

# 非臨床における抗体薬物動態評価の効率化及び 体内動態を改善した改変抗体の創出に関する研究

**Optimization of preclinical PK evaluation of therapeutic  
antibodies and discovery of novel engineered antibodies with  
improved PK properties**

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# Acknowledgement



Gotemba laboratory  
(2008-2013, 2017-present)



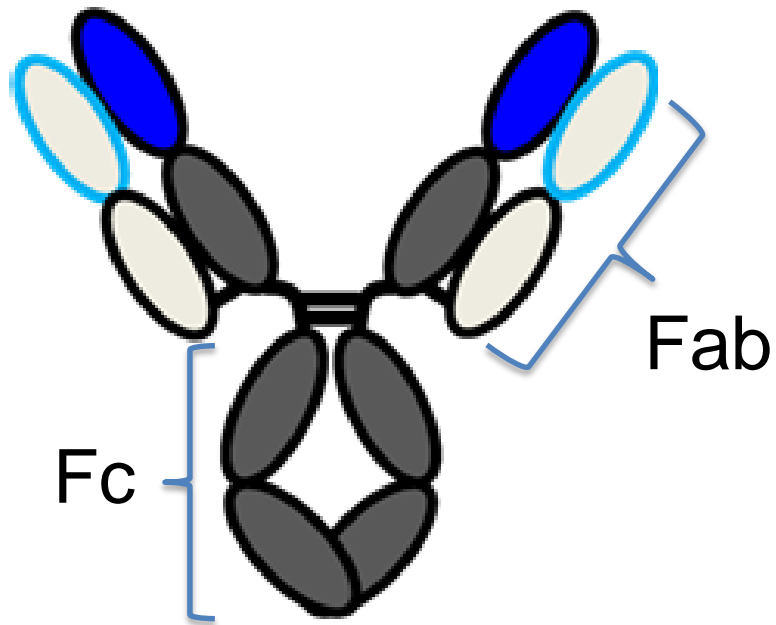
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Chugai Pharmabody Research in Singapore  
(2013-2017)

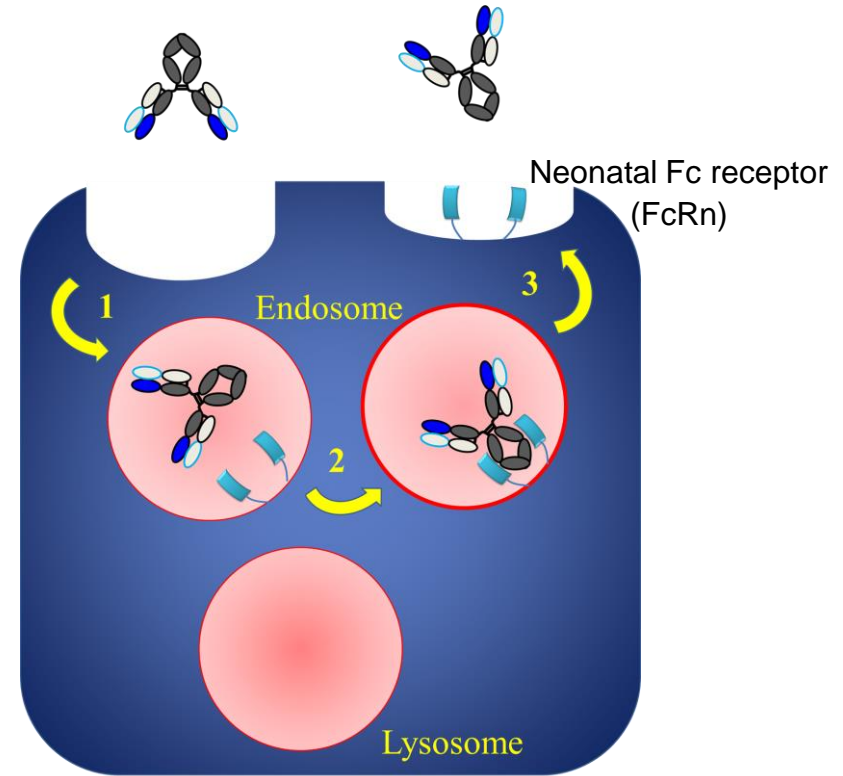


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# Structural and pharmacokinetic features of therapeutic monoclonal antibody



