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Efficacy and safety of omalizumab in patients with moderate-to-severe asthma: An analytic comparison of data from randomized controlled trials between Chinese and Caucasians

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Abstract

Background: Omalizumab has > 15 years of real-world evidence of effectiveness in Caucasian patients. In August 2017, it was approved as an add-on therapy for the management of moderate-to-severe asthma in China.

Objective: To compare the efficacy and safety of omalizumab in Chinese and Caucasian patients.

Methods: This analysis included clinical trial data from a Chinese study (NCT01202903) and four studies with predominantly Caucasian patients (008, 009, EXTRA and INNOVATE). The following outcomes were analyzed: change from baseline in morning peak expiratory flow (mPEF), percentage predicted forced expiratory volume in one second (FEV_1), patient-reported outcomes (PROs), asthma exacerbation and safety. Further, a population pharmacokinetic/pharmacodynamic (PK/PD) was also assessed.

Results: In the Chinese study, omalizumab significantly improved the mPEF from baseline vs placebo at Weeks > 4–8 through > 16–20; however, the change in mPEF did not reach statistical significance at Week 24. A similar trend towards improvement in mPEF was observed in the studies with Caucasians (INNOVATE, 008 and 009). In all studies, omalizumab showed greater improvement in %predicted FEV_1, AQLQ score, and GETE score vs placebo. In addition, asthma symptom scores and seasonal exacerbations were lower, especially during winter, in the Chinese study, and was comparable to studies in Caucasians. PK/PD analyses showed that steady-state PK of omalizumab; free or total immunoglobulin E levels were similar in all studies.

Conclusions: The clinical efficacy and safety of omalizumab was comparable among Chinese and Caucasian patients with moderate-to-severe asthma supporting therapeutic effectiveness, irrespective of race, ethnicity and geographical factors.

Key words: Asthma, omalizumab, Caucasian, Chinese, comparative analysis

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Introduction

An epidemiology analysis in China reports an increasing incidence of asthma, and a relatively high fatality rate associated with asthma exacerbations.[1] In China, a combination of inhaled corticosteroids (ICS) and long-acting β_2-agonist (LABA) is the general physician's preferred choice in the management of patients with moderate or severe asthma.[1] Further, to ensure asthma control, add-on leukotriene-receptor antagonists (LTRAs) and long-acting anti-muscarinic antagonists are used most frequently.[2,3] However, despite treatment with ICS/LABA or with LTRA, a large proportion of Chinese patients remain uncontrolled,[1,3,4] which highlights the need for effective therapeutic approaches to achieve better asthma control.

Omalizumab, a recombinant humanized anti-immunoglobulin E (IgE) antibody that inhibits the activity of free IgE, received approval (August 2017) in China for the management of moderate or severe allergic asthma. This decision was largely supported by a Phase III study, which showed greater improvements in overall health of patients who were administered omalizumab compared with placebo.[5] It was also observed that Chinese patients with higher IgE levels were more likely to respond to omalizumab treatment, irrespective of baseline eosinophil counts.[6]

Omalizumab has had more than 15 years of clinical experience as add-on therapy in moderate-to-severe allergic asthma and is recommended for patients uncontrolled on medium-dose ICS+LABA as per Global Initiative of Asthma (GINA) 2019.[7,8] Previously published prospective and retrospective studies demonstrated the efficacy of omalizumab in asthma control with greater improvements in lung function, patient-reported outcomes (PROs), and reduction in exacerbations and oral corticosteroid (OCS) dose across age groups and ethnicity, predominantly in Caucasian patients.[9-12]

Therefore, a comparative study on efficacy and safety of omalizumab between Chinese and Caucasian patients would help in formulating the country-specific disease management guidelines and treatment algorithms.

Here, we report efficacy, safety and pharmacokinetics/pharmacodynamics (PK/PD) profile of omalizumab in Chinese and Caucasian patients. In order to analyze the Chinese clinical trial data in the context of predominantly Caucasian studies, we performed a comparative analysis with respect to the endpoints morning peak expiratory flow (mPEF), forced expiratory volume in one second (FEV_1), PROs and asthma exacerbations.

Methods

Study design

The Chinese study (ClinicalTrials.gov identifier: NCT01202903) was a 24-week, randomized, double-blind, parallel-group, placebo-controlled study that assessed the efficacy, safety and tolerability of add-on omalizumab versus placebo in adult patients with moderate-to-severe persistent allergic asthma, inadequately controlled despite treatment with GINA 2009 Step 4 therapy. All patients in both treatment groups were on LABA and nearly all of them (99.8%) were using ICS/LABA at baseline. Patients were stratified based on their concomitant use of OCS, theophyllines, leukotriene modifiers, or other asthma concomitant maintenance medications. Data from the China study was compared with four studies (008,[13] 009,[14] EXTRA [ClinicalTrials.gov identifier: NCT00314574][15] and INNOVATE [NCT00046748][16]) that had been conducted in predominantly Caucasian patients. The clinical trials discussed are summarized in **Table 1**.

