

# Pharmacokinetics, Safety and Tolerability of Intravenous Lenzilumab, an Anti-GM-CSF Monoclonal Antibody Drug, in Healthy Korean Subjects

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**Background:** Lenzilumab is a recombinant monoclonal antibody neutralizing human granulocyte macrophage-colony stimulating factor. By modulating proinflammatory cytokine cascade, lenzilumab is expected to be effective in prevention and treatment of cytokine release syndrome. This study aimed to assess the safety, tolerability and pharmacokinetics (PKs) after a single intravenous (IV) administration of lenzilumab in healthy Korean subjects.

**Methods:** A randomized, double-blind, placebo-controlled, single ascending dose study was conducted. The subjects received a single dose of 1, 3 or 10 mg/kg of lenzilumab or placebo via 1-hour IV infusion. Plasma samples for PK analysis were collected up to 69 days after the administration. PK parameters were estimated using noncompartmental analysis and dose-proportionality of lenzilumab was assessed. Adverse events and other safety variables were monitored throughout the whole study period.

**Results:** Among the 20 subjects who completed the study, three received 1 mg/kg of lenzilumab, while six received 3 mg/kg and another six received 10 mg/kg. The remaining five subjects received the placebo. After 1-hour IV infusion, the maximum concentrations of lenzilumab were observed between 2.0 and 3.0 hours. The time-concentration profile of lenzilumab displayed biphasic decline and the terminal half-life ranged from 25.33 to 31.21 days. Lenzilumab exhibited a dose-proportional increase in its systemic exposure across 1 to 10 mg/kg. Nine cases of treatment-emergent adverse events occurred in six subjects receiving lenzilumab. All were mild and spontaneously recovered.

**Conclusion:** The systemic exposure of lenzilumab was dose-proportional across 1 to 10 mg/kg in healthy Korean subjects. A single IV administration of lenzilumab was safe and well tolerated in the dose range between 1 and 10 mg/kg.

**Keywords:** granulocyte-macrophage colony-stimulating factor, monoclonal antibody, pharmacokinetics, phase 1 clinical trial, COVID-19, cytokine release syndrome

## Introduction

Cytokine release syndrome (CRS) refers to excessive systemic inflammatory responses, which can be triggered by several factors including drugs or infections, such as the coronavirus disease 2019 (COVID-19).<sup>1</sup> CRS typically begins with flu-like symptoms including fever, myalgia and fatigue. But it can progress to severe and potentially fatal conditions, such as vasodilatory shock, capillary leakage and multi-organ failure, increasing mortality associated with certain diseases.<sup>2,3</sup> Although the precise mechanism of CRS remains to be fully identified, it is widely attributed to the activation and proliferation of immune cells, followed by the release of proinflammatory cytokines and chemokines. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a type of cytokine secreted by various cells. GM-CSF not only promotes the proliferation and differentiation of bone marrow progenitor cells but also acts as a pro-survival and activating factor for mature myeloid cells, such as macrophage or dendritic cell.<sup>4</sup> GM-CSF was found to play a unique role in the pathogenesis either of severe COVID-19 or of COVID-19 induced CRS. GM-CSF levels exhibited a positive

correlation with COVID-19 severity and were notably elevated only in COVID-19 patients, accompanying IL-6 level elevation.<sup>5</sup>

Lenzilumab is an engineered human immunoglobulin (Ig) G1<sub>k</sub> monoclonal antibody (mAb) for human GM-CSF. It directly binds to human GM-CSF with high affinity and has a slow off-rate. Lenzilumab was developed from its chimeric version, KB002, by Humaneered<sup>®</sup> (Humanigen Inc., NJ, USA), reducing the formation of anti-drug antibodies while preserving its high affinity.<sup>6,7</sup> Lenzilumab is expected to be a novel treatment for severe COVID-19 preventing further progression. In a Phase 3 study conducted in adult COVID-19 patients requiring oxygen supplement but not invasive mechanical ventilation, lenzilumab demonstrated its efficacy by improving survival without the need for mechanical ventilation (SWOV).<sup>8</sup> The likelihood of SWOV decreased as C-reactive protein (CRP) levels increased beyond 150 mg/L, and post-treatment CRP levels were lower in the lenzilumab group compared to the placebo group. Given these, the efficacy of lenzilumab appears to stem from disrupting the positive feedback loop of inflammation and then excessive cytokine release by interfering with GM-CSF.

