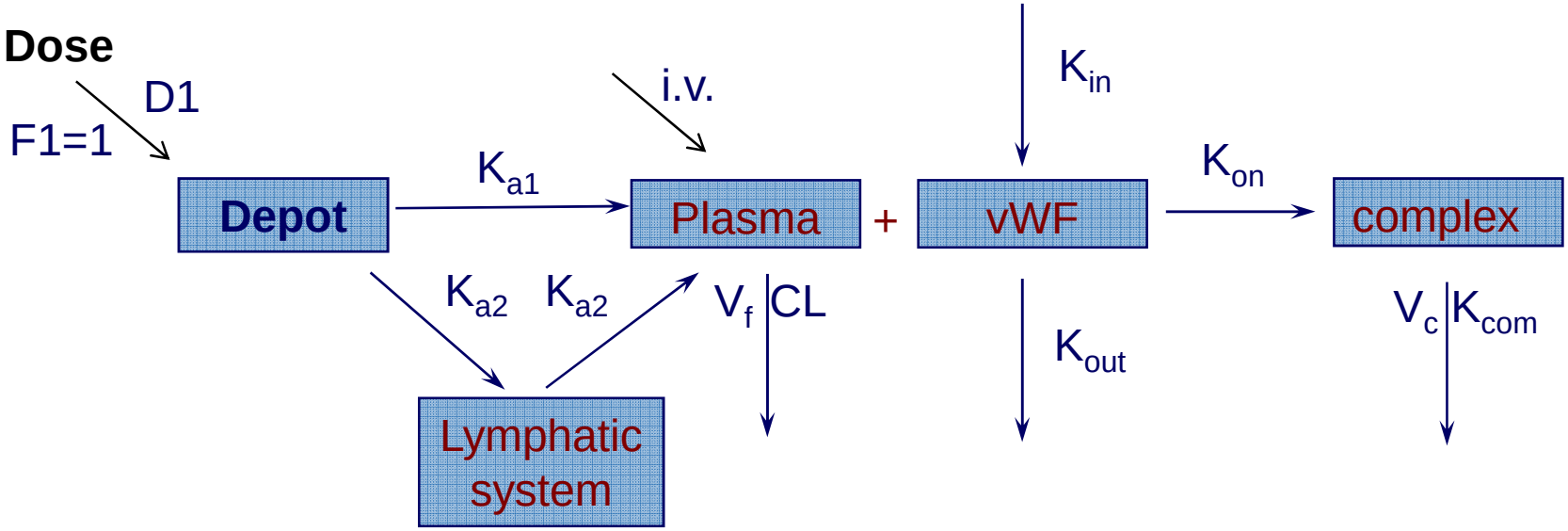


- Substantial variability in PK and PD

ALX-0081/ALX-0681 Pop PK/PD
Raw data



ALX-0081/ALX-0681 Pop PK/PD
Structural model



Assumptions:
- bioavailability is 100%
- K_{off} is negligible

Model	OFV	Delta
3 CMT with 1 Ka	11373.5	-
3 CMT with zero-first order input	11255.6	-117.9
4 CMT with zero-first order input	11212.5	-43.1
Previous + linear time dependent increase of kin	11047.6	-164.9

ALX-0081/ALX-0681 Pop PK/PD
Covariate analysis

- Which covariates are statistically significant:
  - forward addition (plug-in all covariates at once)
  - one by one backward elimination (if increase in OFV > 10.83, keep it in)

Model	OFV	Delta
Full covariate model	10966.9	-
Full – WGT (KA_1)	10979.1	12.2
Full – CRCL (CL)	10992.6	25.7
Full – DST (K_{com})	10997.0	30.1
Full – BLG (Baseline vWF)	10976.2	9.3

ALX-0081/ALX-0681 Pop PK/PD
Final model (estimated parameters)