Table 1. Details of the studies included in this comparative analysis

Study No.	Study Objective; Population Ethnicity	Randomized Patients	Treatment Duration	Medication dose/day	Primary Efficacy Endpoint
PK/PD					
China PK/PD study (A2102)	To evaluate PK and PD of omalizumab in healthy subjects; Chinese	36	Pre-dose and post-dose until Day 85	Single subcutaneous administration 75 mg, 150 mg or 375 mg of omalizumab	Evaluate PK and PD of omalizumab after single subcutaneous administration in healthy Chinese subjects
Global PK/PD study-1 (A2204)	To determine PK and PD of liquid and lyophilised omalizumab in healthy subjects; predominantly Caucasian	155	Pre-dose and post-dose until Day 85	Single subcutaneous administration omalizumab*	To determine PK and PD of liquid and lyophilised omalizumab in subjects with elevated IgE after single subcutaneous administration
Global PK/PD study-2 (A2206)	To determine and compare single-dose PK and PD of omalizumab in Caucasian and Japanese healthy male subjects; Caucasian and Japanese	51	Post-dose until Day 85	Single subcutaneous administration of 150 mg omalizumab	To compare single dose pharmacokinetics of omalizumab in Caucasian and Japanese male subjects after single subcutaneous administration

*Dosed according to body weight and baseline IgE levels;

Table 1. (Continued)

Study No.	Study Objective; Population Ethnicity	Randomized Patients	Treatment Duration	Medication dose/day	Primary Efficacy Endpoint
Clinical efficacy					
Chinese study (A2313)	Efficacy and safety in adults with moderate-to-severe AA; Chinese	616	24 weeks	Omalizumab*/ placeboevery 2 or 4 weeks to ICS + LABA	Mean change from baseline in morning PEF over the 24-week treatment period
008	Efficacy, safety, and ICS reduction in adolescents and adults with moderate-to-severe AA; predominantly Caucasian	525	28 weeks	Omalizumab* every 2 or 4 weeks + ICS + SABA** or placebo + ICS + SABA**	Rate of asthma exacerbation episodes during the 16-week stable steroid and 12 week steroid reduction periods
009	Efficacy, safety, and ICS reduction in adolescents and adults with moderate-to-severe AA; predominantly Caucasian	546	28 weeks	Omalizumab* every 2 or 4 weeks + ICS + SABA** or placebo+ ICS + SABA**	Rate of asthma exacerbation episodes during the 16-week stable steroid and 12 week steroid reduction periods
EXTRA (Q3662g)	Efficacy and safety in adolescent and adult patients with moderate-to-severe persistent AA; predominantly Caucasian	850	48 weeks	Omalizumab* every 2 or 4 weeks + ICS + LABA, or placebo + ICS + LABA	Rate of protocol-defined asthma exacerbations over the 48-week treatment period
INNOVATE (A2306)	Efficacy and safety in adolescent and adult patients with severe AA; predominantly Caucasian	419	28 weeks	Omalizumab* every 2 or 4 weeks + ICS + LABA or placebo + ICS + LABA	Rate of clinically significant asthma exacerbations during the 28-week treatment period

*Dosed according to body weight and baseline IgE levels; **As-needed or regular β_2-agonist treatment.
AA, allergic asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; PK/PD, pharmacokinetics/pharmacodynamics; SABA, short-acting β_2-agonist.

All the studies were approved by institutional review boards or ethics committees at participating centers, and was conducted in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with local regulations applied, and the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

PK/PD modelling

Population pharmacokinetics/pharmacodynamics (PK/PD) modelling was performed to determine whether there were any differences in the PK of omalizumab and PD of free and total IgE between Chinese and Caucasian asthmatic patient populations. PK/PD profiles of omalizumab, free and total IgE concentrations in Chinese subjects were investigated in a single-dose study of omalizumab in healthy Chinese volunteers (China PK/PD [A2102] study), and the Phase III study in Chinese asthma patients. Additionally, a population PK/PD modelling analysis was performed by pooling data from the Phase III China study into a mega-dataset of omalizumab studies used in a previous analysis. Covariates including bodyweight, body mass index (BMI), baseline IgE, gender and Chinese ethnicity was analyzed and the final model was used to simulate the steady-state exposure of free IgE. More details on model structure and methodology are available in previous publications.[17-19]

Patients

The Chinese study included patients aged 18–75 years with moderate-to-severe persistent allergic asthma inadequately controlled on high-dose ICS and LABA.[5] The studies in Caucasians included patients aged 12–75 years with moderate-to-severe allergic asthma (009), or severe allergic asthma (008, EXTRA and INNOVATE) inadequately controlled with high-dose ICS or high-dose ICS and LABA.[13-16]

Assessments

Efficacy

Lung function parameters (Morning PEF and FEV_1)

Morning PEF and FEV_1 were compared between the Chinese and Caucasian populations. The lung function data at Week 24 in the China study were compared with data from Weeks 4 to 16 (i.e., during steroid stabilization phase) in Studies 008 and 009[13,14] and Weeks 12 to > 24 in the INNOVATE study. mPEF was not captured in the EXTRA study.

Patient-reported outcomes (PROs: AQLQ, ACQ and GETE)

Asthma Quality of Life Questionnaire (AQLQ), asthma symptom score, physician's and patient's Global Evaluation of Treatment Effectiveness (GETE) were compared between the Chinese and the Caucasian studies. Data from the PROs at Week 24 in China study was compared with data from Weeks 4 to 16 in Studies 008 and 009, Weeks 12 to > 24 in INNOVATE study, and at Week 48 in EXTRA study.[13-16]

Asthma exacerbation rates

Asthma exacerbation was defined as a worsening of asthma requiring treatment with rescue oral or intravenous corticosteroids. Exacerbation rate was an exploratory endpoint in the China study; however, exacerbations were the primary endpoint in Caucasian studies. In the China study, the proportion

of patients reporting seasonal (summer, autumn, winter and spring) asthma exacerbations was determined between omalizumab and placebo. Further, the results of exacerbation rate ratios were compared between Chinese and predominantly Caucasian patients.

