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Assessing Pharmacokinetics and Safety of Therapeutic Alpha-1-Microglobulin in First-in-Human Kidney Transplantation: A Noncomparative Open-Label Multiple-Dose Phase 1b Study

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Background. RMC-035 is a modified version of alpha-1-microglobulin, an endogenous protein developed as a renoprotective agent. Its intended use is to reduce the risk of irreversible loss of kidney function in cardiac surgery patients and to reduce delayed graft function in kidney transplant recipients. This first-in-human study aimed to evaluate the pharmacokinetics and safety of RMC-035 in kidney transplant recipients. **Methods.** Eight living-donor kidney transplant recipients were included in 2 dose cohorts. The study drug RMC-035 was administered starting with the first dose during transplantation. Four additional doses were administered once daily following transplantation. In the first cohort, all 5 doses of RMC-035 were equal, whereas in the second cohort, the last 3 doses were doubled. Safety monitoring, laboratory tests, and pharmacokinetic measurements were performed according to protocol for 4 d post-transplantation and during the 90-d follow-up period. **Results.** All 5 administrations of the study drug were completed in 5 out of 8 treated participants. Pharmacokinetic concentrations were approximately dose proportional, and AUC_{0-24h} decreased between the first and fifth doses, reflecting improved kidney function and RMC-035 renal clearance over time. No accumulation was observed between the administrations. No clinically significant changes were observed in the hematological or biochemical laboratory parameters, electrocardiogram findings, or vital signs. A total of 22 treatment-emergent adverse events (AEs) were reported in 6 subjects. Mild and transient AEs suggestive of infusion-related reactions, such as chills, were reported in 5 patients. There was a clinically significant reduction in serum creatinine levels, reflecting post-transplant improvement in kidney function. **Conclusions.** Based on the safety data obtained from 8 subjects in the 2 dose cohorts treated with RMC-035, the drug was considered safe. Safety and AE profiles were in line with expectations of the target population, and infusion-related reactions were short-lived and manageable. Dose-limiting toxicity signals were not observed.

(*Transplantation Direct* 2024;10: e1727; doi: 10.1097/TXD.0000000000001727.)

INTRODUCTION

Kidney transplantation from living or deceased donors is the preferred treatment for end-stage renal disease, significantly reducing health risks, enhancing quality of life, and extending lifespan compared with dialysis.[1-3] In addition, it provides cost savings for both the healthcare system and the society.[4]

Received 10 June 2024. Revision received 17 September 2024.

Accepted 17 September 2024.

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This study was sponsored by Guard Therapeutics International AB. J.E.A.N. received a research grant from Westman Foundation.

T.E.L. and S.J.T. are employees, and M.R. is a paid consultant for Guard Therapeutics International AB, Stockholm, Sweden.

J.E.A.N. was the principal investigator of the study, and together with L.M.W., G.N., T.E.L., and M.R. developed the idea, research design, and planned the study layout. J.E.A.N., L.M.W., G.N., and S.J.T. participated in this study. T.E.L., S.J.T., and M.R. were responsible for the primary and exploratory endpoint analyses. All the authors participated in the writing of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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Clinical Trial Notation: EudraCT number 2022-001187-10

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001727

A major complication of kidney transplantation is delayed graft function (DGF), defined as the need for dialysis within the first-week post-transplant, with incidence rates between 10% and 50%.[5,6] DGF is associated with prolonged hospital stay, an increased risk of infection, and reduced long-term graft survival.[7,8] It is often caused by ischemia-reperfusion injury (IRI),[9] which occurs because of the disruption of blood supply during organ procurement and preservation. IRI mechanisms resemble those of acute kidney injury following cardiac surgery,[10] involving hypoxia, hemolysis, oxidative stress, hemodynamic dysfunction, inflammation, and cellular injury.[11]

