

# SKY59, a Long-Acting, Self-Adminstrable Anti-C5 Antibody, Shows Good Safety and Efficacy in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

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# Overview

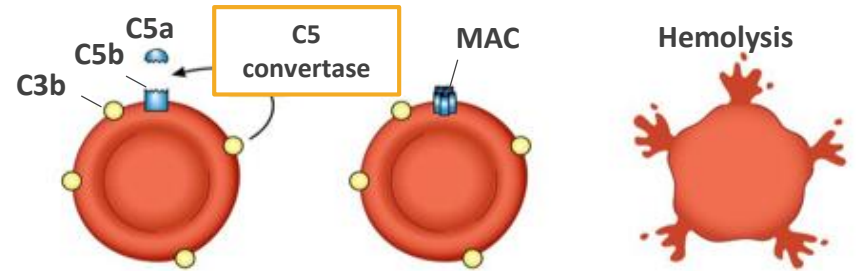
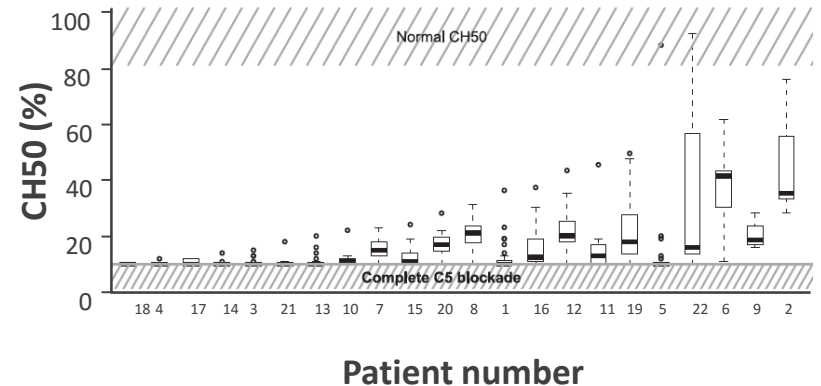
- **SKY59** is an engineered ***anti-C5 monoclonal antibody*** and was designed to support ***maximal C5 inhibition*** by optimizing:
  - ***Enhanced recycling*** of Ab through precision engineering (SMART)
  - ***Reduced C5 accumulation***
  - ***High solubility*** for ***low volume SC administration*** (1-4mL)
- PNH is known to respond to ***anti-C5 therapy***; however, ***breakthrough hemolysis*** and ***treatment burden*** continue to be an unmet need
  - SKY59 binds ***C5 with Arg885His*** polymorphism
  - SKY59 is ***long-acting*** and is ***self-administered subcutaneously***
- SKY59 was tested in ***naive*** and ***previously treated*** patients with PNH in the COMPOSER Phase 1/2 clinical trial

# PNH Treatment: The Unmet Needs

## Limitations of current treatment

- **IV infusion Q2W<sup>1</sup>**
- **Low eculizumab levels** were observed in roughly 16% of patient samples tested<sup>2</sup>
- **Return of hemolysis** with **breakthrough hemolysis**, **return of symptoms**, and **risk of thrombosis** thought to be related to **incomplete C5 blockade** towards the end of the dosing interval or due to infections<sup>2</sup>
- Not effective in patients with **C5 (Arg885His) polymorphism<sup>3</sup>**

## Hemolytic Activity Present in 49% of Eculizumab Treated Patients<sup>2</sup>



Adapted from Brodsky, *Blood*. 2017

1. SOLIRIS® (eculizumab). [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc; 2018. 2. de Latour RP et al. *Blood*. 2015; 125(5): 775-783. 3. Nishimura et al. *NEJM*. 2014; 13;370(7):632-9. 4. Brodsky, R. *Blood*. 2017; 129(8); 922-923

Abbreviations: CH50, 50% hemolytic complement; PNH, paroxysmal nocturnal hemoglobinuria; SNP, single nucleotide polymorphism; Q2W, every 2 weeks

# Precision Engineering (SMART) Elongates Half-Life of SKY59 and Enables SC Administration

## 1 High Affinity Binding

SKY59 is engineered to *optimize binding of C5* in the plasma through *affinity maturation*

## 2 Preferential Antibody Uptake (PI engineering)

SKY59 mAb charge is engineered to favor *increased endocytosis / recycling of antibody bound to 2 molecules of C5*

