Ligelizumab is Well Tolerated and Exhibits a Safety Profile Similar to Omalizumab and Placebo in Patients with Chronic Spontaneous Urticaria

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Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

Type	Company
Employment full time	Novartis Pharma AG, Basel, Switzerland

Conflict of interest
Marcus Maurer has received advisory board, speaker, investigator, grant/research support, and honoraria from Novartis; speaker fees from AlmirallHermal, Bayer, Schering Pharma, Biofrontera, Essex Pharma, Genentech, GSK, Merckle Recordati, Moxie, Sanofi Aventis, Schering-Plough, Leo, MSD, Shire, Symbiopharm, UCB, Uriach, Viropharma. **Gordon Sussman** reports personal fees and grants from Novartis, Aimmune, Aralez, Biocryst, CSL Behring, Dyax, Genentech, GlaxoSmithKline, Green Cross, Kendrion, Merck, Pfizer, and Stallergens. **Ana Giménez-Arnau** has received personal fees from Novartis, Uriach Pharma, Bayer, and Sanofi; has received grants from Intendis-Bayer, Novartis, and Uriach Pharma; and has received travel support from Novartis. **Eva Hua** is a full time employee of Shanghai Novartis Trading Ltd, Shanghai, China. **Reinhold Janocha** is a full time employees of Novartis Pharma AG, Basel, Switzerland.

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Introduction

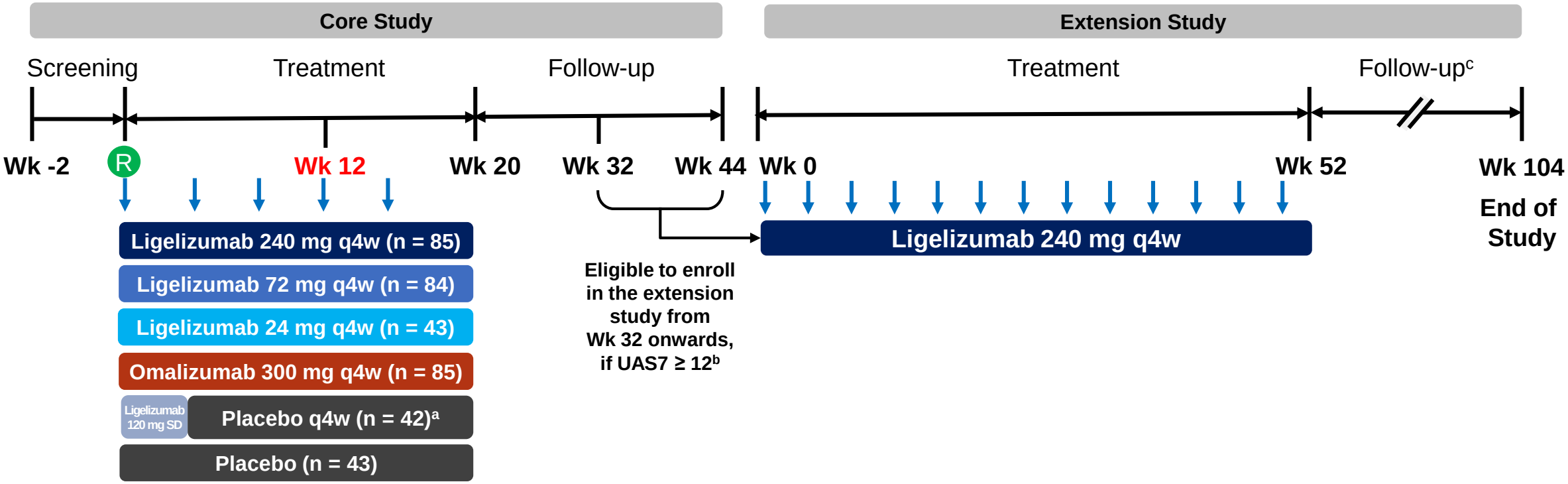
- Chronic spontaneous urticaria (CSU) is a skin disorder characterized by the occurrence of itchy wheals (hives), angioedema, or both for 6 weeks or more in the absence of specific external stimuli,[1] and has a significant negative impact on the quality of life[2]
- Ligelizumab is a next generation high affinity humanized monoclonal anti-IgE antibody which results in rapid, strong and sustained symptom control for patients with CSU
- Ligelizumab was well tolerated and achieved greater control of symptoms of hives, itch and angioedema versus omalizumab and placebo in patients with CSU up to Week 20 in the core Phase 2b study[3]
- Here, we present the safety data of ligelizumab in patients with CSU, and compare it with the safety profile of omalizumab and placebo in a Phase 2b core study, as well as the safety data from the ligelizumab Phase 2b extension study

