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Human Monoclonal Antibody Cocktail for the Treatment or Prophylaxis of Middle East Respiratory Syndrome Coronavirus

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Background. REGN3048 and REGN3051 are human monoclonal antibodies (mAb) targeting the spike glycoprotein on the Middle East respiratory syndrome coronavirus (MERS-CoV), which binds to the receptor dipeptidyl peptidase-4 (DPP4) and is necessary for infection of susceptible cells.

Methods. Preclinical study: REGN3048, REGN3051 and isotype immunoglobulin G (IgG) were administered to humanized DPP4 (huDPP4) mice 1 day prior to and 1 day after infection with MERS-CoV (Jordan strain). Virus titers and lung pathology were assessed. Phase 1 study: healthy adults received the combined mAb (n = 36) or placebo (n = 12) and followed for 121 days. Six dose levels were studied. Strict safety criteria were met prior to dose escalation.

Results. Preclinical study: REGN3048 plus REGN3051, prophylactically or therapeutically, was substantially more effective for reducing viral titer, lung inflammation, and pathology in huDPP4 mice compared with control antibodies and to each antibody monotherapy. Phase 1 study: REGN3048 plus REGN3051 was well tolerated with no dose-limiting adverse events, deaths, serious adverse events, or infusion reactions. Each mAb displayed pharmacokinetics expected of human IgG1 antibodies; it was not immunogenic.

Conclusions. REGN3048 and REGN3051 in combination were well tolerated. The clinical and preclinical data support further development for the treatment or prophylaxis of MERS-CoV infection.

Keywords. first-in-human study; MERS; monoclonal antibodies; safety; tolerability; pharmacokinetics; immunogenicity; animal efficacy.

Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in 2012 in Saudi Arabia with subsequent infections reported across the Arabian Peninsula, Europe, Africa, and Asia [1]. Clinical features range from asymptomatic infection to severe pneumonia. Mortality is high, with the World Health Organization quoting a case-fatality rate of 34.4% among laboratory-confirmed cases of MERS. The risk of developing severe disease increases with age and in patients with preexisting comorbidities [2].

There are currently no approved therapeutics for any human CoV infections including MERS-CoV and the novel

coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), which has resulted in a pandemic of unprecedented scale. This highlights the need for novel therapeutics, such as monoclonal antibodies (mAb), for novel coronaviruses such as MERS. This approach has been successfully used for prophylaxis against other viral diseases including respiratory syncytial virus [3] and for treatment for Ebola virus disease [4].

The viral envelope spike (S) protein is necessary and sufficient for MERS-CoV binding and entry into susceptible cells [5]. The S protein binds to the cellular receptor, dipeptidyl peptidase-4 (DPP4, also known as CD26). DPP4 is expressed in the upper respiratory epithelium of camels but in humans it is expressed primarily in the lower respiratory tract, and is significantly increased in the alveolar cells of both smokers and adults with chronic obstructive pulmonary disease [6].

Regeneron Pharmaceuticals, Inc., Tarrytown, NY developed human antibodies against the S protein of MERS-CoV for the treatment or prophylaxis of MERS-CoV infection using Regeneron's VelocImmune platform [7] and identified 2 lead mAb candidates, REGN3048 and REGN3051 [8]. MERS-CoV

does not replicate in wild-type mice; therefore, a humanized DPP4 (huDPP4) mouse model of MERS-CoV infection was developed using Regeneron's VelociGene technology [8]. Administration of REGN3048 or REGN3051 1 day prior to MERS-CoV infection resulted in reduced virus titers in the lung and reduced lung pathology, with REGN3051 being more potent, in huDPP4 mice. Therapeutic treatment with REGN3051 1 day after MERS-CoV infection was also able to reduce virus titers and lung pathology in huDPP4 mice.

Here, we extend previous preclinical work and describe the prophylactic and therapeutic potential of REGN3048 and REGN3051 coadministered in the huDPP4 MERS-CoV model [8]. We also report results of a first-in-human (FIH) study designed to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of single ascending intravenous (IV) doses of REGN3048 and REGN3051, coadministered in healthy adults.

