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Original article

Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma

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AEs, adverse events; ER, emergency room; EOT, end of the treatment period; ELISA, enzyme-linked immunosorbent

ABSTRACT

Background: Omalizumab is effective and well-tolerated in children with moderate to severe allergic asthma. However, the effects of long-term treatment with omalizumab in this population haven't been well investigated. The objective of this study is to evaluate the long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with uncontrolled severe asthma.
Methods: Thirty-eight Japanese children (aged 7–16 years) who completed the 24-week treatment core study were included in an uncontrolled extension study, in which treatment with omalizumab continued until the pediatric indication was approved in Japan (ClinicalTrials.gov number: NCT01328886).
Results: Thirty-five patients (92.1%) completed the extension study. The median exposure throughout the core and extension studies was 116.6 weeks (range, 46.9–151.1 weeks). The most common adverse events were nasopharyngitis, influenza, upper respiratory tract infection, and asthma. Serious adverse events developed in 10 patients (26.3%), but resolved completely with additional treatments. Incidence of adverse events didn't increase with extended exposure with omalizumab. Twenty-nine patients (76.3%) achieved completely- or well-controlled asthma compared with 9 patients (23.7%) at the start of the extension study. QOL scores, the rates (per year) of hospitalizations and ER visits were significantly improved compared with the baseline of the core study [39.0 vs 48.0 (median), $p < 0.001$ for QOL, 1.33 vs 0.16, $p < 0.001$ for hospitalization, 0.68 vs 0.15, $p = 0.002$ for ER visits]. Remarkably, the mean total IgE level showed a decreasing trend while exposure to omalizumab remained at steady-state.

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assay; FP, fluticasone propionate; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; JPAC, Japanese pediatric asthma control program; JPGL, Japanese pediatric guideline for the treatment and management of asthma; LOCF, last observation carried forward; LTRA, leukotriene receptor antagonist; LABA, long-acting β_2-agonist; QOL, quality of life; SAEs, serious adverse events

Conclusions: Long-term treatment with omalizumab is well-tolerated and effective in children with uncontrolled severe allergic asthma. No new safety findings were identified.

Introduction

Asthma in children is often poorly controlled, usually as a result of under-treatment with controller medications and poor inhaler technique; however, some children have poor asthma control despite current optimal therapies with high-dose inhaled corticosteroid (ICS) plus long-acting β_2-agonist (LABA) or leukotriene receptor antagonist (LTRA) or theophylline.[1,2] Uncontrolled severe asthma results in a high risk of asthma exacerbations and impaired quality of life.[3] Asthma exacerbations are associated with hospital admissions and emergency room (ER) visits,[4] time lost from work and school[5] and decline in lung function.[6] In addition, a history of asthma exacerbation increases the risk of further asthma exacerbations requiring hospitalizations, ER visits or corticosteroids bursts.[7] Asthma exacerbations are frequently treated with systemic [oral or intravenous] corticosteroids, which, if used in multiple bursts over a period of years, could be associated with a reduction in bone mineral accretion and increased risk for osteopenia.[8] Chronic use of high dose ICS was also found to result in a suppression of growth velocity and adrenal function.[8,9]

Omalizumab, a humanized monoclonal anti-IgE antibody, is indicated for the treatment of moderate to severe allergic asthma that is inadequately controlled despite current recommended therapies.[10–12] Several randomized placebo-controlled studies, which have shown a significant decrease in asthma exacerbations, have established omalizumab as an effective and well-tolerated agent for use as add-on therapy in pediatric patients with moderate to severe asthma.[13–15] We also have previously demonstrated the noticeable clinical effects of omalizumab in Japanese children (6–15 years) with severe asthma in a 24-week treatment, single-arm, open-label phase III study.[16] However, especially in childhood asthma population, effects of long-term treatment with omalizumab have remained to be investigated. Therefore, to evaluate comprehensively the long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma in a condition close to a real-life, we conducted a single-arm, open-label phase III extension study following the 24-week core study.[16]

Methods

Study design and patients

This multicenter, single-arm, open-label phase III study, conducted at 15 centers in Japan, was an extension to the 24-week treatment core study in Japanese children (6–15 years) with uncontrolled severe allergic asthma despite ICS (>200 μg/day fluticasone propionate [FP] or equivalent) and two or more controller therapies out of LTRA, LABA, theophylline, sodium cromoglycate, and oral corticosteroid.[16] The extension study consisted of a treatment period and an optional follow-up investigation for anti-omalizumab antibodies at 16 weeks after the last dosing (Fig. 1). The start of the extension study (restarting of treatment with omalizumab) was on the same day of the follow-up investigation for anti-omalizumab antibodies of the core study, and administration of omalizumab continued until the pediatric indication was approved in Japan (20-Aug-2013).

Patients who completed the core study and who in the investigator's clinical judgment benefited from continued treatment with omalizumab were eligible for the extension study. Patients

