


## ARTICLE

# A phase I study to evaluate safety, pharmacokinetics, and pharmacodynamics of respiratory syncytial virus neutralizing monoclonal antibody MK-1654 in healthy Japanese adults

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## Abstract

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection among all infants worldwide and remains a significant cause of morbidity and mortality. To address this unmet medical need, MK-1654, a half-life extended RSV neutralizing monoclonal antibody, is in clinical development for the prevention of RSV disease in infants. This was a phase I, randomized, placebo-controlled, single-site, double-blind trial of MK-1654 in 44 healthy Japanese adults. The safety, tolerability, pharmacokinetics, antidrug antibodies (ADAs), and serum neutralizing antibody (SNA) titers against RSV were evaluated for 1 year after a single intramuscular (i.m.) or intravenous (i.v.) dose of MK-1654 or placebo in five groups (100 mg i.m., 300 mg i.m., 300 mg i.v., 1000 mg i.v., or placebo). MK-1654 was generally well-tolerated in Japanese adults. There were no serious drug-related adverse events (AEs) reported in any MK-1654 recipient and no discontinuations due to any AEs in the study. The half-life of MK-1654 ranged from 76 to 91 days across dosing groups. Estimated bioavailability was 86% for 100 mg i.m. and 77% for 300 mg i.m. One participant out of 33 (3.0%) developed detectable ADA with no apparent associated AEs. The RSV SNA titers increased in a dose-dependent manner among participants who received MK-1654. These data support the development of MK-1654 for use in Japanese infants.

Yuji Orito and Naoyuki Otani have equally contributed to authorship.

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### Study Highlights

#### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

MK-1654 is a half-life extended human monoclonal antibody against respiratory syncytial virus that is being developed for the prevention of infection in infants.

#### WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the safety, tolerability, pharmacokinetics (PKs), neutralization activity, and immunogenicity of MK-1654 in healthy Japanese adults as a surrogate population.

#### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

MK-1654 was well-tolerated with a low incidence of treatment emergent antidrug antibodies (ADAs; 3.0%). An extended elimination half-life (76–91 days) resulted in sustained exposure and pharmacodynamic activity (respiratory syncytial virus serum neutralizing antibody) in healthy Japanese male adults. There was a remarkable increase in SNA following single dose administration of MK-1654 in Japanese healthy adults (compared to placebo). There was no apparent racial difference in the PKs and PDs of MK-1654 between Japanese and non-Japanese adults (historical data) across all dosing regimens.

#### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The results of this study provide a scientific rationale to initiate a global program for MK-1654 involving Japanese and non-Japanese infants without dose adjustment.

## INTRODUCTION

Respiratory syncytial virus (RSV) is a common respiratory pathogen which circulates globally. In temperate climates, RSV viral infections peak in the winter months, and, in tropical climates, infections peak in the hottest months and rainy seasons.<sup>1</sup> Disease can vary in severity. The highest burden of morbidity and mortality occurs in the young and elderly populations. In infants and young children, RSV is the leading cause of lower respiratory tract infections globally.<sup>2</sup> By 1-year of age, over half of infants have been infected, and nearly all children are infected by age 2.<sup>3,4</sup> Upper respiratory tract infections can progress to lower respiratory tract infections (LRTIs) leading to bronchiolitis or pneumonia in ~30% of infections in infants.<sup>5</sup> Moderate or severe LRTIs in young infants and children require a higher level of medical attention; RSV is a leading cause of hospitalization for this age group.<sup>3</sup> Approximately 33 million acute LRTIs, 3.2 million hospitalizations, and >100,000 deaths are caused by RSV annually among children <5 years of age.<sup>2</sup> RSV is the second most common infectious cause of infant mortality after malaria.<sup>6</sup>

In Japan, RSV activity fluctuates seasonally. Peaks of infection have recently shown to change from fall and winter to summer and fall.<sup>7</sup> These seasonal outbreaks are a common cause of hospitalization in infants.<sup>8–10</sup> A large RSV surveillance study conducted in Japan from 2008 to

2015 showed that, excluding the 2009/2010 season, the number of reported RSV infections in young children increased every year, a result of a true increase, increased testing, or both.<sup>8</sup> By the last season of surveillance in that study (2014/2015), there were >40,000 cases of RSV in children reported from clinics and ~25,000 reported from hospitals among the 1372 continuously reporting sites.<sup>8</sup>

A study of the hospital costs for children under 5 years of age with RSV in Japan reported a substantial economic burden as well, with a mean cost of \$3344 for hospitalization and \$4951 for intensive care.<sup>11</sup> To date, there are no approved vaccines or highly effective therapeutics against RSV. Active RSV vaccines have been hindered by safety risks observed in previous trials in infants<sup>12</sup> as well as the general challenges of vaccinating neonates, who have immature immune systems.

