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Montelukast in the treatment of perennial allergic rhinitis in paediatric Japanese patients; an open-label clinical trial

Kimihiro Okubo[a], Yoichi Inoue[b], Hirotaka Numaguchi[b], Kumi Tanaka[b], Itori Saito[b], Nobuyuki Oshima[b], Yuki Matsumoto[b], Marita Prohn[c], Anish Mehta[d], Chisato Nishida[b] and George Philip[d]

[a]Department of Otorhinolaryngology, Nippon Medical School Hospital, Tokyo, Japan; [b]MSD KK, Tokyo, Japan; [c]MSD, Oss, The Netherlands; [d]Merck & Co. Inc., Kenilworth, NJ, USA

ABSTRACT

Background: This study was conducted to evaluate the safety and tolerability, and population pharmacokinetics (PPK) of montelukast as well as efficacy in the treatment of perennial allergic rhinitis (PAR) in paediatric Japanese patients aged between 1 and 15 years.

Methods: In this multi-centre, open-label trial, 87 paediatric Japanese patients with PAR received montelukast 4 mg oral granules (OG) for 4 weeks (1–5-year-olds, $N = 15$), 4 mg OG for 12 weeks (1–5-year-olds, $N = 36$), 5 mg chewable tablets (CT) for 12 weeks (6–9-year-olds, $N = 18$), or 5 mg CT for12 weeks (10–15-year-olds, $N = 18$). Clinical exams and laboratory assessments were conducted at study visits, and adverse events (AE) were monitored throughout the study up to 14 days after the last visit. Population pharmacokinetic approach was used to estimate $AUC_{0-\infty}$, C_{max}, T_{max} and apparent elimination half-life in each age group. Efficacy was assessed based on global evaluations by the subject's caregiver.

Results: There were no serious AEs and one discontinuation due to an AE. The most common AEs in any of the treatment groups were nasopharyngitis, pharyngitis, and acute sinusitis. Montelukast exposure ($AUC_{0-\infty}$) was similar in the 1–5-year-old group and the 6–9-year-old group, but 19% lower in the 10–15-year-old group. Among all patients, the total proportion of patients whose global evaluation was "very much better" was 5.7% (week 2), 11.5% (week 4), and 16.9% (week 12) reflecting improvement in symptoms over time.

Conclusion: Montelukast was generally well tolerated in Japanese children with PAR. $AUC_{0-\infty}$was similar in 1–5 and 6–9-year-olds, while a lower exposure was observed in the 10–15-year-old group likely due to differences in bodyweight. The exposure in Japanese paediatric patients was generally consistent with that in non-Japanese paediatric and adult patients. As assessed by the patients' caregivers, montelukast also demonstrated symptomatic improvement based on global evaluations of PAR.

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Introduction

Allergic rhinitis (AR) is a condition associated with considerable morbidity in paediatric patients and is present as seasonal AR (SAR) or perennial AR (PAR). In addition to respiratory distress caused by AR, the condition is also often associated with concurrent conditions, such as chronic, recurrent rhinosinusitis, otitis media with effusion and asthma. The burden of AR is particularly disruptive in children who experience disturbances of sleep, decrease in school performance due to absenteeism, learning difficulties and distraction, as well as impairment in overall quality of life.[1–4]

The prevalence of AR in the general population has been estimated to be between 10 and 30% with up 40% of children affected worldwide.[5–7] Safe and effective treatment in paediatric populations is important considering the high and increasing prevalence of AR over time. This is of particular importance in Japan where the prevalence of AR has been estimated to be 39% in 2008, which is up from 30% in 1998. Much of this rise in Japan has been attributed to the rise in Japanese cedar pollinosis.[8]

Inflammatory factors that trigger AR symptoms are the primary targets for the treatment of AR. While nasal corticosteroids are the mainstay of treatment for AR, other treatments such as antihistamines and medications that inhibit cysteinyl leukotrienes have also demonstrated efficacy and may be important for comprehensive treatment of the condition.[9,10,11] Montelukast is a selective antagonist of cysteinyl-leukotriene receptor type 1. Although montelukast was

CONTACT Kimihiro Okubo, MD ent-kimi@nms.ac.jp Department of Otorhinolaryngology, Nippon Medical School Hospital, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan

Supplemental data for this article can be accessed here.

originally developed as a treatment for asthma, subsequent research has demonstrated efficacy in the treatment of AR in adults and children.[12,13]

Previous studies have demonstrated that montelukast is generally well tolerated with mild adverse events reported including upper respiratory tract infection, headache, pharyngitis, abdominal pain, nausea, and vomiting at frequencies similar to those observed with placebo in children and in adults.[10,11,14]

Pharmacokinetic evaluations have shown that a 5 mg chewable tablet (CT) in 6–14-year-old non-Japanese children and a 4 mg CT in 2–5-year-old children provide drug exposures (i.e. overall plasma concentrations or $AUC_{0-\infty}$) are similar to that provided by a 10-mg film-coated tablet in non-Japanese adults, which has demonstrated efficacy for the treatment of asthma and AR.[15,16]

This trial was conducted in order to assess the safety and tolerability of montelukast 4 mg oral granules (OG) in 1–5 year-old Japanese patients and 5 mg CT in 6–15 year-old Japanese patients for up to 12 weeks of treatment in subjects with PAR. A population pharmacokinetic (PPK) analysis was conducted based on plasma concentrations of montelukast obtained from these paediatric subjects. To evaluate montelukast 4 mg OG in 1–5-year-olds, a treatment duration of 4 weeks was chosen for the PPK analysis while a treatment duration of 12 weeks was chosen for evaluation of safety and tolerability. Therefore, the caregivers of subjects aged 1–5 years old had the opportunity to select between these two study durations. All 6–15-year-old Japanese patients received 5 mg CT for a 12-week duration, for evaluation of pharmacokinetics as well as safety and tolerability. Finally, efficacy was assessed in each treatment group based on global evaluations by the subject's caregiver.

