Safety, efficacy and pharmacokinetics of palivizumab in off-label neonates, infants, and young children at risk for serious respiratory syncytial virus infection: a multicenter phase II clinical trial

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Summary

Background Pediatric patients with certain rare diseases are at increased risk of severe respiratory syncytial virus (RSV) infection. However, the prophylactic use of anti-RSV antibody (palivizumab) in these patients is not indicated at present in Japan.

Methods This first-in-the-world multicenter, uncontrolled, open-label, phase II clinical trial was carried out between 28 July 2019 and 24 September 2021 at seven medical institutions in Japan to investigate the efficacy, safety, and pharmacokinetics of palivizumab in 23 subjects recruited from among neonates, infants, or children aged 24 months or younger who had any of the following conditions: pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inherited metabolic disease, or neuromuscular disease. At least four continuous doses of palivizumab were administered intramuscularly at 15 mg/kg at intervals of 30 days.

Findings Twenty-three enrolled subjects completed the study. No subject required hospitalization for RSV. Adverse events (AE) did not notably differ from the event terms described in the latest interview form. Five severe AEs required unplanned hospitalization, but resolved without RSV infection. Therapeutically effective concentrations of palivizumab were maintained throughout the study period.

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Trial registration: This study has been prospectively registered in Japan Registry of Clinical Trials (jRCT), which is managed and administered by the National Institute of Public Health (registration number: jRCT2080224862, registration date: September 9, 2019) [https://jrct.niph.go.jp/en-latest-detail/jRCT2080224862].

Interpretation Palivizumab might be well tolerated and effective in preventing serious respiratory symptoms and hospitalization due to severe RSV infection, indicating the prophylactic use in the pediatric patients included in this study.

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Keywords: Airway stenosis; Congenital esophageal atresia; Efficacy; Inherited metabolic disease; Neuromuscular disease; Palivizumab; Pediatric patient; Pulmonary hypoplasia; Respiratory syncytial virus infection

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) is responsible for approximately 50% of pneumonia and 50%–90% of bronchiolitis in infants and young children and is the most common cause of hospitalization for infection in infants and young children. Palivizumab (non-proprietary name), a specific humanized monoclonal antibody, is the only currently approved drug for preventing RSV infection from becoming severe and has been used in more than 70 major Western countries. Overseas efficacy data were validated for the use in Japan, leading to approval of the drug in January 2002. After nationwide questionnaire surveys on RSV infection conducted in Japan showed that immunodeficiency, Down's syndrome, chromosomal aberration, and neuromuscular disease were important underlying diseases associated with severe RSV infection, a clinical study was conducted for additional indications in neonates, infants, and young children with immunodeficiency and Down's syndrome, leading to approval for additional indications in August 2013 in Japan. However, approval for neuromuscular disease and other rare diseases, such as pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, and inherited metabolic disease associated with an increased risk for exacerbated RSV infection is still pending.

Added value of this study

This study comprehensively evaluated the efficacy, safety, and pharmacokinetics of palivizumab in rare groups of pediatric patients with pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inherited metabolic disease, and/or neuromuscular disease, which carry a high risk of severe RSV infection, for which palivizumab is not currently indicated, and which result in reduced ventilatory capacity or difficulty in expectoration due to severe RSV infection.

Implications of all the available evidence

The results of this study suggest that intramuscular administration of palivizumab at a dose of 15 mg/kg body weight every 30 days at least four times might be generally well tolerated and may be effective in preventing serious respiratory symptoms due to severe RSV infection and subsequent hospitalization in neonates, infants, and young children aged 24 months or younger whose primary disease belongs to the above five disease groups studied. The results have direct implications for the approval of palivizumab in these patient groups.

Introduction

Respiratory syncytial virus (RSV) is responsible for approximately 50% of pneumonia and 50%–90% of bronchiolitis in infants and young children and is the most common cause of hospitalization for infection in infants and young children.[1] Currently, there is no drug for RSV infection, thus it is important from the viewpoint of disease management to prevent aggravation of the infection.

Palivizumab (non-proprietary name; sold as SYNAGIS® in Japan, marketed by AbbVie GK), a specific humanized monoclonal antibody, is the only currently approved drug for preventing RSV infection from becoming severe. Palivizumab was developed in the US,[2] and approved for the prevention of severe lower respiratory tract disease caused by RSV infection in pediatric patients at high risk for RSV infection in the US in June 1998 and subsequently in Europe.[3] Palivizumab has been used in more than 70 major Western countries.[4]

In Japan, a bridging study demonstrated the validity of extrapolating overseas efficacy data,[5] leading to approval of the drug in January 2002.[4] Besides, nationwide questionnaire surveys on RSV infection in Japan showed that immunodeficiency, Down's syndrome, chromosomal aberration, and neuromuscular disease

were important underlying diseases associated with severe RSV infection.[6,7] Based on this finding, a clinical study was conducted in neonates, infants, and young children with immunodeficiency and Down's syndrome, leading to approval for additional indications in August 2013 in Japan.[8–10]

However, neuromuscular disease, which is also an underlying condition associated with severe RSV infection according to the aforementioned surveys,[6,7] was not included in the indications additionally approved in 2013. Therefore, the Japan Society of Perinatal and Neonatal Medicine played a central role in calls to extend the indications to pediatric patients with pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inborn errors of metabolism, and neuromuscular disease, who are at high risk for severe RSV infection or inherently too fragile to be treated for severe RSV infection.