Fab : Binding to target antigen  
 Fc : Binding to Fc receptors and C1q



Long half-life due to FcRn mediated endosomal recycling : 5 - 25 days

# Issues in therapeutic antibody development



## 1. Frequent use of cynomolgus monkeys for PK evaluation

- ◆ Inter-species difference of FcRn binding
- ◆ Similar binding to human and cynomolgus monkey FcRn
- ◆ Stronger binding of therapeutic antibody to mouse FcRn compared to human FcRn

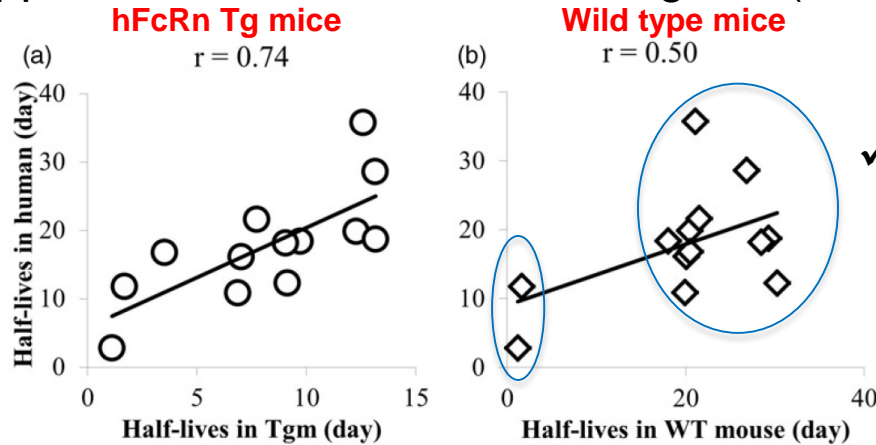
- ✓ Use **human FcRn transgenic mice** for rodent PK evaluation
- ✓ **Estimate CL and s.c. bioavailability (F) without i.v. data** in cynomolgus monkeys, reducing the number of cynomolgus monkeys used
- ✓ Establish **more accurate method of predicting human PK** using monkeys to maximize the value of monkey studies

# Optimization of preclinical *in vivo* study

## Mouse Study

Xenobiotica. 2014. 44(12):1127-34.

### Application of human FcRn transgenic (hFcRn Tg) mice



✓ hFcRn Tg mice can be used as *in vivo* high throughput animal to select candidate with better PK property

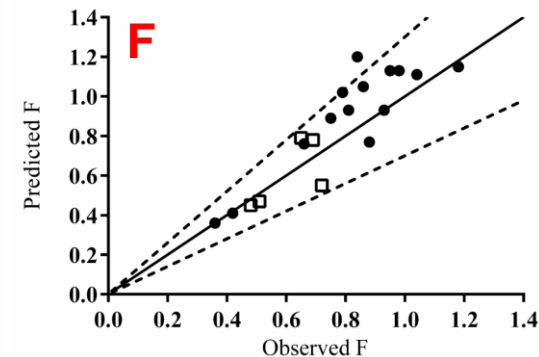
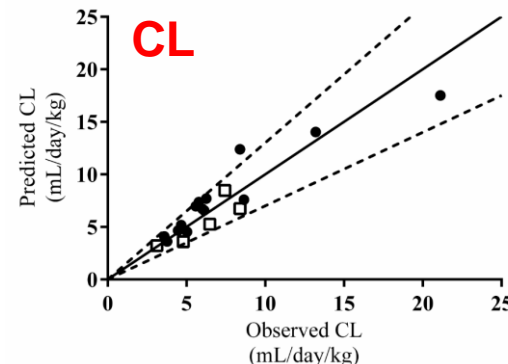
## Monkey Study

Xenobiotica. 2017. 47(3):194-201.

