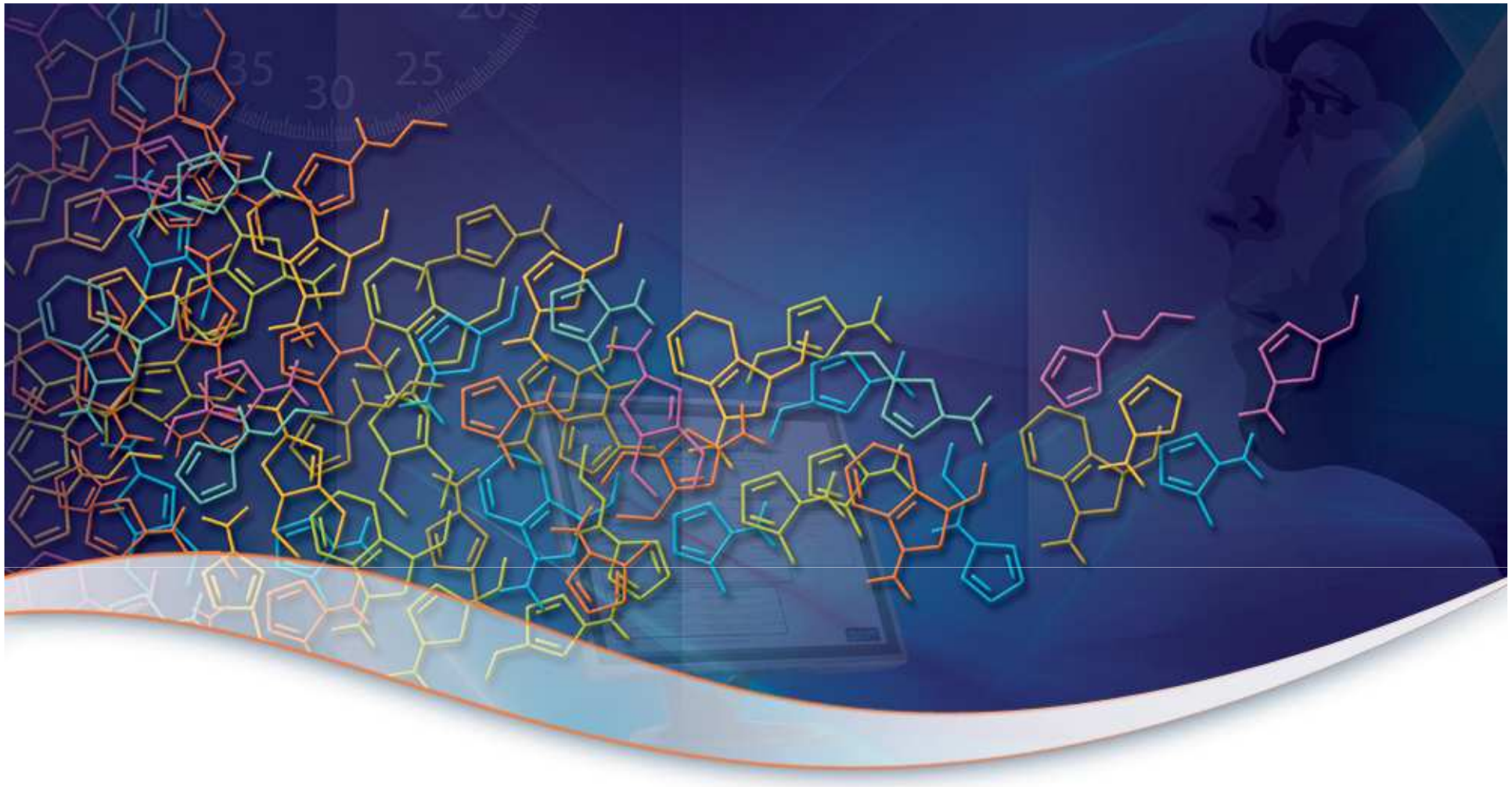

Mechanistic Models to Simulate Dose Response of IgE Suppression Following Dosing of Anti-IgE Monoclonal Antibodies