## 3 Acid-Sensitive Binding

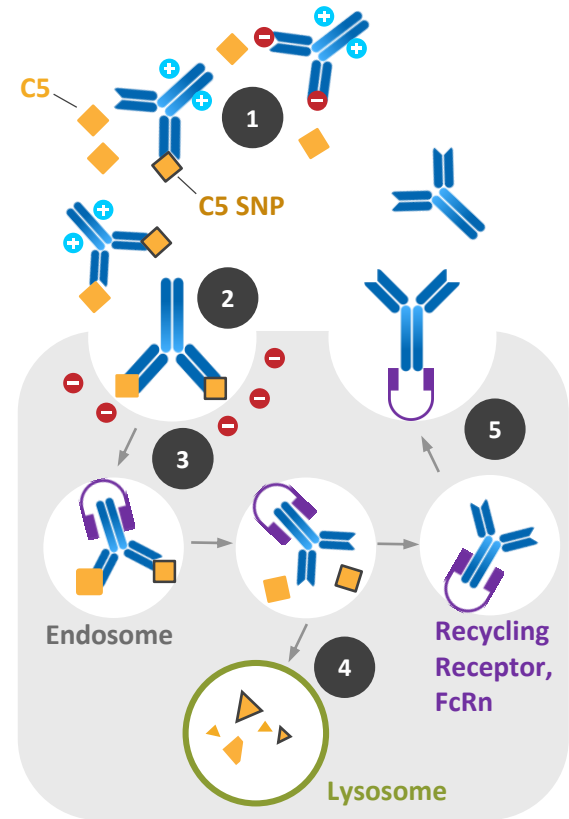
SKY59 is engineered to *dissociate from C5 in the acidic pH of the endosome*

## 4 Antigen Degradation

C5 is degraded in the lysosome

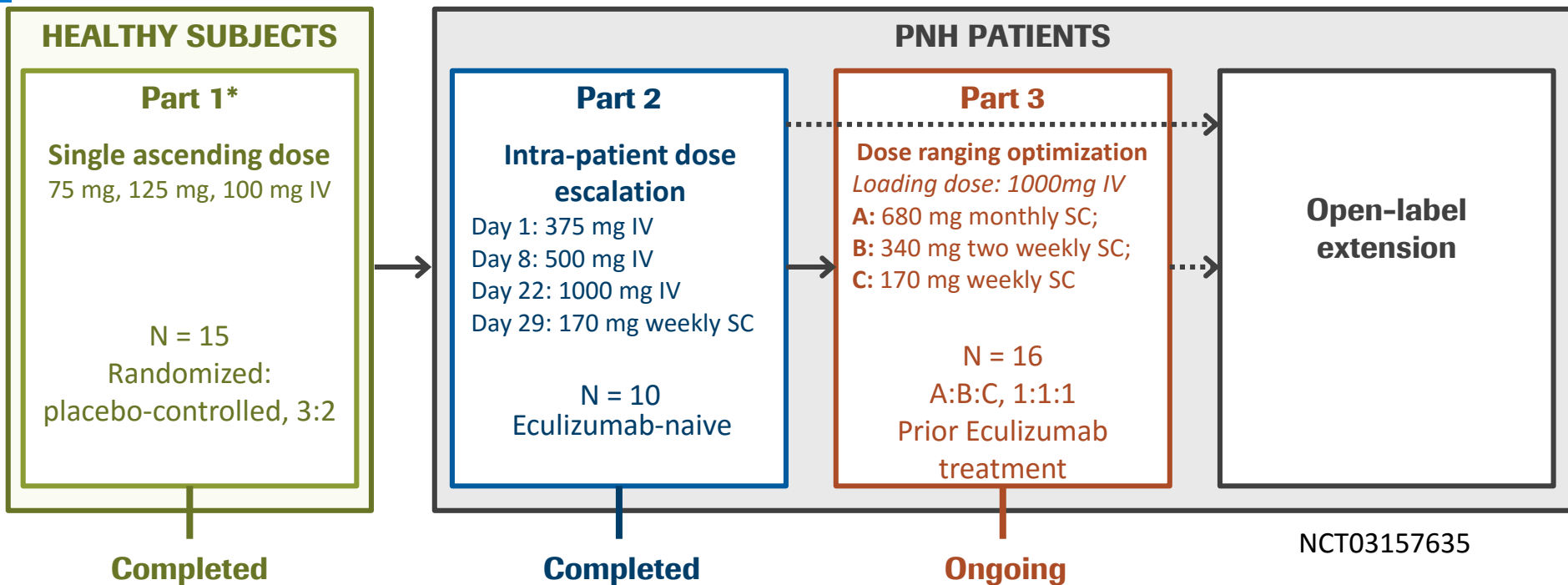
## 5 Antibody Recycling by FcRn engineering

SKY59 is *recycled and returned to the plasma* instead of being degraded; SKY59 mAbs are precision engineered to *favor binding to neonatal Fc receptor (FcRn)*; which protects antibodies from degradation



Adapted from Igawa T et al. *Biochim Biophys Acta*. 2014;1844:1943-1950.