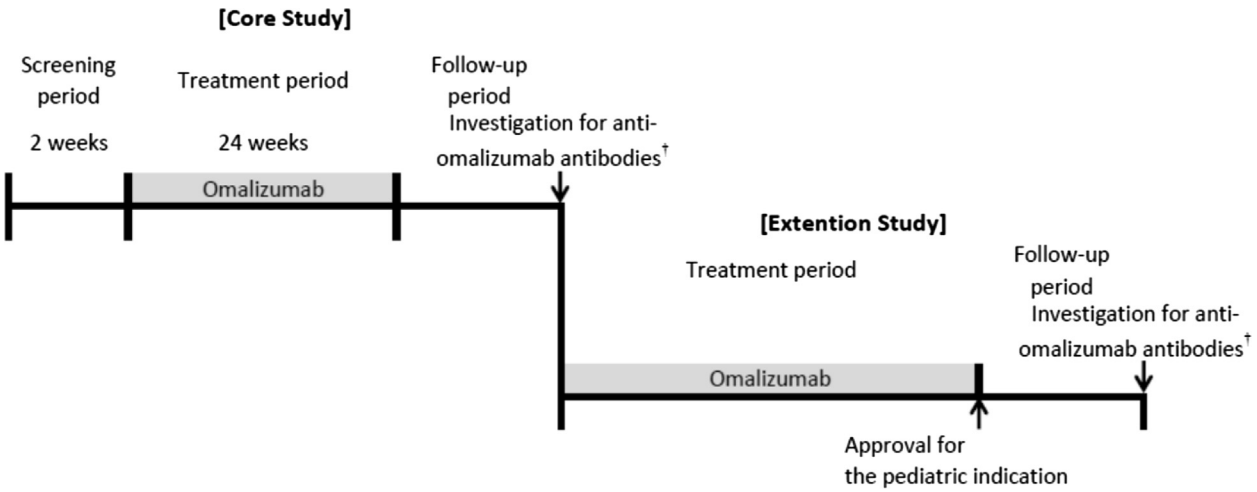

Fig. 1. Study design. This study was extension to the core study which included a 2-week screening period, a 24-week treatment period, and a follow-up investigation for anti-omalizumab at 16 weeks after the last dosing. The extension study consisted of a treatment period and an optional follow-up investigation for anti-omalizumab antibody at 16 weeks after the last dosing. Start of the extension study (restarting of treatment with omalizumab) was at the same day of follow-up investigation for anti-omalizumab antibody of the core study, and the treatment with omalizumab lasted until omalizumab was approved for the pediatric indication in Japan (20-Aug-2013). †16 weeks after the last dosing.

were excluded if they had a serious medical condition (e.g. cancer, hepatic failure, renal failure).

Omalizumab 75–375 mg was administered every 2 or 4 weeks by subcutaneous injection, with a dose and dose frequency the same as in the core study unless there were significant changes in body weight. If a dose adjustment was required, it was determined by the serum total IgE level (IU/mL) at the start of the core study and the updated (current) body weight (kg) according to the standard dosing table.[16]

Use of any asthma medications in line with the Japanese pediatric guideline for the treatment and management of asthma 2008 (JPGL2008)[17] were allowed throughout the extension study. No prohibited medications were applied.

The extension study was conducted in accordance with good clinical practice and the Declaration of Helsinki, and the protocol was approved by each institution's ethics committee. Parents or legal guardians were informed of study procedures and medications, and provided written informed consent before their child's enrollment. The extension study was registered at http://clinicaltrials.gov with the identifier: NCT01328886.

Study assessments

The objectives of the extension study were to evaluate long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma.

The primary outcome was the long-term safety and tolerability of omalizumab. Safety assessments consisted of recording adverse events (AEs) and serious adverse events (SAEs) during the treatment period, vital signs, and any clinically significant changes in laboratory values that were evaluated at 1 month, 3 months and 6 months after the start of the extension study and every 6 months thereafter. Anti-omalizumab antibodies (IgG) were optionally measured at 16 weeks after the final dose using an enzyme-linked immunosorbent assay (ELISA) as previously described.[18]

The other outcomes included asthma control, quality of life (QOL), use of asthma controller medications, and spirometry measurements that were evaluated every 3 months, the number of hospitalizations and emergency room (ER) visits due to asthma, and serum trough concentrations of omalizumab, free and total IgE measured every 6 months.

Asthma control was assessed according to Japanese pediatric asthma control program (JPAC) questionnaire,[19] which consisted of 5 questions scored between 0 and 3 each (0 = severe impairment; 3 = no impairment), using the following scale: Completely controlled (maximum score; 15 points), Well-controlled (12–14 points), Not controlled (11 points or less). QOL was measured using the "QOL questionnaire for pediatric patients with bronchial asthma and their parents or caregivers-short form version 2008 (Gifu)",[20] which consists of a physical (sum of the components of asthma attack, instability of symptoms, exercise load) and an emotional (sum of the components of emotional burden and proper acceptance of asthma) domain, with each component consisting of 2 items each scored between 1 and 5 (1 = severe impairment; 5 = no impairment). Total IgE concentrations were quantified by the ImmunoCAP100 (Phadia, Uppsala, Sweden) and free IgE and omalizumab concentrations were determined using previously reported ELISAs.[21,22]

The evaluation of asthma control based on JPAC questionnaire was conducted during the extension study only and the other assessments were performed throughout the core and extension studies.

Statistical analysis

The all safety and efficacy analyses were performed on the population, which consisted of all patients who received at least one dose of omalizumab during the extension study. The pharmacokinetics and pharmacodynamics variables were analyzed in the population which consisted of all patients who received at least one dose of omalizumab and had at least one serum concentration data during the extension study.

Descriptive statistics were used to summarize safety and efficacy variables. Asthma control evaluated by JPAC scores and mean JPAC scores were summarized by visit. The 95% CIs for the mean change from baseline in JPAC scores were calculated and p-values were provided using the one sample t-test at each post-baseline visit. The frequencies of hospitalizations or ER visits for asthma and QOL scores during the extension study were compared with the baseline of the core study within patient using the Wilcoxon signed-rank test in patients with a value at both baseline and a

Table 1
Demographic and clinical characteristics at the start of the studies.