Safety

The most frequently reported adverse events (AEs), serious/clinically relevant AEs and deaths recorded during the studies were compared between Chinese and Caucasian populations. However, due to differences in study design, and the use of updated revisions of the Medical Dictionary for Regulatory Activities (MedDRA) classification during the clinical development period, pooling of AEs across all studies was not possible.

Comparison in PK/PD profiles

The similarity and differences in PK/PD in terms of maximum concentration (C_{max}), area under curve (AUC), time to maximum plasma concentration (T_{max}), free and total IgE levels were compared between Chinese and healthy, predominantly Caucasian, volunteers.

Analysis

Descriptive statistics was used for comparing the data between the Chinese and Caucasian populations. Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean and standard deviation. Results of the Caucasian studies were adapted from their original results by specific descriptive parameters.[13-16] Data from the Chinese study were matched with results from studies with predominantly Caucasian population, without drawing any statistical inferences.

Results

Baseline characteristics of Chinese versus Caucasian population

The treatment groups in the Chinese study were well balanced in demographic and clinical characteristics. The mean age of the study population was 46.5 years, 94.4% being between 18 to < 65 years of age. There were slightly more females than males (53.9% vs 46.1%) with no difference in gender distribution between the treatment groups. Mean body weight was 62.6 kg (range 38–122 kg), mean height was 163.4 cm (range 142–190 cm), and BMI was 23.4 (range 16.0–43.2 kg/m^2). Most patients in both treatment groups were in stratification group one (i.e. not receiving additional asthma concomitant maintenance medications). The mean total IgE concentration at baseline was 275.4 IU/mL (range 31–698 IU/mL), and was similar between the treatment groups (mean of 271.5 IU/mL and 279.4 IU/mL, respectively, for omalizumab and placebo). The mean age of patients was comparable across the studies. Most of the patients in the Chinese study were in stratification group 1 (i.e. not receiving OCS, theophyllines, leukotriene modifiers or other asthma concomitant maintenance medications); in the Caucasian studies (INNOVATE and EXTRA), patients were distributed between the strata. The mean total IgE level was higher in Chinese patients compared with Caucasians. The mean pre-bronchodilator FEV_1 (% predicted) was comparable across the studies. Patient demographics and clinical characteristics were well matched with regard to age and disease history between the China, EXTRA and INNOVATE studies. The detailed demographic and clinical characteristics are presented in **Supplementary Table 1**.

Supplement Table 1. Demographic and baseline characteristics for the China, EXTRA and INNOVATE studies

Characteristic		China Study		INNOVATE		EXTRA	
		Omalizumab N = 310	Placebo N = 299	Omalizumab N = 245	Placebo N = 237	Omalizumab N=427	Placebo N = 421
Age (years)	Mean	45.8	47.1	42.3	43.0	43.7	45.3
	SD	12.0	11.6	13.8	13.6	14.3	13.9
Age 18 to < 65 years	n (%)	290 (93.5)	285 (95.3)	220 (89.8)	219 (92.4)	379 (88.8)	376 (89.3)
Age 65 to ≤ 75 years	n (%)	20 (6.5)	14 (4.7)	16 (6.5)	11 (4.6)	25 (5.9)	29 (6.9)
Men	**n (%)**	139 (44.8)	142 (47.5)	74 (30.2)	76 (32.1)	165 (38.6)	126 (29.9)
Women	n (%)	171 (55.2)	157 (52.5)	171 (69.8)	161 (67.9)	262 (61.4)	295 (70.1)
Race							
	n (%)	Asian 310 (100)	Asian 299 (100)	Caucasian 187 (76.3)	Caucasian 174 (73.4)	White 313 (73.3)	White 318 (75.5)
	n (%)	Chinese 310 (100)	Chinese 299 (100)	Black 14 (5.7)	Black 15 (6.3)	Black 90 (21.1)	Black 86 (20.4)
				Oriental 3 (1.2)	Oriental 3 (1.3)	Asian/Pacific Islander 12 (2.8)	Asian/Pacific Islander 11 (2.6)

Supplement Table 1. (Continued)