Rapid protection can be achieved using passive immunization with an RSV neutralizing antibody. In Japan, palivizumab, an RSV fusion (F) protein-specific neutralizing antibody, is approved for children at highest risk for RSV morbidity and mortality (e.g., chronic lung disease, chronic heart disease, immunodeficiencies, and Down syndrome). Palivizumab requires monthly doses during RSV season and is thus restricted in use, in part, due to limited cost-effectiveness. It has not been recommended for use in the general infant population, where significant disease burden remains.<sup>13,14</sup> RSV neutralizing monoclonal antibodies (mAbs) with higher potency and

longer half-lives than palivizumab are currently in clinical development. MK-1654 is a recombinant IgG1 human antibody.<sup>15</sup> MK-1654 binds to RSV F protein at antigenic site IV, which is highly conserved across RSV viral genotypes.<sup>15–17</sup> Nirsevimab, another RSV mAb in development, targets antigenic site Ø<sup>18</sup> of the F protein.

MK-1654 demonstrated potent *in vivo* protection from RSV in the cotton rat model, as well as equal *in vitro* potency against a range of clinically derived RSV type A and B strains.<sup>15</sup> The fragment crystallizable region is engineered with three mutations such as YTE (M252Y/S254T/T256E) to extend the elimination half-life. A phase I, first-in-human study of MK-1654 took place in the United States in primarily White participants.<sup>19</sup> In this population, the antibody was well-tolerated with a half-life of 73–88 days.<sup>19</sup> This is approximately four times longer than a typical IgG1 antibody (~21 days).<sup>20</sup> The potent neutralization activity and extended half-life offers the potential for single season dosing to protect the broader infant population against medically attended lower respiratory infection. As of March 2022, MK-1654 is in phase III clinical development to evaluate the safety and efficacy against medically attended lower respiratory infection in healthy pre-term and full-term infants (NCT04767373).

The current study was performed to evaluate the safety, tolerability, pharmacokinetics (PKs), antidrug antibodies (ADAs), and serum neutralizing antibody (SNA) activity of MK-1654 in healthy Japanese male adults.

## METHODS

### Study objectives

The primary objective of the study was to evaluate the safety and tolerability of single intramuscular (i.m.) and intravenous (i.v.) doses of MK-1654 in healthy Japanese male adults. The secondary objectives were to estimate the serum PK profiles and to evaluate the development of ADAs in serum samples after the administration of single doses of MK-1654 in this population. As exploratory objectives, the study evaluated the absolute bioavailability of a single i.m. dose of MK-1654, and the effect of single i.m. and i.v. doses of MK-1654 on RSV SNA titers.

### Study design

This study was a phase I, randomized, placebo-controlled study of MK-1654 in healthy Japanese male adults (Protocol MK-1654-003). The study was conducted in accordance with the ethical principles that have their origin

in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and the applicable regulatory requirements. The protocol was approved by the Oita University Hospital Investigational Review Board before initiation of this study; and written informed consent was obtained from each participant before study entry.

Participants were randomized to receive a single-dose of MK-1654 or placebo (0.9% sodium chloride injection; Japan Pharmacopeia) in a treatment ratio of 3:1 (MK-1654 to placebo). The trial consisted of four panels (panels A to D). Panel A consisted of eight participants (six active and two placebo), and panels B, C, and D consisted of 12 participants in each (nine active and three placebo). The doses in panels A through D were 100 mg i.m., 300 mg i.m., 300 mg i.v., and 1000 mg i.v., respectively. Each participant was only enrolled in one panel in the study; therefore, each received a single dose of MK-1654 or placebo.

The MK-1654 drug product concentration was 100 mg/ml. The i.m. injection was given in the vastus lateralis as either a single bolus injection of 1.0 ml (100 mg) or in two boluses of 1.5 ml (300 mg). The i.v. infusion was given in 250 ml of diluted solution with sterile saline using a volumetric pump for 2.5 h.

Participants were domiciled for ~30 h after initiation of study drug administration for monitoring. There were at least ~2 weeks after dosing participants in a panel before administering the dose in the next panel to evaluate safety, including: local injection (for i.m.) or infusion (for i.v.) site reactions, systemic reactions to injection or infusion, other adverse events (AEs), laboratory safety tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examination. For all panels, participants were evaluated periodically up to ~1-year for safety, serum PKs, ADAs, and RSV SNA titers.

### Population

Healthy Japanese males between the ages of 20 and 55 years (inclusive) with a body mass index (BMI) at screening of  $\geq 18.5$  to  $\leq 32.0$  kg/m<sup>2</sup> who were nonsmokers were eligible for enrollment. Determination of good general health was based on medical history, physical examination, vital sign measurements, and ECG at screening prior to administration of study drug. Key exclusion criteria included acute or febrile illness prior to the administration of study drug on day 1, clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, major neurological abnormalities or diseases, and a history of cancer or severe allergies. Participants were also excluded if they received a vaccination within 30 days of the study, or had a history

of receiving human immunoglobulin, or human blood products, or monoclonal antibodies within 1-year prior to the screening visit.