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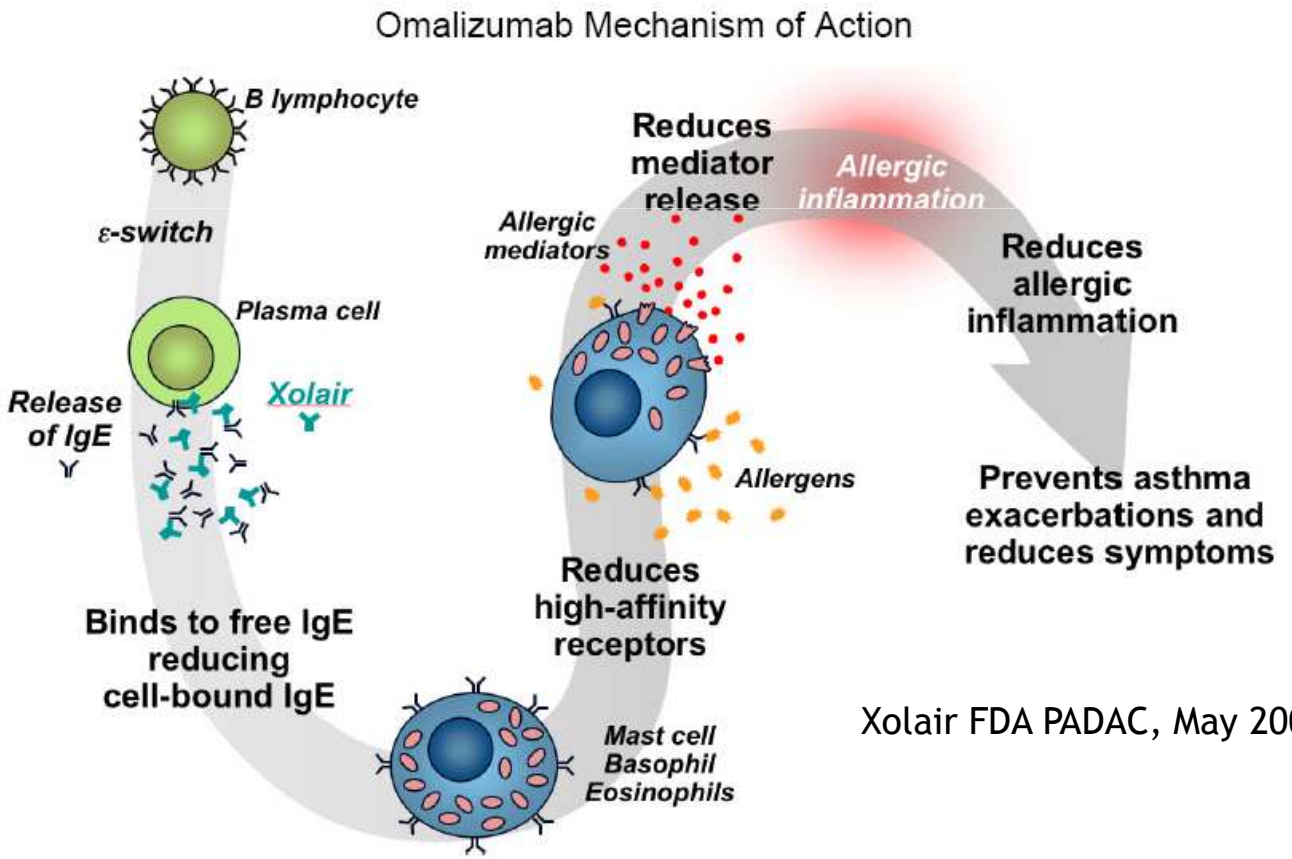
Omalizumab (Xolair™) is a recombinant humanized anti-IgE antibody

Omalizumab inhibits the activity of IgE

Omalizumab is approved in the treatment of moderate to severe persistent asthma for adults and adolescents (≥12 y)



Xolair FDA PADAC, May 2003, Figure 1

Key questions and objective

Key questions

- Is there a potential to develop a new anti-IgE antibody with enhanced affinity to treat the Omalizumab non-treatable population?
- What is the minimum effective dose in the most “difficult to treat” portion of the population?