By 2023, a total of eight clinical studies have been conducted with lenzilumab, reporting its wide therapeutic window and dose-proportional pharmacokinetics (PKs).<sup>7–10</sup> After multiple IV administrations, lenzilumab demonstrated a safety profile similar to that of placebo in adult patients with uncontrolled asthma or severe COVID-19.<sup>7,8</sup> Lenzilumab was also well tolerated in chronic myelomonocytic leukemia patients within a dose range of 200 mg to 600 mg, showing no adverse events of grade greater than 2.<sup>10</sup> In the asthma study, the median half-life of lenzilumab was reported as 29.4 days.<sup>7</sup> All eight studies were conducted outside Korea, providing only limited safety and PK profiles of lenzilumab in Koreans. Although the need for accessible CRS management options, such as lenzilumab, has been rising in Korea, data on the PKs and safety of lenzilumab in Koreans are limited. This study aimed to evaluate the safety, tolerability and PKs of lenzilumab after a single IV administration in healthy Korean subjects.

## Materials and Methods

The protocol of this study (KCT0006851) was reviewed and approved by the Ministry of Food and Drug Safety of Korea, and Institutional Review Board at Seoul National University Hospital (H-2108-184-1248). This study was conducted in accordance with Korean Good Clinical Practice guidelines and Declaration of Helsinki. The investigational product, potential risks, schedule and purpose of the study were fully explained to each subject, and written informed consent was obtained prior to the conduct of any study procedure.

## Study Population

Healthy Korean subjects aged 19 to 45 years with a body mass index (BMI) of 18.5 to 29.9 kg/m<sup>2</sup> were included in this study. Subjects with any history of hypersensitivity to drugs including antibody drugs and Igs were excluded. Given that autoantibodies against GM-CSF were considered as a pathogenic factor for pulmonary alveolar proteinosis (PAP), the exclusion criteria included any evidence of acute and/or chronic pulmonary disease in chest X-ray (CXR) or any abnormal result from pulse-oximetry and/or diffusing capacity of the lung for carbon monoxide (DLCO).

## Study Design

This study had a randomized, double-blind, placebo-controlled, single ascending dose design. The dose levels of 1, 3, and 10 mg/kg were determined based on a previous phase 1 study conducted in healthy non-Korean subjects (unpublished data), which evaluated the pharmacokinetics, safety and tolerability of lenzilumab at these same dose levels. Eight subjects were enrolled in 3 mg/kg and 10 mg/kg cohort, respectively, and four subjects were enrolled in 1 mg/kg cohort, which is a pilot cohort with lower dose than expected effective dose. Subjects were randomly assigned to receive a single IV dose of lenzilumab or placebo in a ratio of 3:1 in each cohort. Lenzilumab or placebo was administered to each subject as a 1-hour IV infusion, with a fasted state maintained for 10 hours before and 5 hours after the start of infusion. Drinking water was not allowed for 1 hour before and 3 hours after the start of infusion. The use of any substance, including over-the-counter drugs, prescription medications, vitamins or herbs, was prohibited from two weeks before the administration of lenzilumab or placebo until the post-study visit. Dose escalation to the next dose proceeded after reviewing the safety data until 7 days post-dose from the previous dose.

## Pharmacokinetic Analysis

Serum samples for PK analysis were collected at baseline (pre-dose) and at 0.5, 1, 3, 5, 9, 13, 25 and 49 hours, as well as 7, 14, 28 and 69 days after the start of IV infusion. For each sampling time point, about 5 mL of blood was collected in serum separating tubes from the arm not used in drug administration and centrifuged at 4°C and 3000 rpm for 10 minutes. Serum was collected from the centrifuged samples and stored at -70°C until analyzed. Serum concentrations of lenzilumab were determined using a validated electrochemiluminescence assay of which quantitation range was 15.0 to 960.0 ng/mL.