# COMPOSER: SKY59 Phase 1/2 Three Part Adaptive Clinical Trials

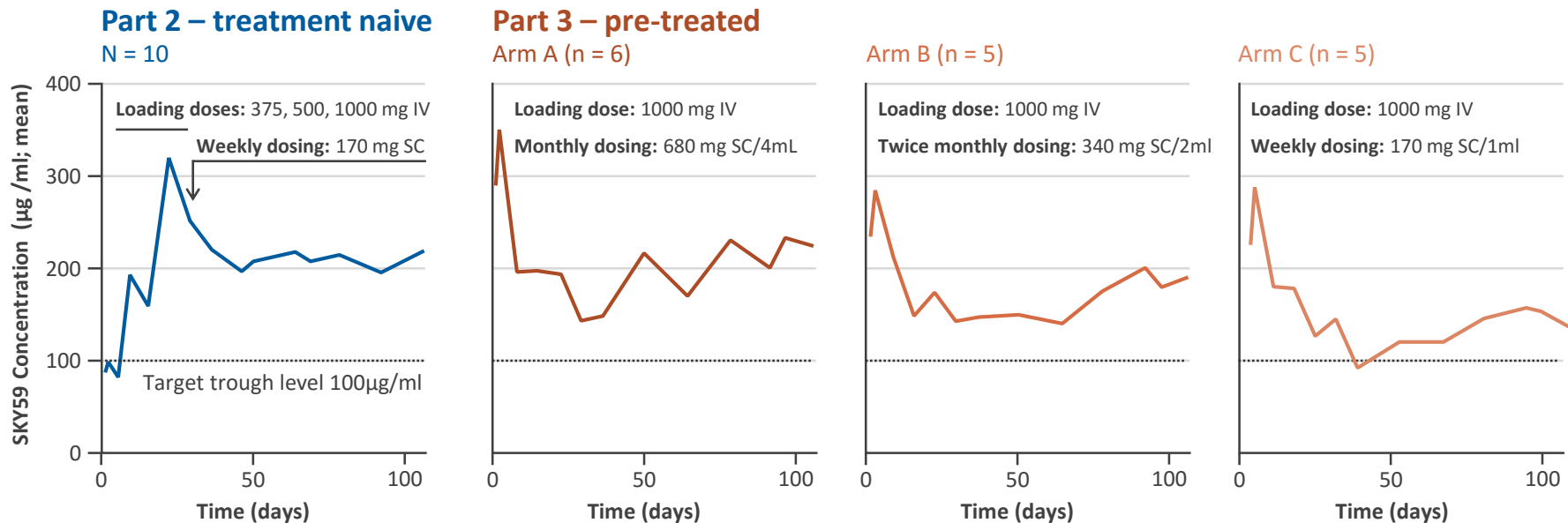


- **Primary Endpoints (Parts 2 and 3):** *Safety and tolerability of SKY59, pharmacodynamic effect* of multiple doses SKY59 on *complement activity* in patients
- **Secondary Endpoints (Parts 2 and 3):** Change in *lactate dehydrogenase (LDH)*, proportion of patients with *stabilized hemoglobin levels*, and *proportion of transfusion-free patients*