METHODS

Preclinical Experiments in huDPP4 Mouse Model

Six- to 8-week-old huDPP4 mice (n = 10 per group) were injected intraperitoneally with a total dose of 2 µg, 20 µg, or 200 µg of individually or coadministered REGN3048 and REGN3051 or immunoglobulin G (IgG) control at 1 day prior to infection or 1 day after infection. Anesthetized mice were inoculated intranasally with either phosphate buffered saline (PBS) or 1×10^5 plaque forming unit (PFU) of MERS-CoV (Jordan strain) diluted into PBS for a total volume of 50 µL. Mice were euthanized at day 2 and day 4 postinfection and lungs harvested for analysis of MERS-CoV viral replication and pathology. The methodology for the preclinical experiments is included in Supplementary Material 1 and has been previously reported [8].

First-in-Human Study in Healthy Adults

Study Design and Participants

A phase 1, FIH, randomized, double-blind, placebo-controlled study was conducted to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of single ascending doses of a combination of REGN3048 and REGN3051, administered IV in healthy adult volunteers.

The study protocol was approved on 4 May 2017 (protocol 15–0109 of the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health). The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and all applicable local regulatory requirements and laws.

Participants provided written informed consent before screening. Subjects were male and female, aged 18–45 years, with a body mass index between 18.5 and 30.0 kg/m^2 inclusive, and in good health. Women were not pregnant or lactating.

A full list of eligibility criteria is included in Supplementary Material 2 (redacted protocol).

Randomization occurred within 6 dosing cohorts (see below) to either active or control in a 3:1 ratio. Further details on randomization and masking can be found in Supplementary Material 1.

Enrolled subjects participated in the study for approximately 21 weeks, including a 4-week screening period, a 3-day inpatient stay (admission on day –1, dosing on day 1, and discharge from the in-patient unit on day 2), and approximately 17-week out-patient follow-up after study product administration. The last follow-up visit was scheduled at day 121.

Study Procedures

A total of 48 subjects were enrolled in the study to 1 of the following 6 sequential ascending IV dose levels of total coadministered REGN3048 and REGN3051: 3, 10, 30, 50, 100, and 150 mg/kg (1.5, 5, 15, 25, 50 and 75 mg/kg of each mAb, respectively). Within each dose cohort, 8 subjects were randomized to receive either the combination of REGN3048 and REGN3051 (n = 6) or placebo (n = 2) (Supplementary Material 1).

Details on the study drug can be found in Supplementary Material 1. The estimated dose was diluted to a final volume of 100 mL for the first dose cohort (3 mg/kg) and 250 mL for the other dose cohorts and was infused IV over 2 hours.

Measurement of mAb Concentrations for Pharmacokinetic Analysis

Serum for pharmacokinetic assays was collected on study day 1 (predose, 1.0 hour after initiation of infusion, at the end of the infusion, and at 1, 3, 7, 23, 47, and 71 hours after completion of the infusion) and on days 8, 15, 29, 43, 57, 91, and 121 or at early termination.

The human serum concentration of REGN3048 and REGN3051 was measured using a validated, multiplexed immunoassay on the U-PLEX platform from Meso Scale Discovery. The bioanalytical method specifically quantitates the levels of each anti–MERS-CoV mAb separately, with no interference from the other antibody. The assay has a lower limit of quantification of 0.078 µg/mL for each analyte in the undiluted serum sample. All samples from the same subject were analyzed in the same assay.

Immunogenicity Assessment

Serum samples for antidrug antibody (ADA) assay were collected at day 1 predose (baseline), on day 57, and on day 121 or early termination. Immunogenicity was examined using 2 specific, titer-based validated bridging assays that detect ADA in serum separately for each study mAb. ADAs were to be measured upon treatment-emergent adverse events (TEAEs) suggestive of acute hypersensitivity reaction or at the end of the study.

Study Outcomes

The primary outcome was safety as measured by the type and frequency of TEAEs experienced by subjects receiving coadministered REGN3048 and REGN3051 compared with placebo. Safety monitoring was conducted by an independent safety monitor included in a safety review committee. In addition, safety oversight was provided by a safety monitoring committee, a group of experts that were separate and independent of study personnel, and an independent institutional review board.