The PK profile of lenzilumab was analyzed using data from subjects who completed the blood sampling for PK and had measurable lenzilumab concentrations, without any major protocol deviations affecting PK analysis. Among PK parameters, the time to reach the maximum concentration ( $T_{max}$ ) and the maximum concentration ( $C_{max}$ ) were recorded as their observed values. The terminal half-life ( $t_{1/2}$ ), clearance (CL), volume of distribution (V), area under the concentration-time curve to the last observed concentration ( $AUC_{last}$ ) and area under the concentration-time curve from time zero to infinity ( $AUC_{inf}$ ) were calculated using non-compartmental methods with Phoenix<sup>®</sup> WinNonlin<sup>®</sup> (Version 8.3, Certara USA Inc., NJ, USA).

## Safety and Tolerability Assessment

For safety and tolerability assessment, adverse events (AEs) were monitored. Safety variables, including clinical laboratory test, 12-lead electrocardiogram, physical examination and vital signs, were also routinely monitored and assessed throughout the 70-day study period. CXRs and DLCO tests were conducted on screening and 28 days after the administration to monitor evidence of PAP. The analysis of safety and tolerability was conducted using data from all subjects who received lenzilumab or placebo. For all collected AEs, their relationship with the investigational drugs was evaluated. AEs for which it is difficult to exclude their relationship with the investigational drugs were categorized as adverse drug reactions (ADRs).

## Statistical Analysis

For PK analysis, the dose-normalized  $C_{max}$  ( $C_{max}/D$ ), the dose-normalized  $AUC_{last}$  ( $AUC_{last}/D$ ) and the dose-normalized  $AUC_{inf}$  ( $AUC_{inf}/D$ ) were compared among the three dose levels using Kruskal–Wallis' test. Dose-proportionality was assessed by a power model using linear regression analyses between the log-transformed dose and log-transformed  $C_{max}$ ,  $AUC_{last}$  or  $AUC_{inf}$ . Dose proportionality was assumed when the 95% confidence interval (CI) of the exponent includes 1. The safety profiles of the three dose levels of lenzilumab and the placebo were compared by analyzing the number of AEs and the change percent of DLCO from baseline using Kruskal–Wallis' test. All statistical analyses were performed via SAS<sup>®</sup> (Version 9.4, SAS Institute Inc., NC, USA).

## Results

### Study Population

Twenty healthy Korean subjects were enrolled in and completed the study. The mean age of subjects was 30 years, and most subjects were male (17/20, 85%). The mean weight, height and BMI of subjects were 73.5 kg, 171.6 cm and 25.2 kg/m<sup>2</sup> (Table 1). The baseline demographics were comparable across the three dose levels of lenzilumab and placebo with no statistically significant differences.

### Pharmacokinetics

The PK profile of lenzilumab was analyzed in 15 subjects who received lenzilumab: 3 subjects in 1 mg/kg and 6 subjects in each of 3 mg/kg and 10 mg/kg.

After a 1-hour IV infusion of lenzilumab, the median  $T_{max}$  ranged from 2.0 to 3.0 hours. Lenzilumab exhibited a biphasic decline after a single 1-hour IV infusion (Figure 1), and its mean  $t_{1/2}$  ranged from 25.33 to 31.11 days. The mean CL and V were consistent across the dose range of 1 to 10 mg/kg, with values of 0.48 to 0.55 L/day and 18.70 to 21.03 L, respectively (Table 2).

**Table 1** Demographics of Healthy Korean Subjects

	Lenzilumab			Placebo (N = 5)
	1 mg/kg (N = 3)	3 mg/kg (N = 6)	10 mg/kg (N = 6)	
Age <sup>a</sup> , years	31.0 [28.0–44.0]	29.5 [22.0–33.0]	29.0 [19.0–45.0]	31.0 [26–39]
Sex				
Male, %	100.0	83.3	66.7	100.0
Weight <sup>b</sup> , kg	81.7 (11.7)	73.3 (15.1)	63.7 (7.6)	80.4 (6.2)
Height <sup>b</sup> , cm	175.7 (2.3)	174.7 (8.7)	164.7 (6.9)	173.8 (3.3)
BMI <sup>b</sup> , kg/m <sup>2</sup>	23.8 (2.8)	23.5 (2.2)	26.7 (2.4)	26.4 (3.2)