# Baseline Characteristics of Patients in Study

Patient Characteristics		Treatment-Naive (Part 2)	Eculizumab Pre-Treated (Part 3)			
		Total N = 10	Total N = 16	Arm A (Q4W) n = 6	Arm B (Q2W) n = 5	Arm C (QW) n = 5
Sex	Male	6 (60%)	10 (62.5%)	1 (20%)	5 (100%)	4 (66.7%)
	Female	4 (40%)	6 (37.5%)	4 (80%)	0 (0%)	2 (33.3%)
Mean age, years (SD)		53.9 (11.8)	50.3 (11.8)	50.4 (11.8)	54.6 (14.8)	46.5 (13.7)
Race	White	7 (70%)	7 (43.8%)	2 (40%)	2 (40%)	3 (50%)
	Asian	3 (30%)	6 (37.5%)	2 (40%)	2 (40%)	2 (33.3%)
	Unknown		3 (18.8)	1 (20%)	1 (20%)	1 (16.7%)
C5 polymorphism		1	1	0	0	1
Mean treatment expo, days (SD)		316 (135)	174 (119)	168 (123)	214 (119)	145 (127)
Clone size [%] (SD)		80 (18)	85 (14)	94 (8)	82 (25)	80 (13)
LDH [U/L] (SD) (ULN=210 U/L)		1160 (608)	315 (225)	238 (54)	346 (215)	353 (323)
Hemoglobin [g/L] (SD)		95.2 (14.7)	102.8 (17.0)	98.6 (4.9)	95.4 (9.1)	112.5 (24.5)

# Subcutaneous Dosing is Supported by SKY59 Pharmacokinetics

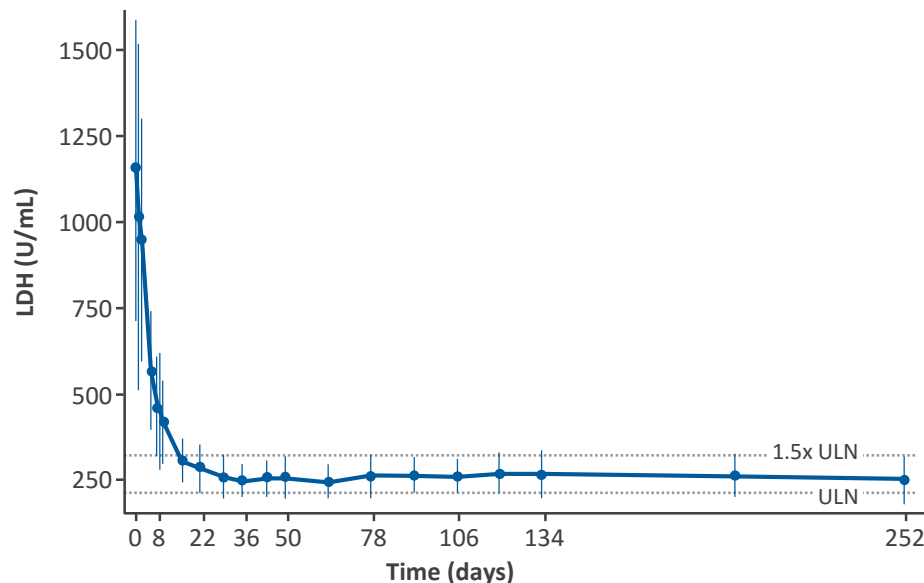


## Part 2 and 3 SC Dosing

- *SC bioavailability estimated at 100%*
- *Median terminal  $t_{1/2}$  estimated at 25 days*
- *Dose proportional exposure*
- *No neutralizing ADA*

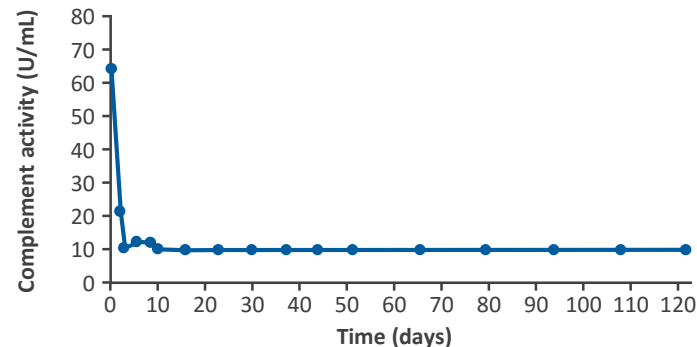
# SKY59 Completely Blocks Complement Activity and Decreases LDH in Treatment-Naive PNH Patients (Part 2; N=10)