Characteristic		China Study		INNOVATE		EXTRA	
		Omalizumab N = 310	Placebo N = 299	Omalizumab N = 245	Placebo N = 237	Omalizumab N=427	Placebo N = 421
Race (Continued)							
				Others 41 (16.7)	Others 45 (19.0)	American Indian/ Alaskan Native 3 (0.7)	American Indian/ Alaskan Native 1 (0.2)
						Native 3 (0.7)	Native 1 (0.2)
						Others 9 (2.1)	Others 5 (1.2)
Weight (kg)	n	310	299	245	237	427	420
	Mean	62.3	62.8	79.2	77.9	87.9	86.2
	SD	11.0	10.4	19.7	17.7	21.2	21.1
Height (cm)	n	310	299	245	237	na	na
	Mean	162.9	164.0	164.4	164.8	na	na
	SD	8.1	7.5	9.7	9.8	na	na
BMI (kg/m^2)	n	310	299			na	na
	Mean	23.4	23.3	29.3	28.7	na	na
	SD	3.5	3.2	na	na	na	na
Stratification group* for China study/Patients at baseline receiving# for INNOVATE and EXTRA, n (%)							
1		291 (93.9)	280 (93.6)	106 (43.3)	111 (46.8)	151 (35.4)	159 (37.8)
2		15 (4.8)	14 (4.7)	83 (33.9)	79 (33.3)	203 (47.5)	191 (45.4)
3		4 (1.3)	5 (1.7)	56 (22.9)	47 (19.8)	73 (17.1)	71 (16.9)
Total IgE (IU/mL)	n	310	299	245	237	427	420
	Mean	271.5	279.4	201.7	190.7	178.7	175.1
	SD	180.4	176.7	153.4	156.3	134.5	133.7
Duration of asthma (years)	n	310	299	245	237	426	420
	Mean	14.3	15.1	22.3	22.1	22.8	24.7
	SD	12.9	13.5	14.8	14.7	15.4	15.8
Smoking history, n (%)							
Never smoked		280 (90.3)	272 (91.0)	185 (75.5)	182 (76.8)	na	na
Ex-smoker		29 (9.4)	27 (9.0)	60 (24.5)	55 (23.2)	na	na
Current smoker		1 (0.3)	0	0	0	na	na
FEV_1 reversibility, (%)	n	310	296	206	207	na	na
	Mean	26.3	27.1	28.9	24.5	na	na
	SD	14.1	13.6	23.3	23.3	na	na

*stratification group; #according to recorded concomitant medication use, rather than the stratification group given in the randomization assignment. Strata 1: Patients not receiving oral corticosteroids (OCS), theophyllines, leukotriene modifiers or other asthma concomitant maintenance medications; Strata 2: Patients receiving one or more of theophyllines, leukotriene modifiers or other asthma concomitant maintenance medications, but not receiving OCS; Strata 3: Patients receiving OCS (with or without other asthma concomitant maintenance medications).

AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; FAS, full analysis set; FEV_1, forced expiratory volume in one second; IgE, immunoglobulin E; na, not available; SD, standard deviation

Supplement Table 1. (Continued)

Characteristic		China Study		INNOVATE		EXTRA	
		Omalizumab N = 310	Placebo N = 299	Omalizumab N = 245	Placebo N = 237	Omalizumab N=427	Placebo N = 421
% predicted FEV_1 (pre-bronchodilator)	N	303	302	245	237	424	418
	Mean	63.5	63.0	63.2	63.0	65.4	64.4
	SD	12.0	12.7	15.8	14.4	15.2	13.9
Baseline AQLQ score	N	251	237	209	210	425	418
	Mean	4.4	4.6	3.9	3.9	4.0	3.9
	SD	1.0	1.0	1.1	1.1	1.1	1.1

Efficacy of omalizumab in Chinese versus Caucasian population

Lung function parameters

Morning PEF

Omalizumab resulted in numerically greater improvement from baseline in mean mPEF compared with placebo after 24 weeks of treatment. However, the least squares mean treatment difference (LSMD) of 8.85 L/min at Week 24 did not reach statistical significance ($p = 0.062$). The treatment difference for omalizumab versus placebo was statistically significant at > 4–8 weeks through > 16–20 weeks (at Week 20, 10.57 L/min, $p = 0.018$); while the per-protocol analysis showed statistically significant improvement in the mean mPEF at all time points from Weeks 4 to 24 (LSMD at Week 24: 11.53 L/min, $p = 0.022$).

Change in mPEF, the exploratory endpoint in the INNOVATE study, was statistically significant following omalizumab treatment between Weeks 12 to 16 (LSMD vs placebo: 10.61 L/min, $p = 0.027$) and Weeks 16 to 20 (9.13 L/min, $p = 0.045$), but not between Weeks 20 to 24 (8.92 L/min, $p = 0.065$). PEF was a secondary endpoint in study 008, where statistically significant differences in favor of omalizumab, relative to placebo, were observed between Weeks 4 to 8 (LSMD: 8.9 L/min, $p = 0.002$), Weeks 8 to 12 (10.7 L/min, $p = 0.001$), Weeks 12 to 16 (11.6 L/min, $p < 0.001$) and at the endpoint visit (11.9 L/min, $p < 0.001$). Similarly, in study 009, statistically significant differences were observed in favor of omalizumab relative to placebo at Weeks 4 to 16, and at the end visit (11.7–15.6 L/min, $p < 0.001$ at all time points) (**Table 2**). PEF was not assessed in EXTRA study.

Forced expiratory lung volume in one second (FEV_1)

In the China study, the LS mean treatment difference between omalizumab and placebo in terms of percent predicted FEV_1 at Week 24 was 4.12% ($p = 0.001$) compared with 2.84% ($p = 0.043$) in INNOVATE study at Week 28 and 2.64% ($p < 0.05$) at Week 16 in EXTRA. In studies 008 and 009, significant differences ($p < 0.05$ and $p = 0.001$, respectively) in the omalizumab versus placebo groups were noted at the end of the steroid stabilization phase (**Table 2**).