	Core study	Extension study
	N = 38	*N* = 38
Age (years), mean (SD)	10.7 (2.46)	11.5 (2.52)
Age distribution (years), *n* (%)		
6–9	14 (36.8)	11 (28.9)
≥10	24 (63.2)	27 (71.1)
Sex, *n* (%)		
Male	23 (60.5)	23 (60.5)
Female	15 (39.5)	15 (39.5)
Duration of asthma (years), mean (SD)	8.4 (3.05)	9.3 (3.08)
Total serum IgE (IU/mL), median (range)	335.5 (33.6–1050.0)	–
$FEV_{1.0}$ (% of predicted), mean (SD)	90.3 (19.34)	89.8 (18.63)[†]
$FEF_{25-75\%}$ (% of predicted), mean (SD)	76.3 (27.23)	75.0 (28.11)[†]
Number of hospitalizations due to asthma in the previous year, mean (SD)	1.4 (1.69)	–
≥1 hospitalizations due to asthma in the previous year, *n* (%)	22 (57.9)	–
Number of ER visits[‡] due to asthma in the previous year, mean (SD)	0.7 (1.09)	–
≥1 ER visits[‡] due to asthma in the previous year, *n* (%)	14 (36.8)	–
Asthma control evaluated by JPAC score		
Completely controlled	–	3 (7.9)
Well controlled	–	6 (15.8)
Not controlled	–	29 (76.3)
ICS dose (μg/day, fluticasone propionate equivalent)		
Mean (SD)	469.7 (199.84)	459.2 (207.58)
Median (range)	500 (250–1000)	450 (200–1000)
Asthma long-term control medications, *n* (%)		
Leukotriene receptor antagonists	37 (97.4)	36 (94.7)
Long-acting β_2-agonists	37 (97.4)	35 (92.1)
Sustained-release theophylline preparations	23 (60.5)	18 (47.4)
Sodium cromoglycate	3 (7.9)	2 (5.3)
Oral corticosteroids	0	0
Dosing regimen of omalizumab, *n* (%)		
Every 2 week	15 (39.5)	15 (39.5)
Every 4 week	23 (60.5)	23 (60.5)

ER, emergency room; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; JPAC, Japanese pediatric asthma program; SD, standard deviation.

[†] *n* = 37.

[‡] If hospitalization and ER visit occurred on the same day, the event is counted as hospitalization.

corresponding time point during the extension study. Comparisons of serum total IgE levels were made using Wilcoxon signed-rank test. For other efficacy variables, the changes during the extension study were summarized to compare with baseline of the core study. In by-visit summaries, missing values were imputed using the last observation carried forward (LOCF) approach, as appropriate. Values at the last visit of the extension study were summarized as the assessment of "the end of the treatment period (EOT)" regardless of the patient's study duration. Percent predicted values of each spirometry measurements were calculated according to the formula developed by the Japanese society of pediatric pulmonology.[23]

Results

Baseline demographics and clinical characteristics

A total of 38 patients completed the core study and entered the extension study. Of these, 35 patients (92.1%) completed the extension study. Three patients (7.9%) discontinued the extension study prematurely due to withdrawal of consent (2 patients) and unsatisfactory therapeutic effect (1 patient). The median exposure to omalizumab in the extension study was almost 2 years [92.4 weeks (range, 22.1–128.0 weeks)] and 13 patients (34.2%) experienced ≥104 weeks (2 years) of treatment, though the duration of exposure to omalizumab varied from patient to patient due to the different time (date) of the entry to the core study. The median exposure throughout the core and extension studies (excluding the follow-up period of the core study) was 116.6 weeks (range, 46.9–151.1 weeks) and 34 patients (89.5%) experienced ≥104 weeks of treatment. During the extension study, dose adjustment (increase) of omalizumab from that of the core study occurred in 17 patients (44.7%) due to significant increases in body weight.

Baseline demographics and clinical characteristics of the core and extension studies are shown in Table 1. No major differences were found between the studies. At the start of the extension study, all patients used ICS, with a mean dose (FP equivalent) of 459.2 μg/day – more than double the maximum approved dose (200 μg/day) for children in Japan – and most patients were using LTRA (94.7%) and LABA (92.1%), respectively. 29 Patients (76.3%) had inadequately controlled asthma as evaluated by the JPAC score.

Safety

All 38 patients experienced at least one AE during the treatment period. The most common AEs (≥30%, preferred term) were nasopharyngitis, influenza, upper respiratory tract infection, and asthma (Table 2A). Incidence of adverse events (system organ class) in every 24 weeks didn't increase with increased exposure to omalizumab (Table 2B).

Ten patients experienced at least one SAE during the treatment period; asthma (asthma exacerbation) in 7 patients (3 exacerbations in one patient; 2 exacerbations in one patient; an exacerbation in each 5 patients) and SAEs other than asthma in 4 patients (Tonsillitis bacterial and viral pharyngitis in one patient; peritonsillar abscess and lymphadenitis in one patient; appendicitis

Table 2A
Incidence of adverse events (preferred term) during the treatment period of the extension study.

	N = 38 *n* (%)
Patients with any adverse event	38 (100.0)
Discontinued due to adverse event	0
Patient with serious adverse events	10 (26.3)
Asthma (asthma exacerbation)	7 (18.4)
Other than asthma (asthma exacerbation)	4 (10.5)
Most frequent adverse events[†]	
Nasopharyngitis	20 (52.6)
Influenza	15 (39.5)
Upper respiratory tract infection	14 (36.8)
Asthma	13 (34.2)
Headache	11 (28.9)
Eczema	10 (26.3)
Pyrexia	9 (23.7)
Contusion	8 (21.1)
Enterocolitis	7 (18.4)
Pharyngitis	7 (18.4)
Stomatitis	7 (18.4)
Gastroenteritis	6 (15.8)
Ligament sprain	6 (15.8)
Vomiting	6 (15.8)
Conjunctivitis allergic	5 (13.2)
Upper respiratory tract inflammation	5 (13.2)
Urticaria	5 (13.2)
Acne	4 (10.5)
Injection site swelling	4 (10.5)
Otitis externa	4 (10.5)
Rhinitis allergic	4 (10.5)
Abdominal pain	3 (7.9)
Bronchitis	3 (7.9)
Constipation	3 (7.9)
Dermatitis allergic	3 (7.9)
Diarrhea	3 (7.9)
Growing pains	3 (7.9)
Hand fracture	3 (7.9)
Migraine	3 (7.9)
Myalgia	3 (7.9)
Pneumonia	3 (7.9)
Patients with any drug-related adverse events	11 (28.9)
Most frequent drug-related adverse events[†]	
Injection site swelling	4 (10.5)

[†] In three or more patients.