Secondary outcomes were the pharmacokinetic profiles of the mAbs and immunogenicity (measurable ADA).

Statistical Methods

The sample size was consistent with a phase 1 healthy volunteer study and power calculations were not considered. The safety analysis set included all randomized subjects who received any study drug and was based on the treatment received. Categorical and continuous data were summarized descriptively (SAS version 9.4; SAS Institute, Inc). Placebo subjects in different dose cohorts were pooled.

The pharmacokinetic population included all treated subjects who were coadministered REGN3048 and REGN3051. Pharmacokinetic noncompartmental analysis was performed using Phoenix WinNonlin version 8.2 (Certara).

The anti-REGN3048 and anti-REGN3051 antibody data were analyzed by calculating a prevalence of treatment-emergent positive ADA response assessed as absolute occurrence and percent of subjects, grouped by study dose.

RESULTS

Preclinical Efficacy of Anti-MERS-CoV mAbs in the huDPP4 Mouse Model
Prophylactic Efficacy

Prophylactic treatment with REGN3048 and REGN3051 reduced virus replication; REGN3051 was more potent than REGN3048. As little as 20 μg of REGN3051 was able to reduce virus replication below the limit of detection at days 2 and 4 after infection, whereas it took 200 μg of REGN3048 to accomplish this (Figure 1). Coadministration of REGN3048 and REGN3051 resulted in higher potency than either antibody used alone. As little as 2 μg of coadministered REGN3048 and REGN3051 showed an almost 100-fold reduction in virus titers 2 days after infection, and by 4 days after infection virus titers were at or below the limit of detection (Figure 1). Coadministration of REGN3048 and REGN3051 at 20 μg and 200 μg of total antibody was even more effective at reducing virus replication with infectious virus titers at or below the limit of detection at 2 and 4 days after infection (Figure 1). These data show that, for prophylaxis, coadministration of REGN3048 and REGN3051 results in no detectable virus 4 days after infection at doses of each antibody (1 μg each antibody, 2 μg total dose) that are more than 10-fold below the doses of each
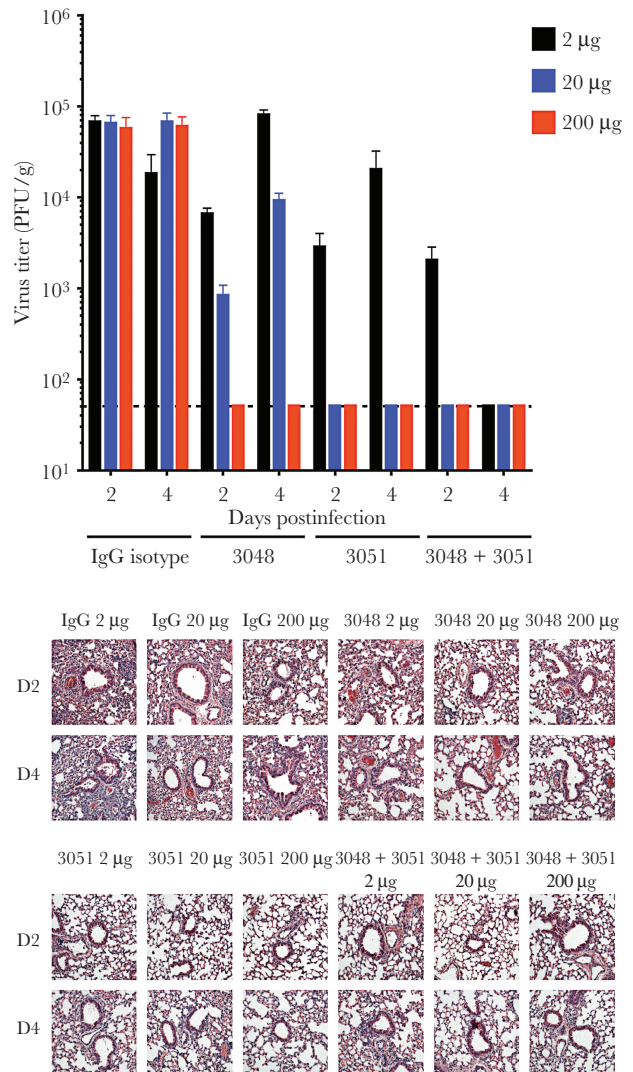
Figure 1. Prophylactic treatment with REGN3048 and REGN3051 protects huDPP4 mice from MERS-CoV infection. Mice (n = 10 per cohort) were intraperitoneally injected with a dose range of isotype control, REGN3051, REGN3048, or a combination of REGN3051 and REGN3048 at 24 hours preinfection with MERS-CoV (Jordan strain). At 2 and 4 days postinfection, lungs were harvested and virus titer quantified by plaque assay reported as plaque-forming unit per gram lung. Error bars indicate standard deviation. Limit of detection was 50 PFU. Formalin-fixed lungs were embedded in paraffin, and 5-μm sections were cut followed by staining with hematoxylin and eosin by the Pathology Electron Microscopy and Histology Laboratory at the University of Maryland School of Medicine. Representative sections from each treatment group at day 2 or 4 post infection are shown. Abbreviations: huDPP4, human dipeptidyl peptidase-4; IgG, immunoglobulin G; MERS-CoV, Middle East respiratory syndrome; PFU, plaque forming unit.