AEs, Adverse events; CSU, Chronic spontaneous urticaria; IgE, Immunoglobulin E; SAEs, Serious adverse events

[1]Zuberbier T et al. *Allergy*, 2018;73(7):1393–1414. [2]Maurer M et al. *Allergy*, 2011;66(3):317–30. [3]Maurer M et al. *N Engl J Med.* 2019;381(14):1321-1332.

Study design

Phase 2b trial and open-label extension study of ligelizumab in patients with CSU inadequately controlled with H_1-antihistamines



R = Randomisation Wk 12 = Primary endpoint ↓ = Treatment visit in the core study

q4w, Every 4 weeks; sc, Subcutaneous; SD, Single dose; Wk, Week

[a]The 120 mg single-dose (SD) arm was chosen to characterise the pharmacokinetics/pharmacodynamics. Data from this arm assesses the duration of the response and correlates this with the concentration of drug in the serum at the time when symptoms reappear. [b]Patients who remained in the follow-up period for at least 12 weeks and had active disease (UAS7 ≥ 12), could enter the extension study from Week 32 onwards. [c]Following the 52-week open label period, patients entered a 52-week treatment free follow up period to assess durability of treatment effect, including potential for disease modification

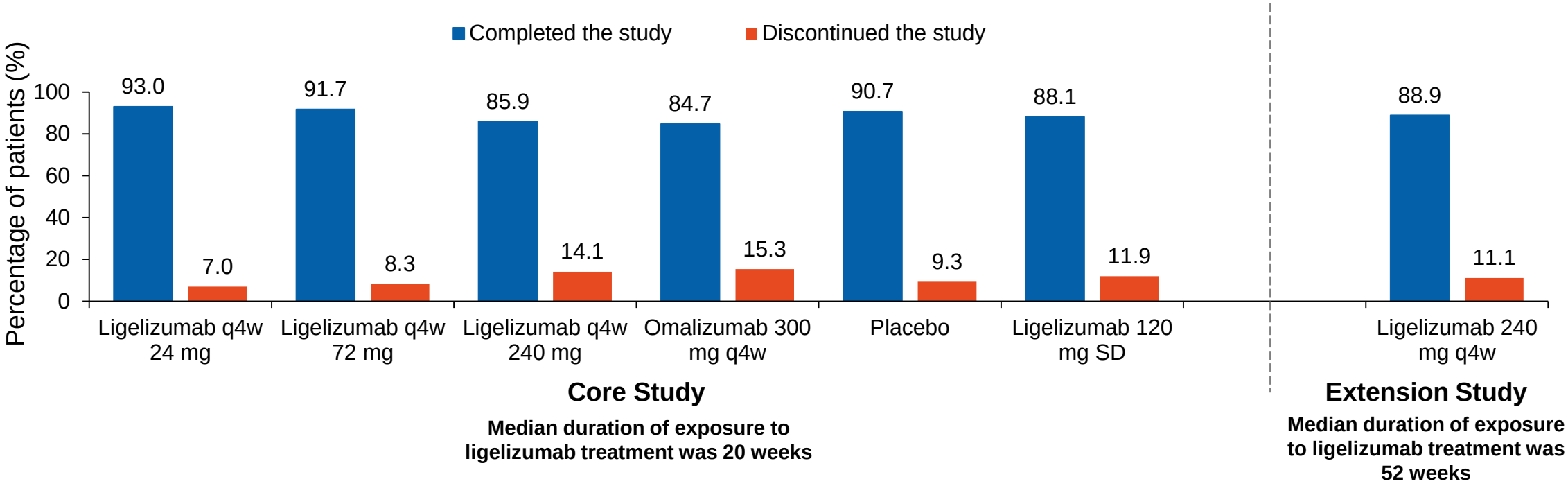