Table 2B
Incidence of adverse events (system organ class) in every 24 weeks during the treatment period of the core and the extension study (In three or more patients in any evaluation period).

Study	Core *N* = 38	Extension *N* = 38			
Period (weeks)	0–24	0–24	>24–48	>48–72	>72–96
	N = 38	*N* = 38	*N* = 36	*N* = 35	*N* = 35
System Organ Class	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total adverse events	36 (94.7)	37 (97.4)	32 (88.9)	30 (85.7)	23 (65.7)
Infections and infestations	31 (81.6)	27 (71.1)	23 (63.9)	19 (54.3)	17 (48.6)
Gastrointestinal disorders	11 (28.9)	11 (28.9)	10 (27.8)	7 (20.0)	7 (20.0)
Respiratory, thoracic and mediastinal disorders	14 (36.8)	9 (23.7)	9 (25.0)	12 (34.3)	2 (5.7)
Skin and subcutaneous tissue disorders	8 (21.1)	6 (15.8)	10 (27.8)	4 (11.4)	5 (14.3)
Injury, poisoning and procedural complications	6 (15.8)	5 (13.2)	7 (19.4)	10 (28.6)	3 (8.6)
General disorders and administration site conditions	11 (28.9)	10 (26.3)	5 (13.9)	3 (8.6)	1 (2.9)
Nervous system disorders	5 (13.2)	8 (21.1)	6 (16.7)	4 (11.4)	1 (2.9)
Musculoskeletal and connective tissue disorders	9 (23.7)	4 (10.5)	3 (8.3)	2 (5.7)	4 (11.4)
Eye disorders	2 (5.3)	4 (10.5)	4 (11.1)	4 (11.4)	1 (2.9)
Psychiatric disorders	0	3 (7.9)	1 (2.8)	0	0

and pneumonia in one patient; foot fracture in one patient). All SAEs were due to hospitalization. One patient discontinued the extension study during the SAE of asthma (asthma exacerbation) due to unsatisfactory therapeutic effect, because the investigator considered omalizumab was not effective for the improvement of asthma symptoms. Only the SAE of peritonsillar abscess was suspected to be drug-related by the investigator. The investigator reported that the event was highly considered due to upper respiratory tract infection because upper respiratory inflammation caused by virus infection had developed 17 days before it and continued. However, as the event developed 5 days after the latest administration of omalizumab, its relation with omalizumab was not completely denied and judged as drug-related (The category of causal relationship with the drug in the extension study was "related" or "not-related"). The event resolved completely in 8 days with additional treatments of hydrocortisone sodium succinate (Saxizon® for injection), sulbactam sodium and ampicillin sodium (Sulbacillin® for injection), and glucose-electrolyte solution (Soldem® 3A).

No AEs of particular clinical interest of anaphylactic reactions, malignancies, serum sickness, Churg-Strauss syndrome, thrombocytopenia, or arterial thromboembolic events were reported during the treatment period. Follow-up investigation for anti-omalizumab antibodies was performed in 10 patients and no anti-omalizumab antibodies were detected.

Asthma control evaluated by JPAC score during the extension study

Treatment with omalizumab led to marked improvements in asthma control as assessed by JPAC score (Fig. 2). At the end of the treatment period, 29 patients (76.3%) achieved complete or well-controlled asthma compared with 9 patients (23.7%) at the start of the extension study. The JPAC score itself also showed a statistically significant improvement. The mean JPAC score (SD) was 9.9 (2.80) at the start of the extension study, and the mean change from baseline (95% CI) was [2.6 (1.5, 3.6), $p < 0.001$ one sample t-test] at week 48, [2.9 (1.9, 3.8), $p < 0.001$ one sample t-test] at week 96, and [3.0 (2.0, 4.0), $p < 0.001$ one sample t-test] at the end of the treatment period, respectively.

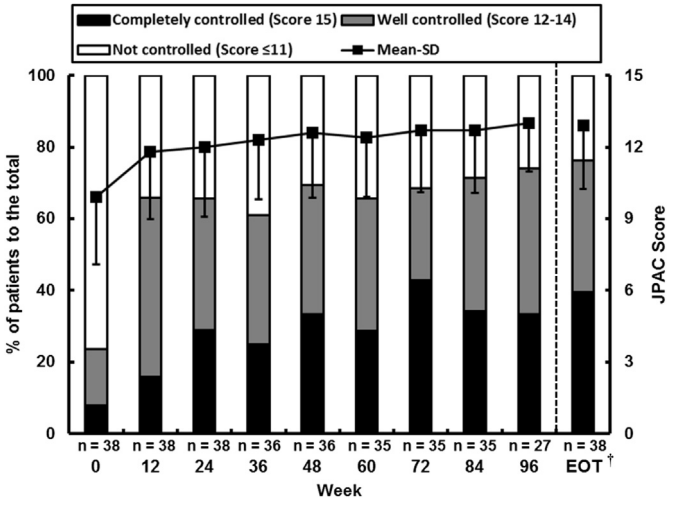

Fig. 2. Patients' asthma control (completely controlled, well controlled, not controlled) and JPAC score over the treatment period of the extension study. Data points are mean and vertical bars are standard deviation in JPAC score. †EOT: Values at the last visit of the extension study were summarized as the assessment of "the end of the treatment period (EOT)" regardless of the patient's study duration.