Strategies to reduce IRI and DGF include machine perfusion of the kidney with preservation solution or blood during storage and pharmacological interventions such as antioxidants to mitigate oxidative stress. Few pharmaceutical options are available to prevent DGF,[12] highlighting the need for effective treatments to improve kidney transplant success, patient and graft outcomes, and overall quality of life. The pharmacologically active molecule RMC-035 is a modified recombinant variant of the endogenous human protein alpha-1-microglobulin (A1M) that retains the key attributes of endogenous A1M with improved solubility and stability.[13-15] A1M protects cells and tissues from various forms of cellular damage caused by oxidative stress, including free radicals and reactive oxygen species (ROS).[16-20] It was initially developed as a renoprotective agent to reduce the risk of irreversible loss of kidney function following cardiac surgery[21] and to reduce DGF and its long-term consequences in kidney transplant recipients. RMC-035 has the following characteristic attributes of an antioxidant and tissue housekeeping protein: reductase activity, radical scavenging, heme binding, mitochondrial binding, and safeguarding. These functions are considered relevant in preventing and protecting against ischemic injuries that occur after donor kidney procurement and subsequent kidney graft revascularization.[16]

RMC-035 has a natural biodistribution in the kidney, including uptake in proximal tubular cells, and targets the key pathophysiological pathways of DGF. Results from previous clinical phase 1 studies of RMC-035 in healthy subjects, renally impaired subjects, and patients undergoing open chest cardiac surgery showed that RMC-035 is safe and generally well tolerated.[21] Pharmacokinetic (PK) analysis demonstrated dose-proportional exposure with rapid initial elimination from the plasma due to renal clearance. Plasma clearance decreased linearly with declining renal function. Since kidney transplant recipients have low or no endogenous renal function at the time of transplantation and kidney graft function may vary significantly post-transplantation, PK evaluation of RMC-035 in this patient population is needed to determine safe and efficacious exposure and dose in subsequent efficacy studies.

MATERIALS AND METHODS

Study Design

This phase 1b, noncomparative open-label, multiple-dose clinical study evaluated the PK and safety of RMC-035 in recipients of kidney transplants performed at 1 clinical site (Department of Transplantation Surgery, Karolinska University Hospital, Huddinge, Stockholm, Sweden). Eight subjects complying with all inclusion criteria and none of the exclusion criteria were allocated to 1 of 2 sequential dose groups of RMC-035 (4 subjects per dose group; cohorts 1 and 2) starting with the lowest dose group. The number of subjects was based on a precedent set by other clinical studies of similar nature, and no formal statistical sample size calculation was performed. The conduct of dosing a third group of subjects was optional and to be confirmed by a Safety Review Committee based upon a prespecified interim analysis of PK parameters and safety findings following completion of treatment of all subjects in both dose groups. All patients provided written informed consent before enrollment in the study. The first patient was included in the study in August 2022, and the last patient completed the study in May 2023. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice E6, the European Union Clinical Trials Directive, and applicable local regulatory requirements. The protocol was approved by the Swedish Ethical Review Authority and Swedish Medical Products Agency.

Inclusion and Exclusion Criteria

Male and female adult patients (≥18 y of age) with dialysis-dependent chronic kidney disease or end-stage renal disease with an estimated glomerular filtration rate (eGFR) ≤ 15 mL/min/1.73 m^2, scheduled to be a recipient of a kidney transplant, were eligible for the study. The exclusion criteria were multiorgan transplantation, active hepatitis B virus infection, hepatitis C virus positivity, and human immunodeficiency virus disease in the donor or recipient. Further exclusion criteria were elevated liver laboratory findings (total bilirubin, alanine aminotransferase, or aspartate aminotransferase levels ≥2 times normal), current or chronic history of liver disease, known hepatic or biliary abnormalities, severe allergic asthma, or other medical conditions that would make participation inappropriate.