Objective: Simulate dose response of IgE suppression for anti-IgE monoclonal antibodies such as Omalizumab versus higher affinity antibodies

Available information: existing models

Two published instantaneous equilibrium drug-IgE binding models for Omalizumab: Hayashi et al., Br J Clin Pharmacol, 2007 and Lowe et al., Br J Clin Pharmacol, 2009

$$\frac{dS}{dt} = -k_a S$$

$$\frac{dX_T}{dt} = k_a S - \frac{CL_X \cdot X}{V_X} - \frac{CL_C \cdot C}{V_C}$$

$$\frac{dE_T}{dt} = R - \frac{CL_E \cdot E}{V_E} - \frac{CL_C \cdot C}{V_C}$$

Lowe et al., 2009

$$C = \left(\frac{K_d V_X V_E}{V_C} + X_T + E_T\right) - \sqrt{\left(\frac{K_d V_X V_E}{V_C} + X_T + E_T\right)^2 - 4 X_T E_T} \Big/ 2$$

where

$$X = X_T - C$$

$$E = E_T - C$$

$$K_d = K_{d0}\left(\frac{X_T}{E_T}\right)^{\alpha}$$

and S is the subcutaneous site; X_T and E_T are molar masses of total omalizumab and IgE; X and E are free omalizumab and IgE; k_a is the absorption rate constant; R is the rate of production (or expression) of IgE; CL_n and V_n are the clearances and volumes of free omalizumab, free IgE and the complex; K_d is the equilibrium binding constant, and α is the change in the affinity of binding between omalizumab and IgE as a function of the molar ratio of total omalizumab to total IgE.

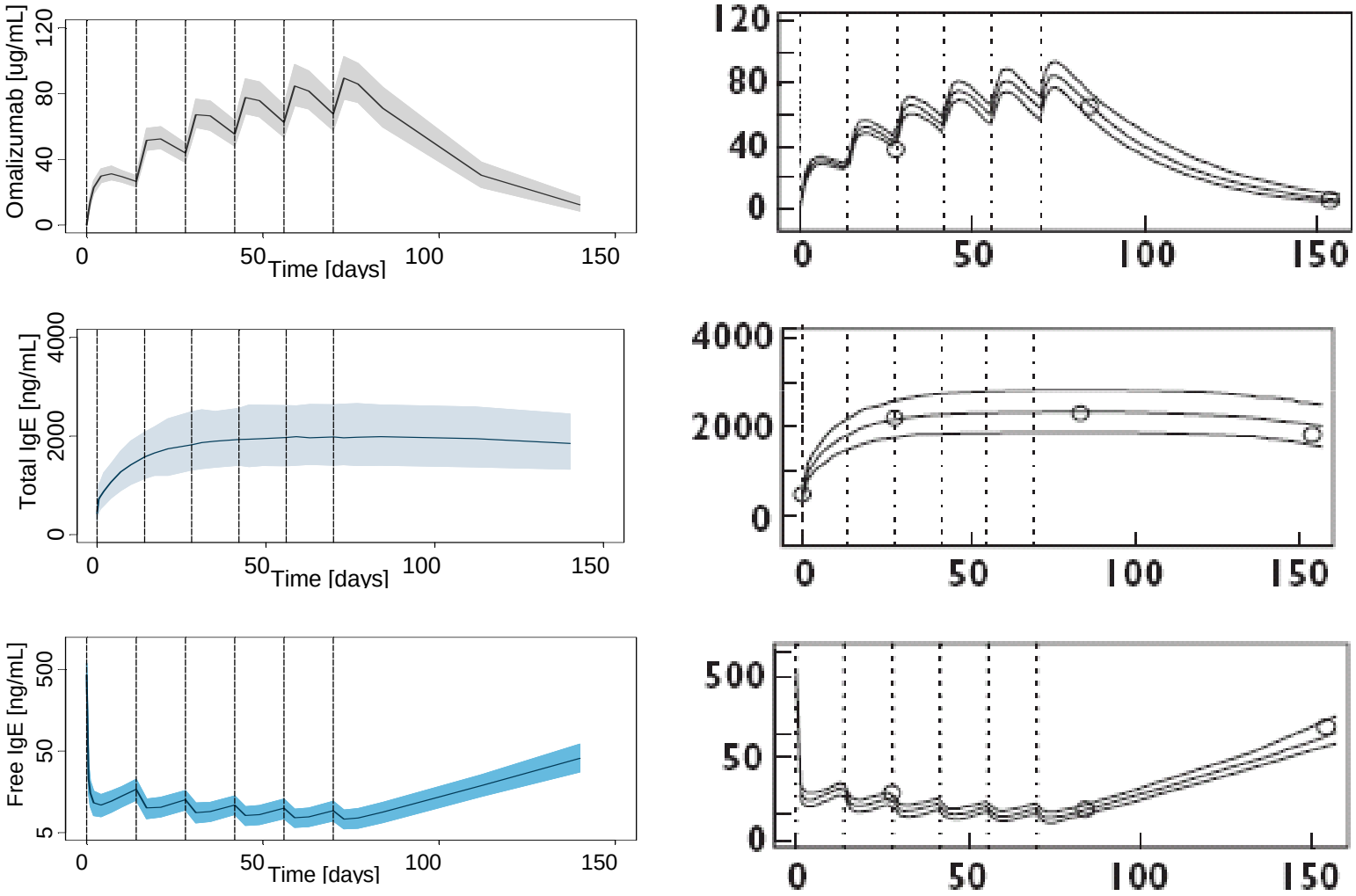
Available information: clinical information