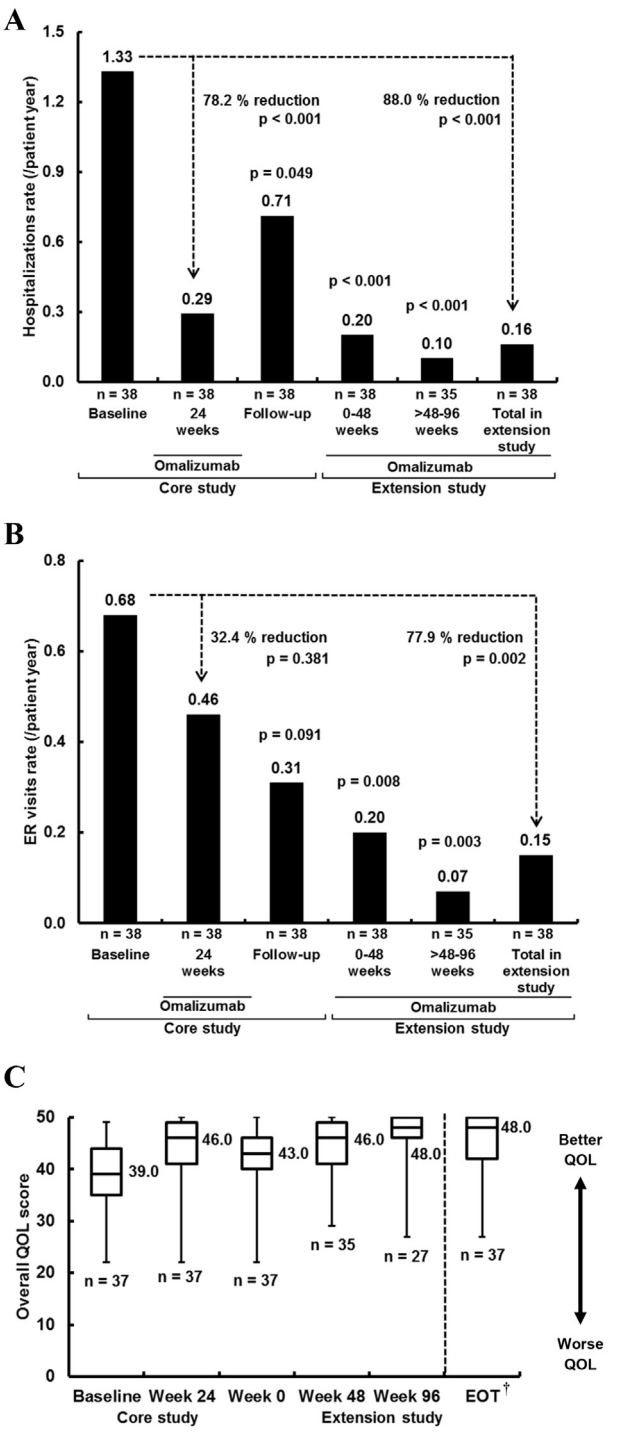

Fig. 3. Rate (per patient-year) of hospitalizations **(A)** and ER visits **(B)** due to asthma over each evaluation periods [core study: baseline (previous 12 months before the start of the core study plus the screening period), 24 weeks of the treatment period, follow-up period, extension study: 0–48 weeks and >48–96 weeks of the treatment period, total treatment period]. Each rate was derived from the total number of events observed during the corresponding evaluation period divided by the total amount time/exposure (in years) of the patients in that period. If hospitalization and ER visit occurred on the same day, the event was counted as a hospitalization. Overall QOL score over the core study and the extension study **(C)**. The boxes indicate the median, the 25th and 75th percentiles, whereas the extremes represent the minimum and maximum values. The analysis was performed in patients who had a baseline and at least one post-baseline assessment of QOL ($n = 37$). QOL was measured using the "QOL questionnaire for pediatric patients with bronchial asthma and their parents or caregivers-short form version 2008 (Gifu)". †EOT: Values at the last visit of the extension study were summarized as the assessment of "the end of the treatment period (EOT)" regardless of the patient's study duration.

Hospitalizations and ER visits due to asthma

The rate of hospitalizations due to asthma per patient-year was 0.16 over the all treatment period during the extension study, compared with 1.33 at baseline of the core study (previous 12 months before the start of the core study plus the screening period), representing a reduction of 88.0% versus baseline ($p < 0.001$ Wilcoxon signed-rank test, Fig. 3A). In addition, the rate of hospitalizations during the two evaluation periods (0–48 weeks, >48–96 weeks) of the extension study and that of the 24-week treatment period of the core study were comparable. The rate of ER visits per patient-year during the all treatment period of the extension study was significantly lower compared with the baseline (0.68 vs 0.15, $p = 0.002$ Wilcoxon signed-rank test, Fig. 3B). In addition, the rates of ER visits during the two evaluation periods (0–48 weeks, >48–96 weeks) of the extension study tended to be lower than that of the 24-week treatment period of the core study, which is insignificant.

Quality of life

Overall QOL scores at week 48, week 96 and the end of the treatment period of the extension study reached almost the upper limit of the ranges (Fig. 3C), and showed statistically significant improvements compared with the baseline of the core study [Median, 39.0 ($n = 35$) vs 46.0 ($n = 35$) for week 48, 42.0 ($n = 27$) vs 48.0 ($n = 27$) for week 96, 39.0 ($n = 37$) vs 48.0 ($n = 37$) for end of the treatment period, $p < 0.001$ respectively, Wilcoxon signed-rank test]. Similar results were obtained in physical domain and emotional domain scores, respectively [e.g. median, 24.0 (baseline, $n = 37$) vs 29.0 (end of the treatment period, $n = 37$) for the physical domain, and 15.0 (baseline, $n = 37$) vs 19.0 (end of the treatment period, $n = 37$) for the emotional domain ($p < 0.001$ respectively, Wilcoxon signed-rank test)].

Use of asthma controller medications

Use of long-term control medications for asthma is summarized in Table 3A. At the end of the treatment period of the extension study, the number of patients who used theophylline was almost half compared with the baseline of the core study [23 patients (60.5%) vs 12 patients (31.6%)]. Fifteen patients (39.5%) stopped at least one asthma long-term control medication compared with the baseline of the core study, while 8 patients (21.1%) at the end of the treatment period of the core study. Although all patients used ICS throughout the core and extension studies, 14 patients (36.8%) had dose reductions of ICS compared with baseline of the core study, while only one patient (2.6%) had a dose increase (increase of 100 μg/day) (Table 3B). The change from baseline of the core study in mean ICS doses (% change) was −64.5 μg/day (−13.2%).