Study Timepoints and Dosing

Prior to the commencement of the study, a 7-d screening period was conducted. The study began with a 5-d treatment period starting at the time of kidney transplantation and concluding 24 h after the final dose. This was followed by a 24-d follow-up period and an additional 60 d of extended follow-up, resulting in a total study duration of 90 d. The study drug was administered via a central venous line as a 30-min intravenous infusion. Cohort 1 subjects were administered 0.3 mg/kg RMC-035 in all 5 doses. The subjects in cohort 2 received 0.3 mg/kg per dose for the initial 2 doses, followed by 0.6 mg/kg for doses 3 through 5. All subjects received the initial study drug dose during surgery, followed by a daily dose for 4 d, amounting to 5 doses. The schedule is illustrated in Figure 1. PK samples were collected as outlined in Table 1.

Primary Endpoint

The primary objective of this clinical study was to assess the key pharmacokinetics of RMC-035 following a 5-d intervention period in kidney transplant recipients. Primary pharmacokinetics were measured by AUC_{0-24h} following the first, second, and fifth doses, as well as C_{max} following each dose administration.

Secondary Endpoints

To evaluate additional pharmacokinetic parameters, the disposition of RMC-035 in plasma was analyzed, including

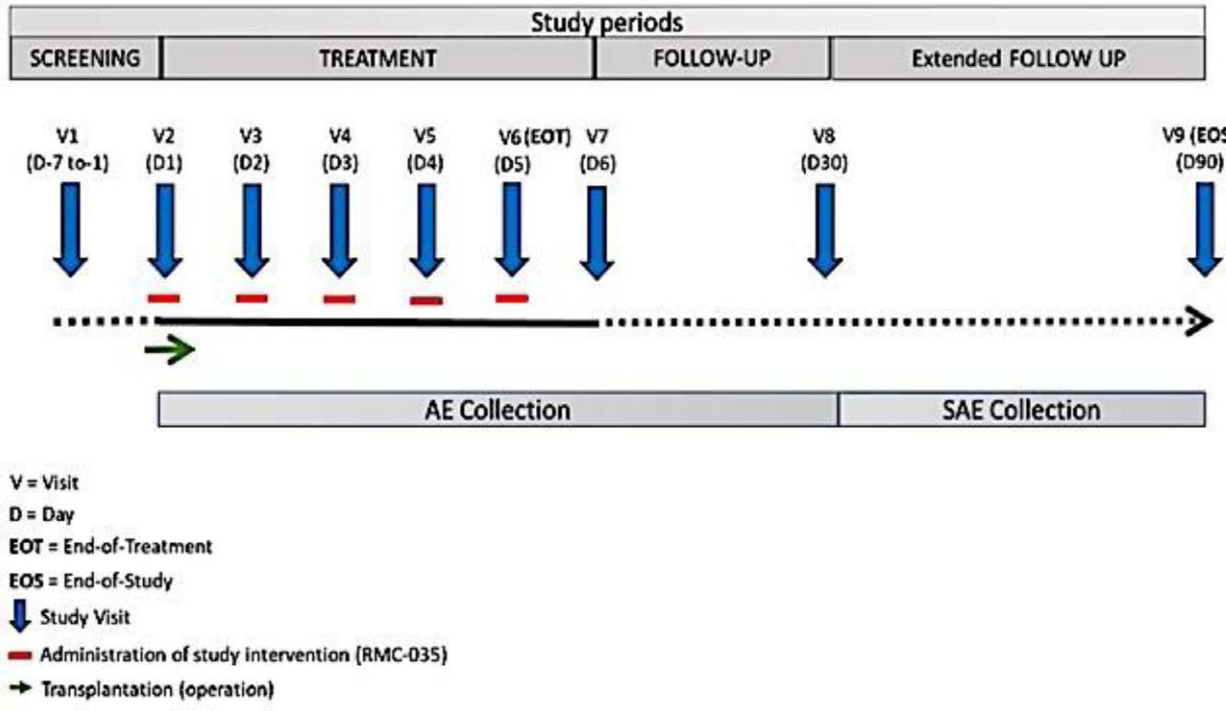

FIGURE 1. Overview of study design.