## Mean LDH Levels

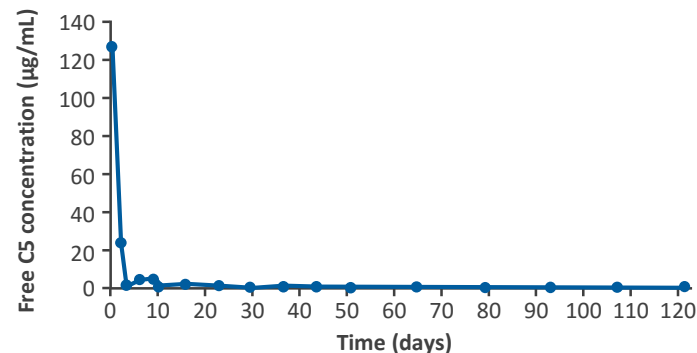


Upper limit of normal (ULN) = 210 U/mL

## Mean Terminal Complement Activity (LIA assay)



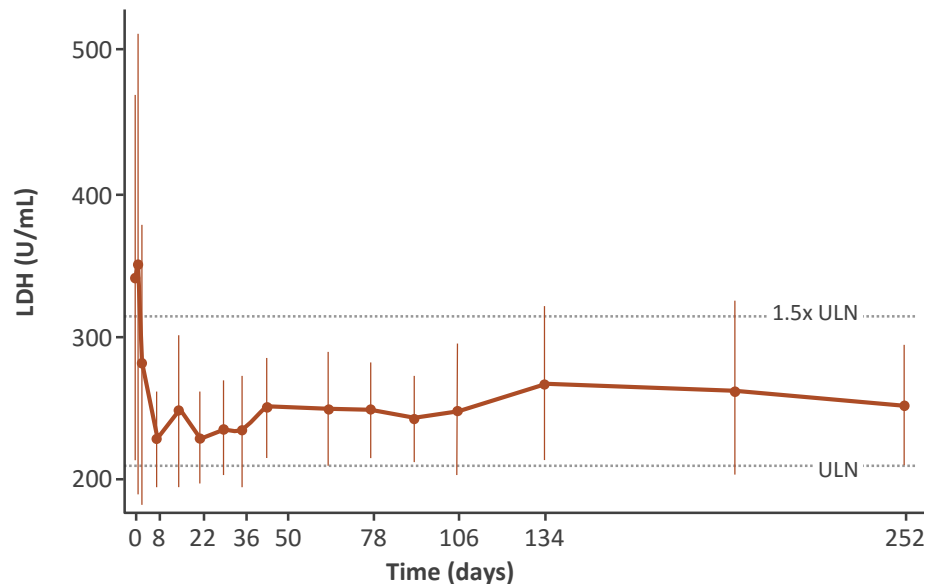
## Mean Free C5 Concentration





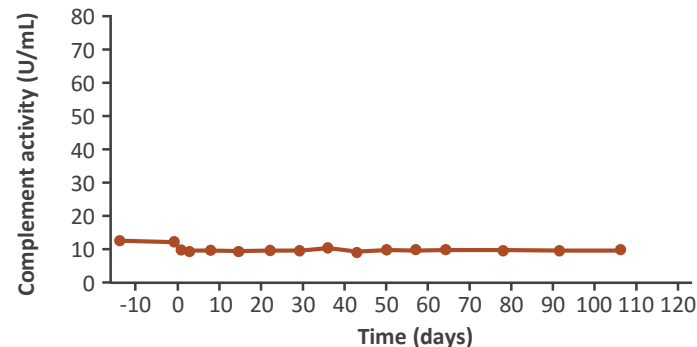
# SKY59 Completely Blocks Complement Activity in Eculizumab Pre-Treated Patients and Maintains LDH levels (Part 3; N=16)