antibody individually required to achieve the same level of virus reduction. Prophylactic coadministration of REGN3048 and REGN3051 also reduced lung inflammation at both 2 and 4 days after MERS-CoV infection (Table 1).

Therapeutic Efficacy

Administration of REGN3048 reduced virus titers at days 2 and 4 after infection with 200 μg of antibody (Figure 2).

Table 1. Overall Inflammation Scores in MERS-CoV–Infected Lungs of Mice Treated Prophylactically or Therapeutically with REGN3048 and REGN3051

Prescription		2 dpi				4 dpi			
Day	Ab, μg	IgG	3048	3051	3048 + 3051	IgG	3048	3051	3048 + 3051
1 d before infection	2	++	++	++	+	++++	++	++	++
	20	++	++	+	+	+++	++	++	+
	200	+++	+	+	+	+++	+	+	+
1 dpi	2	++	++	++	+	++++	+++	+++	+
	20	++	++	++	+	++++	+++	++	+
	200	+++	++	++	+	+++	++	++	++

Scoring scale: no + = no inflammation; + = scant inflammation (<5% multifocal or 1 small focus); ++ = mild inflammation, <25% parenchyma; +++ = moderate inflammation, 25%–50% parenchyma; ++++ = marked inflammation, 50%–75% parenchyma; and +++++ = severe inflammation, >75% parenchyma.

Abbreviations: Ab, antibody; dpi, days postinfection; IgG, immunoglobulin G.

REGN3051 was more potent and reduced virus titers with as little as 20 μg of antibody at days 2 and 4 after infection (Figure 2). Coadministration of REGN3048 and REGN3051 1 day after infection was more effective at reducing virus replication than either antibody alone. A 2-μg dose of the coadministered antibodies reduced virus titers 100-fold as early as 2 days after infection and reduced virus titers below detectable levels by 4 days after infection. Higher doses of 20 or 200 μg of coadministered antibodies resulted in undetectable levels of infectious virus at days 2 and 4 after infection (Figure 2). Therapeutic coadministration of REGN3048 and REGN3051 results in no detectable virus 4 days after infection at doses of each antibody (1 μg each antibody, 2 μg total dose) that are more than 10-fold below the doses of each antibody individually required to achieve the same level of virus reduction. Coadministration of REGN3048 and REGN3051 also reduced the severity of lung inflammation observed 2 and 4 days after infection compared to either antibody alone (Table 1).

First-in-Human Clinical Trial for Anti-MERS-CoV Spike mAbs

Between 19 February 2018 and 21 September 2018, 146 healthy adult subjects were screened at a single site in the United States; 48 eligible subjects were randomly assigned to 6 dose cohorts (Supplementary Figure 1).