TABLE 1.

Plasma PK sampling schedule

Sampling time-point relative to dose [window]	Pre-dose [≤60 min]	+30 min [±5 min]	+1 h [±5 min]	+2 h [±5 min]	+4 h [±10 min]	+24 h [±30 min]
Start of infusion dose 1	x	x	x	x	x	x
Start of infusion dose 2	x	x	x	x	x	x
Start of infusion dose 3	x	x				
Start of infusion dose 4	x	x				
Start of infusion dose 5	x	x	x	x	x	x

h, hour(s); min, minutes; PK, pharmacokinetics.

C_{trough}, CL, PTR, $R_{ac(AUC)}$, $t_{1/2}$, and Vd. Clinical safety was evaluated by recording adverse events (AEs), which were coded according to the Medical Dictionary for Regulatory Activities (MedDRA)[22] system organ class and preferred terms. Adverse events and severe adverse events (SAE) were reported as treatment-emergent AEs (TEAE) that occurred from the administration of the first dose to 72 h after the last dose and post-treatment AEs (PTAE). Safety laboratory tests, including hematological, biochemical, and liver function tests, were performed throughout the treatment and follow-up periods. Additionally, physical examinations were performed, and ECG were recorded.

Exploratory Endpoints

Post-transplant changes in renal function were evaluated using eGFR measurements. Evaluations were conducted on days 7, 30, and 90 after transplantation. The mean AUC_{0-24h} creatinine clearance from days 5 to 6 was measured using urine collection. Dialysis treatment or biopsy-proven graft rejection was also recorded. To identify whether antidrug antibodies (ADA) developed after multiple intravenous administrations, the presence of ADA on day 1 (prior to the first dose of study drug), 30, and 90 post-transplantation were collected. Changes in immunologic biomarkers of complement activation, cytokine release, and mast cell activation were analyzed to explore the background and mechanism of potential infusion-related reactions (IRR), and samples were collected pre- and 2 h post-infusion. These biomarkers were added to the study protocol, while the study was ongoing and were collected from 3 patients in dose cohort 2.

Statistical Analyses

Descriptive statistics included the number of nonmissing data points; arithmetic mean; standard deviation (SD); standard error; and median, minimum, and maximum. Mean and median values are presented in one more decimal place than individual values. Descriptive statistics for PK concentrations included n (number of observed values), arithmetic mean, SD, median, minimum, maximum, and coefficient of variation.

Frequencies and proportions were provided for frequency tabulations. The denominator was the number of participants with nonmissing values in the analysis set.

RESULTS

Study Population

A total of 9 subjects were screened, and 8 subjects were assigned to the study intervention in 2 cohorts. The ninth study subject was excluded because of a screening failure (Figure 2). Eight subjects who provided written informed consent prior to screening for eligibility were allocated in chronological order to 1 of 2 sequential cohorts of RMC-035 (4 subjects per cohort). According to prestudy planning, a third cohort of 4 subjects was optionally planned to receive RMC-035, with the dose determined by PK and safety assessments of the first 2 cohorts. However, this was not required following a review of data from cohorts 1 and 2. A summary overview of the subjects on study treatment by visit is shown in Table S1 (SDC, http://links.lww.com/TXD/A714).

Recipients

The study population consisted of 8 subjects. All the patients received an organ from a living donor. The baseline characteristics of the subjects included in the study, and the transplant characteristics are shown in Table 2.

Living-donor kidney transplantations were performed electively with negative preoperative immunological crossmatching. The surgeries were performed under general anesthesia in a standardized manner. All recipients received standard medical care in all non-study-related aspects, including the immunosuppressive therapies: tacrolimus, mycophenolate mofetil, and corticosteroids.

Donors

All the participating living kidney donors provided written informed consent for basic donor data collection (Table 2). All donors received standard care and underwent robot-assisted laparoscopic donor nephrectomy under general anesthesia.