Demographics

Characteristic	Core Study N=382	Extension Study N=226*
Mean age (years), mean ± SD	43.3 ± 12.5	44.5 ± 12.6
Age group, n (%)		
<65 years	360 (94.2)	211 (93.4)
≥ 65 years	22 (5.8)	15 (6.6)
Gender, n (%)		
Male	96 (25.1)	56 (24.8)
Female	286 (74.9)	170 (75.2)
Race, n (%)		
White	283 (74.1)	163 (72.1)
Asian	76 (19.9)	51 (22.6)
Mean BMI (kg/m^2)	27.9 ± 6.5	28.7 (7.2)
BMI group n (%)		
25-< 30 (kg/m^2)	112 (29.3)	62 (27.4)
≥ 30 (kg/m^2)	116 (30.4)	81 (35.8)

BMI, Body mass index
*For various reasons 44 patients in the core study discontinued the double-blind treatment period and 29 patients discontinued the post-treatment follow-up period

Approximately 90% of patients completed the core and extension study

- For ligelizumab 240 mg treatment, 86% and 89% of patients completed the core and the extension study, respectively



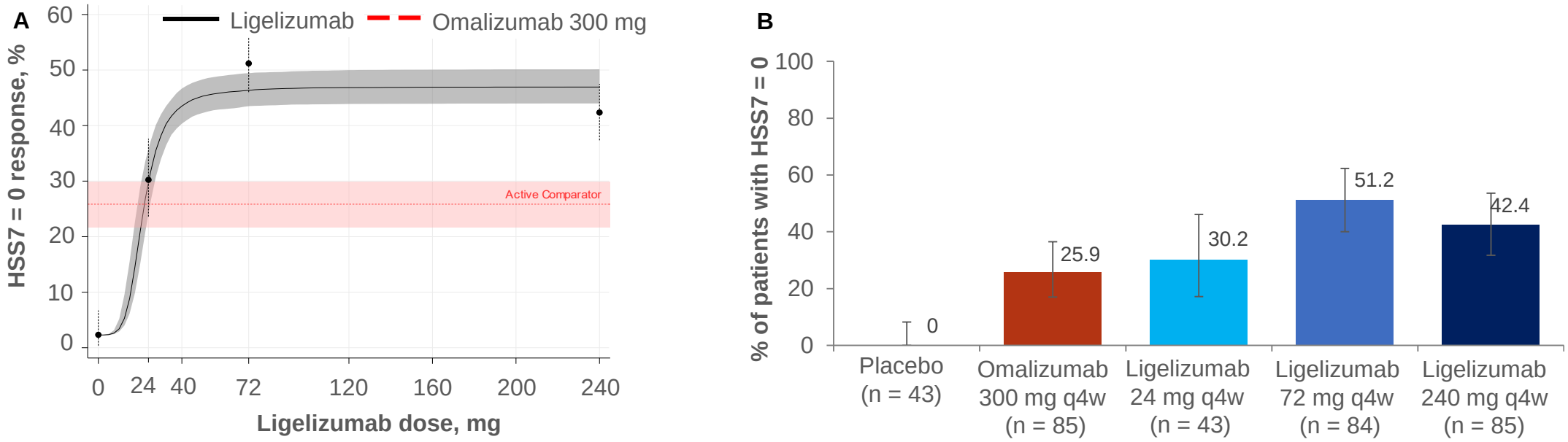
- 86% of patients received the maximum 5 doses of 240 mg of ligelizumab in the core study, whereas 89% of patients received the maximum 13 doses of 240 mg of ligelizumab in the extension study

Duration of exposure in weeks is calculated as (the date of the last treatment visit - the date of first study drug administration + 28) / 7.