Patient-reported outcomes

AQLQ

The change in AQLQ overall score from baseline was statistically significant in patients treated with omalizumab compared with placebo in the China study (LSMD: 0.40; $p < 0.001$). These findings were similar to studies 008, 009, EXTRA and INNOVATE, which reported a mean treatment difference of 0.28 ($p = 0.001$), 0.28 ($p < 0.001$), 0.23 ($p = 0.0047$) and 0.45 ($p < 0.001$), respectively (**Table 3**).

Table 2. Comparison of lung function parameters between the China study and predominantly Caucasian studies

Outcome	Chinese	Predominantly Caucasian			
	A2313 n = 608	008 n = 525	009 n = 546	EXTRA n = 848	INNOVATE n = 419
Morning PEF (L/min)	8.9–11.5* (FAS)/10.8–13.5 (PP); $p < 0.05$	8.9–11.9†; $p < 0.05$	11.7–15.6†; $p < 0.001$	-	3.8–10.6*/8.9‡; $p = 0.065$
FEV_1 % predicted	4.12; $p = 0.001$	-	-	2.25; $p < 0.05$	2.84; $p = 0.043$
FEV_1 absolute values (mL)	114; $p = 0.002$	67–123§; $p < 0.05$	67–124§; $p < 0.05$	-	-

*Week 4–24; †Week 4–16; ‡Weeks 20–24; §Range difference between treatment groups

FAS, full analysis set; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; PP, per protocol analysis.

Table 3. Comparison of change from baseline in AQLQ, ACQ and GETE between the China study and predominantly Caucasian studies

	China Study n = 608	Study 008 n = 525	Study 009 n = 546	EXTRA n = 848	INNOVATE n = 419
AQLQ					
Overall score	0.40*; $p < 0.001$	0.29†; $p = 0.001$	0.28†; $p = 0.002$	0.23‡; $p = 0.005$	0.45†; $p < 0.001$
Symptom score	0.30*; $p = 0.001$	0.32†; $p = 0.001$	0.28†; $p = 0.006$	0.18‡; $p = 0.046$	0.50†; $p < 0.001$
ACQ/Asthma symptom scores	−0.17§; $p = 0.002$ / −0.21¶; $p = 0.048$	$p < 0.05$ (t)¶ $p = 0.026$ (m) $p < 0.05$ (n) $p = 0.010$ (d)	$p = 0.001$ (t)¶ $p = 0.332$ (m) $p < 0.001$ (n) $p = 0.025$ (d)	−0.25§; $p = 0.038$	−0.26§; $p = 0.039$
GETE (%)					
Investigator's GETE responder (OMA vs PBO)	70.3 vs 50.7*; $p < 0.001$	53.1 vs 33.3; $p < 0.001$	66.2 vs 34.8; $p < 0.001$	71.2 vs 57.2‡ $p < 0.001$	60.5 vs 42.8; $p < 0.001$
Patient's GETE responder (OMA vs PBO)	71.9 vs 61.6; $p < 0.006$	60.6 vs 38.1; $p < 0.001$	69.5 vs 42.6; $p < 0.001$	78.8 vs 68.6; $p = 0.0026$	64.3 vs 43.3; $p < 0.001$

§ACQ; ¶Asthma symptom score: t = total, m = morning, n = nocturnal, d = daytime.
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; GETE, Global Evaluation of Treatment Effectiveness; OMA, omalizumab; PBO, placebo.
Note: Least squares mean unless otherwise stated.

Asthma control

Omalizumab showed a significant improvement in ACQ score in the Chinese population (LSMD at Week 24: −0.17; $p = 0.002$). Improvement in total asthma symptom score was observed following omalizumab treatment in both Chinese and Caucasian populations (**Table 3**).

GETE

A higher proportion of patients receiving omalizumab reported treatment effectiveness (excellent/good GETE score) as per investigator's evaluation at Week 16 in the China study ($p < 0.001$) and 008, 009, EXTRA and INNOVATE studies ($p < 0.001$, $p < 0.001$, $p = 0.0001$, and $p < 0.001$, respectively). A similar pattern was seen for the patients' evaluation of treatment response, which showed that patients receiving omalizumab achieved better asthma control compared with placebo across the studies (**Table 3**).

Asthma exacerbations

In the China study, a lower proportion of patients on omalizumab reported exacerbations versus placebo (7.2% vs 10.9%) and the rate ratio of 0.61 showed a trend in favor of omalizumab; however, statistical significance was not achieved ($p = 0.097$). When exacerbations were recorded by seasons in the China study, for spring, summer and autumn there was no difference in exacerbation rates between patients treated with omalizumab compared to those who received placebo. However, winter exacerbations were experienced by only 2 patients in the omalizumab group compared with 21 exacerbations in the placebo group. Overall effect on exacerbations, in terms of rate ratio, was consistent with Caucasian data with highly significant reductions in exacerbations recorded for studies 008 and 009 during the stabilization phase ($p = 0.006$ and $p < 0.001$) and steroid reduction phase ($p = 0.004$ and $p < 0.001$), respectively. In EXTRA and INNOVATE studies, the overall reduction in exacerbations of omalizumab versus placebo was also statistically significant ($p = 0.0058$ and $p = 0.042$, respectively; **Table 4**).