Clinical data on another 2nd generation anti-IgE monoclonal antibody HAE1 showed that with an enhanced affinity, the expected fold reduction in dose is limited to roughly 2-fold (Putnam et al., AAPS J, 2008)

The dosing rationale for Omalizumab is based on a target average free IgE level of 25 ng/mL which should ensure that 95% of patients achieve free IgE level <50 ng/mL (Xolair FDA PADAC, May 2003)

Published models have been successfully implemented

Omalizumab 225 mg q2w: 95% prediction interval of median (18 subjects, 1000 replicates)



Hayashi et al., 2007, Figure 3

Model based simulations according to the EU licensed table (Lowe et al.)

Baseline IgE (ng ml⁻¹)	(IU ml⁻¹)	(c) EU licensed table (for bodyweight and IgE range studied) Body weight (kg) >30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
72.6–242	30–100	75	150	150	150	150	150	300	300
>242–484	>100–200	150	300	300	300	300	300	450	600
>484–726	>200–300	225	300	300	450	450	450	600	750
>726–968	>300–400	300	450	450	450	600	600		
>968–1210	>400–500	450	450	600	600	750	750		
>1210–1450	>500–600	450	600	600	750				
>1450–1690	>600–700	450	600	750					
>1690–1940	>700–800								
>1940–2180	>800–900								
>2180–2420	>900–1000								
>2420–2660	>1000–1100								

q4w regimens

q2w regimens up to 750 mg over 4 weeks: 375 mg q2w

Non treatable

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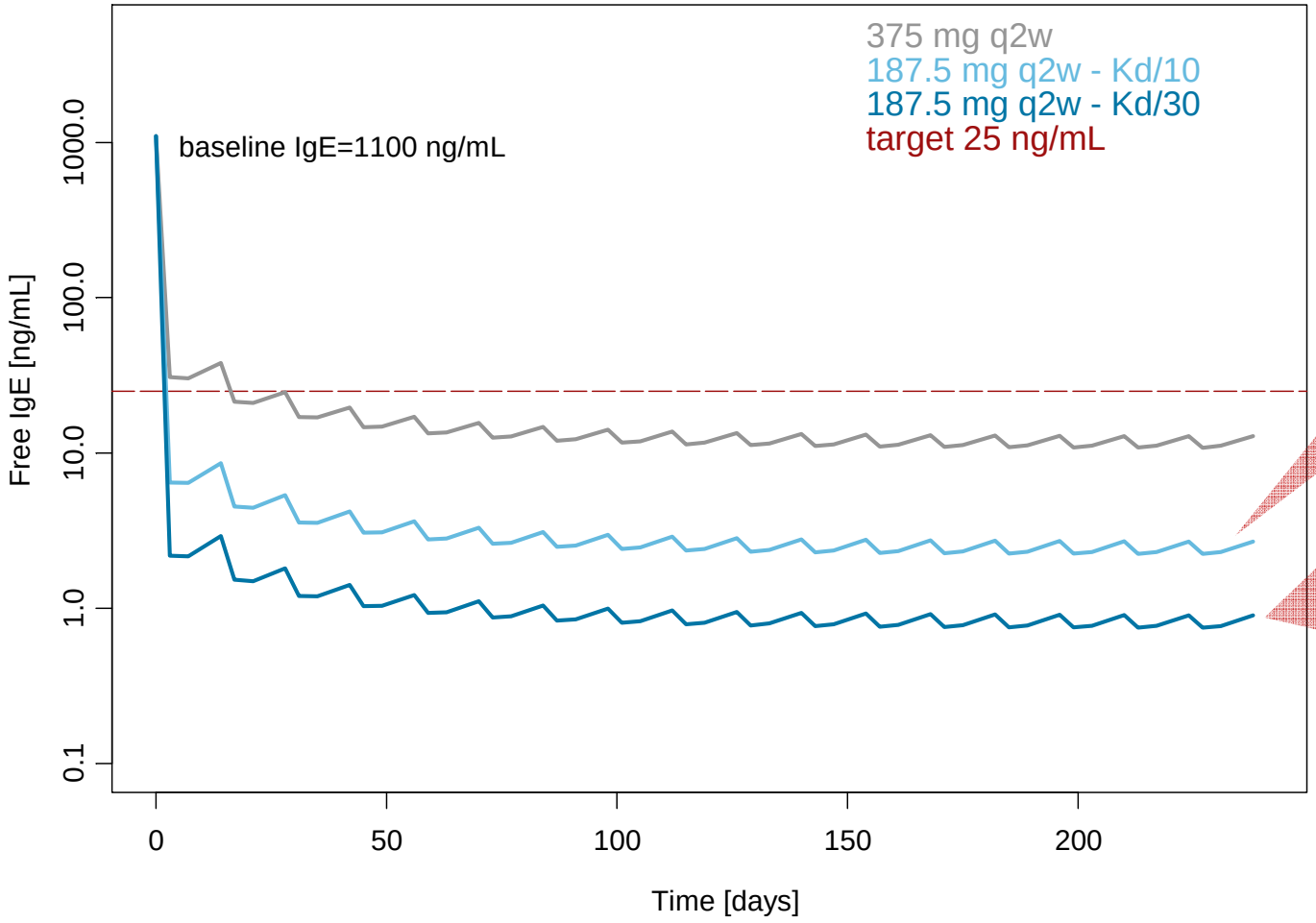
Model based simulations based on Lowe et al. tend to confirm the EU licensed table and the Omalizumab dosing rationale