## Study assessments

Safety was assessed by taking ECGs at baseline, 4 h post-dose, day 2, day 3, and post-study. Vital signs were monitored baseline through baseline to day 7 and at post-study. Standard laboratory values were monitored at baseline, days 2, 3, 7, 14, 90, and 360, and post-study. All AEs were collected through day 90 after dosing and serious adverse events (SAEs) were recorded throughout the 1-year follow-up. The intensity of AEs was categorized by the investigator as mild, moderate, or severe. AEs were determined by the investigator to be related or not related to study treatment. Participants were also monitored for events of clinical interest (abnormalities of liver function test including alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase and hypersensitivity, or cytokine release reaction) throughout the 1-year follow-up.

Serum concentrations of MK-1654 were determined using a validated liquid chromatography–tandem mass spectrometry method, as described in Aliprantis et al.<sup>19</sup> on serum from blood collected at baseline, 0.5, 1, 2.5, 4, 8, 12 h on day 1, and on days 2, 3, 5, 7, 14, 28, 60, 90, 120, 150, 210, 270, and 360. The lower limit of detection for the assay is 0.5 µg/ml.

Antidrug antibodies were evaluated from serum from blood collected predose on day 1 (baseline) and on days 14, 28, 60, 90, 120, 150, 210, 270, and 360. These were measured using a validated electrochemiluminescent assay.<sup>19</sup> A positive titer was defined as greater than or equal to 1:120 (that is, the dilution of the serum into assay reagents/buffers). Confirmed positive samples were analyzed for titer, defined as the reciprocal of the highest dilution that produced a positive signal greater than the cutoff point.

Respiratory syncytial virus subtype A (RSV A) SNA were collected at predose, 0.5, 2.5, and 24 h on day 1 after administration and on days 3, 7, 14, 28, 60, 90, 120, 150, 210, 270, and 360 using a qualified virus reduction neutralization method.<sup>21</sup> Briefly, the test serum is serially diluted three-fold from 1:30 to 1:590,490 and mixed with equal amounts of RSV A (long strain<sup>22</sup>). The serum/virus mixture was incubated for 30 min followed by inoculation of A549 cells. The cells are then incubated for 22–24 h and then fixed with acetone and methanol (1:1). The fluorescent signal is developed using a specific AlexaFluor 488 conjugated anti-RSV antibody. An SNA titer of greater than 30 indicates the presence of RSV neutralizing antibody.

## Data analysis

Formal hypothesis testing was not conducted in this study. All participants who received study intervention were included in the safety assessments. Incidence of AEs were descriptively summarized for all participants.

The PK analysis population consisted of all participants who were compliant with study procedures and had available PK data. A noncompartmental PK analysis was conducted on serum concentrations with actual sampling time using Phoenix WinNonlin (version 6.3; Certara) and evaluated using descriptive statistics. PK parameters of interest included area under the concentration versus time curve from 0 to infinity ( $AUC_{0-\infty}$ ), maximum concentration ( $C_{max}$ ), concentration on day 150 (C150 days), time to maximum concentration ( $T_{max}$ ), and terminal elimination half-life ( $t_{1/2}$ ).  $AUC_{0-\infty}$  was calculated using the linear-up/log-down trapezoidal method. At least three datapoints, excluding the  $C_{max}$ , in the terminal phase were used for the determination of  $t_{1/2}$ . Separately for each PK parameter, individual values of  $AUC_{0-\infty}$ ,  $C_{max}$ , and C150 days at each i.m. and i.v. dose level were natural log-transformed and evaluated with an analysis of variance (ANOVA) model containing a fixed effect for panel (i.e., dose level by route of administration). Ninety-five percent confidence intervals (CIs) for the least squares means for each panel were constructed on the natural log scale and referenced a t-distribution. Exponentiating the least squares means and lower and upper limits of these CIs yielded estimates for the population geometric means and CIs about the geometric means on the original scale. The absolute bioavailability of MK-1654 was estimated as the geometric mean ratio (GMR) (i.m./i.v.) for  $AUC_{0-\infty}$  following i.m. dosing of 100 mg and 300 mg and i.v. dosing of 300 mg, as prespecified in the protocol. Because no i.v. data were available for the 100 mg dose level, the bioavailability for the 100 mg i.m. dose level was estimated using dose-normalization.

The PK parameters ( $AUC_{0-\infty}$ ,  $C_{max}$ , and C150 days) were compared with historical PK data from non-Japanese participants following single i.m. and i.v. administration, using both absolute and dose-normalized values. The historical PK data were previously published in a first-in-human study,<sup>19</sup> which enrolled primarily White participants (84.9% White, 9.9% Black, 2.6% Asian, and 2.6% multiple races), and the population is referred to as the non-Japanese participants in this report. The GMR of Japanese/non-Japanese and corresponding 90% CI were generated from an ANOVA model with a factor for race (Japanese and non-Japanese), group (i.e., dose level by route of administration and route administration) and race by group interaction. In addition,

the analysis including body weight as a covariate in the model was performed, and GMR and corresponding 90% CIs were generated.