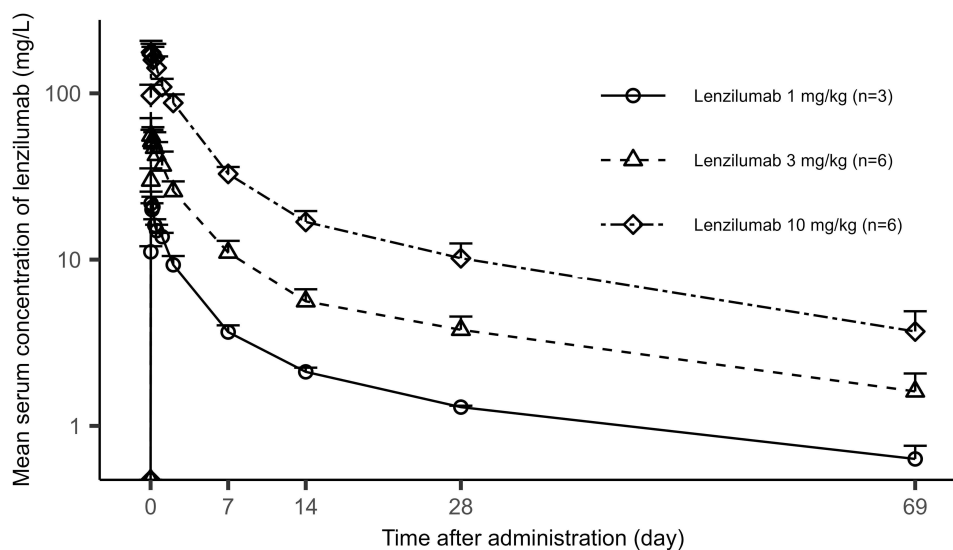
**Note:** <sup>a</sup> Values are represented in median [minimum–maximum]. <sup>b</sup> Values are represented in mean (standard deviation).

**Abbreviation:** BMI, body mass index.

The systemic exposure of lenzilumab increased dose proportionally (Figure 2).  $C_{max}/D$ ,  $AUC_{last}/D$  and  $AUC_{inf}/D$  were not significantly different across the three dose levels ( $p$ -values:  $C_{max}/D = 0.1987$ ,  $AUC_{last}/D = 0.1756$  and  $AUC_{inf}/D = 0.4476$ ). The exponents of power model and their 95% CIs were 1.04 [0.94–1.14] for  $C_{max}$ , 1.06 [0.96–1.16] for  $AUC_{last}$  and 1.02 [0.91–1.13] for  $AUC_{inf}$ , with all 95% CIs including 1.

## Safety and Tolerability

Safety and tolerability were assessed in 20 subjects who received lenzilumab or placebo. A total of 14 treatment emergent AEs (TEAEs) were reported in 9 subjects (45.0%), and all TEAEs were categorized as ADR. The incidence of ADRs did not show a significant difference between subjects receiving lenzilumab and those receiving the placebo ( $p$ -value = 0.3833). Among the three dose levels of lenzilumab, no ADR exhibited a dose-related trend (Table 3). The most frequent TEAEs were somnolence with 2 cases (10.0%). All AEs were mild in their intensity, and SAE did not occur. No clinically significant abnormalities were observed in CXR, DLCO, and other safety parameters. The change percent of DLCO from baseline exhibited no statistical significance between three dose levels of lenzilumab and placebo ( $p$ -value = 0.3992).



**Figure 1** Mean serum concentration-time profiles after a single intravenous infusion of lenzilumab 1, 3, 10 mg/kg in healthy Korean subjects.

**Notes:** The plot is displayed on a semi-logarithmic scale. Each symbol represents the mean serum concentration of lenzilumab at each dose level, and the error bars indicate the standard deviation.