Parameter	Estimate	RSE (%)
KA1 (h^{-1})	0.11	12
V3 (L)	5.18	16
CL ($L.h^{-1}$)	5.12	9
BASE (nM)	49.1	6
Kin ($nM.h^{-1}$)	1.23	10
Kcom (h^{-1})	0.0488	10
Kon ($nM^{-1.93}.h^{-1}$)	0.00691	59
MOL	1.93	5
KA2 (h^{-1})	0.0616	23
RDPR1 (d^{-1})	0.0437	19
DUR (h)	2.33	11
V5 (L)	2.12	7
WGT (KA1)	-2.07	31
CRCL (CL)	1.01	20
DST (Kcom)	0.555	9
IIV KA1	39%	28
IIV V3	48%	50
IIV CL	23%	95
IIV BASE	37%	21
IIV Kin	40%	28
IIV Kcom	22%	62
IIV V5	10%	69
Sigma (PK)	15%	12
Sigma (PD)	18%	13

Free compound distributed in blood and interstitial fluid (>2.5L)

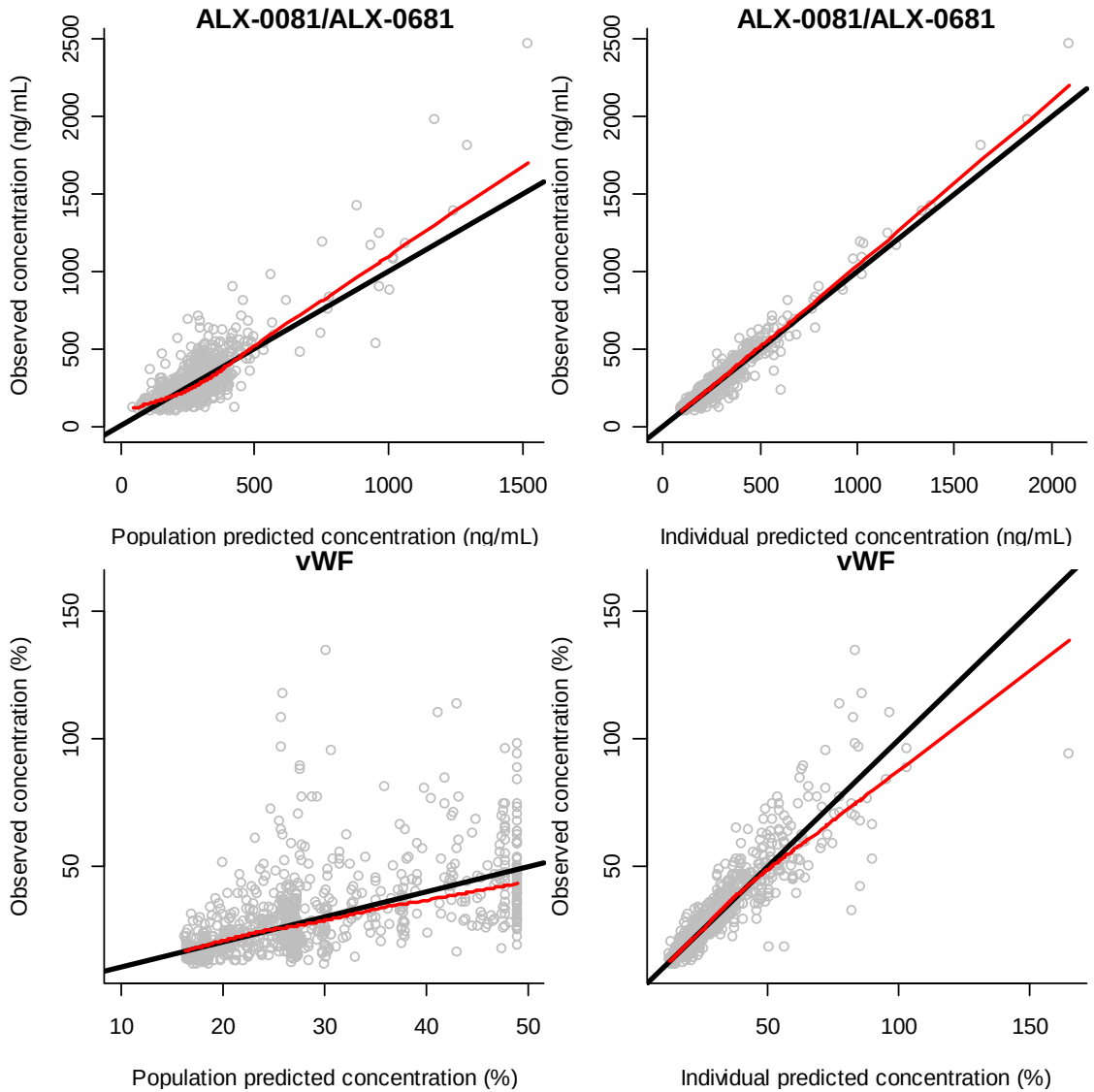
Free compound cleared via glomerular filtration