Table 4. Comparison of asthma exacerbation rates in patients with moderate-to-severe or severe allergic asthma between the China study and predominantly Caucasian studies

Comparison	China Study	Study 008*	Study 009*	EXTRA	INNOVATE†
Rate ratio (95% CI)‡	0.61	0.601	0.384	0.75	0.738
(OMA vs PBO);	(0.34 to 1.09);	(0.40 to 0.90);	(0.26 to 0.56);	(0.61 to 0.92);	(0.55 to 0.99);
p value	0.097	0.014	< 0.0001	0.0058	0.042

*For studies 008 and 009, rates are based on steroid stabilization phases only and analyzed with imputation; †Analysis adjusted for baseline exacerbations; ‡Poisson regression analysis.
CI, confidence interval; OMA, omalizumab; PBO, placebo.

Table 5. Most frequent adverse events, deaths and other serious or significant events in moderate-to-severe or severe allergic asthma between the China study and predominantly Caucasian studies

	China A2313		Study 008		Study 009		EXTRA		INNOVATE	
	Omalizumab N = 310 n (%)	Placebo N = 299 n (%)	Omalizumab N = 268 n (%)	Placebo N = 257 n (%)	Omalizumab N = 274 n (%)	Placebo N = 272 n (%)	Omalizumab N = 428 n (%)	Placebo N = 420 n (%)	Omalizumab N = 245 n (%)	Placebo N = 237 n (%)
Patients with any AE(s)	121 (39.0)	118 (39.5)	239 (89.2)	229 (89.1)	221 (80.7)	213 (78.3)	344 (80.4)	334 (79.5)	177 (72.2)	179 (75.5)
Death	1 (0.3)	0	0	1 (0.4)	0	0	0	3 (0.7)	0	0
SAEs*	8 (2.6)	11 (3.7)	7 (2.6)	7 (2.7)	9 (3.3)	3 (1.1)	40 (9.3)	44 (10.5)	29 (11.8)	37 (15.6)
Asthma exacerbation SAEs	5 (1.6)	7 (2.3)	1 (0.4)	2 (0.8)	0	6 (2.2)	17 (4.0)	13 (3.1)	18 (7.3)	25 (10.5)
Discontinued due to AEs	4 (1.3)	3 (1.0)	2 (0.7)	3 (1.2)	0	5 (1.8)	16 (3.7)	11 (2.6)	10 (4.1)	4 (1.7)

*For studies 008 and 009, SAEs does not include asthma exacerbations. For studies EXTRA and INNOVATE, SAE includes asthma exacerbations
AE, adverse event; SAE, serious adverse event

Supplementary Table 2. Incidence of most frequent adverse events by preferred term from Chinese and studies with predominantly Caucasian population (Study A2313, Study 008, 009, EXTRA and INNOVATE)

	A2313		008		009		EXTRA		INNOVATE	
	Omalizumab N = 310	Placebo N = 299	Omalizumab N = 268	Placebo N = 257	Omalizumab N = 274	Placebo N = 272	Omalizumab N = 428	Placebo N = 420	Omalizumab N = 245	Placebo N = 237
Any AE	121 (39.0)	118 (39.5)	239 (89.2)	229 (89.1)	221 (80.7)	213 (78.3)	344 (80.4)	334 (79.5)	177 (72.2)	179 (75.5)
URTI	40 (12.9)	39 (13.0)	84 (31.3)	76 (29.6)	40 (14.6)	47 (17.3)	96 (22.4)	93 (22.1)	11 (4.5)	13 (5.5)
Sinusitis	-	-	52 (19.4)	56 (21.8)	40 (14.6)	50 (18.4)	81 (18.9)	79 (18.8)	14 (5.7)	18 (7.6)
Pharyngitis	2 (0.6)	0	39 (14.6)	35 (13.6)	32 (11.7)	29 (10.7)	7 (1.6)	9 (2.1)	8 (3.3)	6 (2.5)
Rhinitis	2 (0.6)	2 (0.7)	22 (8.2)	8 (3.1)	26 (9.5)	27 (9.9)	3 (0.7)	1 (0.2)	8 (3.3)	6 (2.5)
Cough	4 (1.3)	2 (0.7)	20 (7.5)	23 (8.9)	17 (6.2)	19 (7.0)	25 (5.8)	29 (6.9)	10 (4.1)	13 (5.5)
Bronchitis	2 (0.6)	1 (0.3)	18 (6.7)	25 (9.7)	23 (8.4)	24 (8.8)	66 (15.4)	60 (14.3)	8 (3.3)	7 (3.0)
Headache	3 (1.0)	4 (1.3)	60 (22.4)	70 (27.2)	66 (24.1)	63 (23.2)	41 (9.6)	34 (8.1)	17 (6.9)	22 (9.3)
Nausea	1 (0.3)	0	18 (6.7)	16 (6.2)	-	-	18 (4.2)	14 (3.3)	11 (4.5)	5 (2.1)
Dyspepsia	-	-	17 (6.3)	31 (12.1)	-	-	5 (1.2)	2 (0.5)	3 (1.2)	1 (0.4)
Diarrhea	1 (0.3)	1 (0.3)	14 (5.2)	15 (5.8)	12 (4.4)	15 (5.5)	14 (3.3)	12 (2.9)	7 (2.9)	5 (2.1)
Viral URTI	0	2 (0.7)	71 (26.5)*	80 (31.1)*	85 (31.0)*	89 (32.7)*	9 (2.1)	13 (3.1)	7 9 (2.9)	11 (4.6)