For the ADA measurement, predose and postdose ADAs were assessed in participants who received an active dose of MK-1654. Postdose samples were defined as samples collected after administration of MK-1654. ADA samples were collected prior to dosing on day 1 (baseline) and on study days 14, 28, 60, 90, 120, 150, 210, 270, and 360. Participants had baseline samples taken prior to dosing to assess for any preexisting immune response that may be detected by the ADA assay and were considered positive if at least one predose or postdose sample was positive in the ADA confirmatory assay. Summary of ADA incidence was provided for participants with at least one ADA sample result.

For the pharmacodynamic marker, the geometric mean (GM) and 95% CIs for SNA titers were tabulated and plotted by time, dose level, and route of administration.

## RESULTS

### Study participants

A total of 44 adult male Japanese participants were randomized to receive a single i.m. or i.v. dose of MK-1654 or placebo in five groups (100 mg i.m. [ $N = 6$ ], 300 mg i.m. [ $N = 9$ ], 300 mg i.v. [ $N = 9$ ], 1000 mg i.v. [ $N = 9$ ], or placebo [ $N = 11$ ]). Participants who received placebo were pooled across i.m. and i.v. panels. All participants (100%) completed the study. Baseline characteristics are shown in Table 1. Per study design, all participants were male adults and of Asian race. The mean age of the total participants was 34 years (range 20–46 years), and the mean weight was 66.9 kg (range 51.3–91.2 kg). The age, weight, and BMI were generally consistent across study groups.

### Safety

A total of 19 participants who received MK-1654 (57.6%), and seven who received placebo (63.3%) reported one or more AEs (Table 2). A total of four participants in the study reported an AE (diarrhea) that was considered to be treatment related (one participant each from the following groups: placebo i.m., MK-1654 100 mg i.m., MK-1654 300 mg i.m., and MK-1654 1000 mg i.v.). There were no deaths in the study and no discontinuations due to any AE or SAE. One SAE was reported by a participant in the MK-1654 300 mg i.v. group, which was a tendon rupture that occurred while playing soccer. This SAE was determined to be not related to study intervention by the investigator and subsequently resolved. The most commonly reported treatment-emergent AEs in participants that received MK-1654 were nasopharyngitis (27.3%) and diarrhea (12.1%), as shown in Table 3. No dose-dependent pattern of intervention-related AEs were observed. Most AEs were transient and considered mild to moderate in intensity. Further, there were no clinically meaningful dose-related trends observed as a function of study intervention for laboratory safety tests, vital signs, or ECGs, and no AEs of clinical interest were reported in the study. MK-1654 i.m. and i.v. were generally well-tolerated in terms of local reactogenicity, with no participants reporting injection/infusion site reactions after MK-1654 administration.

### Pharmacokinetics

The mean serum concentration-time profiles of MK-1654 appeared to increase in a manner that was dose-proportional; and the apparent terminal elimination phases were parallel for all i.m. and i.v. groups (Figure 1). The median  $T_{max}$  observed across doses was 6.0 and 9.5 days for 100 mg and 300 mg i.m. groups, respectively, and 2.5 to 4.0 h post-infusion for 300 mg and 1000 mg i.v. groups. The 4-h timepoint is the first

**TABLE 1** Participant baseline characteristics

	Placebo <sup>a</sup>	MK-1654				Total
		100 mg i.m.	300 mg i.m.	300 mg i.v.	1000 mg i.v.	
	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)
Participants	11	6	9	9	9	44
Mean age, years [range]	33.3 [24–44]	35.7 [24–45]	31.6 [20–46]	36.3 [20–46]	33.7 [21–41]	34.0 [20–46]
Mean weight, kg [range]	70.1 [58.9–91.2]	63.1 [51.3–82.2]	66.3 [58.5–79.0]	66.2 [54.1–79.5]	66.8 [52.3–75.6]	66.9 [51.3–91.2]
Mean BMI, kg/m <sup>2</sup> [range]	23.1 [18.9–28.1]	21.9 [19.0–24.5]	22.4 [19.6–25.9]	22.6 [19.3–26.1]	23.3 [19.1–26.9]	22.7 [18.9–28.1]

Abbreviation: BMI, body mass index.

<sup>a</sup>Participants who received placebo were pooled across i.v. and i.m. panels.

**TABLE 2** Adverse event summary

	MK-1654					Placebo <sup>a</sup>
	100 mg i.m.	300 mg i.m.	300 mg i.v.	1000 mg i.v.	Total MK-1654	
	n (%)	n (%)	n (%)	n (%)	n (%)	
Participants in population	6	9	9	9	33	11
With ≥1 AE	2 (33.3)	7 (77.8)	3 (33.3)	7 (77.8)	19 (57.6)	7 (63.3)
With drug-related <sup>b</sup> AE	1 (16.7)	1 (11.1)	0 (0.0)	1 (11.1)	3 (9.1)	1 (9.1)
With ≥1 SAE	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.0)	0 (0.0)

Abbreviations: AE, adverse event; SAE, serious adverse event.