1.9 vWF molecules binds to 1 ALX molecule

Complex only present in the blood (≈2.5L)

$t_{1/2}$ of complex in:
HV = 14h
PAT = 26h

ALX-0081/ALX-0681 Pop PK/PD
Final model (GOF plots)



ALX-0081/ALX-0681 Pop PK/PD
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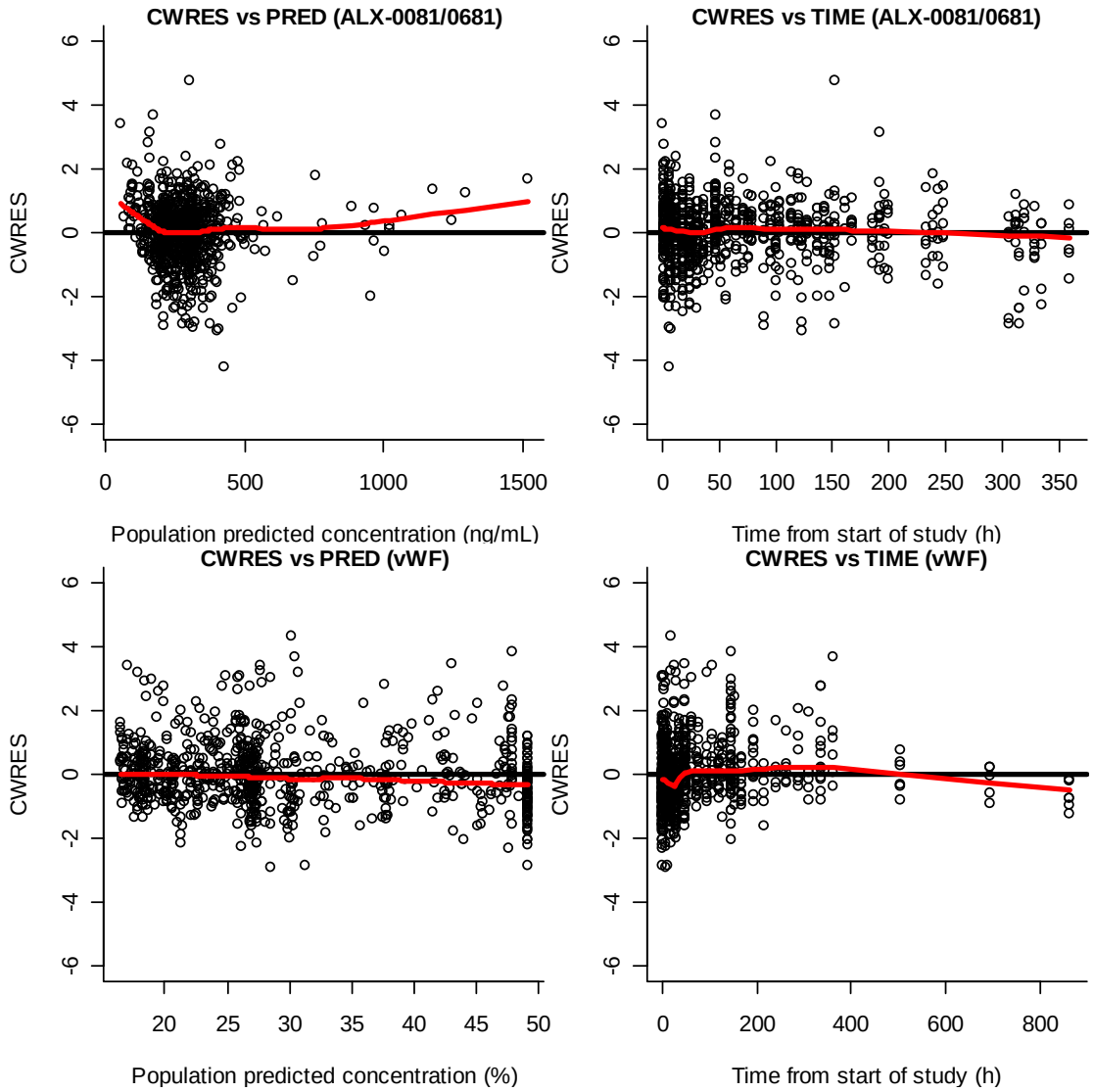
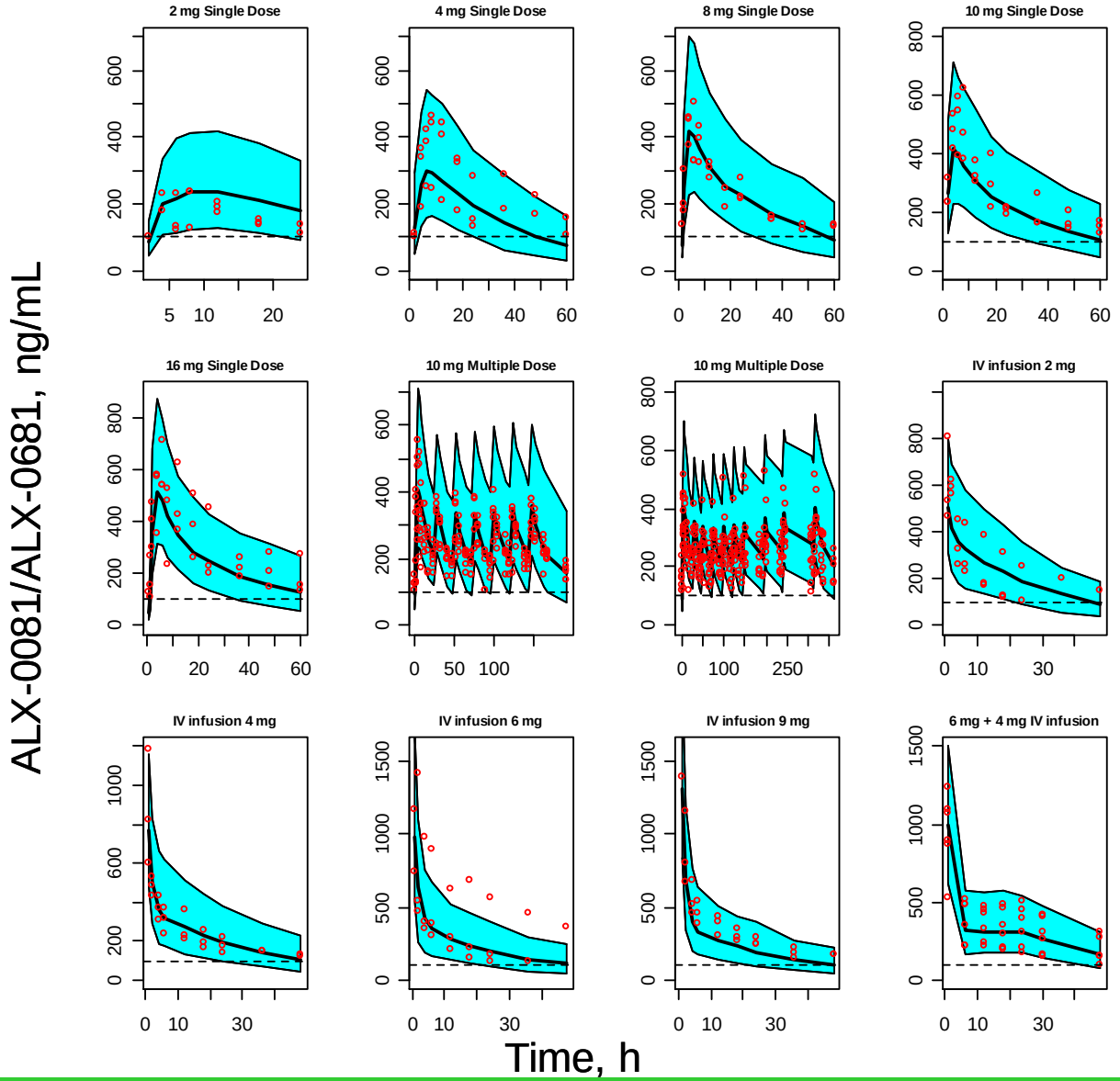
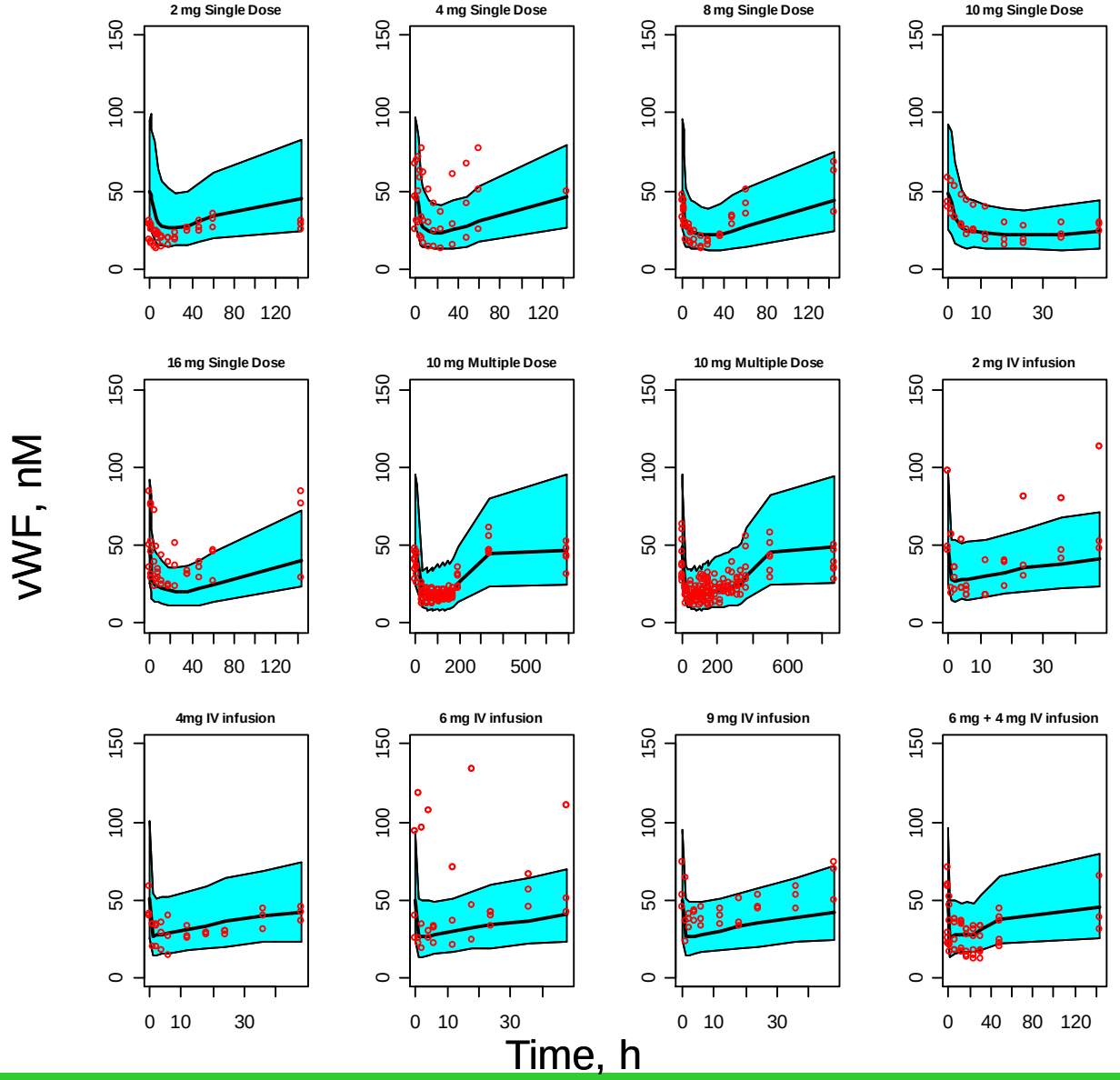