Here, we comprehensively evaluated the efficacy, safety, and pharmacokinetics of palivizumab in pediatric patients falling within any of the five disease groups mentioned above in order to provide evidence for the safety of palivizumab in these patients and to expand indications for these conditions.

Methods

Study design and participants

This multicenter, uncontrolled, open-label, phase II clinical trial was carried out between 28 July 2019 to 24 September 2021 at seven medical institutions in Japan, and is the first such study in the world. Participants were recruited at outpatient clinics from among neonates, infants, or children aged 24 months or younger with conditions categorized under any of the following disease groups: pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inherited metabolic disease, or neuromuscular disease. In particular, in children with congenital metabolic disorders, respiratory failure may occur due to complications of progressive neuromuscular disease, or a metabolic crisis may occur under catabolic stress due to RSV infection, resulting in muscle weakness and difficulty controlling breathing due to retention of neurotoxic substances and decreased blood sugar levels, resulting in inadequate ventilation. Given the rarity of the target diseases, the number of subjects per disease group was set at a minimum of three, with analysis set for at least 15 subjects in the five disease groups combined. The target sample size was set at 18 subjects to allow for dropouts. A detailed description of the individual diseases within the above disease groups, the reason why they predispose to higher risk of severe RSV aggravation, estimated patient numbers in Japan, and the rationale for the target sample size determination were previously published.[11]

Participant selection criteria

Inclusion criteria were (1) written informed consent from the legally authorized representative; (2) subject age of 24 months or younger at the time of informed consent, and a disease classified under any of the following disease groups at the time of informed consent and requiring prophylactic palivizumab: pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inherited metabolic disease, and neuromuscular disease; and (3) continuous management on an outpatient basis at the time of informed consent.

Exclusion criteria were (1) classified in any patient category for which palivizumab has already been approved in Japan 1[11]; (2) receipt of palivizumab or another investigational product within 3 months prior to administration of palivizumab in this study, or receipt of palivizumab within less than five times the blood half-life of another investigational product; (3) active infection, including RSV infection, during the screening period; (4) requirement for oxygen inhalation, artificial ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other respiratory support during the screening period (children who have been receiving oxygen inhalation due to an underlying disease for at least 2 weeks before enrollment with a stable oxygen flow rate may be enrolled); (5) serious concurrent disease other than immunodeficiency and renal failure; (6) history of apnea (central or transient apnea is acceptable); (7) history of hypersensitivity to any component of the study drug; (8) history of serious adverse reaction or allergy to immunoglobulin preparations; (9) history of hypersensitivity to immunoglobulin preparations, blood products, or other protein products; (10) not expected to survive for at least one year after the start of study treatment; and (11) considered ineligible for participation in the study for any other reason.

Discontinuation criteria were (1) the subject dies; (2) further participation in the study is considered inappropriate due to an adverse event or due to an inadequate response to study treatment; (3) the investigator considers that further participation in the study is inappropriate; and (4) the legally authorized representative does not wish further participation in the study and the subject has received three or fewer doses of study drug when a decision to discontinue participation is made.

Study procedures

Baseline characteristics were age at the time of informed consent, sex, ethnicity, race, gestational age, single/multiple pregnancy, height, weight, prior medication/therapy, and medical/surgical history. During the screening period, primary disease, reason for requiring prophylactic palivizumab, past medical/surgical history, concurrent disease, and family structure were

investigated and entered in the case report form (CRF). Further baseline characteristics were vital signs (pulse rate, systolic/diastolic blood pressure, respiratory rate, body temperature), laboratory tests and a RSV test. In this study, prior and concomitant therapy were regarded to have little impact on the study endpoints. Hence, there were no restrictions on these therapies.

Palivizumab (recombinant), with the non-proprietary name Palivizumab (recombinant), provided as a solution for intramuscular administration (injection) containing 100 mg of palivizumab (recombinant) per vial, was obtained from AbbVie GK. Lot numbers 190801 and 191,102 were used. Palivizumab was intramuscularly administered at a dose of 15 mg/kg body weight every 30 days at least four times during the RSV season. It was administered in divided doses if the injection volume exceeded 1 mL. Five or more doses could be given during the same season up to March at the request of the legally authorized representative if deemed necessary. The dosage and administration described in the package insert of palivizumab were used as reference.[4]

Outcomes

The following outcomes were obtained in this study; (1) primary endpoint; efficacy: percentage of subjects requiring RSV-related hospitalization between the first dose of palivizumab and 30 days after the last dose (as primary endpoint), (2) second endpoints; 1) efficacy: percentage of subjects requiring oxygen inhalation, artificial ventilation, membrane oxygenator, continuous positive airway pressure, other assisted ventilation, or management in an intensive care unit (ICU) owing to RSV infection between the first dose of palivizumab and 30 days after the last dose and duration of hospitalization, oxygen inhalation, artificial ventilation, membrane oxygenator use, continuous positive airway pressure, other assisted ventilation, or management in an ICU (as secondary endpoints); 2) safety: adverse events (AE) and adverse drug reactions (ADRs) will be summarized by grade, seriousness, and timing of onset using the number of subjects with events/reactions, and the incidence and number of events/reactions; 3) pharmacokinetics; serum palivizumab concentrations (trough values) 30 days after the first, 4th, and last doses of palivizumab.