Methods

This study (Clinical Trials Registry # NCT01852812, Sponsor Protocol P520) was conducted at 12 trial centres in Japan from Jun-2013 to Dec-2013. The protocol for the study was approved by local institutional review boards and ethical review committees and was conducted according to principles of Good Clinical Practice. Parents or legal guardians provided informed consent prior to participation in the study; patients provided consent if they were able to do so. This study was designed by MSD KK, Tokyo, Japan. Statistical analyses and PPK analyses were performed by the Clinical Biostatistics and Pharmacokinetics, Pharmacodynamics and Drug Metabolism departments of MSD KK, MSD Netherlands, and Merck & Co. Inc., respectively.

Subjects

Japanese male and female subjects with a diagnosis of perennial allergic rhinitis (classified as "Nasal blocked type" or "combined type"[8]) between the ages of 1 and 15 years old were enrolled in this study. Subjects were to be $\geq$8 kg. Female subjects who have begun menstruating were to demonstrate a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test and agreed to remain abstinent from heterosexual activity, or to use two adequate barrier methods of contraception to prevent pregnancy during this trial.

Subjects were excluded if they were diagnosed with asthma (past or present), acute rhinitis, simple (non-allergic) rhinitis, congestive rhinitis, atrophic rhinitis, sinusitis with purulent nasal discharge, rhinitis medicamentosa, or other types of nonallergic rhinitis (e.g. vasomotor rhinitis, eosinophilic rhinitis). A medical history of inferior concha mucosal resection, submucous resection of inferior Tubinates or other surgery on the nasal mucosa (including electrocoagulation, cryoextraction or application of trichloroacetic acid) led to exclusion from the trial. Use of the following treatments and procedures were prohibited within seven days of randomisation: antihistamine, leukotriene receptor antagonist, chemical mediator release inhibitor, steroids, biological preparations (e.g. immunoglobulin with histamine), anticholinergic, prostaglandin D2 receptor antagonist, thromboxane A2 receptor antagonist, β2-stimulants, decongestants for nasal/eye use, herbal medicine for anti-allergy, nebuliser (nasal/oral), or nasal therapeutic procedures (e.g. aspiration and irrigation). Treatment with any other clinical study drug within three months prior to screening was prohibited. The following conditions also led to exclusion from the trial: a total bilirubin $\geq$3.0 mg/dl, or AST or ALT $\geq$2.5-fold upper limit normal for the institution, a serum creatinine $\geq$2.0 mg/dl within 14 days before allocation; a clinically significant, active disease of the cardiovascular, or hematologic systems; or uncontrolled hypertension (1–5-year-olds; >120/70 mmHg, 6–9-year-olds; >130/80 mmHg, 10–15-year-olds; >140/85 mmHg), a medical history of stunted growth, or a serious drug allergy.

Study design

This multi-centre, open-label trial assessed the safety and pharmacokinetics of montelukast in Japanese paediatric subjects aged 1–15 years old with PAR. Approximately 1–2 weeks before allocation (screening period), potential subjects were evaluated to determine that they fulfilled the entry requirements. Treatment started from week 0 to week 4 or to week 12. There were four treatment groups in the trial: (1) 1–5-year olds receiving 4 mg OG (in a single sachet) for 4 weeks; (2) 1–5-year olds receiving 4 mg OG for 12 weeks; (3) 6–9-year olds receiving 5 mg CT (as a single tablet) for 12 weeks; (4) 10–15-year olds receiving 5 mg CT for 12 weeks once daily at bed time.

Blood samples for pharmacokinetic (PK) analysis were drawn around C_{max} and in elimination phase in two sampling groups: group A was at 1 h (allocation visit) and 22 h (week 4); group B was at 3 h (allocation visit) and 14 h (week 4) after treatment. At the allocation visit, subjects were assigned in a ratio of 1:1 to each sampling group by the central registration centre according to a computerised randomisation schedule.

The treatment period for subjects receiving 4 weeks of treatment included four study visits; visit 1 was 14 to 7 days before treatment (screening), visit 2 was Day 0 of the treatment period (baseline/allocation visit), visit 3 was Day 14/week 2, and visit 4 was Day 28/week 4. If a subject who