EU Table: percentage of patients achieving target free IgE<50 ng/mL
based on a pre dose steady state free IgE level (week 29)

	Body weight							
Baseline IgE (ng/mL)	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
72.6-242	**q4w**				93.5		98.2	
>242-484	94.3							
>484-726			93.4	98.5				97.9
>726-968			97.9	96.3				
>968-1210	q2w					97.7		
>1210-1450					97.1	95.6		
>1450-1690		97.8						83.5
>1690-1940			97.5					
>1940-2180				94.6	92.3		84.5	
>2180-2420		97.8				88.2		
>2420-2660					89.0			67.1

According to this rationale and based on the model from Lowe et al., the treatable population with Omalizumab 375 mg q2w could be a little bit expanded to higher baseline IgE values and higher body weights than those mentioned in the EU-licensed table (Lowe et al.)

However deterministic simulations with the instantaneous equilibrium models (Lowe et al.) denoted the need for a physiological model for PK-PD translation across anti-IgE antibodies with various affinities



A much more than 2-fold reduction in dose expected with a 10-fold enhanced affinity

No apparent saturation on free IgE suppression expected with a further enhanced affinity

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Switch to a Target Mediated Disposition model

The Target Mediated Disposition model (Agoram et al. Br. J. Clin. Pharmacol, 2009) was implemented and extended as follows:

Units: nmol, L, d
X: free Omalizumab amount
$Conc_E$ and $Conc_C$: free IgE and complex conc.

$$\frac{dS}{dT} = -ka.S$$

$$\frac{dX}{dT} = ka.S - Kon.X.Conc_E - \frac{CLx}{Vx}.X + Koff.Vx.Conc_C$$

$$\frac{dConc_E}{dT} = -Kon.\frac{X}{Vx}Conc_E - \frac{CLe}{Ve}.Conc_E + \frac{R}{Ve} + Koff.Conc_C$$

$$\frac{dConc_C}{dT} = Kon.\frac{X}{Vx}Conc_E - \frac{CLc}{Vc}.Conc_C - Koff.Conc_C$$