## Mean LDH Levels

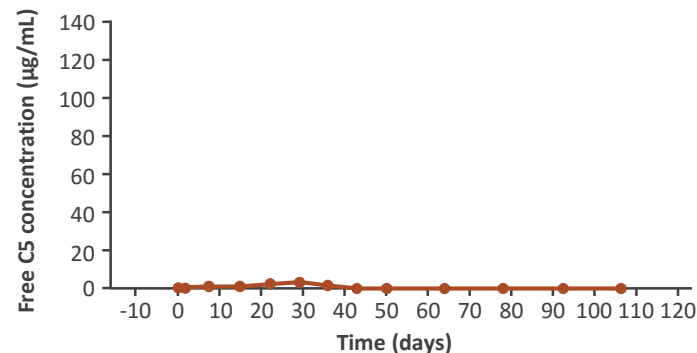


Upper limit of normal (ULN) = 210 U/mL

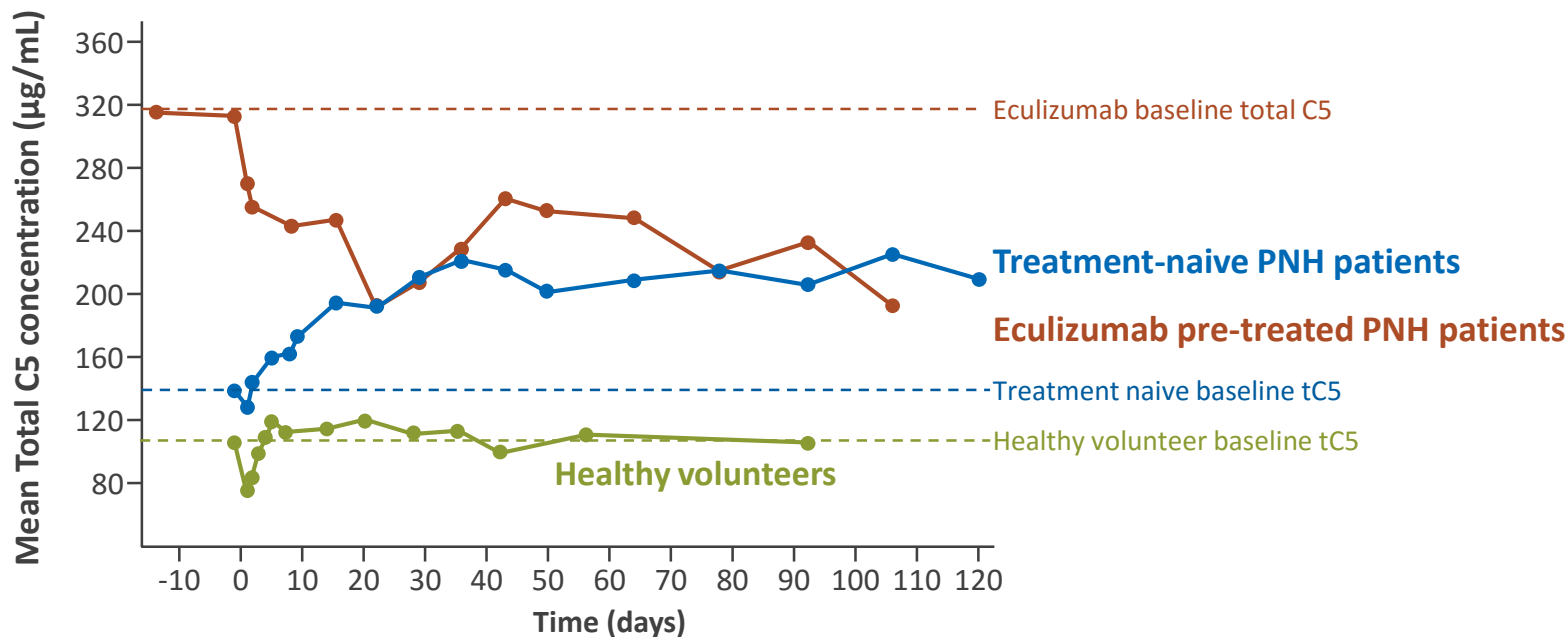
## Mean Terminal Complement Activity (LIA assay)