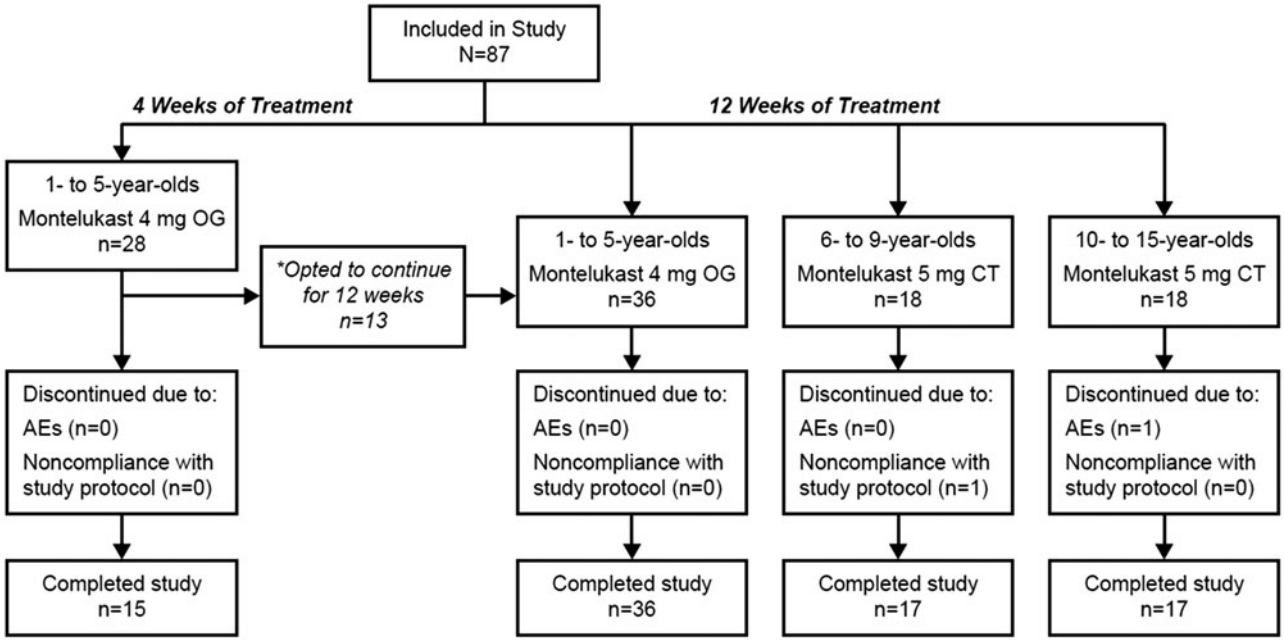

Figure 1. Account of patients throughout the study (CONSORT diagram). *13 of the 28 subjects allocated to the 1–5-year-old group receiving 4 weeks of treatment opted to continue to 12 weeks of treatment; the total number of 1–5-year-old subjects receiving 12 weeks of treatment is 36 including those who opted to extend their treatment period.

agreed initially to 4 weeks of treatment then agreed to extend treatment to 12 weeks, informed consent for 12 weeks treatment must have been obtained before proceeding after week 4. For patients who entered the 12-week treatment period or extended to 12 weeks of treatment, additional visits included visit 5 on Day 56/week 8, and visit 6 on Day 84/week 12. To assess for any serious adverse events (AE)s during 14 days after the last study drug administration, the subjects' caregiver was required to be in contact with investigator or trial staff by phone call.

The identity of the study medication and dosage was included on labels, so the subjects, study site personnel, and the study sponsor were not blinded to treatment. The design of this study is illustrated in Supplemental Figure 1.

Sample size

The sample size for this study was estimated using a one-compartment PK model to determine the number of subjects needed for PPK analysis. The target was to estimate the population AUC in each age group with a percent coefficient of variation (CV%) of ∼10%. With the proposed sampling scheme (two samples per subject), subject numbers needed for the PPK analysis were 40 for 1–5-year-olds, 14 for 6–9-year-olds and 14 for 10–15-year-olds. Thus, taking drop out (20%) into account, enrollment subject numbers were determined to be 48 for 1–5-year-olds, 18 for 6–9-year-olds and 18 for 10–15-year-olds.

Study objectives, hypotheses and endpoints

The first primary objective of this trial was to evaluate the safety and tolerability of montelukast 4 mg OG for 1–5-year-old children and 5 mg CT for 6–15-year-old children. The second primary objective of the trial was to conduct a population pharmacokinetic (PPK) analysis in children aged 1–15 years. The hypothesis for this trial was that the dose regimen of montelukast of 4 mg OG for 1–5 years old and 5 mg CT for 6–15 years old provides similar exposure of montelukast to historical PK data in previous paediatric PK studies of montelukast [15,17] based on the PPK analysis. The pharmacokinetic parameters included $AUC_{0-\infty}$, C_{max}, T_{max} and apparent elimination half-life ($t_{1/2}$) in each age group.

The exploratory objective of the trial was to assess the efficacy of montelukast by Global Evaluation of allergic rhinitis at week 2, 4 and 12. Caregivers assessed Global Evaluation of allergic rhinitis, although subjects provided assessments if the investigator approved; the person making the assessment was to be consistent throughout the trial. The Global Evaluation included six levels that included the following: (1) very much better; (2) somewhat better; (3) a little better; (4) the same; (5) worse; (6) unable to assess.

Safety evaluations

Safety was evaluated by conducting clinical examinations and laboratory tests at screening, week 4 or week 12 and monitoring AEs throughout the study. Investigators evaluated each AE to determine degree of severity and whether there was a relationship with the study medication. The percentage of patients with AEs and change in baseline in laboratory parameters was evaluated. Liver function tests that indicate drug-induced liver injury included AST or ALT levels three times higher than upper limit of normal range, total bilirubin levels at least two times higher than upper limit of normal

range, and alkaline phosphatase levels less than twice the upper limit of normal range.