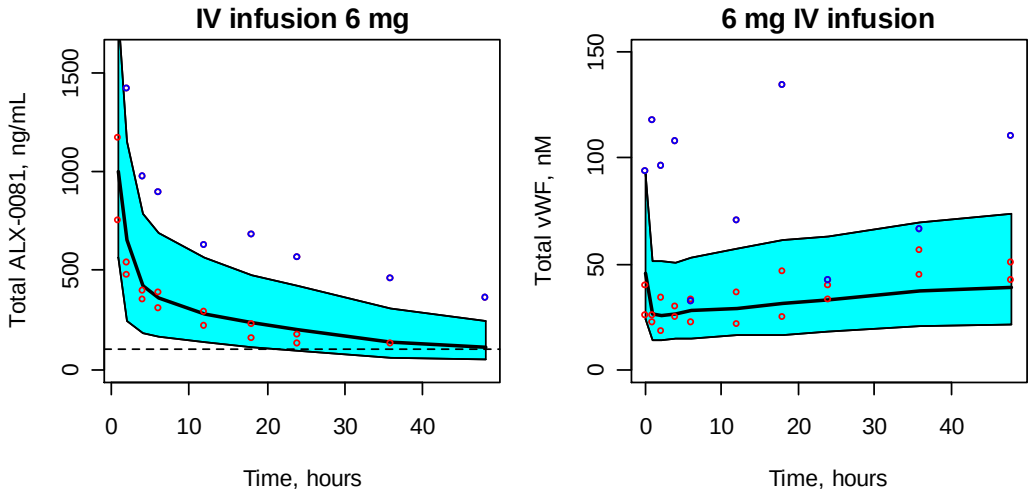
ALX-0081/ALX-0681 Pop PK/PD
Visual predictive check (PK)