*Viral infections were included for studies 008 and 009. AE, adverse event; URTI, upper respiratory tract infection

Safety analysis of omalizumab in Chinese versus Caucasian population

In Chinese patients, approximately 39% in both treatment groups experienced at least one AE during 24 weeks of treatment (**Table 5**). The most frequently reported AEs (≥ 5% in any class) were upper respiratory tract infection, asthma exacerbation and nasopharyngitis. In the Chinese patients, the incidence of death, SAEs, asthma exacerbations and discontinuations due to AEs was low and comparable between the treatment groups except for the preferred term of asthma (exacerbation), which was reported more frequently in the placebo group (2.3%) than in the omalizumab group (1.0%). Discontinuations due to SAEs, while infrequent, were slightly more common in the omalizumab group versus the placebo group (1.0% vs 0.3%). AEs leading to hospitalization or prolonged hospitalization were observed more frequently with placebo versus omalizumab (3.3% vs 1.9%). A lower proportion of Chinese (39%) versus predominantly Caucasian populations (study 008, 89.2%; study 009, 80.7%; EXTRA, 80.4% and INNOVATE, 72.2%) experienced an AE. The proportion of patients who experienced SAEs among the Chinese patients (2.6%) was similar to those in studies 008 (2.6%) and 009 (3.3%), but lower compared to those in EXTRA (9.3%) and INNOVATE (11.8%). One death due to asthma exacerbation was reported in the Chinese study, the patient having taken one dose of omalizumab the previous day. Although, the event was suspected to be related to study drug by the investigator, anaphylaxis was not cited as the reason. No deaths were reported in the omalizumab groups of the compared studies in predominantly Caucasian patients.

An overview of deaths, SAEs, asthma exacerbations and discontinuations due to AEs in the China and Caucasian studies are presented in **Table 5**. An overview of the most frequently reported AE by preferred term across studies were presented in **Supplementary Table 2**. The overall safety profile of omalizumab was comparable between Chinese and predominantly Caucasian populations.

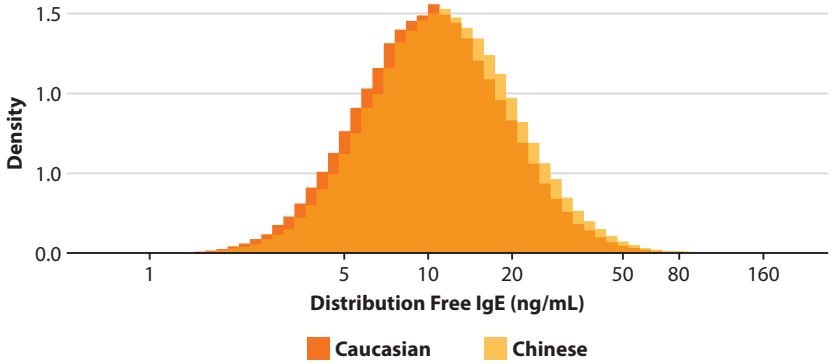
PK/PD profiles of omalizumab in Chinese versus Caucasian population

Mean maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to the time of the last quantifiable concentration point (AUC_{last}) after a single dose of omalizumab (150 mg) were higher in Chinese healthy subjects compared with an equivalent predominantly Caucasian population (**Table 6**). In Chinese subjects, the mean % decrease in free IgE at T_{min} was similar to that in predominantly Caucasian subjects, whereas the mean % increase of total IgE at T_{max} was similar to the A2204 study and higher in A2206 study. Population PK/PD analysis showed that, compared with Caucasian patients, Chinese patients exhibit 29% faster clearance of free omalizumab, 42% faster clearance of omalizumab-IgE complex and 20% increase in the equilibrium dissociation constant. Simulation was conducted using the final model to evaluate the impact of these differences on free IgE level in Chinese patients. As represented in **Supplementary Figure 1**, control of free IgE under steady state is very similar in Chinese and Caucasian patients. The observed small shift in free IgE distribution is negligible compared with variability in patients.

Table 6. Cross study comparison of PK/PD parameters between Chinese and predominantly Caucasian subjects following single subcutaneous dose of omalizumab 150 mg

	Chinese subjects	Predominantly Caucasian subjects	
	China PK/PD study N = 36	Global PK/PD study-1 N = 52	Global PK/PD study-2 N = 19
C_{max} (μg/mL)	22.0 ± 3.4	15.9 ± 4.4	14.2 ± 1.9
AUC_{last}, d*μg/mL	744 ± 95.4	594 ± 155	593 ± 65.3
AUC_{inf}, d*μg/mL	780 ± 106	659 ± 184	673 ± 86.3
T_{max}, median days (range)	5 (2–10)	7 (1–14)	7 (3–10)
$T_{1/2}$, days	**21.0 ± 6.0**	23.8 ± 4.3	25.5 ± 4.0
Free IgE C_{min}, ng/mL	7.46 ± 5.45	6.64 ± 3.66	5.92 ± 2.72
Total IgE C_{max}, ng/mL	624 ± 278	798 ± 392	810 ± 225
% decrease of free IgE at T_{min}	94.2 ± 1.9	94.9 ± 2.9	94.8 ± 2.4
% decrease of free IgE at T_{max}	436 ± 102	490 ± 253	714 ± 263

Data are mean ± standard deviation unless stated; AUC_{last}, area under the concentration-time curve from time zero to the time of the last quantifiable concentration point; AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum serum concentration; C_{min}, trough concentration; d, days; IgE, immunoglobulin E; PD, pharmacodynamics; PK, pharmacokinetics; $T_{1/2}$, half-life; T_{max}, time at which the maximum serum concentration is achieved; T_{min}, time at which the minimum concentration of serum free IgE is achieved.