Subjects were followed until 14 days after the last study drug administration in order to assess any additional AEs that arose upon discontinuation of study medication.

Sample handling and montelukast analysis

Blood samples were collected in glass tubes containing K_2EDTA. Samples were centrifuged immediately; plasma samples were stored at −70 °C and protected from exposure to light. Montelukast plasma concentration was determined using high-performance liquid chromatography with tandem mass spectrometry detection. The assay had a lower limit of quantitation of 5.0 ng/mL. Data below the lower limit of quantitation were assigned a value of 0 ng/mL. All assays were performed at PPD Inc. (Richmond, VA).

Statistical analysis of population pharmacokinetic parameters

The All-Subjects-Pharmacokinetically-Evaluable (ASPE) group was used for the pharmacokinetic analyses. The ASPE group consisted of all subjects from the All Patients-as-Treated (APaT) group, for whom at least one pharmacokinetic parameter can be calculated according to the protocol and who did not have any protocol violation interfering with pharmacokinetics.

A PPK analysis was conducted to estimate the mean montelukast pharmacokinetic profiles ($AUC_{0-\infty}$, C_{max}, T_{max} and $t_{1/2}$) within each age group. To accommodate the limited amount of data acquired (two observations per patient), a population pharmacokinetic model was used to fit the montelukast plasma concentrations over time. Previous analyses in paediatric patients showed that a one-compartment model with first-order absorption and first-order elimination provides a good fit of the data.[17] The PPK model was built using a nonlinear mixed-effect modelling approach as implemented in NONMEM v7.2 (ICON Development Solutions, Ellicott City, MD). The model's PK parameters included absorption rate constant (Ka), apparent clearance (CL/F) and apparent volume of distribution (V/F). Inter-individual variability was assumed to be log-normally distributed and was included on CL/F and V/F. A proportional error model was used to describe residual variability.

A covariate analysis was conducted to evaluate the influence of body weight on CL/F and V/F. Measured individual body weight was included as a covariate on CL/F and V/F when its inclusion was associated with a decrease in the objective function associated with a p value of ≤ 0.05. The effect of body weight on CL/F or V/F was included as a centred power function (e.g. CL/F_pop = theta * (WT/median WT)$^{0.75}$). If a satisfactory covariate model was obtained, representative CL/F and V/F for each age group was determined based on the representative (defined as the median) body weight for that age group. The population mean estimates of $AUC_{0-\infty}$, C_{max}, T_{max} and $t_{1/2}$ together with their standard errors and corresponding 95%CIs in each age group were derived using the parameters from the one-compartmental model.

Efficacy evaluation

The Full Analysis Set (FAS) population was serving as the population for the analysis of efficacy data. The FAS population consisted of all patients who took at least one dose of treatment, and had at least one post baseline observation. The subjects or subjects' caregivers assessed the Global Evaluation of PAR. These classifications were based on subjective observations at weeks 2, 4, and 12 compared with the allocation visit.

Statistical analysis of safety and efficacy measurements

The All-Patients-as-Treated (APaT) population was used for safety analyses. Descriptive statistics were used to summarise AEs, laboratory parameters (haematology, biochemistry and urinalysis). Safety results were tabulated for all patients and 4 mg OG for 4 weeks of treatment, 4 mg OG for 12 weeks of treatment and 5 mg CT groups. The Full Analysis Set (FAS) population was used for exploratory efficacy analyses. The FAS population consisted of all patients who took at least one dose of treatment, and had at least one post baseline observation. The number and percentage of patients in each category of Global Evaluation at each visit were summarised for patients receiving 4 mg OG (1–5-year-old subjects), 5 mg CT (6–9-year-old subjects), 5 mg CT (10–15-year-old subjects), and all patients.

Results

Subjects

There were 87 subjects who were enrolled in the study: 15, 36, 18, and 18 in the montelukast 4 mg (1–5-year-olds) for 4 weeks group, montelukast 4 mg (1–5-year-olds) for 12 weeks group, montelukast 5 mg (6–9-year-olds) for 12 weeks group, and montelukast 5 mg (10–15-year-olds) for 12 weeks group, respectively. Of these, 85 subjects completed the study; there was one discontinuation due to an AE (epistaxis) and another discontinuation due to non-compliance with the study protocol (Figure 1). Patient characteristics are shown in Table 1.

Safety and tolerability

AEs occurred in 67% of subjects (53% in the 4-week montelukast 4 mg group, 83% in the 12-week montelukast 4 mg group, and 56% in montelukast 5 mg group) (Table 2). There were no serious AEs and no subject died. Only 2 AEs were determined to be drug-related by the investigator; both of these AEs were in the montelukast 4 mg group and included photophobia and diarrhoea. One subject discontinued treatment due to an AE (epistaxis) in the montelukast 5 mg group; the patient recovered 8 days after discontinuation and the epistaxis was determined to not be related to study medication.