Since the target study population is patients with rare diseases, at least 18 patients, including at least 3 for each disease group, were included in the study to allow for some dropouts. The efficacy outcome of the study, therefore, was comprehensively evaluated based on results on the above efficacy, safety, and pharmacokinetic endpoints.

Safety evaluation

Safety measurements assessed were AEs, laboratory values, vital signs, and weight. An AE was defined as any unfavorable or unintended sign, symptom, disease, or abnormal change in laboratory values, vital signs, and weight meeting any of the criteria listed below that occurred in a subject between the first dose of the study drug and 30 days after the last dose or treatment discontinuation, whichever occurred later. An event (sign, symptom, or disease) observed before study treatment was regarded as an AE if it was judged to have worsened after the start of study treatment. If an AE was observed during a medical examination, appropriate action and all possible measures were taken. Abnormal changes seen in laboratory values, vital signs, and weight measurements were assessed for clinically significance, and an "abnormal change" was handled as an AE.

AEs were assessed continuously throughout the study by identification and grading using the Japanese version of the Common Terminology Criteria for Adverse Events v 5.0 (JCOG version of the CTCAE v 5.0).[12,13] Grade was determined to be the one closest to the definition of Grades 1 to 5. If a specific intervention is described in the grade, the grade was determined based on the clinical need for the intervention. If the CTCAE and its Japanese version had been revised in line with the revision of the Medical Dictionary for Regulatory Activities (MedDRA)[14] and its Japanese version (MedDRA/J),[15] safety was evaluated using the corresponding latest version of the CTCAE in combination with the MedDRA/J. In this study, concurrent disease observed during the screening period was considered an AE if it worsened by at least one grade according to CTCAE v 5.0. Laboratory abnormalities were assessed in the same manner.

An event meeting the criteria for a "SAE" was handled in accordance with the procedures specified in the study protocol. AEs were followed up in affected subjects as necessary. AEs in subjects not treated with the study drug were not followed up. AEs that had not resolved within 30 days after the last dose of the study drug were followed up until it was determined that no further follow-up was medically necessary. ADRs were followed up until resolution. Follow-up results were reported to the coordinating investigator. Follow-up results were entered in the CRF approximately 30 days to four weeks after the last dose of study drug. This did not apply if symptoms due to exacerbation of primary disease or concurrent disease became chronic or if continuous observation was difficult due to hospital transfer or other reasons.

Laboratory tests were performed at visits 1, 5, and 30 days after the last dose. Parameters measured were white blood cell count, red blood cell count, hemoglobin, hematocrit, and platelet count, differential leukocyte count, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, urea nitrogen, creatinine, and c-reactive protein, glucose, protein, and occult blood. Vital signs and weight were

measured at visits 1, 2, 3, 4, 5, and 6 or later, 30 days after the last dose, and at discontinuation. Testing for RSV infection was carried out during the screening period at the clinical laboratory of the study site using a rapid RSV test (immunochromatographic assay) kit, and was planned during hospitalization for severe RSV infection. The presence or absence of RSV infection was confirmed by polymerase chain reaction assay. The timing of observations, tests, and investigation items is shown in Table 1.

Measurement of serum palivizumab and anti-palivizumab antibody concentrations

Palivizumab concentration: venous blood was collected before the first dose of palivizumab, 30 days after the first dose (before the second dose of study drug), 30 days after the fourth dose, and 30 days after the last dose. The concentration was measured four times per subject, but three times if the fourth dose was the last dose. Anti-palivizumab antibody concentrations: venous blood was collected 30 days after the fourth dose (before the fifth dose of study drug) and 30 days after the last dose. For subjects who received four doses of study drug, in whom the fourth dose was the last dose, the antibody concentration was measured once.

If blood collection was scheduled on the same day as study drug administration, blood was collected before study drug administration. Serum was prepared according to standard laboratory procedures, frozen at –80 °C or below within 2 h of collection and stored at the study site until retrieval. Palivizumab concentrations and anti-palivizumab antibody concentrations were measured by AbbVie GK.

Blood palivizumab concentrations (trough) were similar 30 days after the first dose and 30 days after the fourth dose in premature infants, pediatric patients treated for bronchopulmonary dysplasia, hemodynamically abnormal coronary heart disease, and immunodeficiency, for whom palivizumab is approved. Therefore, it was considered appropriate to determine efficacy in the present study comprehensively by measuring blood drug concentrations and visually comparing similarities with existing data.