ALX-0081/ALX-0681 Pop PK/PD
Visual predictive check (PD)

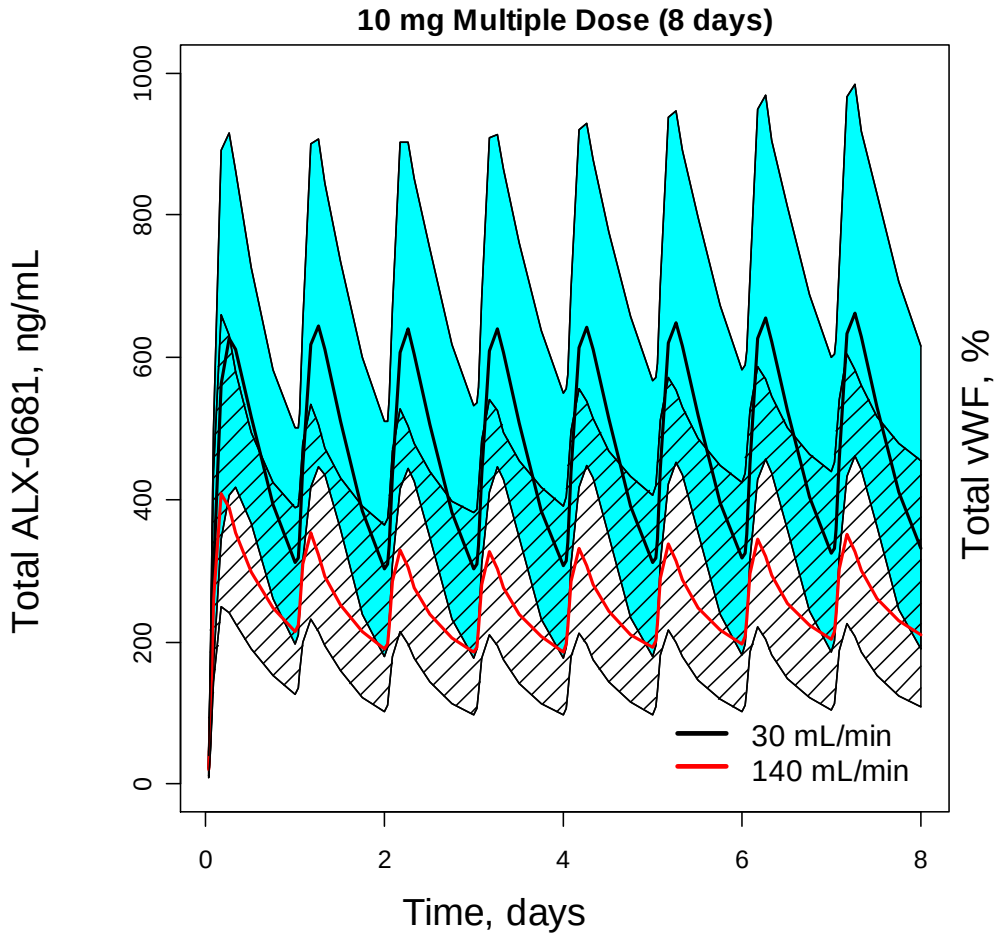


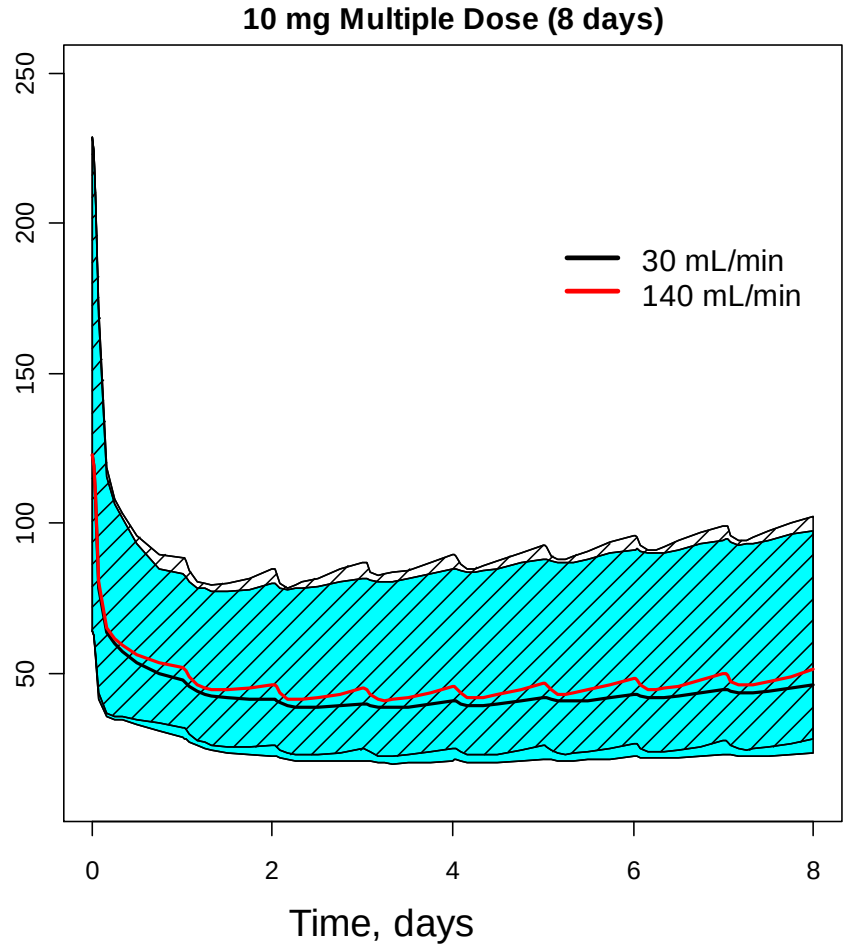
ALX-0081/ALX-0681 Pop PK/PD
Visual predictive check



- Same subject outside the 90% prediction interval for PK and PD
  - vWF level is very high in this case which lead to high total ALX-0081 concentrations