## Mean Free C5 Concentration



# Mean Total C5 (tC5) in Healthy Volunteers, Treatment-Naive and Eculizumab Pre-Treated Patients

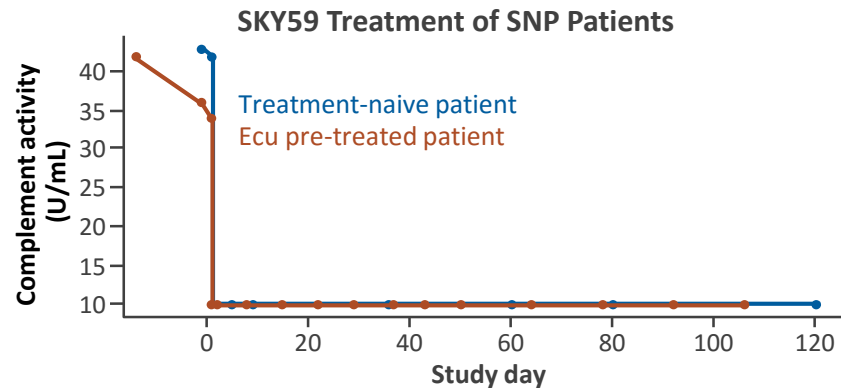
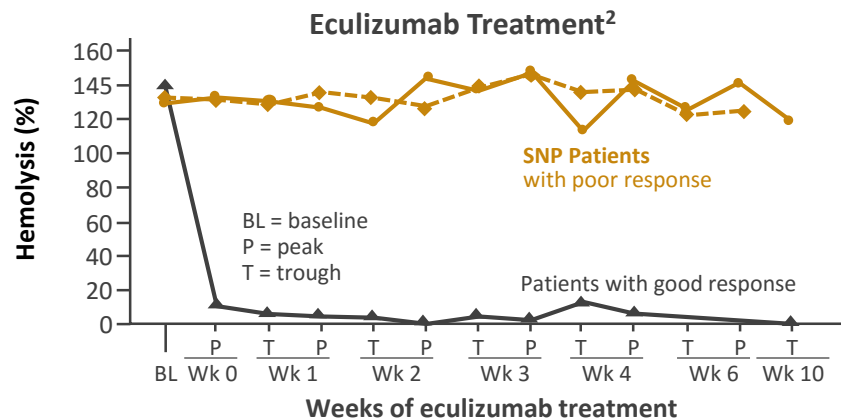
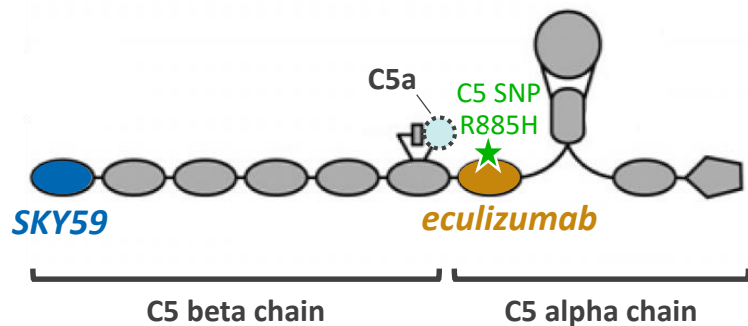


- *Limited accumulation of tC5 in treatment-naive patients*
- *Reduction of tC5 in eculizumab pre-treated patients*

# SKY59 is Effective in Patients With C5 Polymorphism Who do not Respond to Eculizumab

- SKY59 binds to a **different C5 binding site** than eculizumab and ravulizumab<sup>1</sup>, and **blocks hemolysis** in patients who have a **single missense C5 heterozygous mutation**

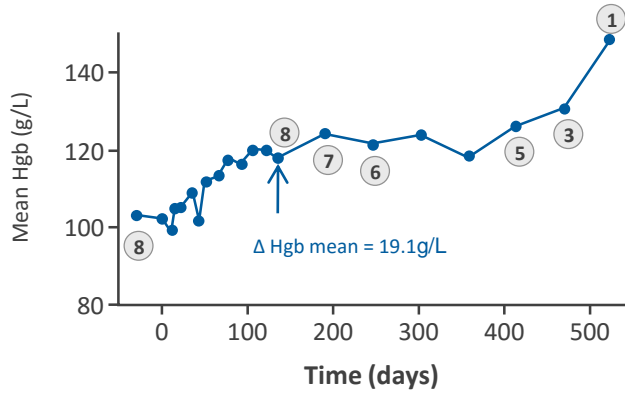
## SKY59 Binding Region



# Hemoglobin Response in subgroups of COMPOSER Patients

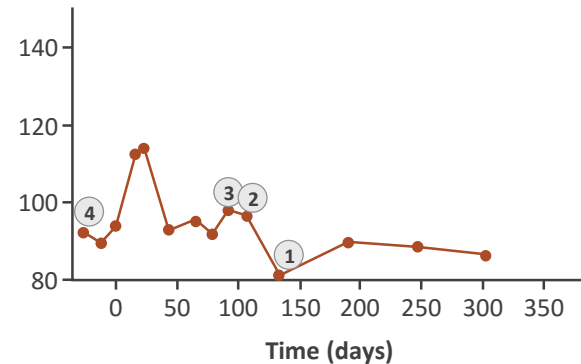
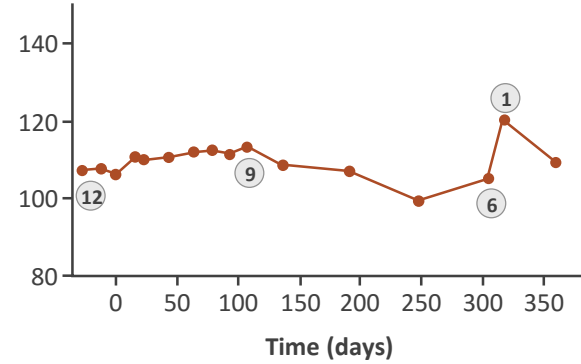
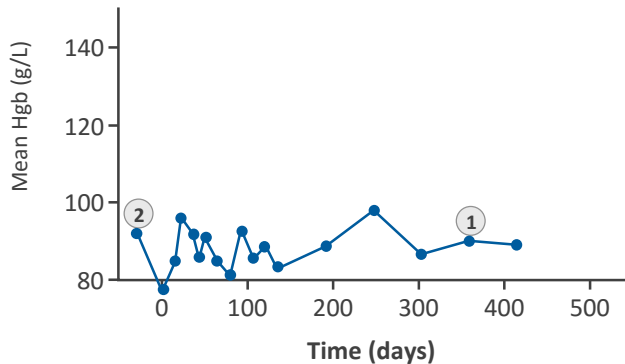
## Part 2 – Treatment-Naive