Assessment	Screening period	Study treatment period								
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[e]	Visit 6 or later[e]	30 days after the last dose	RSV infection during hospitalization due to severe RSV infection	At discontinuation
		Day 1	Day 31	Day 61	Day 91	Day 121	–	–	–	–
Acceptable range (days)	–28 to 0	–	±5	±5	±5	±5	±5	±5	±5	±3
Informed consent	●					▲[f]				
Subject baseline characteristics	●									
Eligibility determination[a]	●									
Past medical history/concurrent disease	●									
Concomitant medication/therapy	●	●	●	●	●	●	●	●	●	●
Medical examination/interview		●	●	●	●	●	●	●	●	●
Test for RSV infection	●[d]								●[h]	
Vital signs		●	●	●	●	●	●	●	●	●
Height	●									
Weight		●	●	●	●	●	●	●	●	●
Laboratory tests (blood/urine collection)[b]		●				●		●	●	
Blood collection for blood drug concentration measurement[c]		●	●			●		●		
Blood collection for anti-palivizumab antibody						(●)[g]		(●)[g]		
Study drug administration		●	●	●	●	●	●			
Adverse event		←	←	←	←	←	←	←	←	←

[a]Subject eligibility will be determined during the screening period. [b]Hematology, blood chemistry, and urinalysis. [c]Blood for blood drug concentration measurement will be collected before study drug administration. [d]A rapid RSV test (immunochromatographic assay) kit will be used for testing for RSV infection during the screening period. [e]If a fifth or later dose of study drug is administered, efficacy and safety will be assessed and tested on the day of administration. [f]If extended treatment is desired, written informed consent to extended treatment will be obtained before administration at Visit 5. [g]After checking the subject's condition, blood collection for laboratory tests should be given the highest priority, followed by blood collection for blood drug concentration measurement. Then, blood for anti-palivizumab antibody measurement will be collected if possible. [h]A polymerase chain reaction (PCR) assay will be used for testing for RSV infection during hospitalization for severe RSV infection. Table 1 was adapted from Mori et al.[3]

Table 1: **Study observations/tests/assessments and timing.**

Statistical analysis

The number and proportion (%) of subjects requiring hospitalization for RSV infection or any in-hospital treatment due to RSV infection between the start of palivizumab treatment and 30 days after the last dose were calculated, and the 95% confidence interval (CI) was calculated by the Clopper-Pearson method. In addition, summary statistics were calculated for the duration of each intervention. For laboratory tests, the number and incidence of subjects with abnormal changes in laboratory values were presented. For hematology and blood chemistry, a summary at each time point was calculated. For serum drug concentrations, summary statistics at each time point were presented for serum palivizumab concentration along with 95% confidence interval, and the number and proportion of subjects in each category at each time point of blood collection were presented for serum anti-palivizumab antibody. For safety evaluation, the analyses described below were performed on the safety analysis set (SAS), i.e., 23 subjects. MedDRA/J version 24.0[16] was used to code AEs according to the MedDRA/J. Regarding AEs, ADRs, fatal AEs, and AEs leading to discontinuation of study treatment, the number of subjects, incidence (%), and number of events are presented by grade (1, 2, 3, 4, 5, and overall) overall, and for each MedDRA system organ class (SOC) and each SOC/preferred term (PT). SOCs and PTs are presented in descending order of the number of subjects with AEs of all grades. In addition, for AEs by grade, ADRs by grade, fatal AEs by grade, AEs leading to discontinuation of study treatment by grade, and laboratory tests, the number of subjects and the incident cases (%) are presented. Missing data were not imputed in the analyses.

Role of the funding source

Neither AbbVie GK nor AMED had any role in the design of the study; the collection, analysis, or interpretation of the data; or in the decision to publish this paper.

Results

Demographic and other baseline characteristics

Twenty-three eligible participants were recruited, enrolled, and completed the study. The proportion of male/female subjects was 52.17%/47.83%. At the time of informed consent, mean age was 9.0 months, and mean height and weight were 68.82 cm and 7.61 kg, respectively. Ethnicity was Japanese in 100.00%, and race was Asian in 100.00% of subjects. The disease group of the primary disease was congenital esophageal atresia in 26.09%, airway stenosis in 21.74%, neuromuscular disease in 21.74%, inherited metabolic disease in 17.39%, and pulmonary hypoplasia in 13.04% of the subjects. Detailed subject baseline characteristics are shown in Table 2. The 23 subjects distributed over the seven study sites as shown in Supplementary table.

There were no children who received palivizumab in two consecutive seasons in this study according to exclusion criteria.

Treatment frequency

Palivizumab was administered to 23 of 23 subjects. The mean number of doses given (range [minimum to maximum]) was 4.3 (4–6), with the most common number being 4 in 18 of 23 subjects. Study treatment was not interrupted in any subject (Table 3).

Efficacy evaluation

Number of hospitalizations for RSV infection and in-hospital interventions

The number of hospitalizations and subjects hospitalized for RSV infection were zero and 0/23 subjects (0.00%, 0.00–0.15 for 95% confidence interval), respectively, Table 4. No interventions during hospitalization for RSV infection were recorded.