Ligelizumab demonstrated a dose-response relationship with complete hives response rate at Week 12

- **The primary objective** of the study was achieved, with ligelizumab demonstrating a dose-response relationship with respect to complete hives response rate at Week 12 ($p<0.001$)
- HSS7 = 0 response rates at Week 12 were 30%, 51%, and 42% for ligelizumab 24, 72, and 240 mg, respectively, vs. 26% for omalizumab, and 0% for placebo

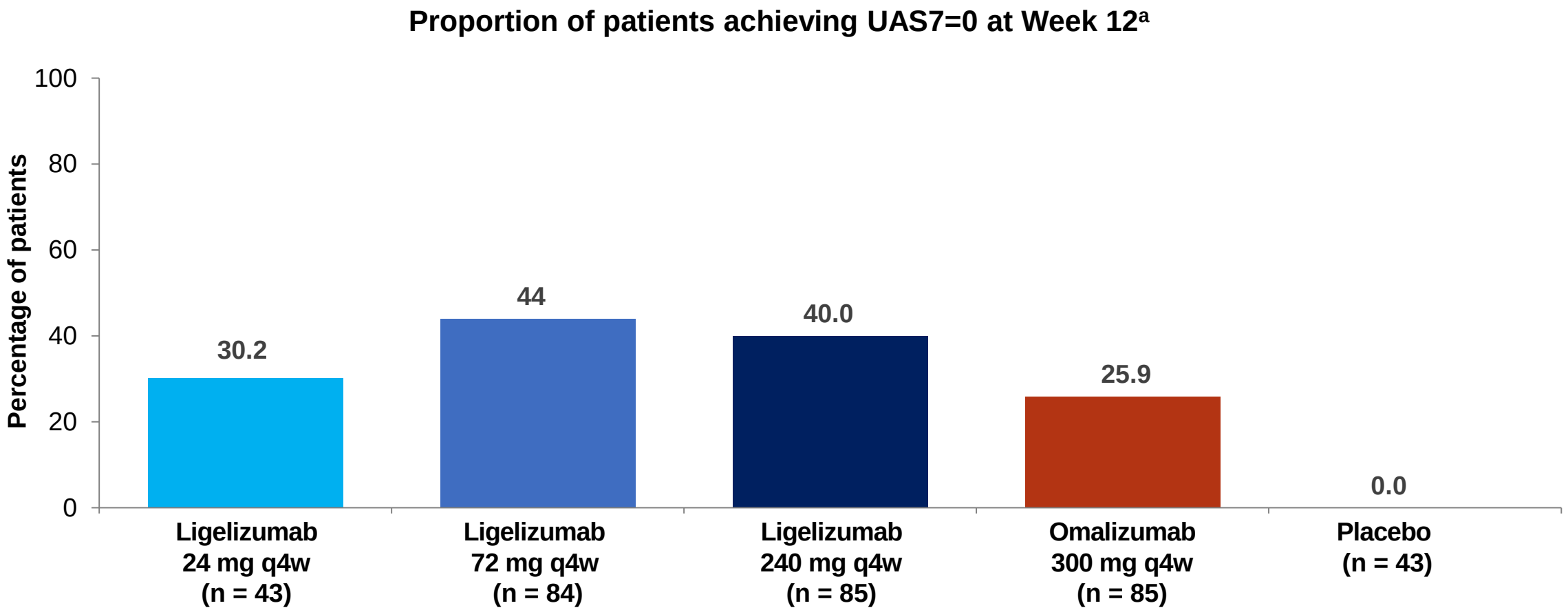
(A) Dose-response curve and (B) the proportion of patients achieving HSS7=0[a] at Week 12 (primary endpoint)



[a]Data are reported using non-responder imputation

Maurer M et al. *N Engl J Med.* 2019 Oct 3;381(14):1321-1332.