On SKY59 treatment  
transfusion  
independent



## Part 3 – Pre-Treated

On SKY59 treatment  
Transfusion  
dependent



# SKY59 Demonstrates Good Tolerability and Safety

Number of Patients with Event	Treatment-Naive		Eculizumab Pre-Treated	
	Mild	Moderate	Mild	Moderate
Hypersensitivity				
Infections and infestations	4	1	5	1
Musculoskeletal and connective tissue disorders	1	3	3	
Nervous system disorder – all AEs		2	5	1
Nervous system disorder – headache only		2	1	1
Gastrointestinal disorders	2	1	3	
General disorders and administration site conditions	1	1	3	
Injury, poisoning, and procedural complications	1	1	2	
Investigations		2	1	
Respiratory, thoracic, and mediastinal disorders	1	1	3	
Blood and lymphatic system disorders				2
Renal and urinary disorders			2	
Hepatobiliary disorders			1	
Cardiac disorders		1		
Ear and labyrinth disorders	1			
Vascular disorders				1
Skin and subcutaneous tissue disorders	1	1	4	
Serious AEs (all non-related)		1		1
Related AEs	1	1	6	2

Abbreviation: AE, adverse event:

SAE: Part 2: Atrial fibrillation and Abdominal Pain; Part 3: Hemolysis at study day 15;

## SKY59: Switching from Eculizumab is Feasible

- **16 patients** were switched from *eculizumab* to *SKY59*
- As expected, **transient development** of **drug-target-drug complexes (DTDC)** was **observed in all switch patients**
- **Two non-serious, non-severe skin adverse events** likely related to DTDC were observed in **2 patients**
- Both patients **continued to receive SKY59** without interruption or recurrence

## Summary

- **SKY59** is *well tolerated and efficacious* in the treatment of *naive and eculizumab pre-treated PNH patients*
- Application of **SMART technology** leads to *favorable C5/PK ratio*, with *less total C5 accumulation* than current standard of care
- **Complete complement inhibition** was achieved for all patients on trial with *infrequent low volume SC dosing*
- **Good control of intravascular hemolysis** was shown along with *rapid reduction of LDH* in treatment-naive patients, and *maintenance of low levels of LDH* in patients previously treated with eculizumab
- **Efficacy and safety profile** support *continued development* and *initiation of pivotal trials*

# Thank you

*We thank*

**All patients  
and relatives**

*We thank*

**All participating sites,  
physicians, nurses and  
study personal**



# Paroxysmal Nocturnal Hematuria: Clinical Triad of PNH



Hemolytic Anemia

## Intravascular Hemolysis<sup>1,2</sup>

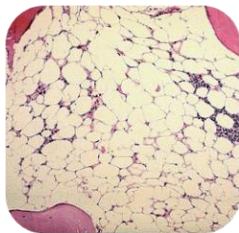
- Hemoglobinuria (only one third of patients as presenting symptom)
- Fatigue
- Dyspnea
- Abdominal pain
- Dysphagia
- Erectile dysfunction



Thrombophilia

## Thrombosis

- Involving unusual sites: liver or brain (venous), arterial
- 40% of all PNH patients<sup>1</sup>
- Leading cause of morbidity and mortality before introduction of anti-C5 treatment



Cytopenia

## Bone Marrow Failure<sup>3</sup>

- Variable degree from isolated thrombocytopenia to aplastic anemia
- Often precedes PNH
- Selection/growth advantage of PNH clones