Thirty-six subjects were randomized to the active arm and 12 were randomized to placebo. All subjects received their intended study medications. Five subjects withdrew from study participation between study day 15 and day 122, all for personal reasons; 3 subjects received placebo and 2 received active treatment. No subject withdrew due to an adverse event (AE). Subject demographics and characteristics are listed in Supplementary Table 2.

Safety Profile of Anti-MERS-CoV mAbs in Humans

No deaths, serious AEs, TEAEs leading to early termination, or infusion-related reactions occurred during the study (Table 2). The most common TEAEs in the active arms were abnormal laboratory investigations deemed to be of no clinical significance and self-limited.

Overall, 12 (100%) subjects in the combined placebo cohort and 33 (92%) subjects in the combined active cohort experienced at least 1 TEAE (Table 2). Seven severe (grade 3) TEAEs were reported in 6 subjects: 4 AEs in 4 subjects (11.1%) who received REGN3048 and REGN3051 and 3 AEs in 2 subjects (16.7%) who received placebo. Six of the 7 severe TEAEs were laboratory abnormalities that were assessed as not related to study treatment. One severe TEAE of pruritus that was assessed as related to study treatment, occurred in a 24-year-old man at 50 mg/kg (25 mg/kg of each mAb) dose level. This subject first reported intermittent pruritus on day 29 that had started on day 6, affecting his bilateral proximal upper extremities, bilateral lower extremities, calves, chest, bilateral shoulders, and thoracic back area. Pruritus did not interfere with sleep or daily activities and no self-treatments were used. No triggers could be identified by medical history. Physical examination did not reveal any skin rashes on study days 2, 4, 8, 15 and 29. Laboratory test results on these study days were within normal limits, including eosinophil counts, except for a mild decrease of hemoglobin on day 29. The same subject reported a maculopapular rash bilaterally on the posterior aspect of the lower extremities and left upper arm at various times intermittently with onset on day 39, and it was confirmed on physical examination on day 43. The event was assessed as moderate in severity and related to study treatment. Hydrocortisone 1% cream and hydrogen peroxide were used for symptomatic relief. Both AEs of pruritus and rash were fully resolved by day 91. ADA levels were below limit of detection throughout the study.

There were 2 additional AEs reported as skin disorders, 1 event in each of 2 subjects treated with 100 mg/kg (50 mg/kg of each mAb). One subject had keratosis pilaris on the upper arms and back and the other subject had rash due to mosquito bites on the extremities. Both events were assessed as mild and not related to the study treatments.