<sup>a</sup>Participants who received placebo were pooled across i.v. and i.m. panels.

<sup>b</sup>Determined by the investigator to be related to the drug.

**TABLE 3** Adverse events (incidence ≥1 in total MK-1654 participants)

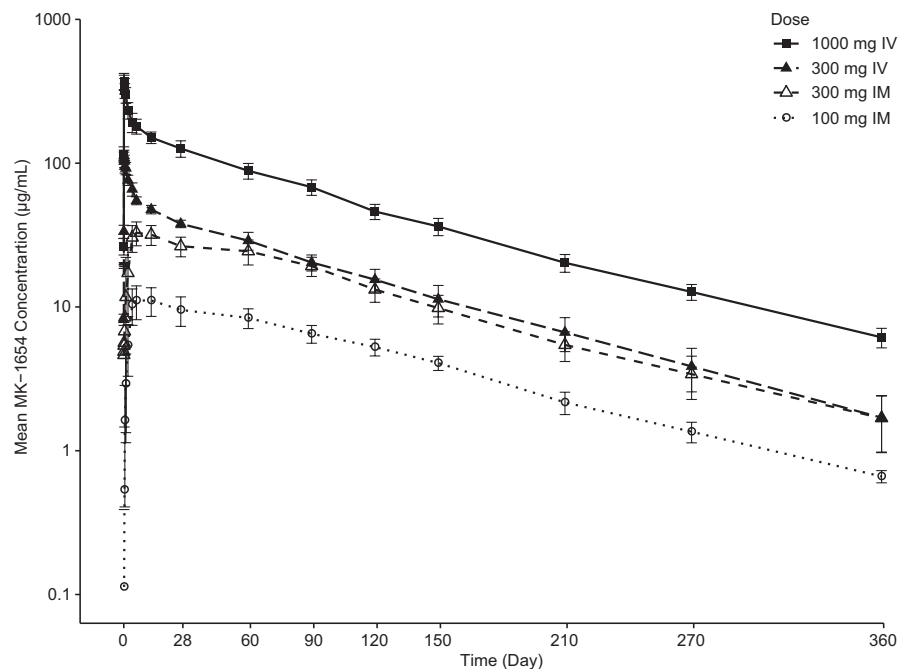
	MK-1654					Placebo
	100 mg i.m.	300 mg i.m.	300 mg i.v.	1000 mg i.v.	Total MK-1654	
	n (%)	n (%)	n (%)	n (%)	n (%)	
Participants in population	6	9	9	9	33	11
Abdominal discomfort	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.0)	0 (0.0)
Diarrhea	2 (33.3)	1 (11.1)	0 (0.0)	1 (11.1)	4 (12.1)	1 (9.1)
Hemorrhoids	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.0)	0 (0.0)
Nausea	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Adenoviral conjunctivitis	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	3 (33.3)	1 (11.1)	5 (55.6)	9 (27.3)	3 (27.3)
Pharyngotonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.0)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Skin abrasion	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.0)	1 (9.1)
Tendon rupture	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.0)	0 (0.0)
Limb discomfort	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Headache	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.0)	0 (0.0)

reliable measurement for post-infusion serum concentrations in the i.v. group because the i.v. infusions took place over a minimum of 2.5 h. The GM terminal elimination half-life of MK-1654 in Japanese adults ranged from 76 to 91 days and was comparable across study groups (Table 4). The bioavailability was ~86% for 100 mg i.m. and ~77% for 300 mg i.m. groups as estimated using data from participants that received the 300 mg i.v. as the reference.

The Japanese participant data from the current study was compared to non-Japanese data from the first-in-human study.<sup>19</sup> Japanese participants had slightly

higher exposures relative to non-Japanese (Table 5). The GMRs of Japanese/non-Japanese participants following single i.m. and i.v. doses for  $AUC_{0-\infty}$ ,  $C_{max}$ , and C150 days ranged from 1.08 to 1.27, 1.01 to 1.15, and 0.97 to 1.42, respectively. After adjustment for body weight, any differences in exposure between Japanese and non-Japanese were much less apparent (Table 5). The GMRs of Japanese/non-Japanese participants for  $AUC_{0-\infty}$ ,  $C_{max}$ , and C150 days after adjusting for body weight ranged from 0.94 to 1.01, 0.84 to 0.98, and 0.83 to 1.13, respectively. The 90% CIs around the GMRs contained one in almost all comparisons.