ALX-0081/ALX-0681 Pop PK/PD
Effect of renal clearance on PK and PD





Conclusions

- A popPK/PD model is developed that describes the total ALX-0081/ALX-0681 and total vWF profiles
  - ALX-0081/ALX-0681 is going into the systemic circulation via two pathways i.e. directly and indirectly (e.g. lymphatic system)
  - free ALX-0081/ALX-0681 is distributed outside the central compartment
  - ALX-0081/ALX-0681 in complex stays in the blood
  - rapid clearance of free ALX-0081/ALX-0681 via glomerular filtration
  - low accumulation potential of the drug

- Three covariates are clinically relevant
  - weight on Ka1
  - CRCL on CL
  - disease status on K_{com}

- Model can be used to guide dose and dosing regimen in special populations (Renal impaired subjects, pediatric population)

Acknowledgements

- Pharmacology
  - ML Sargentini-Maier
  - J Baumeister
  - H Ulrichts
  - S Priem

- Clinical
  - JB Holz
  - C Duby
  - D Tersago
  - K Vercruysse
  - C Lyssens

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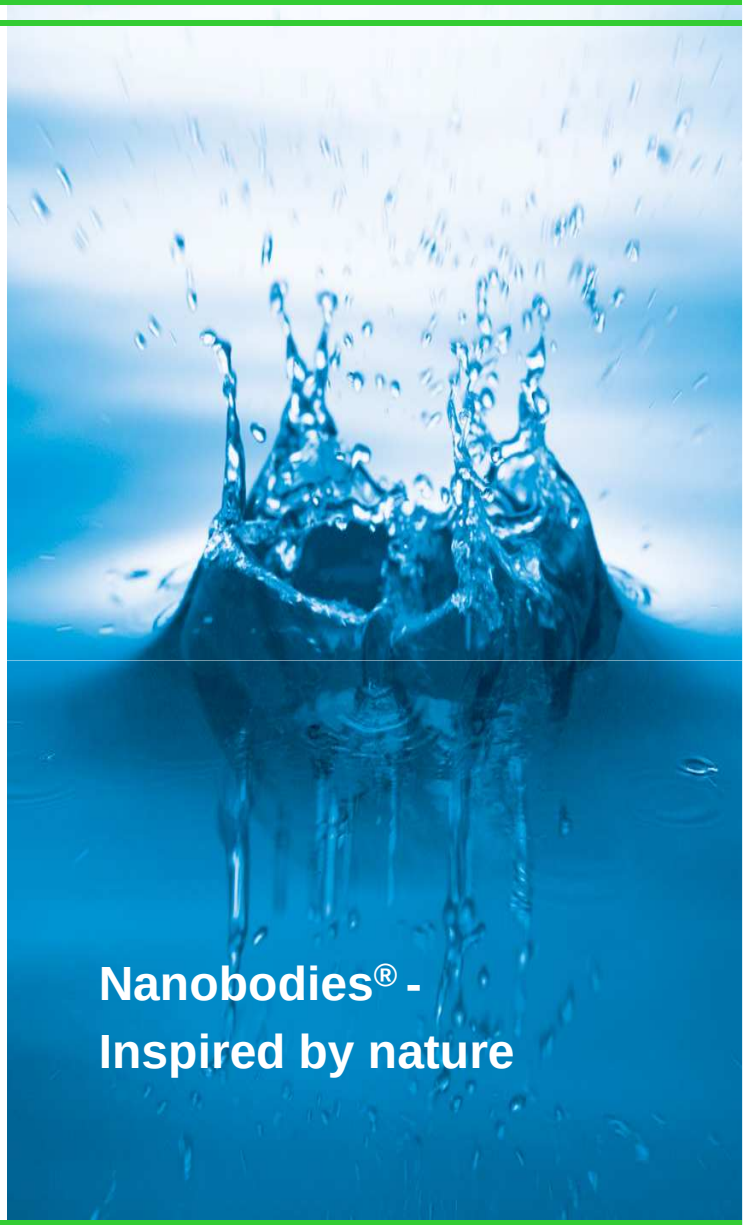
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