### Estimating CL and F with only s.c. data in cynomolgus monkeys

#### Strategy

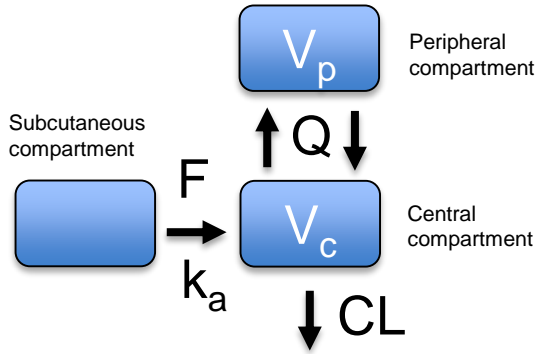
1. Fix Q (18.9 mL/day/kg), V1 (40.3 mL/kg), V2 (45.1 mL/kg) by geometric mean of reported 23 antibodies
2. Fit CL and F using PK profile after s.c. injection



✓ No need for i.v. data to estimate CL and F in cynomolgus monkeys

# Human PK profile prediction after i.v. and s.c. injection from cynomolgus monkeys

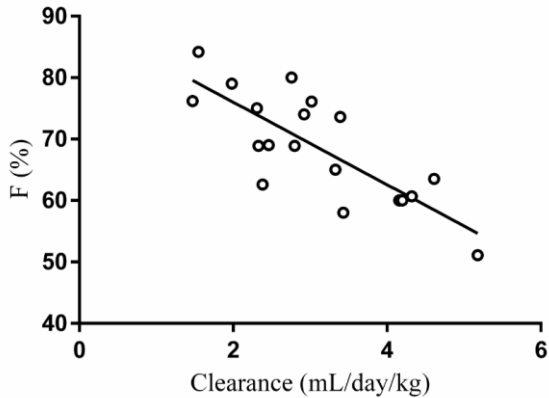
## 2 compartment model with s.c. compartment



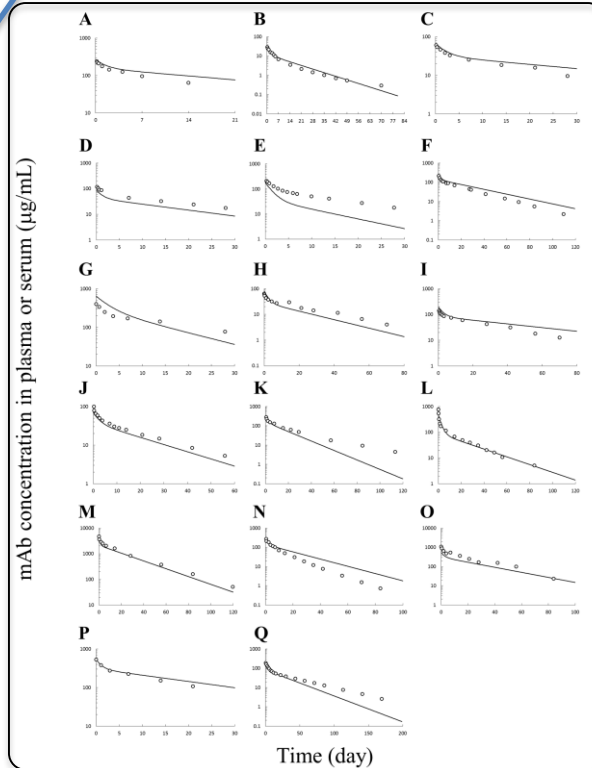
CL, Q,  $V_c$ ,  $V_p$  : allometric scaling using optimized exponents from monkeys

$k_a$  : Geometric mean of 19 reported antibodies in human

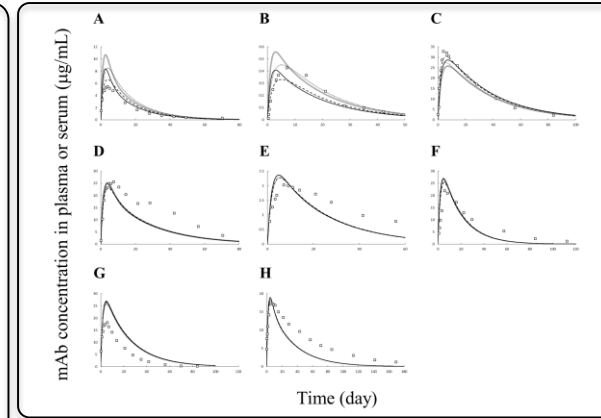
F : Estimation from predicted CL in humans



