

(1) Certara – CDDS, Basel, Switzerland; (2) Galderma R&D, Zug, Switzerland , (3) Galderma R&D, Dallas, USA

Pharmacokinetic/Pharmacodynamic framework to support the subcutaneous dosing regimen of nemolizumab* in subjects with moderate-to-severe atopic dermatitis.

Background & Objective

- Nemolizumab, a humanized anti-IL-31 receptor A monoclonal antibody was developed for treatment of atopic dermatitis (AD).
- The selected subcutaneous (SC) dose for the Phase 3 pivotal studies was:
 - 30 mg Q4W with a 60-mg loading dose (LD)
- Aim:**
 - To characterize the PK/PD relationships between nemolizumab concentrations and the clinical efficacy; the eczema area and severity index (EASI: 0-72 scale), the investigator global assessment (IGA: 0-4 scale) and the weekly average peak pruritus numerical rating scale (PP NRS: 0-10 scale).
 - To assess the exposure-response for safety (adverse events)
 - To support the proposed dosing regimen in AD

Data

Table 1: Observations and subjects included in the analysis

Study	Dosing regimen	PK	EASI	PP NRS	IGA
Phase 1	0.03-0.3 mg/kg	542 (N=27)	222 (N=116)	-	-
Phase 2	0.1-2mg/kg Q4W	3385 (N=248)	2188 (N=264)	-	1932 (N=264)
Phase 2	10 mg (LD 20 mg) Q4W 30 mg (LD 60 mg) Q4W 90 mg Q4W	1455 (N=169)	2272 (N=225)	5842 (N=225)	2044 (N=225)
Phase 2	30 mg (LD 60 mg) Q4W	87 (N=18)	116 (N=20)	302 (N=20)	98 (N=20)
Phase 3	30 mg (LD 60 mg) Q4W	3213 (N=594)	4470 (N=937)	13103 (N=937)	3552 (N=937)
Phase 3	30 mg (LD 60 mg) Q4W	2743 (N=499)	3673 (N=776)	11008 (N=776)	2910 (N=776)
Total		11425 (N=1555)	12941 (N=2338)	30255 (N=1958)	10537 (N=2222)

Abbreviations: LD=Loading dose; N = number of subjects; Q4W=every 4 weeks.

Models

PK-EASI and PK- PP NRS models:
Structural model: indirect-response model including placebo effect

PK

Dose

K_a

C_p

CL/V

Placebo effect

Placebo

$Eff = \frac{I_{max} \cdot C_p}{C_p + IC_{50}}$

$Eff_2 = \frac{2 \cdot \exp(Eff + Plac)}{1 + \exp(Eff + Plac)}$

$\frac{dA_3}{dt} = R_{in} \cdot (1 - Eff_2) - k_{out} \cdot A_3$

EASI/PP NRS

$EASI = 72 \cdot (2 \cdot \exp(A_3) / (1 + \exp(A_3)) - 1)$
 $PP\ NRS = 10 \cdot (2 \cdot \exp(A_3) / (1 + \exp(A_3)) - 1)$

PK-IGA
Structural model: Continuous Time Markov Model (CTMM)

PK

Dose

K_a

C_p

CL/V

E_{desc}

0/1

2

3

4/5

λ_{21}

λ_{12}

λ_{32}

λ_{23}

λ_{43}

λ_{34}

IGA

$E_{desc} = (1 + C_p) \cdot (1 + \theta_{Female})$
 $\frac{dP_1}{dt} = \lambda_{21} \cdot E_{desc} \cdot P_2(t) - \lambda_{12} \cdot \theta_{B4/5} \cdot P_1(t)$
 $\frac{dP_2}{dt} = \lambda_{12} \cdot \theta_{B4/5} \cdot P_1(t) + \lambda_{32} \cdot E_{desc} \cdot P_3(t) - (\lambda_{21} \cdot E_{desc} + \lambda_{23} \cdot \theta_{B4/5}) \cdot P_2(t)$
 $\frac{dP_3}{dt} = \lambda_{23} \cdot \theta_{B4/5} \cdot P_2(t) + \lambda_{43} \cdot E_{desc} \cdot P_4(t) - (\lambda_{32} \cdot E_{desc} + \lambda_{34} \cdot \theta_{B4/5}) \cdot P_3(t)$
 $\frac{dP_4}{dt} = \lambda_{34} \cdot \theta_{B4/5} \cdot P_3(t) - \lambda_{43} \cdot E_{desc} \cdot P_4(t)$
 λ_{asc} =rate constant for ascending transitions; λ_{desc} =rate constant for descending transitions;

Simulations – Clinical Efficacy Endpoints

- Population:** 1000 subjects per arm resampled from the Phase 3 subjects - EASI baseline>16 and IGA>3
- Clinical assessment:** EASI, PP NRS and IGA measured at W4, W8, W12 and W16
- Clinical endpoints:** EASI75, PP NRS and IGA responders
- Outputs:** Responder rate at W16 for the 3 clinical endpoints over 100 replicates.