Spirometry measurements (FEV_1 and $FEF_{25–75\%}$)

Little changes were observed in mean FEV_1 (% predicted) and $FEF_{25–75\%}$ (% predicted) values throughout the core and extension studies [e.g. mean (SD), 90.3 (19.34)% at the baseline of the core study vs 89.2 (15.83)% at the end of the treatment period of the extension study for FEV_1 (% predicted), and 76.3 (27.23)% at the

Table 3A
Summary of usage of asthma long-term controller medications.

Asthma long-term medications	Core study $N = 38$, n (%)		Extension study $N = 38$, n (%)			
	Baseline	End of treatment	Week 0	Week 48	Week 96	End of treatment
	$N = 38$	$N = 38$	$N = 38$	$N = 36$	$N = 27$	$N = 38$
Inhaled corticosteroid	38 (100)	38 (100)	38 (100)	36 (100)	27 (100)	38 (100)
Leukotriene receptor antagonists	37 (97.4)	35 (92.1)	36 (94.7)	33 (91.7)	25 (92.6)	35 (92.1)
Long-acting β_2-agonists	37 (97.4)	34 (89.5)	35 (92.1)	31 (86.1)	24 (88.9)	33 (86.8)
Sustained-release theophyllines	23 (60.5)	19 (50.0)	18 (47.4)	12 (33.3)	9 (33.3)	12 (31.6)
Sodium cromoglycate	3 (7.9)	2 (5.3)	2 (5.3)	0	0	0
Patients with stopping any medications compared to baseline	–	8 (21.1)	8 (21.1)	15 (41.7)	12 (44.4)	15 (39.5)
≥3 medications stopped	–	1 (2.6)	1 (2.6)	1 (2.8)	0	1 (2.6)
2	–	0	0	2 (5.6)	2 (7.4)	3 (7.9)
1	–	7 (18.4)	7 (18.4)	12 (33.3)	10 (37.0)	11 (28.9)
Patients with adding any medications compared to baseline	–	0	1 (2.6)	0	0	0

Table 3B
Summary of usage of Inhaled corticosteroid (ICS).

	Core study $N = 38$, n (%)		Extension study $N = 38$, n (%)			
	Baseline	End of treatment	Week 0	Week 48	Week 96	End of treatment
	$N = 38$	$N = 38$	$N = 38$	$N = 36$	$N = 27$	$N = 38$
No of patients with ICS	38 (100)	38 (100)	38 (100)	36 (100)	27 (100)	38 (100)
Mean (SD), (μg/day)	469.7 (199.84)	455.3 (211.11)	459.2 (207.58)	430.6 (202.58)	392.6 (243.65)	405.3 (210.79)
Median (range), (μg/day)	500 (250–1000)	450 (200–1000)	450 (200–1000)	400 (200–1000)	350 (200–1000)	400 (200–1000)
No of patients with reduction of ICS doses compared to the baseline	–	4 (10.5)	5 (13.2)	9 (25.0)	12 (44.4)	14 (36.8)
>400 (μg/day) of reduction	–	0	1 (2.6)	1 (2.8)	1 (3.7)	1 (2.6)
>200–400 (μg/day)	–	1 (2.6)	1 (2.6)	1 (2.8)	3 (11.1)	3 (7.9)
>100–200 (μg/day)	–	1 (2.6)	1 (2.6)	3 (8.3)	2 (7.4)	2 (5.3)
>50–100 (μg/day)	–	0	0	0	1 (3.7)	2 (5.3)
>0–50 (μg/day)	–	2 (5.3)	2 (5.3)	4 (11.1)	5 (18.5)	6 (15.8)
No of patients with increase of ICS doses compared to the baseline	–	0	2 (5.3)	1 (2.8)	0	1 (2.6)

ICS, inhaled corticosteroid.