High complete and well controlled response with ligelizumab at Week 12 during the core study

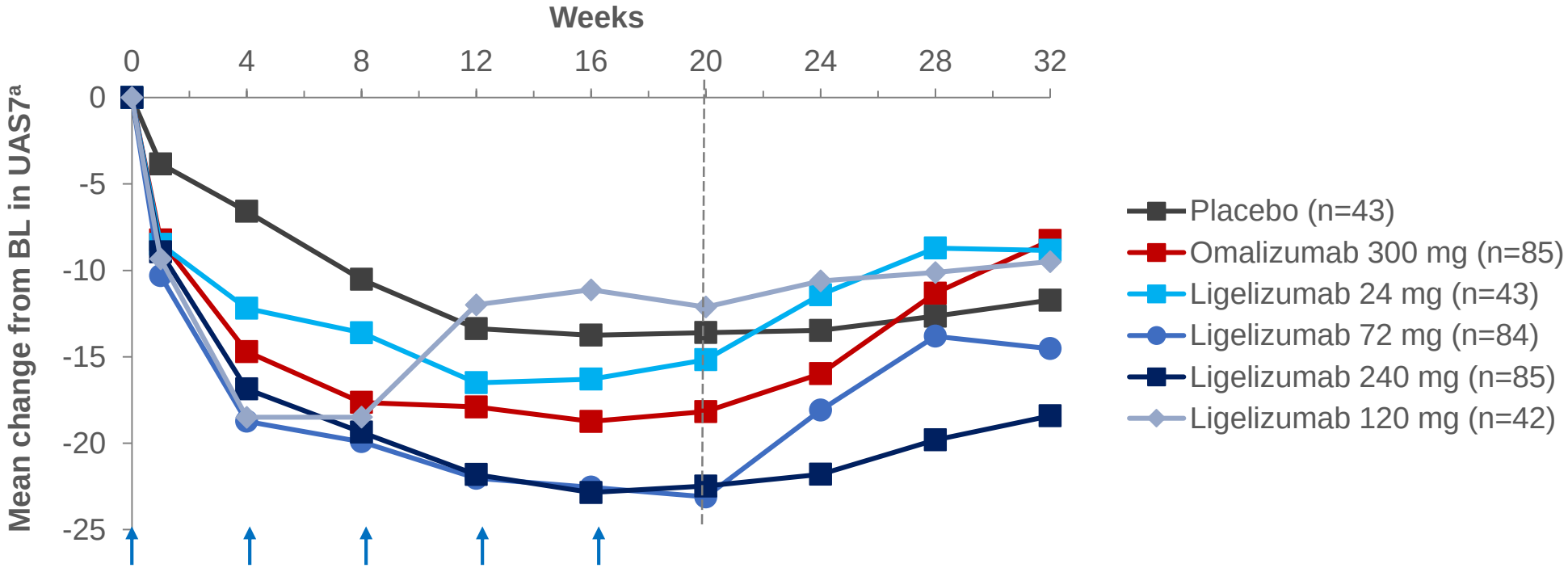


UAS7, 7-day urticaria activity score

[a]The proportion of patients achieving UAS7=0 at Week 12 was a key secondary endpoint of the core study

Higher changes from baseline in UAS7 with ligelizumab 72 and 240 mg vs. omalizumab and ligelizumab 24 mg

- Higher changes from baseline in UAS7 were observed with ligelizumab 72 and 240 mg vs. omalizumab and ligelizumab 24 mg; the benefit in favor of ligelizumab 72 and 240 mg was sustained up to Week 32 and was more pronounced in the 240 mg group



Data are reported as observed. The dashed vertical line indicates the end of treatment period. Ligelizumab 120 mg was given as a single dose at Week 4.
[a]UAS7 is a composite of ISS7 and HSS7 (scale 0–42); BL, Baseline; HSS7, Urticaria Activity Score (UAS7)
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All ligelizumab doses were well tolerated with a safety profile similar to omalizumab/ placebo