Table 1. Subject characteristics (all allocated subjects)

	Montelukast sodium 4 mg 4-weeks treatment		Montelukast sodium 4 mg 12-weeks treatment		Montelukast sodium 5 mg		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Subjects in population	15		36		36		87	
Gender								
Male	7	(46.7)	20	(55.6)	23	(63.9)	50	(57.5)
Female	8	(53.3)	16	(44.4)	13	(36.1)	37	(42.5)
Age (years)								
1–5 years	15	(100.0)	36	(100.0)	–		51	(58.6)
6–9 years	–		–		18	(50.0)	18	(20.7)
10–15 years	–		–		18	(50.0)	18	(20.7)
1 years	1	(6.7)	4	(11.1)	–		5	(5.7)
2 years	2	(13.3)	6	(16.7)	–		8	(9.2)
3 years	1	(6.7)	8	(22.2)	–		9	(10.3)
4 years	6	(40.0)	3	(8.3)	–		9	(10.3)
5 years	5	(33.3)	15	(41.7)	–		20	(23.0)
6 years	–		–		5	(13.9)	5	(5.7)
7 years	–		–		1	(2.8)	1	(1.1)
8 years	–		–		5	(13.9)	5	(5.7)
9 years	–		–		7	(19.4)	7	(8.0)
10 years	–		–		3	(8.3)	3	(3.4)
11 years	–		–		9	(25.0)	9	(10.3)
12 years	–		–		4	(11.1)	4	(4.6)
13 years	–		–		1	(2.8)	1	(1.1)
14 years	–		–		1	(2.8)	1	(1.1)
15 years	–		–		0	(0.0)	0	(0.0)
Mean	3.8		3.5		9.6		6.1	
SD	1.3		1.5		2.1		3.4	
Median	4.0		3.5		9.5		5.0	
Range	1–5		1–5		6–14		1–14	
Body weight (kg)								
Subjects with data	15		36		36		87	
Mean	15.65		15.44		32.82		22.67	
SD	3.16		3.43		11.21		11.45	
Median	16.40		15.20		31.25		18.40	
Range	9.4–20.2		9.4–23.4		18.4–83.2		9.4–83.2	

Table 2. Adverse event summary (all subjects as treated)

	Montelukast sodium 4 mg 4-weeks treatment $N = 15$		Montelukast sodium 4 mg 12-weeks treatment $N = 36$		Montelukast sodium 5 mg 12-weeks treatment $N = 36$		Total $N = 58$	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Summary of AEs								
With 1 or more AEs	8	(53.3)	30	(83.3)	20	(55.6)	58	(66.7)
With serious AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinuation due to AEs	0	(0.0)	0	(0.0)	1	(2.8)	1	(1.1)
Drug-related AEa	0	(0.0)	2	(5.6)	0	(0.0)	2	(2.3)
Clinical AEs in >1 patient in any treatment group								
Nasopharyngitis	4	(26.7)	18	(50.0)	12	(33.3)	34	(39.1)
Pharyngitis	2	(13.3)	7	(19.4)	3	(8.3)	12	(13.8)
Acute sinusitis	0	(0.0)	6	(16.7)	0	(0.0)	6	(6.9)
Diarrhoea	0	(0.0)	4	(11.1)	0	(0.0)	4	(4.6)
Bronchitis	0	(0.0)	3	(8.3)	3	(8.3)	6	(6.9)
Otitis media	1	(6.7)	3	(8.3)	1	(2.8)	5	(5.7)
Gastroenteritis	0	(0.0)	3	(8.3)	1	(2.8)	4	(4.6)
Hand-foot-and-mouth disease	0	(0.0)	3	(8.3)	0	(0.0)	3	(3.4)
Arthropod sting	1	(6.7)	1	(2.8)	2	(5.6)	4	(4.6)
Dermatitis infected	0	(0.0)	2	(5.6)	0	(0.0)	2	(2.3)
Enteritis infectious	0	(0.0)	2	(5.6)	0	(0.0)	2	(2.3)
Impetigo	0	(0.0)	2	(5.6)	0	(0.0)	2	(2.3)
Otitis media acute	1	(6.7)	2	(5.6)	0	(0.0)	3	(3.4)
Epistaxis	0	(0.0)	0	(0.0)	2	(5.6)	2	(2.3)
Miliaria	0	(0.0)	0	(0.0)	2	(5.6)	2	(2.3)
Rash	1	(6.7)	1	(2.8)	0	(0.0)	2	(2.3)

[a]Determined by the investigator to be related to the drug.

Table 3. Summary statistics of derived PK parameters (all-subjects-pharmacokinetically-evaluable)

Total *N*:	1–5 years old *n* = 51	6–9 years old *n* = 18	10–15 years old *n* = 18	All *n* = 87
$AUC_{0-\infty}$ (ng·h/mL)				
Mean (SD)	4300 (890)	4350 (760)	3500 (620)	4140 (870)
Median (range)	4020 (3000–7600)	4320 (3000–5900)	3440 (2400–5000)	3990 (2400–7600)
C_{max} (ng/mL)				
Mean (SD)	510 (84)	438 (82)	344 (61)	461 (100)
Median (range)	501 (340–690)	437 (280–590)	340 (220–470)	464 (220–690)
$t_{1/2}$ (h)				
Mean (SD)	1.27 (0.56)	2.0 (0.75)	2.08 (0.66)	1.59 (0.73)
Median (range)	1.08 (0.77–3.6)	2.01 (1–3.8)	1.87 (1.3–3.7)	1.41 (0.77–3.8)
t_{max} (h)				
Mean (SD)	2.74 (0.6)	3.55 (0.71)	3.65 (0.6)	3.1 (0.75)
Median (range)	2.56 (2.1–4.9)	3.63 (2.5–5)	3.49 (2.8–5)	2.99 (2.1–5)