Exposure

Subjects in cohort 1 received RMC-035 at doses ranging from 19.2 mg to 30.3 mg per dose. Administrations to individual subjects were performed over a duration of 30–37 min. In cohort 2, subjects received 20.1–46.2 mg per dose and the duration of individual administrations were 28–33 min.

Compliance with Study Intervention

Of the 8 subjects, 5 (62.5%) completed all 5 administrations of the study drug per protocol. Two (25.0%) subjects withdrew consent for treatment with the study drug after 2 doses and missed the 3 subsequent doses. One subject (12.5%) missed the administration of doses 2 and 5 because the dose-hold criteria (low urine output and hemodialysis) were met. The number of subjects administered each dose is presented in Table S1 (SDC, http://links.lww.com/TXD/A714).

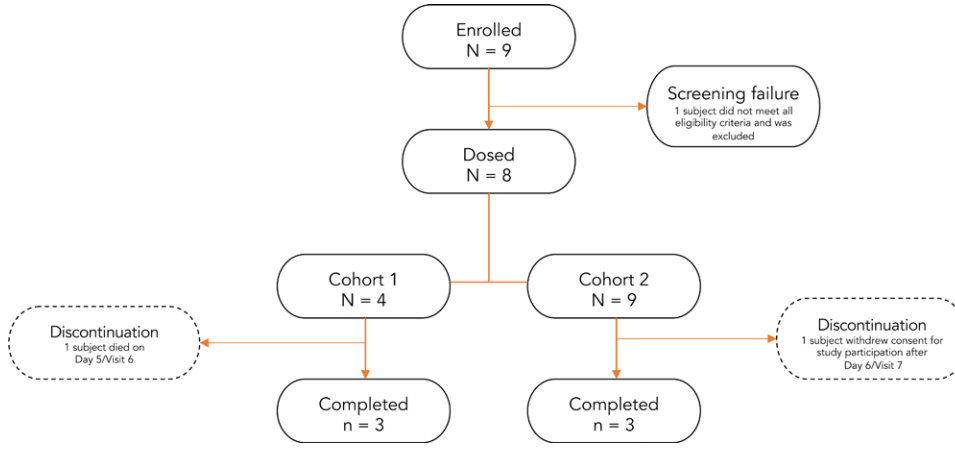

FIGURE 2. Disposition of subjects.

TABLE 2.

Recipient, donor, and transplant characteristics

	Recipients cohort 1 (n = 4)	Recipients cohort 2 (n = 4)	Donors cohort 1 (n = 4)	Donors cohort 2 (n = 4)
Sex (female)	1	1	2	3
Sex (male)	3	3	2	1
Age, y	50.5 (3.7)	50.3 (10.6)	46.8 (7.6)	47.8 (7.3)
BMI, kg/m^2	26.0 (5.9)	24.1 (1.8)	25.4 (2.3)	25.7 (3.6)
Surgery, min	350.8 (89.9)	414 (72.8)		
CIT, min	62 (29.2)	75.8 (14.4)		
WIT, min	39 (6.9)	34.8 (5.6)		

The results are presented as mean (SD) for continuous variables or n for categorical variables.
BMI, body mass index; min, minutes; CIT, cold ischemia time; WIT, warm ischemia time.

TABLE 3.

C_{max}, $AUC_{0–24h}$ and C_{trough} of RMC-035 following first, second, and fifth dose

Cohort no.	Dose no.	Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{0–24h}$ (h * µg/mL)	C_{trough} (µg/mL)
1 and 2	1	0.3	4.79 (1.409)	11.37 (2.554)	Not applicable
(n = 8)			3.53, 7.49	8.95, 15.02	
1 and 2	2	0.3	4.62 (1.182)	8.33 (1.636)	0.028 (0.009401)
(n = 7)			3.42, 7.11	6.65, 11.37	0.01356, 0.03814
1	5	0.3	3.54(0.9847)	7.35 (1.050)	0.028 (0.01316)
(n = 3)			2.77, 4.65	6.41, 8.48	0.01880, 0.04730
2	5	0.6	7.79 (1.316)	13.53 (1.327)	0.032(0.0008839)
(n = 2)			6.86, 8.72	12.60, 14.47	0.03126, 0.03251

The results are presented as mean (SD), minimum and maximum range.