Category	Phase 2b Core Study							Extension
	Ligelizumab q4w			Omalizumab 300 mg q4w (N= 85)	Placebo (N = 43)	Ligelizumab 120 mg SD (N = 42)	Total (N = 382)	Ligelizumab 240 mg q4w (N = 226)
	24 mg (N = 43)	72 mg (N = 84)	240 mg (N = 85)					
At least one TEAE	36 (83.7)	63 (75.0)	63 (74.1)	62 (72.9)	34 (79.1)	37 (88.1)	295 (77.2)	190 (84.1)
Mild	16 (37.2)	31 (36.9)	32 (37.6)	36 (42.4)	15 (34.9)	22 (52.4)	152 (39.8)	94 (41.6)
Moderate	16 (37.2)	27 (32.1)	28 (32.9)	21 (24.7)	12 (27.9)	13 (31.0)	117 (30.6)	81 (35.8)
Severe	4 (9.3)	5 (6.0)	3 (3.5)	5 (5.9)	7 (16.3)	2 (4.8)	26 (6.8)	15 (6.6)
At least one serious TEAE	3 (7.0)	2 (2.4)	2 (2.4)	3 (3.5)	4 (9.3)	4 (9.5)	18 (4.7)	15 (6.6)
TEAEs leading to discontinuation	0 (0.0)	1 (1.2)	1 (1.2)	2 (2.4)	1 (2.3)	2 (4.8)	7 (1.8)	6 (2.7)
At least one TEAE possibly related to treatment	5 (11.6)	18 (21.4)	24 (28.2)	7 (8.2)	12 (27.9)	6 (14.3)	72 (18.8)	54 (23.9)

TEAE, Treatment-emergent adverse event; SD, Single dose; q4w, Every 4 weeks. Data presented as n (%)

No new safety findings emerged in the extension study
Ligelizumab was well tolerated up to 1 year

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	24 mg (N = 43)	72 mg (N = 84)	240 mg (N = 85)		
Administration site conditions (PT)					
Injection site reaction	0 (0.0)	3 (3.6)	5 (5.9)	0 (0.0)	10 (4.4)
Injection site erythema	0 (0.0)	2 (2.4)	4 (4.7)	1 (2.4)	13 (5.8)
Most frequent TEAEs (≥10% in any group, PT)					
Upper respiratory TEAEs*	12 (27.9)	21 (25.0)	28 (32.9)	19 (45.2)	84 (37.2)
Viral upper respiratory tract infection*	7 (16.3)	13 (15.5)	17 (20.0)	10 (23.8)	6 (2.7)
Upper respiratory tract infection*	7 (16.3)	7 (8.3)	10 (11.8)	9 (21.4)	23 (10.2)
Nasopharyngitis*	0 (0.0)	1 (1.2)	2 (2.4)	1 (2.4)	57 (25.2)
Headache	7 (16.3)	9 (10.7)	7 (8.2)	1 (2.4)	29 (12.8)

TEAE, Treatment emergent adverse event; PT, Preferred term; q4w, Every 4 weeks; SD, Single dose. Data presented as n (%).
*Upper respiratory AEs include viral upper respiratory tract infection (URTI), URTI, and nasopharyngitis

Treatment emergent adverse events of special interest during treatment period of the extension study

Treatment emergent adverse events of special interest	n (%)
Acute allergic reaction	1 (0.4)
Injection site reactions (HLT)	25 (11.1)
Eosinophilic conditions (CMQ)*	4 (1.8)
Myalgia (PT)	2 (0.9)
Wheezing (PT)	1 (0.4)
Hypersensitivity vasculitis (PT)	1 (0.4)
Malignancies (SMQ)*	3 (1.3)
Pancytopenia (PT)*	1 (0.4)

- Injection site reactions were mostly non-serious, mild to moderate in severity and did not require use of concomitant medications or lead to any discontinuation of the study treatment
- One death in a patient with metastatic pancreatic cancer was reported in the extension study. The patient had a history of breast cancer and chemo-radiation therapy. The investigator assessed the death as not related to ligelizumab treatment

CMQ, Customized MedDRA Queries; HLT, High level term; PT, Preferred term; SMQ, Standardised MedDRA quieries.
*All cases were not related to the study treatment

Conclusions

- In the CSU Phase 2b core study, all tested doses of ligelizumab showed an evolving safety profile comparable to omalizumab
- No adverse events of clinical relevance were observed during the core study, and no new safety signals were identified in the extension study where all patients received the highest dose (240 mg) of ligelizumab
- In patients with CSU inadequately controlled with standard of care including H_1-AH, ligelizumab 240 mg q4w treatment seems to be well tolerated for up to 52 weeks, consistent with data from the 20 weeks of treatment in the core study

CSU, Chronic spontaneous urticaria; H_1AH, H_1-antistamines; q4w, Every 4 weeks.

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