Supplementary Figure 1. Distribution of simulated free immunoglobulin E concentration (ng/mL) in Chinese and Caucasian asthma patients treated with omalizumab
IgE, immunoglobulin E

Discussion

This is the first comparative analysis between omalizumab -treated Chinese and Caucasian populations. In the Chinese study and four studies with predominantly Caucasian population, omalizumab has been shown to be effective, with a favorable safety profile in patients with moderate-to-severe allergic asthma. Omalizumab had a positive effect on lung function, as demonstrated by improvements in mPEF and FEV_1, with simultaneous improvements in health status and symptom scores.[20]

The efficacy of omalizumab was comparable in both Chinese and Caucasian populations. The four studies (008, 009, EXTRA and INNOVATE) were selected as all had been conducted in a similar patient population in terms of severity of allergic asthma, and background therapy at baseline as the Chinese study, namely ICS and LABA. Reference was also made to the two studies, 008 and 009,[13,14] which were conducted from 1998–1999 when the use of ICS and LABA and ICS/LABA combinations were less consistent. Most patients in studies 008 and 009 were taking short-acting β_2-agonists with an ICS; hence, the concomitant medications differ from the more recent clinical studies. Since studies 008 and 009 were conducted, there have been significant changes in medical practice and international treatment guidelines. Despite this, these two double-blind randomized placebo-controlled studies provide high quality, valuable data for a number of clinical evaluations to compare with the China study.

The clinical efficacy in Chinese patients is strikingly similar to data observed in Caucasian patients in the pivotal studies. Although the mPEF marginally missed reaching statistical significance, there were statistically significant improvements in lung function (trough FEV_1), symptom control (ACQ) and health-related quality of life (AQLQ), which met or exceeded the threshold for clinically meaningful improvement. The investigator's and the patient's global evaluations of treatment effectiveness (GETE) scores were significantly greater in the omalizumab group compared to placebo in the Chinese study, which was consistent with the results in Caucasian patients.[13-16,21]

Although the Chinese study was not powered to detect a difference in the rate of pre- and post-treatment exacerbations, there was a numeric trend in the omalizumab-treated patients in terms of reduction of exacerbations and a risk reduction that was consistent with Caucasian data,[13-16,21] although this did not reach statistical significance. Of interest is the finding that during the winter season there were 21 patients on placebo who experienced exacerbations compared to only 2 patients on omalizumab. Omalizumab demonstrated statistically significant benefit in the four Caucasian studies that were designed to study exacerbations. Omalizumab was proven to be effective in Chinese patients in concordance with the pivotal studies on Caucasian patients.

Compared with Caucasian studies, the safety profile of omalizumab remains unaltered in light of the outcomes in Chinese patients. The overall incidence of AEs, including asthma exacerbations, was comparable between the two treatment groups in Chinese patients with a similar trend observed in the predominantly Caucasian patients.[13-16,21] SAEs, AEs leading to discontinuation, and other clinically significant AEs occurred at low rates in both treatment groups and showed no clinically meaningful trends. There was no consistent indication of a higher incidence for any system organ class or preferred term with omalizumab versus placebo in Chinese patients.

In support of the similarity of clinical efficacy and safety in Chinese patients compared with other populations, PK/PD analysis showed a similar exposure to omalizumab and inhibition of free IgE. Most importantly, simulation with the final population PK/PD model showed that both Chinese and Caucasian patients had sufficient suppression of free IgE for clinical benefit, with median free IgE below 25 ng/mL, and below 50 ng/mL in over 95% patients.[22] The comparisons in the current analysis were aligned with published efficacy and safety findings of omalizumab.[23-28]

In our study, we found that omalizumab showed similar efficacy and tolerability in both Caucasian and Chinese patients. Therefore, Chinese patients are likely to respond to omalizumab when administration is based on the GINA strategy and clinically tested algorithms for managing Caucasian patients.[29] However, the comparative analysis was not statistically tested and efficacy and safety were measured at different time points across studies. Moreover, although 24 weeks is a reasonable study period to assess lung function and patient reported outcomes, it is too short to measure exacerbation rates. Therefore, we recommend caution while interpreting these results.

More adequately powered prospective studies in Chinese versus predominantly Caucasian patients are required to draw a clearer conclusion.

Conclusions

Omalizumab showed comparable effectiveness and safety in Chinese and Caucasian populations. This was further supported by the results from PK/PD model. Overall data indicate a favorable benefit-risk profile, and are in line with the previous findings of omalizumab which supports its use for the treatment of moderate-to-severe allergic asthma in Chinese patients.

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Declaration of interest

- Ioannis Kottakis is an employee and stockholder of Novartis Pharma AG. Jing Yang,
- Linda Wang, Abhijit Pethe, Xinting Wang and Robert Fogel are employees of Novartis.
- Michael Humphries was an employee of Novartis during the conduct of the study.
- All other authors have nothing to disclose.

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Author Contributions

All authors contributed to the conception of the study and were involved in the development and final approval of the manuscript.

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