No other clinically significant safety issues were observed with respect to vital signs results, physical examination data, clinical laboratory testing, or electrocardiogram (ECG) measurements.
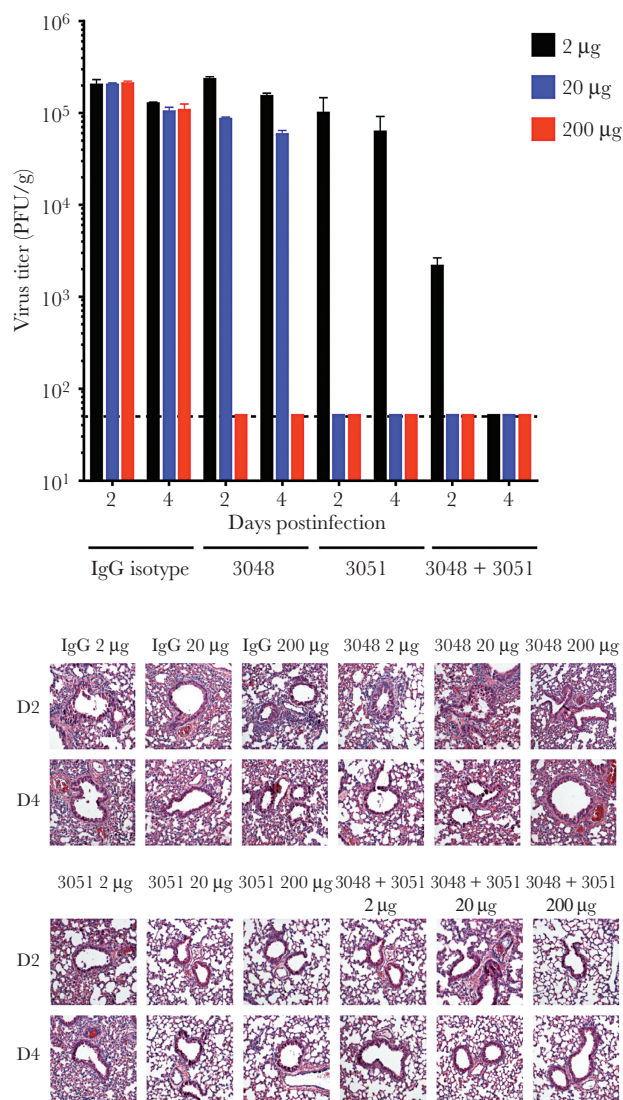
Figure 2. Therapeutic treatment with REGN3048 and REGN3051 protects huDPP4 mice from MERS-CoV infection. Mice (n = 10 per cohort) were intraperitoneally injected with a dose range of isotype control, REGN3051, REGN3048, or a combination of REGN3051 and REGN3048 at 24 hours postinfection with MERS-CoV (Jordan strain). At 2 and 4 days postinfection, lungs were harvested and virus titer quantified by plaque assay reported as plaque-forming unit per gram lung. Error bars indicate standard deviation. Limit of detection was 50 PFU. Formalin-fixed lungs were embedded in paraffin, and 5-µm sections were cut followed by staining with hematoxylin and eosin by the Pathology Electron Microscopy and Histology Laboratory at the University of Maryland School of Medicine. Representative sections from each treatment group at day 2 or 4 post infection are shown. Abbreviations: huDPP4, human dipeptidyl peptidase-4; IgG, immunoglobulin G; MERS-CoV, Middle East respiratory syndrome; PFU, plaque forming unit.

Pharmacokinetic Profile of Anti-MERS-CoV mAbs in Humans

Following IV coadministration of REGN3048 and REGN3051, the serum concentration over time of each mAb exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase (Figure 3 and Supplementary Table 1, Supplementary Material 3). Both REGN3048 and REGN3051 displayed a dose-proportional,

linear pharmacokinetic profile as indicated by the similar dose-normalized maximum concentration and area under the curve from time 0 to infinity across all dose cohorts. The mean biological half-life of REGN3048 and REGN3051 was dose independent; the mean half-life observed for REGN3048 ranged from 18.8 to 24.2 days and for REGN3051 ranged from 17.8 to 22.1 days.

Immunogenicity

No subjects developed detectable levels of anti-REGN3048 or anti-REGN3051 antibodies during the study.

DISCUSSION

REGN3048 and REGN3051 are human mAbs that bind to noncompeting sites on the S protein and neutralize virus infectivity by blocking interaction with the cellular receptor DPP4 on target cells. The combined use of 2 independently neutralizing antibodies is likely to reduce the risk of treatment failure from the development of virus escape mutants or new variants that may arise during an outbreak. In this report, coadministration of REGN3048 and REGN3051 in a humanized model of MERS-CoV given either before or after intranasal infection of huDPP4 mice was more effective than either antibody administered alone and led to potent reductions in infectious virus titers and lung pathology. Similar observations were made in the marmoset, another animal model of MERS-CoV in which the combination of REGN3048 and REGN3051 was more effective than each mAb individually in the prevention, and to a lesser extent therapy, of the infection [9]. These data further support the clinical development of these antibodies for both prophylactic and therapeutic indications.

In the FIH study, the coadministration of REGN3048 and REGN3051 was generally well tolerated at all dose levels. The majority of TEAEs were mild in severity. The most common TEAEs with coadministration of REGN3048 and REGN3051 were transient abnormalities in laboratory data that were not dose-dependent and were considered to be not medically significant. There were no safety concerns regarding ECGs and vital signs and no treatment-emergent ADAs were detected. The pharmacokinetic parameters of REGN3048 and REGN3051 indicated that both antibodies had pharmacokinetic profiles that were not substantially different and were consistent with that of a human IgG1 antibody in healthy subjects who lack an endogenous target.