Pharmacokinetic Results

Results for $AUC_{0–24h}$, C_{max}, and C_{trough} are shown in Table 3. Following infusions at a dose level of 0.3 mg/kg, the mean C_{max} decreased from 4.79 µg/mL at the first dose to 4.62 µg/mL at the second dose and 3.54 µg/mL at the fifth dose. Similarly, the mean $AUC_{0–24h}$ was 11.37 h*µg/mL at the first dose, 8.33 h*µg/mL at the second dose, and 7.35 h*µg/mL at the fifth dose. The mean C_{trough} was similar (rounded to 0.03 µg/mL) for the second and fifth doses in cohort 1 and for the fifth dose in cohort 2, indicating negligible accumulation and near-complete clearance in both 0.3 and 0.6 mg/kg dose levels. For the 0.6 mg/kg dose level, the mean C_{max} was 7.79 µg/mL and the mean $AUC_{0–24h}$ was 13.53 h*µg/h (based on the results of the 2 subjects completing this dose level), both measured following the fifth administration, more than threefold lower than the exposure cap derived from the cumulative mean $AUC_{0–24h}$ exposure (42.1 h*µg/mL) in a previous multiple ascending dose study in healthy subjects (19-ROS-02; Table S2, SDC, http://links.lww.com/TXD/A714, and data on file). The accumulation ratio ($R_{ac(AUC)}$) for the first versus fifth dose was 0.59 in cohort 1. In cohort 2, the ratio of AUCs between day 5 and day 1 was 1.43, reflecting the combined effect of a double dose and increased renal clearance on day 5 (Table 4).

Immunological Biomarkers and Immunogenicity

Changes in immunological biomarkers were assessed in 3 patients following an amendment to the study protocol. To measure mast cell and complement activation, tryptase, complement factor 5a (C5a), and interleukin-1β (IL-1β) levels were analyzed. These levels did not increase following RMC-035 infusion. However, the levels of the inflammatory biomarkers interleukin-6 (IL-6), and -8 (IL-8), and tumor necrosis factor alpha (TNFα) increased 2 h after RMC-035 infusion in 2 subjects, as shown in Figure 3. Both subjects who displayed marked increases in these inflammatory markers withdrew consent following the second RMC-035 infusion after experiencing IRRs as AEs. All ADA results were negative.

Safety Results

A total of 22 TEAEs were reported in 6 subjects, accounting for 75% of the study population. The details of TEAEs are presented in Table 5. Twelve TEAEs were deemed related to the study intervention, all of which were of mild intensity.

TABLE 4.

Ratio of AUC day 5/day 1

Cohort no.	$AUC_{0–24h}$ (h* µg/mL)	AUC_{last} (h* µg/mL)
1	0.59 (0.16)	0.59 (0.17)
(n = 3)		
2	1.43 (0.03)	1.43 (0.03)
(n = 2)		

The results are presented as mean (SD).

The remaining 5 mild TEAEs were unrelated to the study intervention. The 3 moderate TEAEs were *Klebsiella* sepsis, *Staphylococcus*-positive blood culture, and decreased urine output. Two severe TEAEs—oliguria and respiratory failure—occurred in the same patient. Both moderate and severe TEAEs were assessed as unrelated to the study intervention. The incidence and nature of TEAEs were consistent with those expected in patients undergoing kidney transplantation, except for IRRs, chills, and feelings of cold, which were categorized as mild, transient, and typically occurred within 1 h of administration of the study drug.