### Prediction of i.v. data



### Prediction of s.c. data



✓ High predictability of PK profile after both i.v. and s.c. injection in humans

# Issues in therapeutic antibody development

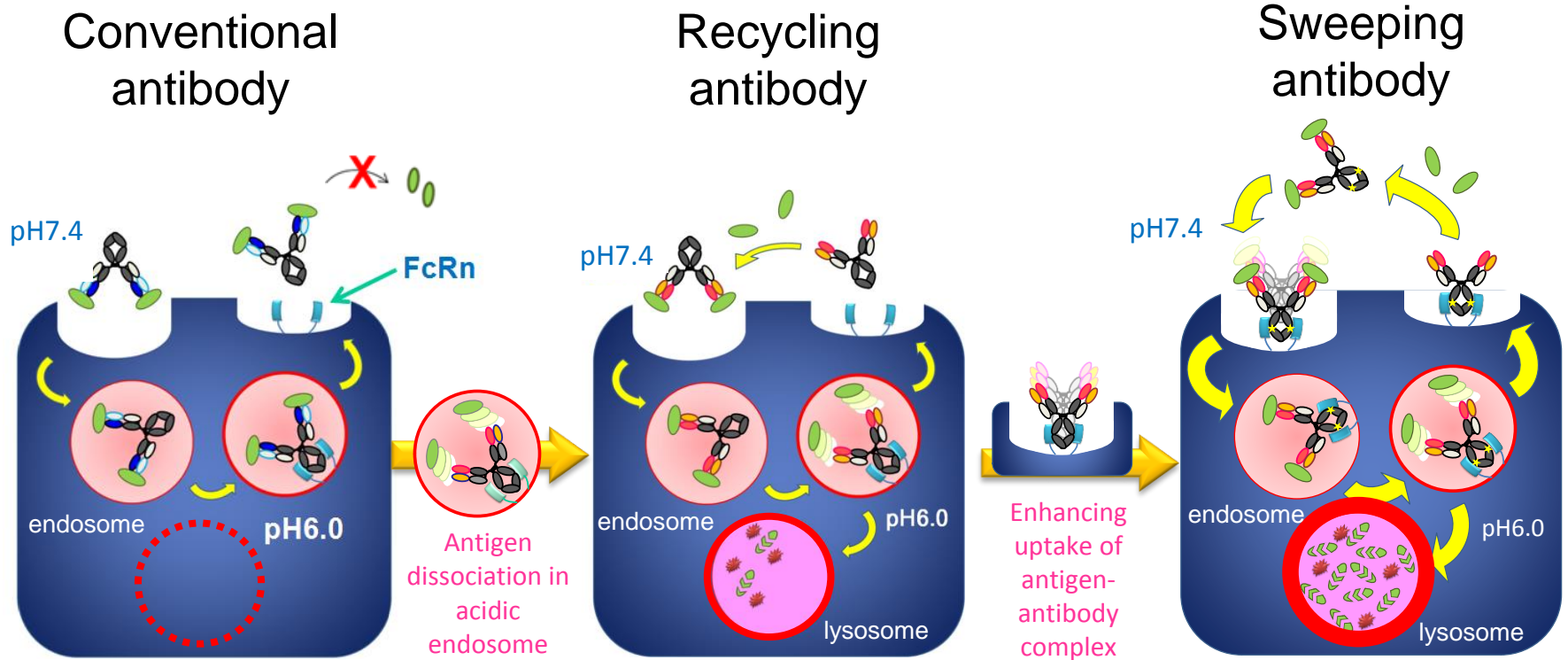


## 2. Severe competition in development of therapeutic antibodies

- ◆ Global high sales of several therapeutic antibodies
- ◆ Generalization of antibody generation methodology
- ◆ Limited target antigens in extracellular space

- ✓ Differentiate by developing novel antibody engineering technologies (recycling antibody and sweeping antibody)
- ✓ Efficiently select targets for novel antibodies using mechanistic PKPD analysis
- ✓ Generation of subcutaneously injectable anti-complement C5 recycling antibody, SKY59/Crovalimab