Safety evaluation

AEs and ADRs

A summary of AEs and ADRs is presented in Table 5. The incidence and number of AEs were 86.96% and 46, respectively. The incidence and number of serious AEs (SAEs) were 21.74% and 5, respectively; all of these events required hospitalization or prolongation of existing hospitalization for treatment (seriousness 5). Most of the adverse events were Grade 2, and the incidence and number of Grade 2 events were 73.91% and 30, respectively, with no Grade 4 or 5 events reported. No ADRs were observed.

A breakdown of AEs observed during the evaluation period is presented in Table 6. The SOCs of AEs reported in at least 20% of subjects were “infections and infestations” in 69.57% and “skin and subcutaneous tissue disorders” in 39.13% of subjects. AEs reported in at least 5% of subjects were “upper respiratory tract infection” in 43.48%, “nasopharyngitis” in 17.39%, “gastroenteritis” in 8.70%, “eczema infantile” in 17.39%, “eczema” in 13.04%, “dermatitis diaper” in 8.70%, and “diarrhea” in 8.70% of subjects. We evaluated the RSV infection in “infections and infestations” of the adverse events, but none suffered from RSV infection.

AEs were coded to lower level terms (LLT) according to the Japanese version of the ICH Medical Dictionary for Regulatory Activities (MedDRA/J) Version 24.0. The PT was used for tabulation, and the SOC was used for organ classification. A breakdown of serious AEs is shown in Table 7. All serious AEs observed in this study were carefully investigated and treated, and were judged to be unrelated to the study treatment.

AEs by grade are presented in Table 8. The incidence of AEs by grade was 26.09% for Grade 1, 73.91% for Grade 2, and 13.04% for Grade 3, with no Grade 4 or 5 events reported. None of the AEs led to discontinuation of study treatment during the evaluation period.

Parameter (unit)	Statistics/category	Unit (%)	
Age (months)	Number of subjects	23	
	Mean	9.0	
	Standard deviation	6.3	
	Maximum	23	
	Median	7.0	
	Minimum	2	
Sex	Male	12	(52.17)
	Female	11	(47.83)
Height	Number of subjects	23	
	Mean	68.82	
	Standard deviation	7.88	
	Maximum	82.3	
	Median	70.40	
	Minimum	57.1	
Weight (kg)	Number of subjects	23	
	Mean	7.611	
	Standard deviation	1.651	
	Maximum	10.21	
	Median	7.500	
	Minimum	4.91	
Ethnicity	Japanese	23	(100.00)
Race	Asian	23	(100.00)
Primary disease: Disease group	Congenital esophageal atresia	6	(26.09)
	Airway stenosis	5	(21.74)
	Neuromuscular disease	5	(21.74)
	Inherited metabolic disease[a]	4	(17.39)
	Pulmonary hypoplasia	3	(13.04)
Primary disease: Disease name	Congenital esophageal atresia	6	(26.09)
	Propionic acidemia	2	(8.70)
	Pharyngeal stenosis	2	(8.70)
	Laryngomalacia	2	(8.70)
	Congenital diaphragmatic hernia	2	(8.70)
	Duchenne muscular dystrophy	1	(4.35)
	Pharyngeal stenosis/laryngomalacia	1	(4.35)
	Very long-chain acyl-coenzyme A dehydrogenase deficiency	1	(4.35)
	Myotonic dystrophy	1	(4.35)
	Spinal muscular atrophy	1	(4.35)
	Congenital myopathy	1	(4.35)
	Congenital myopathy (suspected Bethlem myopathy)	1	(4.35)
	Congenital cystic lung disease	1	(4.35)
	Medium-chain acyl-coenzyme A dehydrogenase deficiency	1	(4.35)

[a]Propionic acidemia (2 cases), medium-chain acyl-CoA dehydrogenase (1 case), deficiency very-long-chain acyl-CoA dehydrogenase (1 case).

Table 2: **Subject characteristics.**

Evaluation of laboratory parameters

The summary statistics of laboratory values at each time point are presented in Table 9.

No abnormal changes in laboratory values were observed.

Pharmacokinetic evaluation

Serum palivizumab concentrations

Summary statistics for serum palivizumab concentrations (trough) at each time point are presented in Table 10. Mean serum palivizumab concentration (range, 95% CI, number of subjects) was 66.89 (40.0–89.2, 61.015–72.759, n = 23), 116.82 (49.5–167.0, 102.719–130.916, n = 23), and 153.00 (153.00, not calculated, n = 1) μg/mL at Visit 2, 30 days after the fourth dose, and 30 days after the fifth dose, respectively. The lower limit of the 95% CI at each time point, except for 30 days after the fifth dose, was >10 μg/mL, which is below the lower limit of quantification, indicating that serum palivizumab concentrations reached trough levels throughout the study period. The target drug concentration of >30 μg/mL for each study in the

Parameter (unit)	Statistics/category	Unit (%)	
Number of doses of palivizumab given (continuous variable)	Number of subjects	23	
	Mean	4.3	
	Standard deviation	0.7	
	Maximum	6	
	Median	4.0	
	Minimum	4	
Number of doses of palivizumab given (frequency)	7 doses	0	(0.00)
	6 doses	3	(13.04)
	5 doses	2	(8.70)
	4 doses	18	(78.26)
	3 doses	0	(0.00)
	2 doses	0	(0.00)

Table 3: **Palivizumab treatment.**

Category	Number of events	n	(%)	95% CI
Number of hospitalizations for RSV infection	0	0	(0.00)	(0.00–0.15)

FAS, full analysis set.