**FIGURE 1** Mean serum concentration-time profiles after a single intravenous (i.v.) or intramuscular (i.m.) dose of MK-1654 in healthy Japanese male adults. Arithmetic mean serum concentrations for each group versus time in days after administration. Error bars represent the standard deviation. Data include the 1000 mg i.v. group ( $N = 9$ ), 300 mg i.v. group ( $N = 9$ ), 300 mg i.m. group ( $N = 9$ ), and 100 mg i.m. ( $N = 6$ ). IM, intramuscular injection; IV, intravenous infusion over 2.5 h



**TABLE 4** Summary statistics of pharmacokinetic parameter values of MK-1654

PK Parameter	100 mg i.m.	300 mg i.m.	300 mg i.v.	1000 mg i.v.
N	6 <sup>e</sup>	9	9	9
AUC <sub>0-∞</sub> (µg·day/ml) <sup>a</sup>	1539 (1356, 1746)	4168 (3759, 4620)	5386 (4859, 5971)	17,310 (15,614, 19,190)
C150 (µg/ml) <sup>a</sup>	4.05 (3.35, 4.91)	9.60 (8.33, 11.1)	11.0 (9.51, 12.7)	36.0 (31.2, 41.5)
C <sub>max</sub> (µg/ml) <sup>a</sup>	11.2 (9.80, 12.8)	33.2 (29.7, 37.1)	112 (101, 125)	370 (331, 413)
<i>t</i> <sub>1/2</sub> (day) <sup>b</sup>	90.6 (14.6)	86.4 (21.0)	75.9 (18.8)	91.2 (6.94)
<i>T</i> <sub>max</sub> (day) <sup>c</sup>	9.53 [4.02, 27.1]	6.03 [0.104, 13.2]	0.167 [0.104, 0.167]	0.104 [0.104, 0.167]
Bioavailability (%) <sup>d</sup>	85.7	77.4	-	-

Abbreviations: AUC<sub>0-∞</sub>, area under the concentration versus time curve from 0 to infinity; C150, concentration at 150 days; C<sub>max</sub>, maximum plasma concentration; PK, pharmacokinetic; *t*<sub>1/2</sub>, terminal half-life; *T*<sub>max</sub>, time to maximum concentration.

<sup>a</sup>Back-transformed least squares mean and 95% confidence interval from the analysis of variance model performed on natural log-transformed values.

<sup>b</sup>Geometric mean (GM %CV).

<sup>c</sup>Median (minimum, maximum).

<sup>d</sup>Calculated using dose-normalized 100 mg and 300 mg i.m. geometric mean AUC<sub>0-∞</sub>/300 mg i.v. geometric mean AUC<sub>0-∞</sub>.

<sup>e</sup>*n* = 5 for C150.

## Evaluation of antidrug antibody

One participant (100 mg i.m. group) of 33 who received MK-1654 (3.0%) developed a treatment-emergent ADA. The participant had a negative sample at baseline and developed positive samples following administration of MK-1654 beginning on day 90. The magnitude of the response increased at later timepoints with a maximum titer of 240 measured at day 210. This ADA titer was low and close to the detection limit of the assay (titer of 120). There were no apparent AEs associated with the treatment-emergent ADA in this participant, and the participant demonstrated a PK profile comparable to the ADA-negative participants.

## RSV SNA

Serum neutralization titers, as a pharmacodynamic measure, were evaluated at baseline and at timepoints up to 1-year after dosing (Figure 2). All participants had detectable SNA titers at baseline, which is expected, as all adults have typically had prior RSV infection. A rise in RSV SNA was detected in all MK-1654 treated groups and titers increased in a dose-dependent manner. The placebo group demonstrated minimal change over time. The SNA titers peaked earlier in the groups given MK-1654 i.v. (day 1), as compared to those given MK-1654 i.m. (day 7). In the groups given MK-1654 300 mg, the GM SNA titers were comparable between the i.v. and

**TABLE 5** Comparison of MK-1654 exposures in healthy Japanese participants compared to healthy non-Japanese participants following single i.m. or i.v. administrations

MK-1654 dose	Japanese <i>N</i>	Non-Japanese <i>N</i>	Ratio (Japanese/non-Japanese)		
			$AUC_{0-\infty}$	$C_{max}$	C150
			GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
Without body weight adjustment					
100 mg i.m.	6 <sup>b</sup>	12	1.27 (1.05, 1.53)	1.01 (0.87, 1.18)	1.42 (0.98, 2.08)
300 mg i.m.	9	48 <sup>c</sup>	1.21 (1.06, 1.39)	1.08 (0.96, 1.20)	1.20 (0.92, 1.55)
i.m. (100 mg + 300 mg) <sup>a</sup>	15 <sup>d</sup>	60 <sup>d</sup>	1.25 (1.12, 1.39)	1.06 (0.97, 1.16)	1.28 (1.04, 1.58)
300 mg i.v.	9	12	1.08 (0.91, 1.27)	1.05 (0.91, 1.20)	0.97 (0.71, 1.33)
1000 mg i.v.	9	30	1.14 (0.99, 1.32)	1.15 (1.02, 1.29)	1.04 (0.80, 1.37)
i.v. (300 mg + 1000 mg) <sup>a</sup>	18	42	1.13 (1.02, 1.26)	1.12 (1.03, 1.22)	1.02 (0.84, 1.25)
With body weight adjustment					
100 mg i.m.	6 <sup>b</sup>	12	1.01 (0.86, 1.19)	0.84 (0.74, 0.96)	1.13 (0.78, 1.63)
300 mg i.m.	9	48 <sup>c</sup>	0.98 (0.86, 1.10)	0.90 (0.82, 0.99)	0.93 (0.72, 1.21)
i.m. (100 mg + 300 mg) <sup>a</sup>	15 <sup>d</sup>	60 <sup>d</sup>	0.99 (0.90, 1.10)	0.88 (0.81, 0.96)	1.00 (0.80, 1.25)
300 mg i.v.	9	12	0.95 (0.82, 1.09)	0.94 (0.84, 1.05)	0.83 (0.62, 1.13)
1000 mg i.v.	9	30	0.94 (0.83, 1.07)	0.98 (0.88, 1.08)	0.83 (0.63, 1.09)
i.v. (300 mg + 1000 mg) <sup>a</sup>	18	42	0.95 (0.86, 1.04)	0.97 (0.89, 1.04)	0.83 (0.68, 1.02)