The three most commonly reported AEs in any of the treatment groups were nasopharyngitis (22 subjects in 4 mg OG group [43.1%], 12 in 5 mg CT group [33.3%]), pharyngitis (9 subjects in 4 mg OG group [17.6%], 3 in 5 mg CT group [8.3%]) and acute sinusitis (6 subjects in 4 mg OG group [11.8%], 0 in 5 mg CT group [0%]) (Table 2). All AEs were mild in intensity with the exception of one moderate case of pharyngitis in the 4 mg OG group. These AEs were not unexpected. No clinically meaningful changes in laboratory values were observed. A 10% change from baseline was observed for total bilirubin, monocyte count, neutrophil count, white blood cell count, basophil count, and eosinophil count; changes in other laboratory safety parameters were small. Liver function tests did not identify any subject with drug-induced liver injury.

Pharmacokinetics

Montelukast plasma concentrations in this study are well-described by a first-order absorption, one-compartment elimination model, with CL/F and V/F, increasing with body weight.

PK parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$) were derived for each individual. A summary of PK parameters are shown in Table 3. The median Tmax was estimated at 2.99 (range 2.09–5.03) h and the mean $t_{1/2}$ was estimated at 1.59 (range 0.77–3.8) h. Mean predicted $AUC_{0-\infty}$ was similar in the 1-5 year-old and 6-9 year old age groups (4300 and 4350 3500 ng.h/mL, respectively) and decreased to 3500 ng·h/mL in patients 10–15 years old, which constituted on average a 19% reduction as compared to the 1–5 year old group. The mean predicted C_{max} decreased from 510 ng/mL in 1–5 year old to 438 ng/mL in 6–9 year old to 344 ng/mL in 10–15 year old patients. Due to the relationship between plasma concentration and body weight, and the strong correlation between body weight and age in this population, the montelukast plasma concentrations were on average reduced with increasing age (Figure 2).

Global efficacy evaluations

The number (%) of subjects in the 1–5 year-old montelukast 4 mg OG group reporting improved ("very much better"; "somewhat better"; or "a little better") Global Evaluation of allergic rhinitis was 39 (76.5%), 44 (86.3%), and 35 (97.2%) at week 2, week 4, and week 12, respectively. The number (%) of subjects in the 1–5 year-old montelukast 4 mg group reporting no change or worsening of symptoms was 12 (23.5%), 5 (9.8%), and 1 (2.8%) at week 2, week 4, and week 12, respectively. The number (%) of subjects in the 6–9 year-old montelukast 5 mg CT group reporting improved Global Evaluation of allergic rhinitis was 17 (94.4%), 16 (88.9%), and 17 (100%) at week 2, week 4, and week 12, respectively; the number (%) of subjects reporting no change or worsening was 1 (5.6%), 2 (11.1%), and 0 (0%) at week 2, week 4, and week 12, respectively. The number (%) of subjects in the 10–15 year-old montelukast 5 mg CT group reporting improved Global Evaluation of allergic rhinitis was 13 (72.2%), 13 (72.2%), and 12 (66.7%) at week 2, week 4, and week 12, respectively; the number (%) of subjects reporting no change or worsening was 5 (27.8%), 5 (27.8%), and 6 (33.3%) at week 2, week 4, and week 12, respectively. Results for all subjects and by each evaluation category are illustrated in Figure 3.

Discussion

The primary objective of this trial was to determine whether montelukast was safe and well tolerated in paediatric Japanese patients with PAR. The AEs observed in this trial were all mild in intensity with only one AE that was moderate in intensity. There were no serious AEs and only one patient discontinued due to an AE, which was not related to montelukast. Nasopharyngitis, pharyngitis, and acute sinusitis were reported as the most common AEs. These AEs are fairly consistent with what was previously reported in non-Japanese paediatric patients with PAR.[18] The tolerability demonstrated in this study reflects that montelukast was generally well tolerated in Japanese paediatrics, as previously reported in other patient populations.[10,11,14]

We also conducted a PPK analysis in this study of Japanese paediatric patients with PAR in order to evaluate different paediatric age groups who may be treated with montelukast. This type of analysis helps to study the sources and correlates of variability in drug concentrations among individuals receiving clinically relevant doses of a drug.[19]