Table 4: **Number of hospitalizations for RSV infection (FAS).**

	(N = 23)		
	n	(%)	Number of events
Adverse events	20	(86.96)	46
Grade			
1	6	(26.09)	13
2	17	(73.91)	30
3	3	(13.04)	3
4	0	(0.00)	0
5	0	(0.00)	0
Seriousness			
Non-serious	19	(82.81)	41
1	0	(0.00)	0
2	0	(0.00)	0
3	0	(0.00)	0
4	0	(0.00)	0
5	5	(21.74)	5
6	0	(0.00)	0
7	0	(0.00)	0
Adverse drug reactions	0	(0.00)	0

Table 5: **Summary of adverse events and adverse drug reactions.**

interview form of palivizumab was achieved as early as Visit 2, when the drug concentration was measured, indicating that the target drug concentration was achieved from Visit 2 onwards.

Serum anti-palivizumab antibody concentrations

The number and proportion of subjects in each category of serum anti-palivizumab antibody at each time point are presented in Table 11. The serum anti-palivizumab antibody concentration was <30 μg/mL at 30 days after the fourth dose and 30 days after the fifth dose in all subjects tested. The production of anti-drug antibody possible to result reducing the efficacy of the drug especially considerable in drugs which will be administrated repeatedly in couple of months, such as palivizumab. The result of very low level of anti-palivizumab antibody production after 4 doses of palivizumab will support the efficacy in the subject group in this study, as well as children who are documented in indication of palivizumab.

Discussion

This study was conducted to evaluate the efficacy, safety, and pharmacokinetics of palivizumab in pediatric patients with pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inherited metabolic disease, and/or neuromuscular disease, which carry a high risk of severe RSV infection, for which palivizumab is not currently indicated, and which result in reduced ventilatory capacity or difficulty in expectoration due to severe RSV infection.

Twenty-three subjects with any of the above disease groups were enrolled in the study and received at least four doses of palivizumab every 30 days. No subjects required hospitalization for RSV infection between the start of palivizumab treatment and 30 days after the last dose. There were three to six subjects per disease group, and efficacy did not differ among the disease groups. A total of 46 AEs occurred in 20 of 23 subjects during the study. These AEs were not notably different from the event terms described in the latest interview form. Five

MedDRA version 24.0			
System organ class (SOC), Preferred term (PT)	**(N = 23)**		
	n	(%)	Number of events
Any adverse event	20	(86.96)	46
Infections and infestations	16	(69.57)	26
Upper respiratory tract infection	10	(43.48)	13
Nasopharyngitis	4	(17.39)	7
Gastroenteritis	2	(8.70)	2
Bronchitis	1	(4.35)	1
Otitis media acute	1	(4.35)	1
Pneumonia bacterial	1	(4.35)	1
Sinusitis	1	(4.35)	1
Skin and subcutaneous tissue disorders	9	(39.13)	11
Eczema infantile	4	(17.39)	4
Eczema	3	(13.04)	4
Dermatitis diaper	2	(8.70)	2
Eczema asteatotic	1	(4.35)	1
Gastrointestinal disorders	3	(13.04)	4
Diarrhoea	2	(8.70)	2
Gastroesophageal reflux disease	1	(4.35)	1
Vomiting	1	(4.35)	1
Respiratory, thoracic and mediastinal disorders	2	(8.70)	2
Rhinitis allergic	1	(4.35)	1
Chronic respiratory failure	1	(4.35)	1
General disorders and administration site conditions	1	(4.35)	1
Pyrexia	1	(4.35)	1
Injury, poisoning and procedural complications	1	(4.35)	1
Thermal burn	1	(4.35)	1
Nervous system disorders	1	(4.35)	1
Seizure	1	(4.35)	1

SAS, safety analysis set; MedDRA, medical dictionary for regulatory activities.

Table 6: **Breakdown of adverse events (SAS).**

MedDRA version 24.0			
System organ class (SOC), Preferred term (PT)	**(N = 23)**		
	n	(%)	Number of events
Any adverse event	5	(21.74)	5
Infections and infestations	3	(13.04)	3
Bronchitis	1	(4.35)	1
Otitis media acute	1	(4.35)	1
Pneumonia bacterial	1	(4.35)	1
Respiratory, thoracic and mediastinal disorders	1	(4.35)	1
Chronic respiratory failure	1	(4.35)	1
Nervous system disorders	1	(4.35)	1
Seizure	1	(4.35)	1

SAS, safety analysis set; MedDRA, medical dictionary for regulatory activities.