**Table 2** Summary of Pharmacokinetic Parameters After a Single 1-Hour Intravenous Infusion of Lenzilumab 1, 3, 10 mg/kg in Healthy Korean Subjects

Parameter	1 mg/kg	3 mg/kg	10 mg/kg
	Mean (SD) (N = 3)	Mean (SD) (N = 6)	Mean (SD) (N = 6)
$T_{max}^a$ (h)	3.0 [1.0–5.0]	2.0 [1.0–5.0]	2.0 [1.0–9.0]
$C_{max}$ (mg/L)	22.80 (3.61)	56.88 (15.08)	187.67 (29.24)
$AUC_{last}$ (h*mg/L)	2967.14 (578.01)	9350.39 (1670.73)	27,326.51 (3281.80)
$AUC_{inf}$ (h*mg/L)	3619.43 (711.19)	11,156.57 (2300.00)	30,775.58 (4459.17)
$t_{1/2}$ (day)	25.33 (12.19)	31.21 (6.31)	25.90 (4.94)
CL (L/day)	0.55 (0.06)	0.48 (0.08)	0.50 (0.07)
V (L)	19.67 (8.36)	21.03 (1.70)	18.70 (4.58)

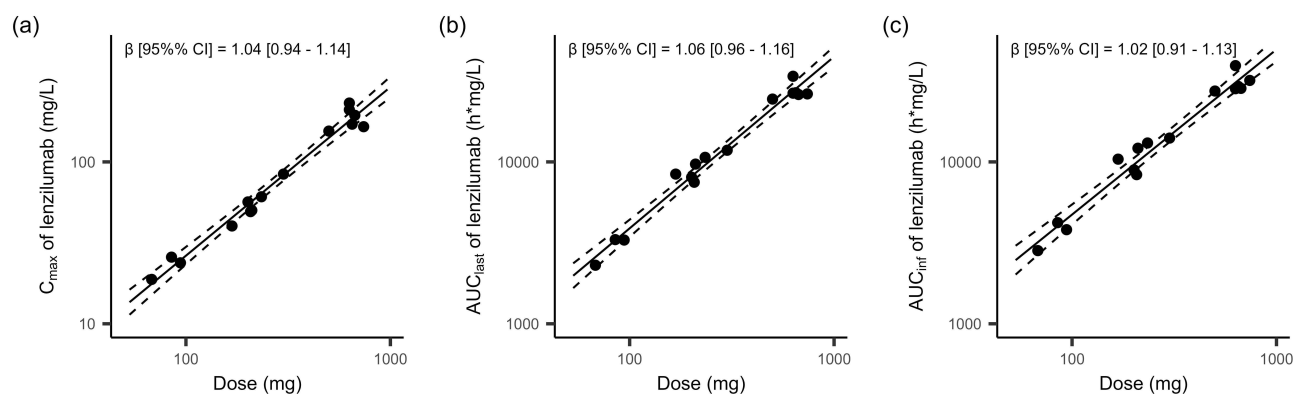
**Note:** <sup>a</sup>  $T_{max}$  is represented in median [minimum-maximum].

**Abbreviations:** SD, standard deviation;  $T_{max}$ , time to reach the maximum concentration;  $C_{max}$ , the maximum concentration;  $AUC_{last}$ , area under the curve from 0 to the time of the last measurable concentration;  $AUC_{inf}$ , area under the curve from 0 to infinity;  $t_{1/2}$ , half-life; CL, clearance; V, volume of distribution.

## Discussion

As lenzilumab was administered intravenously, its  $T_{max}$  after a 1-hour IV infusion was expected to match the infusion duration. However, the median  $T_{max}$  ranged from 2.0 to 3.0 hours, exhibiting a delay of 1 to 2 hours from the end of the infusion (Figure S1). A delay in  $T_{max}$  is also observed in other IV-infused mAbs, including trastuzumab,<sup>11,12</sup> and is hypothesized to result from local adsorption of the biotherapeutics to the vascular wall near the infusion site. Joannes et al simulated the physiological conditions during and after IV infusion of trastuzumab using artificial veins lined with human umbilical vein endothelial cells.<sup>13</sup> In their experiment, high concentration trastuzumab was first perfused through the artificial vein, followed by perfusion with low concentration trastuzumab. Trastuzumab initially bound to the endothelium or extracellular matrix through the high concentration perfusion and was subsequently washed out by the low concentration perfusion. Through adsorption and subsequent release, the vascular wall near the infusion site functioned as a depot, resulting in a delayed  $T_{max}$ . Given that endothelial cells express GM-CSF,<sup>14</sup> the delayed  $T_{max}$  of lenzilumab is assumed to be resulted from a similar mechanism.