Using the minimal effective dose observed in the preclinical animal studies along with data from the FIH study, a probable dosing regimen for prophylaxis in humans can be estimated. Serum drug concentrations were not measured in the preclinical mouse model. However, based on the preclinical data (Figure 1), using 20 µg total of coadministered mAbs (as 10-fold above the minimally effective dose of 1 µg per mAb or 2 µg total), the concentration of drug in serum at this dose level can be estimated.

Table 2. Cumulative Unsolicited Adverse Events in First-in-Human Study in Healthy Adults Receiving REGN3048 and REGN3051

Characteristic	No. (%) of Healthy Adults								
	Placebo (n = 12)	Any Dose (n = 36)	Dose Cohort A (n = 6)	Dose Cohort B (n = 6)	Dose Cohort C (n = 6)	Dose Cohort D (n = 6)	Dose Cohort E (n = 6)	Dose Cohort F (n = 6)	All Subjects (n = 48)
At least 1 AE	12 (100)	33 (92)	6 (100)	5 (83)	6 (100)	6 (100)	5 (83)	5 (83)	45 (94)
At least 1 related AE, mild, grade 1 or worse	8 (67)	19 (53)	5 (83)	5 (83)	2 (33)	4 (67)	1 (17)	2 (33)	27 (56)
At least 1 related AE, moderate, grade 2, or worse	0	3 (8)	1 (17)	0	0	2 (33)	0	0	3 (6)
At least 1 related AE, severe, grade 3	0	1 (3)	0	0	0	1 (17)	0	0	1 (2)
At least 1 SAE, any	0	0	0	0	0	0	0	0	0
At least 1 SAE, related	0	0	0	0	0	0	0	0	0
At least 1 AE leading to early termination	0	0	0	0	0	0	0	0	0
MedDRA system organ class									
Gastrointestinal disorders	2 (17)	1 (3)	0	0	0	1 (17)	0	0	3 (6)
General disorders and administration site conditions	0	2 (6)	0	1 (17)	0	0	0	1 (17)	2 (4)
Infections and infestations	3 (25)	7 (19)	1 (17)	1 (17)	1 (17)	0	1 (17)	3 (50)	10 (21)
Investigations[a]	11 (92)	31 (86)	5 (83)	5 (83)	6 (100)	5 (83)	5 (83)	5 (83)	42 (88)
Nervous system disorders	1 (8)	1 (3)	0	0	0	1 (17)	0	0	2 (4)
Reproductive system and breast disorders	0	1 (3)	0	0	0	0	1 (17)	0	1 (2)
Respiratory, thoracic, and mediastinal disorders	0	3 (8)	0	0	1 (17)	1 (17)	0	1 (17)	3 (6)
Skin and subcutaneous tissue disorders	0	3 (8)	0	0	0	1 (17)	2 (33)	0	3 (6)

Dose cohort A, 3 mg/kg (1.5 mg/kg of each mAb); dose cohort B, 10 mg/kg (5 mg/kg of each mAb); dose cohort C, 30 mg/kg (15 mg/kg of each mAb); dose cohort D, 50 mg/kg (25 mg/kg of each mAb); dose cohort E, 100 mg/kg (50 mg/kg of each mAb); and dose cohort F, 150 mg/kg (75 mg/kg of each mAb).