$$S(0) = 0$$

$$X(0) = 0$$

$$Conc_E(0) = IgE_{baseline}$$

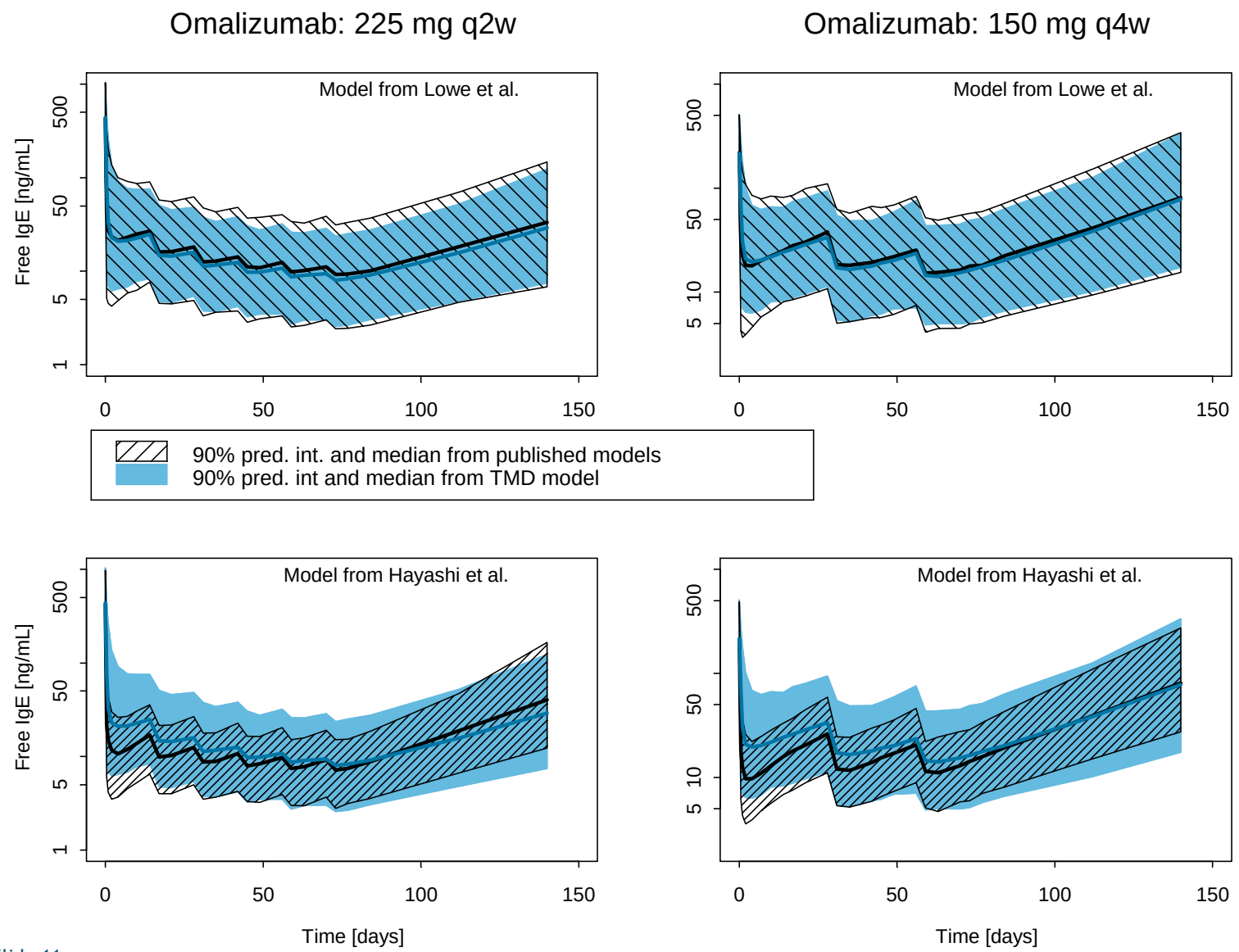
$$Conc_C(0) = 0$$

$$Koff = \frac{CLc}{Vc}.4$$

$$Kon = \frac{Koff}{Kd_0}.\left(\frac{Conc_E.Ve + Conc_C.Vc}{X + Conc_C.Vc}\right)^{\alpha}$$

- Parameterization in terms of Koff and Kon instead of Kd (Kd=Koff/Kon)
- Molar ratio (total Omalizumab/total IgE) implemented on Kon
- Parameter estimates, baseline IgE, correlations, covariates relationships from Lowe et al.
  - Estimated model parameters: CLx, CLc, Cle, Vx=Ve, Vc, R, ka, Kd_0, α

Simulations performed at usual Omalizumab dosing regimens with the TMD model are consistent with those from published instantaneous equilibrium models