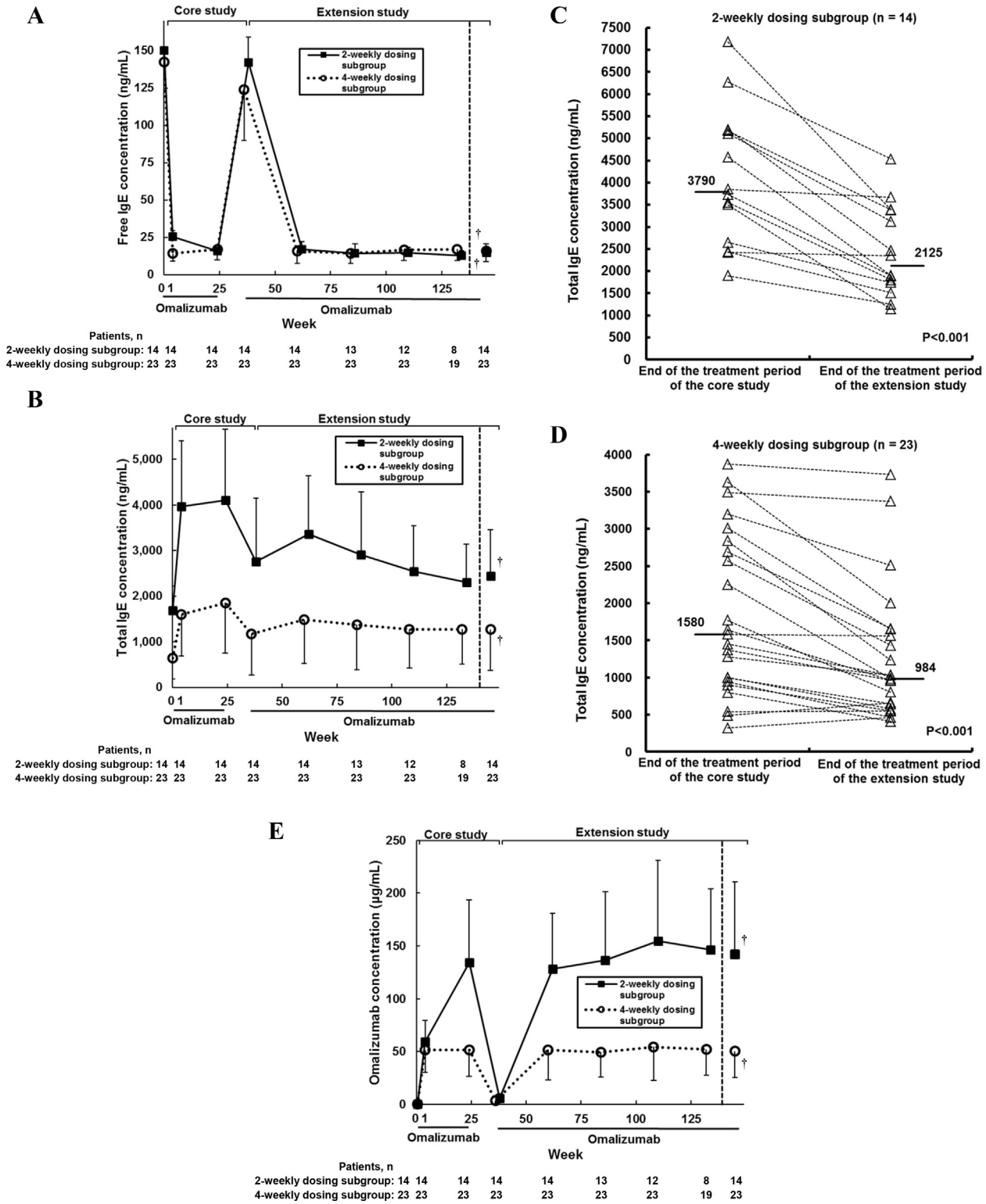

Fig. 4. Mean (SD) plots over the core study and the extension study in **(A)** Free IgE concentrations (ng/mL), **(B)** Total IgE concentrations (ng/mL) and **(E)** omalizumab concentrations (μg/mL) in dosing subgroups (every 2 weeks or 4 weeks dosing). For free IgE, if an observed value exceeded an upper limit of quantification, 150 (ng/mL), the value was summarized as 150 (ng/mL). Comparison of serum total IgE levels between the end of the treatment period of the core study (week 24) and that of the extension study in dosing subgroups of every 2 weeks **(C)** and every 4 weeks **(D)**. Each symbol shows an individual value; horizontal bars are median values. The analyses were performed in patients who received at least one dose of omalizumab and had at least one serum concentration data during the extension study ($n = 37$). †EOT: Values at the last visit of the extension study were summarized as the assessment of "the end of the treatment period (EOT)" regardless of the patient's study duration.

baseline of the core study vs 75.1 (23.71)% at the end of the treatment period of the extension study for $FEF_{25-75\%}$ (% predicted)].

Serum free IgE, total IgE and omalizumab levels

In both dosing subgroups (every 2 weeks or 4 weeks), mean serum free IgE levels prior to the first dose of the extension study (at the end of the washout of omalizumab during the follow-up period of the core study) increased to 125–150 ng/mL (Fig. 4A). After restarting treatment with omalizumab, the mean serum free IgE levels were again suppressed below 25 ng/mL throughout the treatment period of the extension study.

Mean serum total IgE levels during the extension study were lower than those in the core study and exhibited a decrease with time in both dosing subgroups which was more noticeable for those taking omalizumab every 2 weeks (Fig. 4B). Serum total IgE levels at the end of the treatment period of the extension study showed a 43.9% reduction in 2-weekly dosing subgroup and 37.7% reduction in 4-weekly dosing subgroup respectively, compared with that at the end (week 24) of the treatment period of the core study [Median, 3790 ng/mL vs 2125 ng/mL, $p < 0.001$, for 2-weekly dosing subgroup (Fig. 4C), 1580 ng/mL vs 984 ng/mL, $p < 0.001$, for 4-weekly dosing subgroup (Fig. 4D)].

Mean trough omalizumab levels during the extension study were comparable to those in the core study (Fig. 4E).

Discussion

This is, to the author's knowledge, the first study to investigate, comprehensively, the clinical safety, efficacy and pharmacological effects of long-term treatment with omalizumab in children with uncontrolled severe asthma. Almost 90% of the patients received ≥104 weeks of treatment with omalizumab throughout the core and extension studies, though the duration of exposure to omalizumab varied from patient to patient.

At the start of the extension study approximately 80% of the patients had inadequately controlled asthma evaluated by JPAC score, although all patients used ≥200 μg/day of ICS (corresponding to high dose ICS in JPGL2008) and 90% or more patients used LTRA and LABA, respectively. In addition, some of the efficacy parameters including QOL score and rate of hospitalization seemed to worsen compared with those at the end of the 24-week treatment period (week 24) of the core study. This might be due to the 16-week-follow-up after the last dosing of omalizumab in the core study, in which omalizumab was not administered, enabling free IgE levels to return toward baseline. This is consistent with the previous report showing that withdrawal of omalizumab after less than a year of treatment resulted in a return to the pre-treatment clinical state within a few months.[24]

The safety profile of omalizumab in the extension study was comparable to that observed in previous studies,[13–16] and no new safety concerns were identified. In addition, there was no trend toward an increase in incidence of adverse events with prolonged exposure to omalizumab. Of all SAEs, peritonsillar abscess was suspected to be drug-related, but completely resolved with additional treatments. To the author's knowledge, there is no evidence that omalizumab induces increased susceptibility to viral or bacterial infection, where it might be associated with a modest increase in helminth infection rate in patients at chronic high risk of it.[25] In randomized placebo-controlled studies in children with asthma,[13–15,26] incidences of adverse events associated with viral or bacterial infections (e.g. nasopharyngitis, upper respiratory tract infection and influenza) in omalizumab groups were comparable with those in placebo groups. In addition, allergic asthma children have impaired antiviral response via IgE-dependent mechanism,[27,28] increasing the chance of frequent and severe virus-induced exacerbations,[29] and thus it may be possible that omalizumab affects that process.