The primary PK parameters of lenzilumab were comparable across a dose range of 1 to 10 mg/kg after a single 1-hour IV infusion, with systemic exposure showing dose-proportional increase. Although the 3 mg/kg cohort exhibited longer  $t_{1/2}$  compared with the other two cohorts, the difference did not reach statistical significance (Kruskal–Wallis’s test,  $p$ -value = 0.2889). This may be attributable to the small number of subjects. Drugs with high affinity and specificity for target molecules that have limited binding capacity may exhibit nonlinear PKs due to target-mediated drug disposition



**Figure 2** Exposure-dose profiles after a single intravenous infusion of lenzilumab 1, 3, 10 mg/kg in healthy Korean subjects.

**Notes:** (a)  $C_{max}$  versus dose; (b)  $AUC_{last}$  versus dose; (c)  $AUC_{inf}$  versus dose. Plots are displayed on a logarithmic scale. Dots represent individual subjects’ exposure values, solid lines indicate regression lines, and dashed lines denote the upper and lower limits of 95% confidence intervals.

**Abbreviations:**  $\beta$ , exponent of power model; 95% CI, 95% confidence interval;  $C_{max}$ , maximum concentration;  $AUC_{last}$ , area under the concentration-time curve to the last observed concentration;  $AUC_{inf}$ , area under the concentration-time curve from time zero to infinity.

**Table 3** Summary of Adverse Drug Reactions After a Single 1-Hour Intravenous Infusion of Lenzilumab in Healthy Korean Subjects

Adverse Drug Reactions	Lenzilumab			Placebo (N = 5)
	1 mg/kg (N = 3)	3 mg/kg (N = 6)	10 mg/kg (N = 6)	
All	2 (66.7) [3]	2 (33.3) [3]	2 (33.3) [3]	3 (60.0) [5]
Leukopenia	1 (33.3) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Abdominal discomfort	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (20.0) [1]
Dyspnea	0 (0.0) [0]	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]
Nausea	0 (0.0) [0]	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]
COVID-19	1 (33.3) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
White blood cells urine positive	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]	0 (0.0) [0]
Back pain	1 (33.3) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Somnolence	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]	1 (20.0) [1]
Depressive symptom	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (20.0) [1]
Oligomenorrhoea	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]	0 (0.0) [0]
Cough	0 (0.0) [0]	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]
Dyspnea	0 (0.0) [0]	0 (0.0) [0]	1 (16.7) [1]	0 (0.0) [0]
Hypertension	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (20.0) [1]

**Note:** Values are represented in number of subjects (percentage of subjects in each group) [number of events].

**Abbreviation:** COVID-19, Corona virus disease of 2019.

(TMDD).<sup>15</sup> In addition, IgG mAbs are likely to exhibit dose-dependent elimination if the dose range reaches a level that saturates neonatal Fc receptors (FcRn). Lenzilumab, an mAb drug for GM-CSF, may also show nonlinear PKs by aforementioned mechanisms. However, the behavior related to TMDD, such as increased clearance at low concentrations, was not observed (Figure 1). This suggests that GM-CSF, the target of lenzilumab, may have been saturated by lenzilumab starting from the lowest dose. In contrast, the FcRn may not have been saturated up to the highest dose. This explanation is reasonable considering the study by Kanji et al, which demonstrated that most serum GM-CSF in healthy subjects is in protein-bound state.<sup>16</sup>