Table 7: **Serious adverse events (SAS).**

SAEs, including infection, required unplanned hospitalization, but resolved without RSV infection. No AEs led to discontinuation from the study.

All 23 subjects enrolled in the study received palivizumab at a dose of 15 mg/kg body weight every 30 days for four consecutive doses. Mean serum palivizumab

	(N = 23)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event	6 (26.09)	17 (73.91)	3 (13.04)	0 (0.00)	0 (0.00)
Infections and infestations	2 (8.70)	14 (60.87)	2 (8.70)	0 (0.00)	0 (0.00)
Upper respiratory tract infection	1 (4.35)	10 (43.48)	0 (0.00)	0 (0.00)	0 (0.00)
Nasopharyngitis	1 (4.35)	3 (13.04)	0 (0.00)	0 (0.00)	0 (0.00)
Gastroenteritis	0 (0.00)	2 (8.70)	0 (0.00)	0 (0.00)	0 (0.00)
Bronchitis	0 (0.00)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)
Otitis media acute	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Pneumonia bacterial	0 (0.00)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)
Sinusitis	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Skin and subcutaneous tissue disorders	4 (17.39)	6 (26.09)	0 (0.00)	0 (0.00)	0 (0.00)
Eczema infantile	0 (0.00)	4 (17.39)	0 (0.00)	0 (0.00)	0 (0.00)
Eczema	3 (13.04)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Dermatitis diaper	0 (0.00)	2 (8.70)	0 (0.00)	0 (0.00)	0 (0.00)
Eczema asteatotic	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Gastrointestinal disorders	2 (8.70)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Diarrhoea	2 (8.70)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Gastroesophageal reflux disease	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Vomiting	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	0 (0.00)	1 (4.35)	1 (4.35)	0 (0.00)	0 (0.00)
Rhinitis allergic	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Chronic respiratory failure	0 (0.00)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)
General disorders and administration site conditions	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Pyrexia	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Injury, poisoning and procedural complications	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Thermal burn	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Nervous system disorders	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Seizure	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)

SAS, safety analysis set.

Table 8: **Adverse events by grade (SAS).**

concentrations at Visit 2, 30 days after the fourth dose, and 30 days after the fifth dose, indicated that blood concentrations of ≥30 μg/mL–the therapeutically effective concentration of palivizumab–were maintained from the first dose to 30 days after the last dose.

This study has some limitations. Firstly, the number of cases in this study cohort is relatively small to assess efficacy. A previous systematic review and meta-analysis[17] found that the NNT (number needed to treat or prevent) of palivizumab for RSV-related hospitalizations was 18.1 (palivizumab: 44/1000 versus placebo: 98/1000). Based on this data, 0–2 cases are likely to occur in this cohort (23 patients). Secondly, the incidence of breakthrough RSV infection in the recipient or her history of past RSV exposure was not investigated. Thirdly, the RSV activity during the study was limited due to the duration of the study during the COVID-19 pandemic. So, the exact efficacy may not have been fully assessed in this study design.

These efficacy, safety, and pharmacokinetic results comprehensively suggest that intramuscular administration of palivizumab at a dose of 15 mg/kg body weight every 30 days at least four times might be generally well tolerated and may be effective in preventing serious respiratory symptoms due to severe RSV infection and subsequent hospitalization in neonates, infants, and young children aged 24 months or younger whose primary disease belongs to the five disease groups studied in this study. The findings have direct implications for the approval of palivizumab in these patient groups.

Contributors

MM: conceptualization, study design, study supervision, project administration, manuscript draft, study protocol discussion with the Pharmaceuticals and Medical Devices Agency (PMDA).

KY: study supervision, manuscript draft, manuscript revision.

SW: conceptualization, study supervision.

MIshige: conceptualization, study design, study supervision, manuscript revision.

AHinoki: study supervision, manuscript draft, manuscript revision.