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

[a]Clinical laboratory test concept (including biopsies), radiologic test concept, physical examination parameter, and physiologic test concept (eg, pulmonary function test).
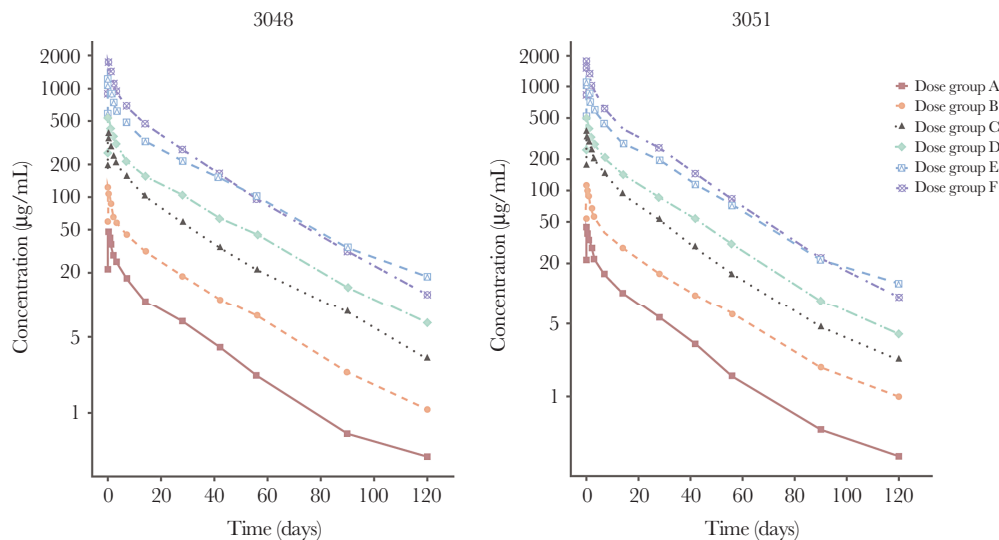
Figure 3. Mean concentration of REGN3048 and REGN3051 in human serum over time. CV% of C_{max} ranged from 7% to 29% across all dose cohorts for REGN3051 and from 10% to 25% across all dose cohorts for REGN3048. Dose cohort A, 3 mg/kg (1.5 mg/kg of each mAb); dose cohort B, 10 mg/kg (5 mg/kg of each mAb); dose cohort C, 30 mg/kg (15 mg/kg of each mAb); dose cohort D, 50 mg/kg (25 mg/kg of each mAb); dose cohort E, 100 mg/kg (50 mg/kg of each mAb); dose cohort F, 150 mg/kg (75 mg/kg of each mAb). Abbreviations: C_{max}, maximum concentration; CV, coefficient of variation; mAb, monoclonal antibody.

The weight-normalized volume of distribution (50 mL/kg) as well as the mean weight of humanized mice (20 g) would lead to a volume of distribution in the mouse of 1 mL and an approximate total concentration at time of mAb coadministration of 20 µg/mL (10 µg/mL per antibody) [10]. This provides a putative target concentration for each mAb (10 µg/mL) above which drug concentration should be maintained for prophylaxis and treatment. In humans, the time above this putative target, or duration of prophylactic coverage, at a given single IV dose of either REGN3048 or REGN3051 can be interpolated from the serum concentration over time of REGN3048 and REGN3051 (Figure 3). For example, using data in Supplementary Table 1 (Supplementary Material 3) and Figure 3, which shows similar pharmacokinetic profiles of both REGN3048 and REGN3051, at a dose of 25 mg/kg per mAb (dose cohort D), the time above a putative target concentration of 10 g/mL of each mAb is approximately 100–110 days, corresponding to approximately 14–16 weeks of prophylactic coverage.

In summary, coadministered REGN3048 and REGN3051 was generally well-tolerated, with no observed immunogenicity when administered in a single IV dose up to 150 mg/kg. The preclinical study in a huDPP4 mouse model supports the continued development of REGN3048 and REGN3051 for the prophylaxis and treatment of MERS-CoV infection and the minimally effective dose identified falls well within the human range of tolerability determined in the FIH study. The study demonstrated the potential efficacy and utility of mAb therapy for the prevention or treatment of MERS-CoV and lays the groundwork for the development of S-targeted mAb therapies for other infectious disease threats, including SARS-CoV-2.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributors. S. S., L. L., G. A. S., M. F., K. K., and G. Y. were responsible for first-in-human study design. G. A. S., and DVC clinical project management team oversaw writing of the protocol and were responsible for study implementation and enrolment of participants at WCCT Global. C. A. K., G. Y., and N. S. were responsible for preclinical development. M. F. and K. K. were responsible for the preclinical mouse studies. M. H., M. A. K., G. S., and C. E. were responsible for immunogenicity and pharmacokinetic assays and/or analysis of

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