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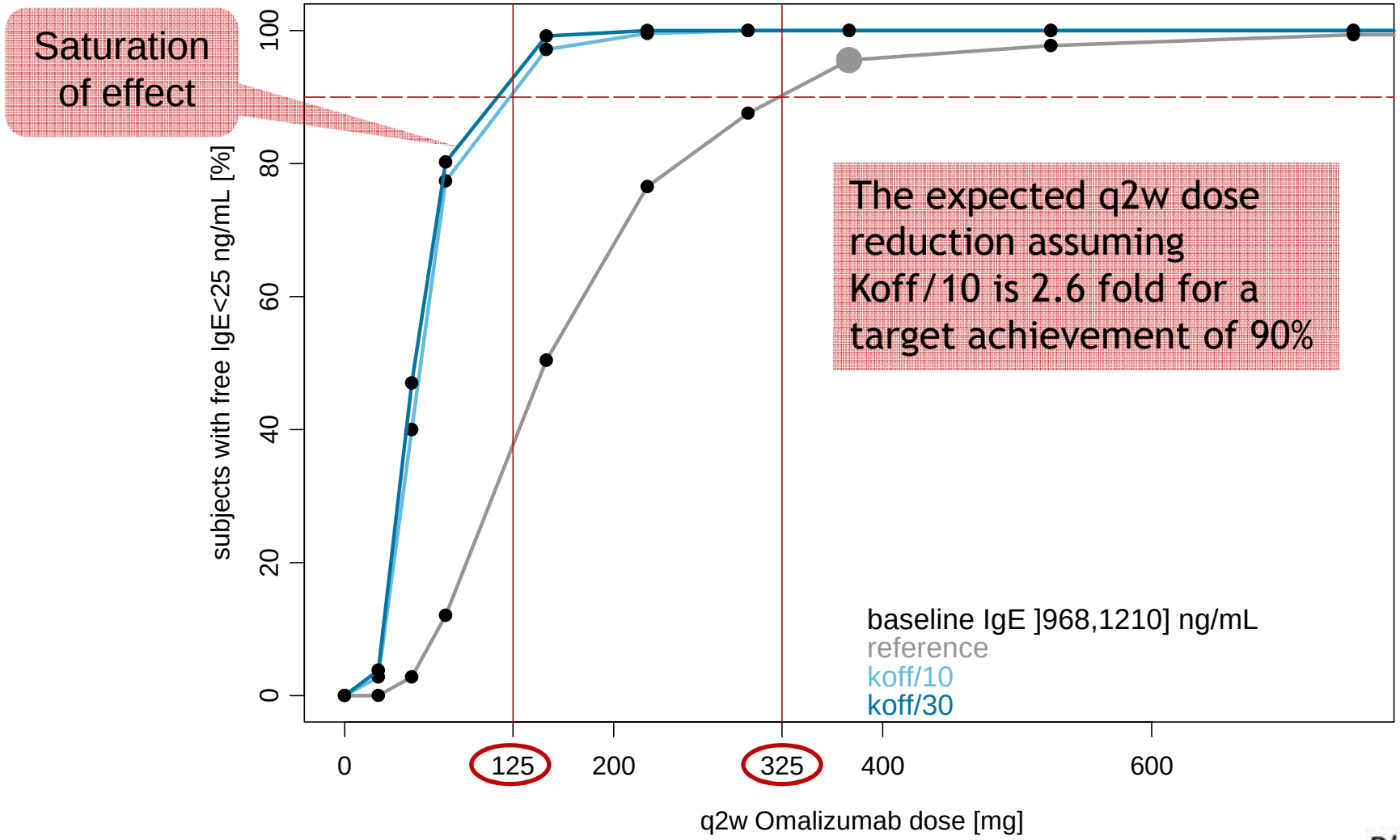
Based on the TMD model, a 10-fold reduction in Koff is expected to result in a 2 to 3-fold dose reduction



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Conclusions

Model based simulations using the model from Lowe et al. confirm the EU licensed table and the Omalizumab dosing rationale

A fully mechanistic TMD model is required for PK-PD translation across anti-IgE antibodies of different affinities

The TMD model seems to provide reliable results:

- In line with both published instantaneous equilibrium models
- In line with clinical data on a 2nd generation anti-IgE monoclonal antibody (Putnam et al.)