Table 2: Simulation details

Arm	Subject BW Range	Dose	Regimen*
1	Overall subject population (BW range observed in the clinical studies)	30 mg (LD 60 mg)	Q4W
2	Low BW subject population (BW range: 31 to <90 kg)	30 mg (LD 60 mg)	Q4W
3	High BW subject population (BW range: ≥90 to 171 kg)	30 mg (LD 60 mg)	Q4W

*16-week treatment with the last administration Week 12, Abbreviations LD=Loading dose; Q4W=every 4 weeks.

EASI-75 responder:	Subjects with at least a 75% decrease of the EASI score compared to baseline at week 16
PP NRS responder:	Subjects with at least a 4-point improvement from baseline score at week 16
IGA responder:	Subjects with an IGA score of 0 or 1 and at least a 2-point improvement from baseline IGA score at week 16

Figure 1: EASI-75 responder rate at W₁₆ by bodyweight

Figure 2: PP NRS responder rate at W₁₆ by bodyweight

Figure 3: IGA responder rate at W₁₆ by bodyweight and sex

Figure 4: IGA responder rate at W₁₆ by bodyweight and IGA baseline

Table 3: PopPK and PKPD Model parameters

Parameter	Point Estimate	%RSE	IIV	%RSE
Population PK model				
CL/F (L/day)	0.263	1.3	0.109	2.2
V/F (L)	7.67	1.3	0.11	6.2
Ka (1/day)	0.476	7.7	0.344	10
lag-time (day)	0.043	23		
Weight effect on CL/F ⁽¹⁾	0.662	6		
Weight effect on V/F ⁽¹⁾	0.802	5.3		
Covariance (CL/F and V/F)	0.068	9.97		
PK - EASI				
K _{OUT} (1/day)	0.0328	4.1	0.946	3.7
Placebo effect (P ₁)	1.43	4.5	2.18	2.7
I _{max}	1.4	20.8		
IC ₅₀ (µg/mL)	4.27	43.1		
PK - PP NRS				
tPP NRS0	1.82	0.76	0.132	1.5
KOUT (1/day)	0.0396	2.5	1.28	2.5
Placebo effect (P1)	0.545	8.1	2.34	1.8
I _{max}	2.23	0.6		
IC ₅₀ (µg/mL)	0.654	2.6		
IGA				
λ ₁₂ (day ⁻¹)	0.00794	7.8		
λ ₂₁ (day ⁻¹)	0.00708	6.4	0.444	5.3
λ ₂₃ (day ⁻¹)	0.00909	5.8		
λ ₃₂ (day ⁻¹)	0.012	5.1	0.444	5.3
λ ₃₄ (day ⁻¹)	0.00334	6.9		
λ ₄₃ (day ⁻¹)	0.0266	6.2	0.444	5.3
Slope/1000	0.0964	14		
Baseline effect (4/5)	2.25	6.9		
Sex effect (female)	0.12	16		

(1) Only weight is reported in this table - other covariates were not clinically relevant.

Exposure-Safety Analysis

- Data:** Phase 3 data - 1719 subjects (1135 treated with Nemolizumab and 584 with placebo)
- PK metrics:** Nemolizumab C_{trough} at W₁₆
- Clinical Endpoints:** Dermatitis atopic, Newly diagnosed asthma, Facial and peripheral edema
- Analysis:** Logistic regression
- There was no trend exposure and incidence of safety endpoints

Figure 5: Exposure-Safety Analysis: Logistic regression A) Dermatitis atopic; B) Newly diagnosed asthma; C) Facial edema; D) Peripheral Edema

Conclusions

- Population PK model and PKPD efficacy models were updated with Phase 3 data
 - The exposure of nemolizumab decreases with increasing BW (popPK model)
 - Baseline IGA score and Gender were the only significant covariates in the PK-IGA model
- Exposure-safety analysis did not evidence significant ascending relationship between nemolizumab exposure and the incidence of AEs
- PK/PD simulations support the SC dosing regimen in patients with AD with no dose adjustment based on BW

* Galderma is investigating the use of nemolizumab and has not received approval for any indication in any country
Acknowledgment: Special appreciation is extended Maria Luisa Sardu, Emilie Schindler for their contributions