Post-treatment Adverse Events

A total of 15 PTAEs occurred in 7 subjects; that is, all subjects entering the follow-up period experienced a PTAE. Of the PTAEs, 5 events occurring in 3 subjects were reported as SAEs. None of the PTAEs were assessed as related to the study intervention.

Patient Mortality

One case of fatality occurred during the study. It occurred on study day 5 and was assessed as unrelated to the study intervention. The fatal event was the result of respiratory failure in a patient with a medical history of heart transplantation and several comorbidities including type I diabetes and chronic ischemic heart disease caused by chronic allograft vasculopathy. Autopsy findings revealed massive bronchopneumonia and pulmonary edema, causing acute and fatal respiratory failure.

Serious Adverse Events

Six SAEs occurred in 4 of 8 (50%) patients, all of which were assessed as unrelated to the study intervention. Apart from the fatal SAE described above, all SAEs were PTAEs of mild-to-moderate severity, as shown in Table 6.

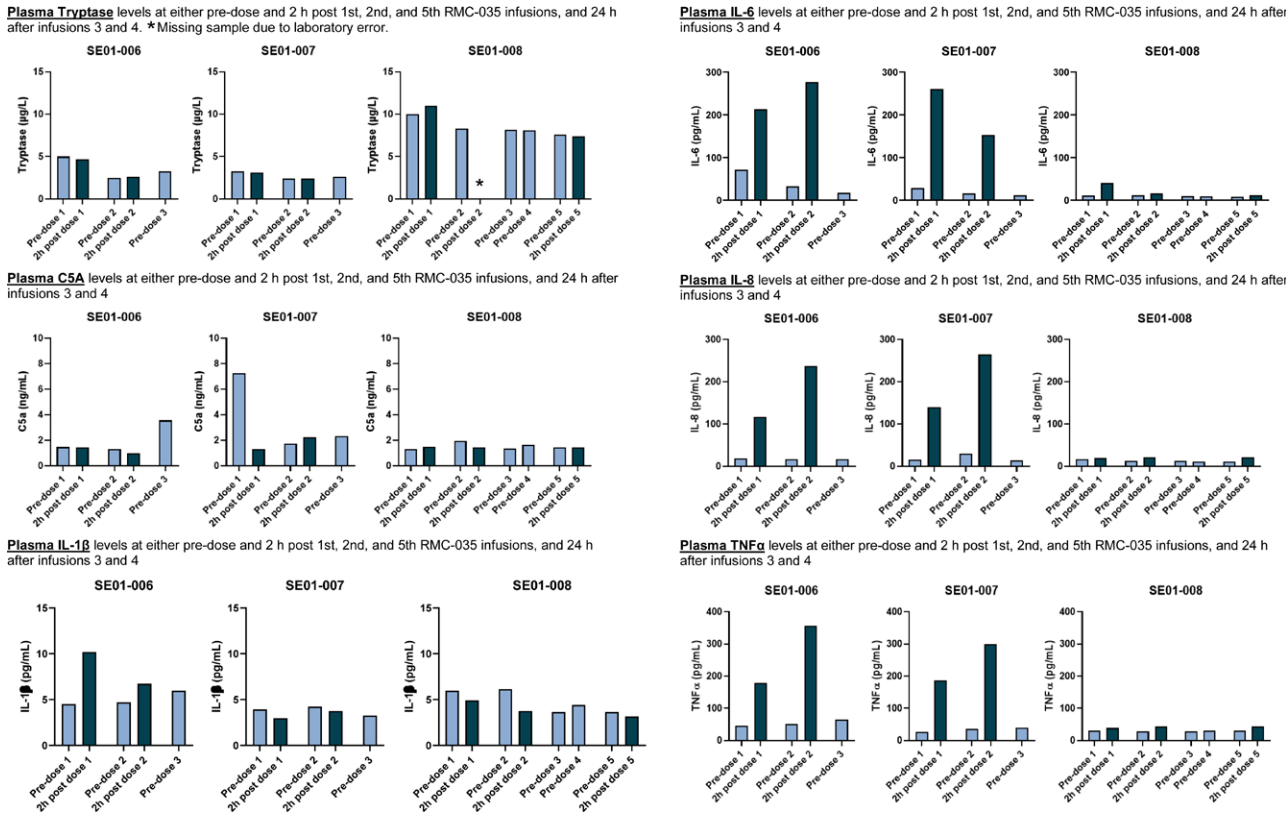

FIGURE 3. Immunological biomarkers. µg/L, microgram per liter; ng/mL, nanogram per milliliter; pg/mL, picogram per milliliter; C5A, complement factor 5a; IL-1β, interleukin-1-beta; IL-6, interleukin-6; IL-8, interleukin-8; TNFα, tumor necrosis factor alpha.

Other Safety Evaluations

There were no clinically significant changes in hematology, biochemistry, liver function parameters, or other safety observations in this study.

Efficacy Results

No formal efficacy evaluation was performed in this phase 1 study of 8 subjects with no comparator arm. The evolution of serum creatinine, cystatin C, eGFR, and creatinine clearance showed general postoperative improvements in kidney function (Figure 4; Tables S3–S6, SDC, http://links.lww.com/TXD/A714).

DISCUSSION

This noncomparative open-label study met the primary objective of evaluating the PK and safety in kidney transplant recipients treated with RMC-035. Exposures at comparable time points were approximately dose proportional, where a doubling of the dose from 0.3 to 0.6 mg/kg resulted in an approximate doubling of the plasma concentrations. Plasma exposure (AUC_{0-24h}) decreased between the first and fifth doses, reflecting improved kidney graft function and RMC-035 renal clearance over time. No drug accumulation was observed during or after drug administration.