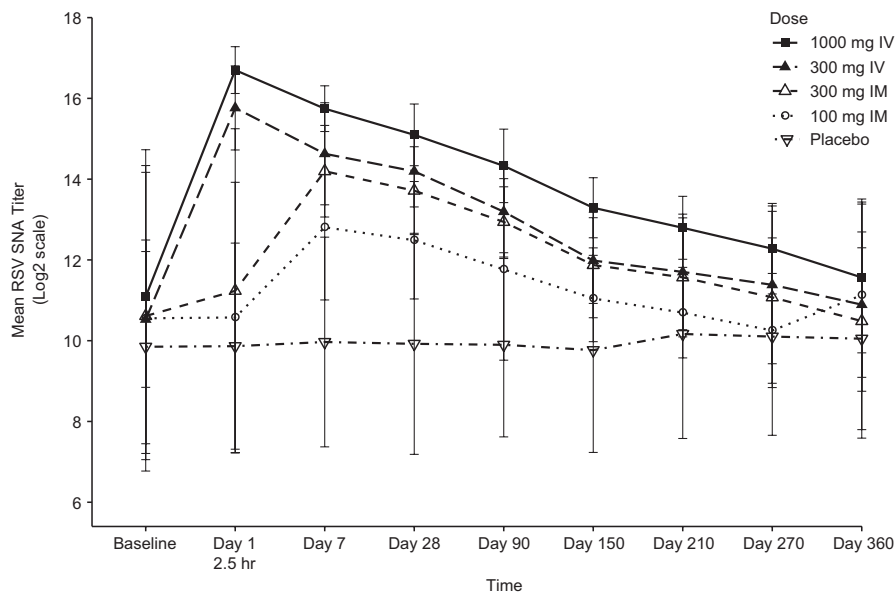
Abbreviations:  $AUC_{0-\infty}$ , area under the concentration versus time curve from 0 to infinity; C150, concentration at 150 days; CI, confidence interval;  $C_{max}$ , maximum plasma concentration; GMR, geometric mean ratio.

<sup>a</sup>Calculated using dose-normalized pharmacokinetic parameters.

<sup>b</sup> $n = 5$  for C150.

<sup>c</sup> $n = 47$  for C150.

<sup>d</sup>Japanese participants,  $n = 14$  for C150; non-Japanese participants,  $n = 59$  for C150.



**FIGURE 2** RSV-neutralizing antibody titers following a single intravenous (i.v.) or intramuscular (i.m.) administration of MK-1654 or placebo in healthy Japanese male adults. RSV serum neutralization 50% inhibitory concentration ( $IC_{50}$ ) titers in log<sub>2</sub> scale versus time. A titer of greater than 30 (4.9 in log<sub>2</sub> scale) indicates the presence of RSV neutralizing antibody. Points represents the geometric mean of each group and error bars represent the 95% confidence intervals. Data include the 1000 mg i.v. group ( $N = 9$ ), 300 mg i.v. group ( $N = 9$ ), 300 mg i.m. group ( $N = 9$ ), 100 mg i.m. ( $N = 6$ ) and placebo (combined i.m. and i.v.,  $N = 11$ ). IM, intramuscular injection; IV, intravenous infusion over 2.5 h



i.m. groups after day 7. The GM SNA titers in all MK-1654 treated groups declined over time to near baseline levels by day 360.

## DISCUSSION

Here, we present the results of the first study of the neutralizing RSV mAb, MK-1654, conducted in healthy Japanese adults. This study was performed to measure safety, tolerability, PK, ADA, and SNA of MK-1654 in Japanese adults prior to starting studies in the target pediatric population. The results reported here can be compared to the findings in the first-in-human study conducted in the United States.<sup>19</sup>

Single doses of MK-1654 (100 mg i.m., 300 mg i.m., 300 mg i.v., and 1000 mg i.v.) were generally well-tolerated in healthy Japanese adult males. There were no deaths, serious drug-related AEs, or discontinuation due to any AEs in the study. The safety profile across all MK-1654 treated participants were similar to that of the placebo recipients. These safety findings are consistent with those in a non-Japanese cohort.<sup>19</sup> Overall, no clinically meaningful differences in safety findings between the studies in non-Japanese and Japanese adults were observed.