A similar phase 1 study with a single 1-hour IV infusion of lenzilumab in healthy non-Korean subjects was conducted prior to this study (unpublished data). A delay in  $T_{max}$  was observed in these subjects as well, with median values ranging from 1.0 to 5.0 hours after a 1-hour IV infusion. The systemic exposure of lenzilumab was dose-proportional across the dose range of 1.0 to 10.0 mg/kg, and no behavior related to TMDD was observed. No significant difference in systemic exposure was observed between healthy Korean and non-Korean subjects across the 1.0 to 10.0 mg/kg dose range, with geometric mean ratios below 2.0 (Table S2). The observed small difference in systemic exposure, despite being non-significant, may be explained by the following factors: 1) the small number of subjects, 2) differences in bioanalysis laboratory for serum lenzilumab concentration determination, and 3) ethnic difference between Korean and non-Korean subjects. Given that ethnic difference is rarely significant covariates for PK of mAbs<sup>17,18</sup> and the demographic profiles of the two ethnic groups were similar (Table S1), the ethnic difference unlikely contributes to the observed difference in systemic exposure. To accurately evaluate these findings, additional studies specifically designed to compare different ethnicities should be considered. Moreover, even if ethnic difference in systemic exposure exists, further investigation is warranted to determine whether such difference have any clinical impact on the efficacy or safety of lenzilumab.

PAP is a rare lung disease characterized by reduced respiratory function resulting from the accumulation of surfactants in the alveoli. Since alveolar macrophages rely on GM-CSF for pulmonary surfactant homeostasis, there is a hypothesis that autoantibodies against GM-CSF contribute to the development of PAP by impairing macrophage-mediated surfactant clearance.<sup>19,20</sup> Accordingly, respiratory safety was monitored following lenzilumab administration, through CXR and DLCO assessments at screening and post-study visit. Across a dose range used in this study, no significant change was observed both in CXR and DLCO. One subject in 10 mg/kg reported dry cough and dyspnea

beginning two days after drug administration, which resolved spontaneously within 3 days of onset. Given the absence of significant findings in clinical laboratory tests, physical examination, vital signs, CXR or DLCO, the likelihood of PAP was considered low. Overall, the safety profile, including hematologic or immunologic AEs, was comparable to that of the placebo.

This study is limited by the absence of an anti-drug antibody (ADA) assessment. However, no subject exhibited dramatic increase in clearance or outlying PK parameters. While this does not rule out the emergence of ADA, it suggests that ADA affecting the pharmacokinetics of lenzilumab is unlikely after a single IV dose across the dose range of 1 to 10 mg/kg. This assumption is supported by a previous study in patients with uncontrolled asthma, where the rate of ADA emergence was 9%.<sup>7</sup>

## Conclusions

The systemic exposure of lenzilumab was dose-proportional across 1 to 10 mg/kg in healthy Korean subjects. A single IV administration of lenzilumab was safe and well tolerated in the dose range between 1 and 10 mg/kg.

## Abbreviations

ADA, anti-drug antibody; ADR, adverse drug reaction; AE, adverse event;  $AUC_{inf}$ , area under the concentration-time curve from time zero to infinity;  $AUC_{inf}/D$ , the dose-normalized area under the concentration-time curve from time zero to infinity;  $AUC_{last}$ , area under the concentration-time curve to the last observed concentration;  $AUC_{last}/D$ , the dose-normalized area under the concentration-time curve to the last observed concentration; BMI, body mass index; CI, confidence interval; CL, clearance;  $C_{max}$ , the maximum concentration;  $C_{max}/D$ , the dose-normalized maximum concentration; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; CXR, chest X-ray; DLCO, diffusing capacity of the lung for carbon monoxide; FcRn, neonatal Fc receptors; GM-CSF, Granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; IV, intravenous; mAb, monoclonal antibody; PAP, pulmonary alveolar proteinosis; PK, Pharmacokinetic; SWOV, survival without the need for mechanical ventilation;  $t_{1/2}$ , terminal half-life; TEAE, treatment emergent adverse event;  $T_{max}$ , the time to reach the maximum concentration; TMDD, target-mediated drug disposition; V, volume of distribution.

## Ethics Approval and Informed Consent

The protocol of this study (KCT0006851) was reviewed and approved by the Ministry of Food and Drug Safety of Korea, and Institutional Review Board at Seoul National University Hospital (H-2108-184-1248). This study was conducted in accordance with Korean Good Clinical Practice guidelines and Declaration of Helsinki. The written consent forms were obtained from each subject before any procedures of study.

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## Disclosure

The authors have neither financial nor non-financial competing interest to disclose.

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