Assuming Koff/10, a dose of 225 mg q2w is expected to ensure a free IgE level <50 ng/mL in more than 95% of patients within the most "difficult to treat" portion of the population (highest body weight and baseline IgE values)

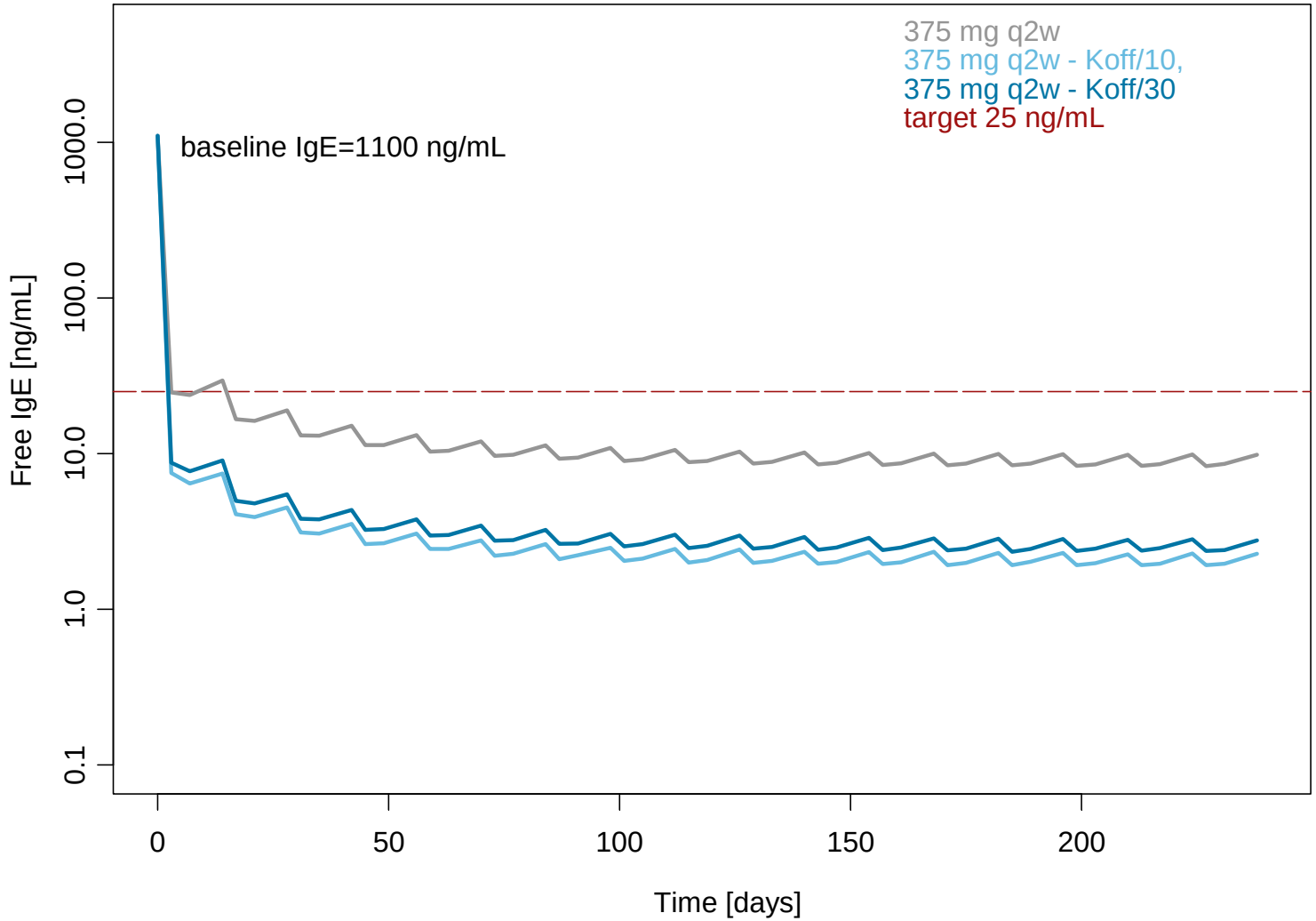
There is potential to treat a larger patient population with a higher potency anti-IgE antibody and a more convenient dosing paradigm

Back-up slides

Model based simulations based on Lowe et al. tend to confirm the EU licensed table and the Omalizumab dosing rationale

EU Table: mean pre dose steady state free IgE level (week 29)								
	Body weight							
Baseline IgE (ng/mL)	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
72.6-242	q4w				22		14.9	
>242-484	21.3							
>484-726			22.4	14.7				16.1
>726-968			16.5	18.8				
>968-1210	q2w					16.8		
>1210-1450					17.5	19.8		
>1450-1690		16.5						32.4
>1690-1940			17.2					
>1940-2180				21.4	23.9		31.9	
>2180-2420		17.1				28.7		
>2420-2660					27.3			45.7

For increased affinity the TMD model shows results consistent with the clinical data (Putnam et al.)



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