Long-term treatment with omalizumab in the extension study led to marked and sustained improvements in asthma control evaluated by JPAC score, QOL, frequencies of hospitalizations and ER visits due to asthma, and use of asthma controller medications. In addition, the rates of hospitalizations and ER visits due to asthma during the two evaluation periods (0–48 weeks, >48–96 weeks) of the extension study were comparable with or lower than those in the 24-week treatment period of the core study. These results indicate that there is no loss of efficacy with increased exposure to omalizumab. Whether longer treatment with omalizumab provides more beneficial clinical effects or not should be further investigated.

Some previous studies investigated the ICS sparing effects of omalizumab[13–15,26,30] and the extent of ICS dose reduction differed according to the study designs and severity of the patients. However, as children with severe asthma are usually treated with high dose ICS and other controller medications, dose reduction of not only ICS but also other controller medications should be evaluated. At the end of the treatment period of the extension study, approximately 40% of the patients stopped at least one asthma long-term control medication and reduced ICS doses compared with baseline of the core study, respectively. Order and amount of reduction in asthma controller medications in the extension study was based on investigator's decision, and therefore, presenting the most appropriate scheme of reduction of asthma controller medications would be an important upcoming question.

The mean serum free IgE level was suppressed below 25 ng/mL (target level of suppression) throughout the treatment period of the extension study, supporting the long-term efficacy of omalizumab as described above.

Though there is the limitation of interpretation due to the small sample size and the study design (single-arm, open-label), these consistent improvements in asthma control with long-term treatment with omalizumab, which were first demonstrated in this extension study, would strongly support the role of omalizumab in the management of children with severe allergic asthma.

Overall, omalizumab was associated with little change in lung function throughout the core and extension studies though other clinical variables were markedly improved. It raises several possible hypotheses. One is that as study patients had early-onset (the mean age and duration of asthma at the baseline of the core study were 10.7 years and 8.4 years, respectively) severe persistent asthma, having frequent exacerbations despite receiving the current recommended therapies, they are thought to have less reversible changes in airway wall stricture.[31,32] Omalizumab, which is not a direct bronchodilator, might not be effective enough to show improvement in lung function in stable condition in such population though it has been shown to reduce allergen-induced bronchoconstriction in patients with mild or moderate asthma.[33,34] Another is that though spirometry is currently the most commonly used test to measure lung functions, impulse oscillometry, which is an alternative, noninvasive, and effort-independent approach[35,36] and could have greater sensitivity to detect peripheral airway obstruction,[37,38] has newly been developed. Therefore, it may be worth to be performed to find an effect undetectable by spirometry. The other is that considering a progressive decline in lung function over time observed in children and adolescents with severe asthma,[2,39] omalizumab could have benefit to prevent it, which requires much more time in follow-up to be proved.

Several randomized studies have established omalizumab is effective and well-tolerated as add-on therapy in pediatric patients

with moderate to severe allergic asthma,[13–15] but the impact of long-term treatment with omalizumab on the natural course of asthma has not been well-investigated. There is some evidence that omalizumab might have a disease-modifying effect. Nopp *et al.* reported that most of the patients who had stopped omalizumab after approximately 6 years of treatment had stable or improved asthma control for 3 years after stopping.[40] Lowe *et al.* have suggested by using the model-based pharmacokinetic–pharmacodynamic analysis that IgE production in patients with allergic asthma might be reduced during long-term treatment with omalizumab.[41] It is generally known that after initiation of omalizumab treatment, serum total IgE level is increased due to differences in metabolic pathways between free IgE and IgE-omalizumab complexes (longer metabolic half-life of IgE-omalizumab complexes than that of free IgE), kept at a constant increased level during the treatment of omalizumab, and decreased to the baseline level after cessation of omalizumab.[24,42] In the core study, serum total IgE level changed as previously reported. However, in this extension study, after restarting of treatment with omalizumab, serum total IgE levels was at first increased, but then demonstrated a decreasing trend, while exposure to omalizumab remained at a steady state. As a result, serum total IgE levels at the end of the treatment period of the extension study showed approximately 40% reduction compared to that at the end of the treatment period (week 24) in the core study. Considering that trough omalizumab levels were kept constant during the core and extension studies and that serum IgE levels in patients with asthma in childhood generally show an increasing trend,[43,44] this new observation of change in serum total IgE levels in the extension study may also indicate that longer exposure to omalizumab could reduce IgE production. There is a possibility that the decreasing trend of serum total IgE correlates with sustainable asthma control after cessation of omalizumab treatment; or growing out of asthma. However, after the extension study most patients continued treatment with omalizumab (Xolair®), and therefore, asthma control, total and free IgE levels after stopping long-term treatment with omalizumab could not be investigated. Further detailed study on IgE production and disease prognosis of asthma over long-term treatment with omalizumab should be required.

In conclusion, this study indicates that long-term treatment with omalizumab as add-on therapy to current standard of care is well-tolerated and effective in children with uncontrolled severe allergic asthma. Increase in safety risks or loss of efficacy with extended exposure to omalizumab was not identified.

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Conflict of interest

SN served as medical consultant funded by Novartis Pharma. NSa and NSe are employees of Novartis Pharma. The rest of the authors have no conflict of interest.

Authors' contributions

HO contributed to implementation of the study, interpretation of the data, and drafting the manuscript. ME, TN, TF, AA, KI, SD, KY, TK, KK, TT, KS, MN, AH, and SY contributed to implementation of the study, interpretation of the data and reviewing the manuscript. NSa contributed to the study design, implementation of the study, interpretation of the data, and drafting the manuscript. NSe contributed to analysis of the data and drafting the manuscript. SN gave advice on the study design, implementation of the study, interpretation of the data, and drafting the manuscript. All authors read and approved final manuscript.

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