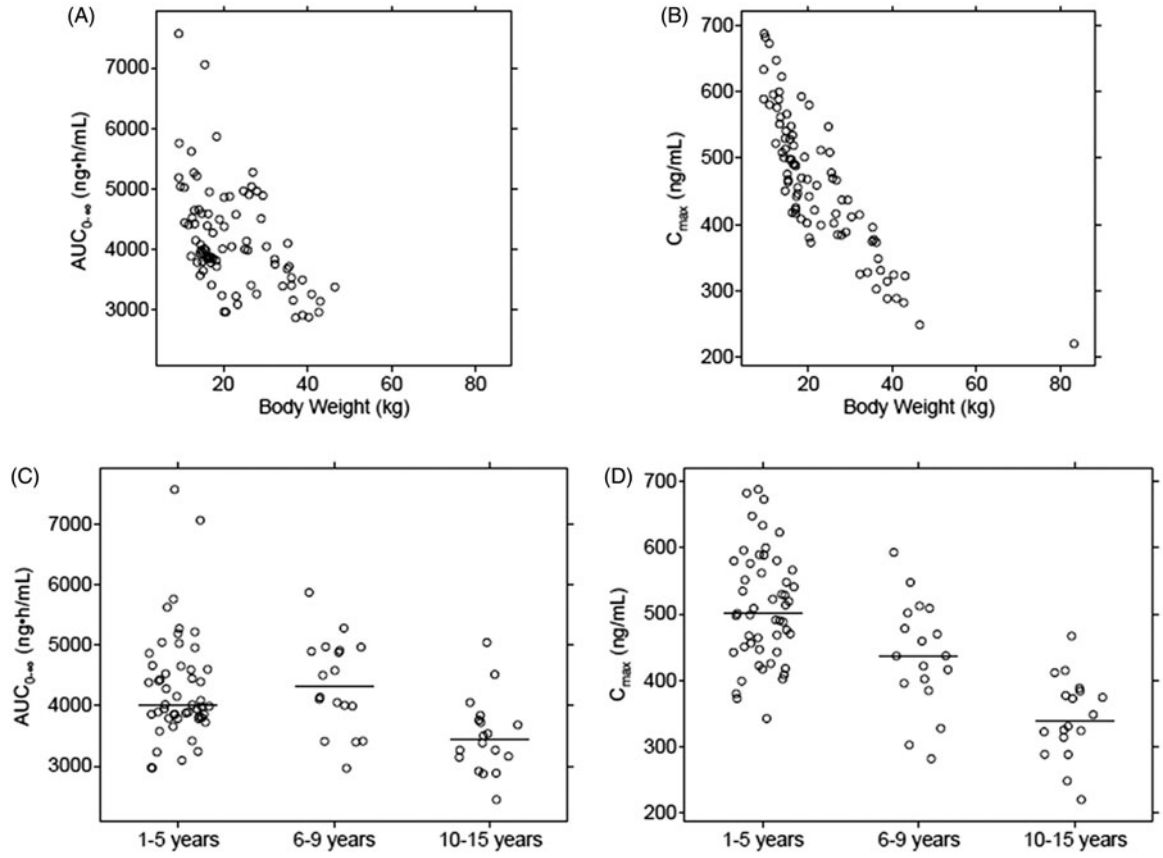

Figure 2. Individual PK parameter estimates of the final model versus body weight and age group. (A) $AUC_{0-\infty}$ versus body weight, (B) Cmax versus body weight, (C) $AUC_{0-\infty}$ versus age group, (D) C_{max} versus age group.

The PK of montelukast in this study was found to be consistent with a 1st-order absorption and 1-compartment elimination model with CL/F and V/F increasing with body weight and a proportional error structure. These results were similar to those from a previous study [20] and a previous PPK analysis in non-Japanese paediatric patients.[17] We observed that montelukast plasma concentrations decreased slightly with age and that the relationship between PK and age is likely explained by the underlying relationship between age and body weight. The exposures in Japanese paediatric patients were similar to those in non-Japanese paediatric and adult patients. In a previous non-Japanese paediatric study of 4 mg CT in 2–5 year-old paediatric patients with asthma (median weight of 17 kg), geometric mean AUC_{pop} was 2721 ng.h/mL and mean C_{max} was 471 ng/mL; this was deemed comparable to adult asthma patients taking 10 mg montelukast film-coated tablets (geometric mean AUC_{pop} 2595 ng·h/mL and C_{max} of 283 ng/mL). Another study of 9- to 14-year-old subjects with asthma who received 6 mg montelukast film coated tablets, $AUC_{0-\infty}$ was 2929 ngh/mL with a C_{max} of 444 ng/mL in subjects weighing 45 kg or less and $AUC_{0-\infty}$ was 3528 ng/mL with a C_{max} of 526 ng/mL in subjects weighing over 45 kg.[15,16] The 1–5-year-old subjects in our study had mean $AUC_{0-\infty}$ of 4300 ng.h/mL and C_{max} 510 ng/mL.

Global evaluations of efficacy suggested that paediatric subjects demonstrated improvement in PAR symptoms with montelukast treatment in each treatment and age group. Increased improvement was observed over time in the 1–5-year-old group of subjects receiving montelukast 4 mg OG; however, it should be noted that this increase in improvement may appear greater due to the number of subjects who ended treatment according to their 4-week treatment assignment and the small number who elected to continue to week 12 (thus introducing a small number of self-selected subjects). In the montelukast 5 mg CT subjects, both age groups improved; however, the younger age group exhibited a greater proportion with improvement while the older age group exhibited a greater proportion of subjects who had no change or worsening of symptoms. Although further research is needed to definitively demonstrate the efficacy of 4 mg and 5 mg montelukast in paediatric Japanese patients with PAR, the data from this trial in conjunction with efficacy and PK data from previous studies in non-Japanese patients suggest that the doses of montelukast evaluated in this trial would provide symptom improvement in paediatric Japanese AR patients.[15,16]

There are limitations to this study that should be considered. Behavioural AEs have been reported in association with montelukast in post-marketing experience. However, this study was not designed and was not large enough to evaluate these types of AEs; analyses of adult and paediatric clinical trials, pooling numerous available studies to provide a large enough patient sample, did not demonstrate an association.[21] Additionally, this was an open label study and efficacy was determined using subjective global evaluation