The GMRs of MK-1654 PK parameters (i.e.,  $AUC_{0-\infty}$  and  $C_{max}$ ) reported here indicate modestly higher exposures compared to historical estimates of exposures in the non-Japanese cohort.<sup>19</sup> Body weight is a known covariate of MK-1654 PK and its impact on clearance and volume of distribution has been described using population PK modeling.<sup>23</sup> After adjusting for the lower body weight observed in Japanese compared to non-Japanese participants, GMRs suggest that exposures were largely comparable between the two cohorts. This finding suggests a lack of PK differences based on race and indicates that subsequent infant studies do not require a dose adjustment between Japanese and non-Japanese infants because there are no major differences in the distribution of body weight by age in children born in Japan<sup>24</sup> compared to those born in the United States.<sup>25</sup>

MK-1654 demonstrated linear PK and geometric mean half-life values ranging from 76 to 91 days in healthy Japanese adult men, which is a similar finding to that reported in the non-Japanese cohort (73–88 days).<sup>19</sup> This half-life is approximately four-fold longer as compared to palivizumab in adults.<sup>26</sup> Studies of other YTE-engineered mAbs evaluated in adults reported a similar range. Nirsevimab, motavizumab-YTE, and MEDI4893 reported half-lives of 85–117 days,<sup>18</sup> 70–100 days,<sup>27</sup> and 80–112 days,<sup>28</sup> respectively.

The estimated bioavailability of (~77%) for the 300 mg i.m. dose in Japanese adults is similar to the result

measured from the 300 mg i.m. dosed group in the non-Japanese cohort (~69%).<sup>19</sup> The demonstrated extended half-life and high bioavailability of MK-1654 are important because those enable the potential for a single prophylactic immunization with i.m. administration to cover an RSV season.

Levels of ADA are important to understand both potential effects on drug PKs as well as safety. In the current study, only one participant of all MK-1654 treated (3.0%) demonstrated treatment-emergent ADA. This participant did not report any AEs during this study. This ADA result in Japanese participants is consistent with the study in non-Japanese adults, where 2.6% of MK-1654 participants demonstrated treatment-emergent ADA.<sup>19</sup> In both studies, there were no apparent associated AEs in the participants who had treatment-emergent ADAs.

Increases in SNA are important to achieve RSV viral neutralization and protection from disease. SNA levels can rise quickly with passive immunization of a neutralizing mAb because there is no need for an active immune response to evolve to achieve titers. Here, we measured peaks in SNA around the  $T_{max}$  (2.5 h in the i.v. MK-1654 dosed groups and at day 7 in the i.m. dosed MK-1654 group). All doses of MK-1654 in the study showed the robust neutralizing activity compared to placebo, in a manner that is consistent with the non-Japanese cohort.<sup>19</sup> A recently published RSV model-based meta-analysis described how SNA titers were used to support dose selection in infants. A dose of greater than or equal to 75 mg of MK-1654 in infants was predicted to provide high protection against LRTI (>75% for 5 months).<sup>23</sup> Because no clear differences exist in the SNA response observed in Japanese participants compared to non-Japanese participants following MK-1654 administration, it is reasonable to conclude that the same dose can be used for Japanese and non-Japanese infants alike.

One limitation to the current study is that MK-1654 was evaluated in healthy male adults only. More diverse studies including the target infant population and in both sexes will be required to fully evaluate the antibody.

In summary, MK-1654 was generally well-tolerated in healthy Japanese male adults. No clinically meaningful differences in safety, tolerability, PK, ADA, and SNA profiles were observed between the present study in Japanese participants compared to the previous evaluation in a non-Japanese cohort. The results of this study provide a scientific rationale for continued global development of MK-1654 in Japanese and non-Japanese infants without dose adjustment for race.

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### CONFLICT OF INTEREST

Y.O., Y.M., K.F., N.O., B.M.M., L.C., and A.O.A. are employees (or were at the time of the study) of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may hold stock in Merck & Co., Inc., Rahway, NJ, USA. K.S.C. is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, may hold stock in Merck & Co., Inc., Rahway, NJ, USA, and is named on an issued patent related to the discovery of the RSV antibody. N.U. reports payments as a Primary Investigator for the study, is a paid consultant to MSD K.K. for general clinical pharmacology matters at the time of the conduct study, and holds stock in Merck & Co., Inc., Rahway, NJ, USA. All other authors declared no competing interest for this work. As an Associate Editor for *Clinical & Translational Science*, Naoto Uemara was not involved in the review or decision process for this paper.

### AUTHOR CONTRIBUTIONS

Y.O., N.O., K.F., A.O.A., K.S.C., N.U., and Y.M. wrote the manuscript. Y.O., K.F., L.C., A.O.A., Y.M., and B.M.M. designed the research. Y.O., N.O., K.F., M.K., H.K., O.T., H.I., N.U., and Y.M. performed the research. Y.O., N.O., A.O.A., and Y.M. analyzed the data.

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