# Recycling antibody and sweeping antibody



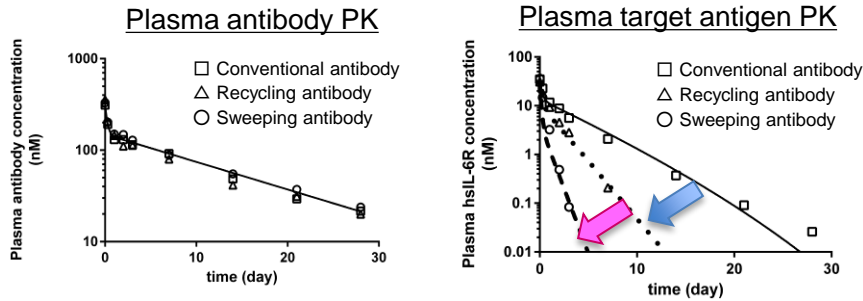
Drug Metab Pharmacokinet. 2019. 34(1):25-41.  
 Immunol Rev. 2016. 270(1):132-51.  
 PLoS One. 2013. 8(5):e63236.



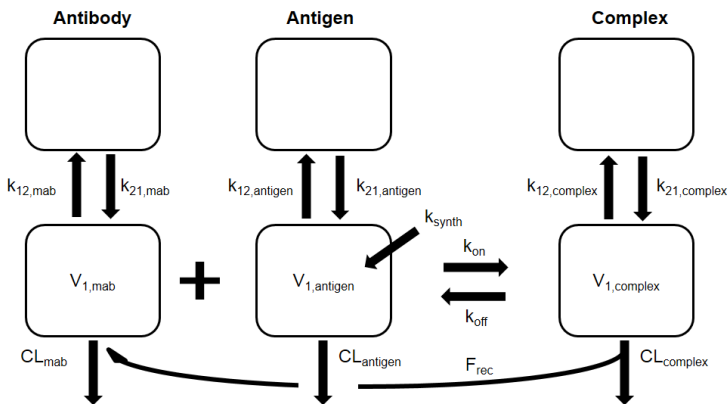
# Target antigen selection by target mediated drug disposition (TMDD) model based PKPD analysis

## hFcRn Tg mice PKPD study

- Intravenous injection of mixture of antibody (conventional, recycling, sweeping antibodies) and soluble target antigen

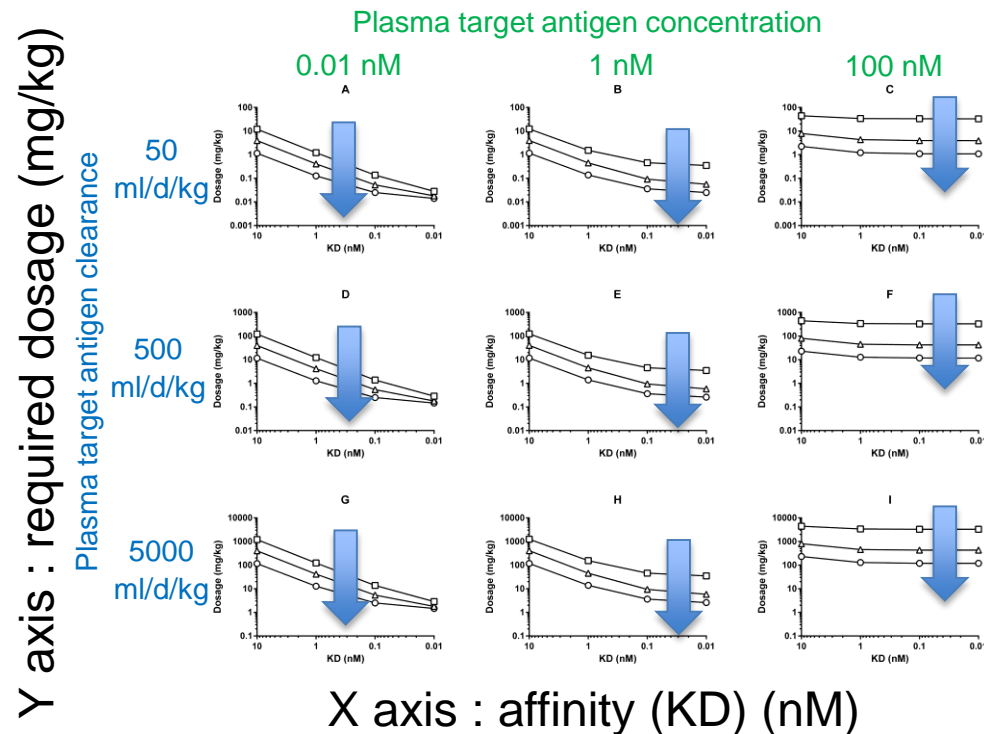


## TMDD model with recycling mechanism



## Simulation of required dosage to achieve 90% neutralization for 1 month for different antigen

- Conventional antibody
- △ Recycling antibody
- Sweeping antibody



- ✓ Antigen with high plasma concentration are more efficacious targets for recycling and sweeping antibody