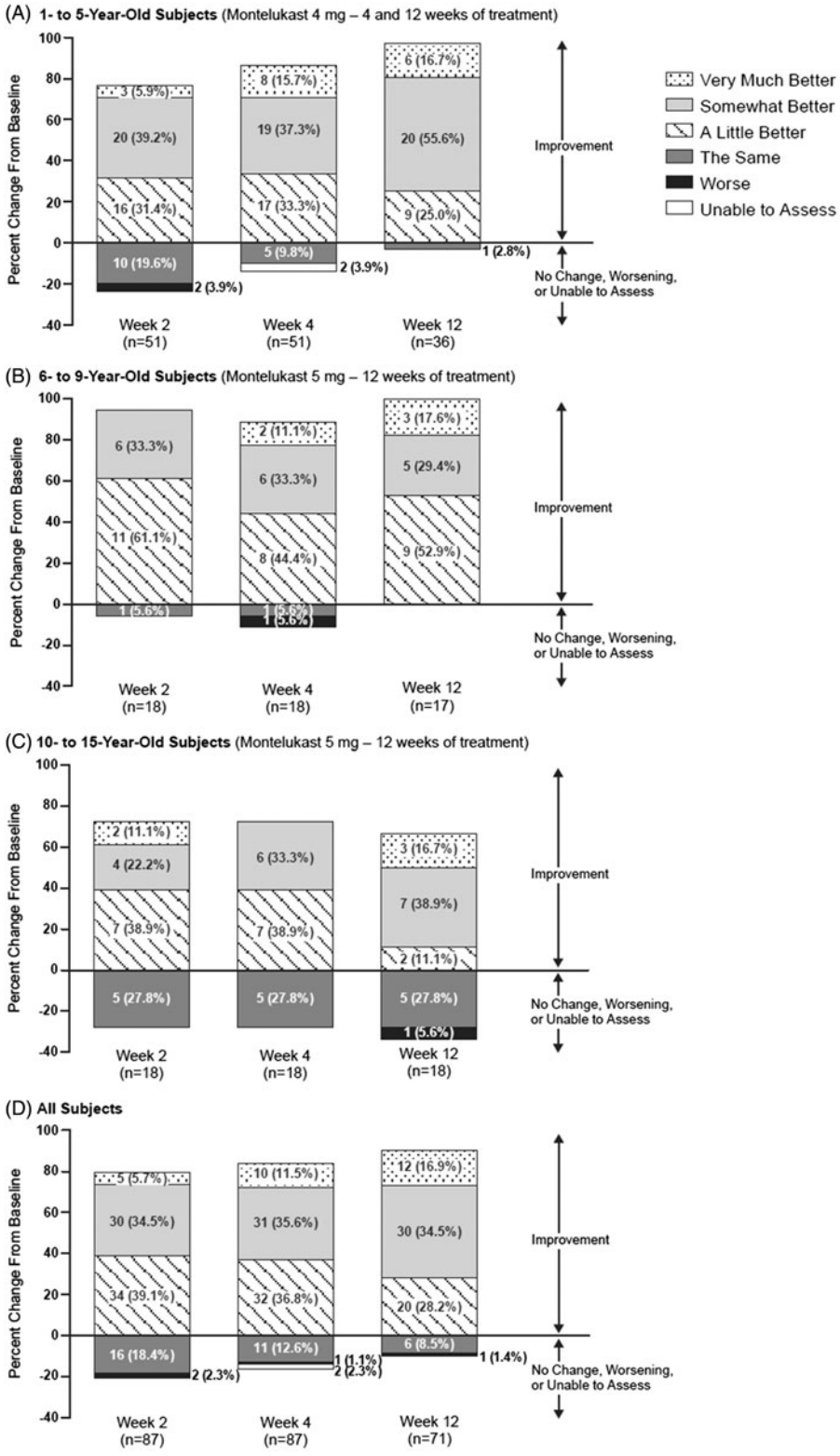

Figure 3. Summary of global evaluation of PAR (full analysis set). (A) Montelukast 4 mg group (1–5-year-old subjects); (B) Montelukast 5 mg group (6–9-year-old subjects); (C) Montelukast 5 mg group (10–15-year-old subjects); (D) All treatment groups.

assessments based on patients' impression of nasal symptoms. There were also no statistical analyses to assess a relationship between drug exposure levels and efficacy. Further, this study was limited in that it did not evaluate montelukast in combination with other treatments for PAR; combination therapy with montelukast and inhaled corticosteroids or antihistamines has previously been suggested as an optimal method to maximise efficacy while minimising dose levels of individual medications.[12] However, the data from this study suggest that montelukast provides symptomatic effect in the treatment of PAR in Japanese paediatric patients. In particular, montelukast has previously been shown to provide

benefits with regard to improvement in night-time symptoms of children with PAR and decreasing inflammation reflected by exhaled nitric oxide levels.[22–24]

Conclusion

In conclusion, the data from our study provide evidence that montelukast at the doses of 4 mg oral granules for ages 1–5 years and 5 mg chewable tablets for ages 6–15 years in Japanese paediatric patients with PAR would lead to drug exposure consistent with efficacy and tolerability similar to that achieved in other populations. A positive tolerability profile and apparent symptomatic improvement were observed in this trial. It should be noted that this study had a limited number of patients and larger studies that are designed to better assess efficacy and tolerability outcomes would be needed to confirm our results. However, these data suggest that Japanese paediatric patients would benefit from a similar level of efficacy and tolerability that has long been established with montelukast in other patient populations.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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