Test parameter (unit)	Time of testing	Statistics					
		Number of subjects	Mean	Standard deviation	Minimum	Median	Maximum
White blood cell count (10^9/L)	Visit 1	23	10.380	3.091	6.40	9.500	18.60
	Visit 5	5	11.320	1.264	9.60	11.200	13.10
	30 days after the last dose	21	11.254	2.747	6.40	10.930	16.40
Red blood cell count (10^{12}/L)	Visit 1	23	4.676	0.533	3.65	4.570	5.89
	Visit 5	5	4.822	0.230	4.50	4.840	5.11
	30 days after the last dose	21	4.890	0.365	4.16	4.890	5.60
Hemoglobin (g/L)	Visit 1	23	122.8	9.7	103	122.0	146
	Visit 5	5	122.2	7.0	114	121.0	133
	30 days after the last dose	21	127.1	11.7	110	127.0	157
Hematocrit (%)	Visit 1	23	36.70	3.20	31.9	36.20	44.2
	Visit 5	5	37.90	2.07	36.1	37.00	41.1
	30 days after the last dose	21	38.37	3.37	32.0	37.80	45.8
Platelet count (10^4/L)	Visit 1	23	43.85	12.09	29.3	39.20	76.1
	Visit 5	5	50.88	9.20	40.2	53.60	59.6
	30 days after the last dose	21	37.74	11.39	20.7	34.40	70.6
Differential leukocyte count:	Visit 1	22	25.60	10.62	10.0	26.35	51.0
Neutrophils (%)	Visit 5	5	24.18	6.94	16.0	26.00	33.0
	30 days after the last dose	21	27.69	9.97	11.5	28.00	49.0
Differential leukocyte count:	Visit 1	22	3.10	1.81	0.0	2.90	7.0
Eosinophils (%)	Visit 5	4	3.50	2.74	0.5	3.25	7.0
	30 days after the last dose	21	3.46	2.96	0.0	3.00	10.5
Differential leukocyte count:	Visit 1	21	0.55	0.60	0.0	0.40	2.0
Basophils (%)	Visit 5	2	0.55	0.07	0.5	0.55	0.6
	30 days after the last dose	18	0.50	0.41	0.0	0.50	1.0
Differential leukocyte count:	Visit 1	22	65.00	11.79	42.5	65.90	87.0
Lymphocytes (%)	Visit 5	5	66.22	6.46	60.0	65.00	77.0
	30 days after the last dose	21	63.96	9.93	44.0	63.00	85.0
Differential leukocyte count:	Visit 1	22	4.47	3.17	1.0	3.15	10.5
Monocytes (%)	Visit 5	5	5.50	2.12	4.0	4.50	9.0
	30 days after the last dose	21	3.99	2.12	0.0	3.50	7.9
Total bilirubin (mg/dL)	Visit 1	23	0.462	0.548	0.10	0.400	2.90
	Visit 5	5	0.272	0.037	0.21	0.280	0.30
	30 days after the last dose	22	0.324	0.130	0.10	0.300	0.60

Table 9: **Summary of laboratory test values.**

Time	Statistics						
	Number of subjects (number of non-missing data)	Mean	SD	Min	Median	Max	95% CI (upper–lower)
Visit 1	23 (23)	10.00	0.00	10.0	10.0	10.0	
Visit 2	23 (23)	66.89	13.58	40.0	63.90	89.2	(72.759–61.015)
30 days after the fourth dose	23 (23)	116.82	32.60	49.5	114.00	167.0	(130.916–102.719)
30 days after the fifth dose	4 (1)	153.00		153.0	153.00	153.0	

FAS, full analysis set. Data are shown in [μg/mL] unless otherwise stated.

Table 10: **Serum palivizumab concentrations (trough) over time (FAS).**

TK: study supervision, manuscript draft, manuscript revision.

TT: conceptualization, study supervision, manuscript draft, manuscript revision.

HH: conceptualization, study supervision, manuscript draft, manuscript revision.

TH: study supervision, manuscript draft, manuscript revision.

NT: conceptualization, manuscript draft, manuscript revision.

KK: study supervision, manuscript draft, manuscript revision.

AHirakawa: statistical analysis, manuscript review.

TN: project administration, manuscript draft, manuscript revision.

MImai: study design, study protocol discussion with PMDA, project administration, manuscript draft, manuscript revision.

RK: study design, study protocol discussion with PMDA, project administration, manuscript draft, manuscript revision.

Time point	Category	(N = 23)	
		n	(%)
30 days after the fourth dose	<30	22	(95.65)
30 days after the fifth dose	<30	2	(8.70)

FAS, full analysis set. Data are shown in [μg/mL] unless otherwise stated.

Table 11: **Analysis of serum anti-palivizumab antibodies (FAS).**

KH: conceptualization, manuscript draft, manuscript revision.

SK: conceptualization, manuscript draft, manuscript revision.

All authors had access to the raw data, reviewed and approved the final manuscript, and agreed to the submission for publication.

Data sharing statement

The study protocol and statistical analysis plan can be accessed.[11] De-identified participant data that underlie the results reported in this Article will be made available upon request. Proposals should be directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigators, and collaborators on the basis of scientific merit. After approval of a proposal, data requestors will need to sign a data access agreement. Data can be requested indefinitely.

Ethical approval and consent to participate

This study was conducted in compliance with the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, the Ministerial Ordinance on Good Clinical Practice (GCP), and the protocol, taking into account the ethical principles based on the Declaration of Helsinki.

The study protocol was approved by the Institutional Review Board, Tokyo Medical and Dental University Hospital of Medicine, approval number 2019-1001. Written informed consent was obtained from the legally authorized representatives of all subjects before the start of the study and again during the course of the study whenever the consent form was revised or amended with new information. Legally authorized representatives had the option to withdraw participation at any time.

Declaration of interests

MM received research grants from AbbVie GK during the conduct of the study. HH received lectures fee from Astra Zeneca KK. SK received lectures fee from AbbVie GK and Astra Zeneca KK. The rest of the authors declare that they have no conflict of interests. Neither AbbVie GK nor AMED have any role in the design of the study; the collection, analysis, or interpretation of data; or in the decision to publish this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100847.

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