# Generation of SKY59/Crovalimab, pH dependent anti-complement C5 recycling antibody

## Drawback of conventional C5 antibody

- High plasma C5 concentration: about 400 nM
- Conventional anti-C5 antibody (Eculizumab) requires high dosage (900-1200mg) and frequent i.v. injection (Q2W) in clinic.

Utilization of recycling antibody technology to generate subcutaneous injectable anti-C5 antibody.

## Generation of anti-C5 recycling antibody

CFA0305 from rabbit

Antibody engineering

- ✓ Humanization & deimmunization
- ✓ Optimizing C5-binding property
- ✓ Surface-charge engineering
- ✓ Improving stability

Variable region of SKY59

Human IgG<sub>1</sub> κ

Antibody engineering

- ✓ Silencing FcγR & C1q binding
- ✓ Enhancing FcRn binding at acidic pH
- ✓ Abrogating RF binding
- ✓ Reducing heterogeneity

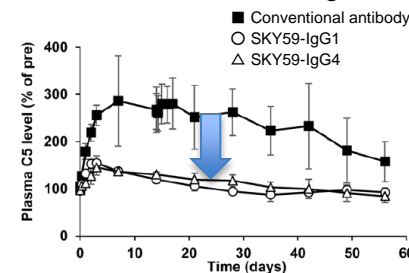
Constant region of SKY59



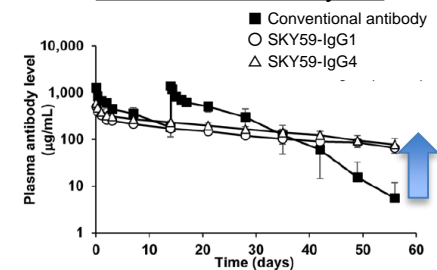
## Cynomolgus monkey PKPD study 1

Conventional antibody: 40 mg/kg i.v. at day 0 and 14  
SKY59: 20 mg/kg i.v. at day 0

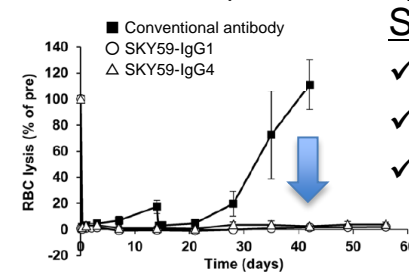
### A. Plasma C5 change



### B. Plasma antibody PK



### C. Plasma complement activity



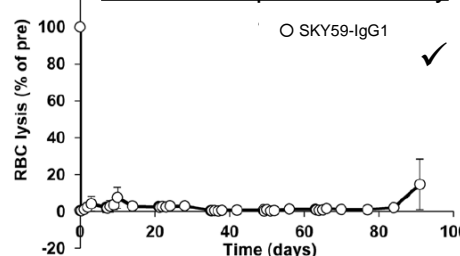
### SKY59

- ✓ Total C5 reduction
- ✓ Improved PK (CL and T<sub>1/2</sub>)
- ✓ Long lasting suppression of complement activity

## Cynomolgus monkey PKPD study 2

SKY59 : 5 mg/kg i.v. at day 0 and 2 mg/kg s.c. at day 7, 21, 35, 49, 63

### Plasma complement activity



- ✓ Complete suppression of complement activity by biweekly s.c. injection

# Summary

## Optimization of preclinical PK evaluation

- Use of hFcRn Tg mice for PK evaluation
- Estimation of F and CL without i.v. data in cynomolgus monkeys
- Accurate method of predicting human PK using cynomolgus monkeys

## Discovery of novel engineered antibodies (recycling antibody and sweeping antibody)

- Selection of target antigens using TMDD-based PKPD analysis
- Generation of SKY59/Crovalimab, a subcutaneously injectable anti-complement C5 recycling antibody

Innovation all for the patients



**CHUGAI PHARMACEUTICAL CO., LTD.**



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