The PK data were in line with those of previous studies (Table S2, SDC, http://links.lww.com/TXD/A714), and the C_{max} and AUC showed dose linearity. A decrease in AUC_{0-24h} was observed over time, reflecting a postoperative improvement in kidney function. In addition, the AUC_{0-24h} exposures were predictable between subjects without renal function and healthy subjects. No significant accumulation was observed, as determined by C_{trough}. Peak exposures (C_{max}) or AUC_{0-24h} exposures with single dose of either 0.3 or 0.6 mg/kg are not close to any safety limits or levels achieved in previous clinical phase 1 studies (Table S2 http://links.lww.com/TXD/A714, SDC; data on file).

Overall, the AE profiles were in line with expectations for the study population,[23,24] except for events suggestive of IRRs. Two patients withdrew from the study after experiencing IRRs (chills). However, these events were mild in intensity and transient in nature without the need for medical intervention. Four patients reported SAEs unrelated to the intervention. No clinically significant changes in safety laboratory parameters were observed. There was a clinically significant reduction in serum creatinine levels, reflective of post-transplant improvement in kidney function.

The increased levels of the inflammatory biomarkers IL-6, IL-8, and TNFα in the 2 subjects experiencing AEs, suggestive of IRR, indicate a possible immunogenic response to treatment. No relevant changes were observed in biomarkers of complement and mast cell activation. However, the results obtained from only 2 patients were difficult to interpret, and any response related to immune activation requires further assessment.

The findings on the renal function parameters reflected the expected improvement in kidney function after transplantation. Given the low number of patients and the absence of a comparator group, no further conclusions are possible regarding the preventive or therapeutic potential of RMC-035 in kidney transplant patients.

Results from this first-in-human kidney transplantation trial showed that apart from manageable IRR, the safety

TABLE 5.

Incidence of TEAEs by MedDRA system organ class and preferred term

		Cohort 1 (n = 4)	Cohort 2 (n = 4)	Total (n = 8)
System organ class	**Preferred term**	**n**	**n**	**n**
Gastrointestinal disorders		1	2	3
	Ileus paralytic	1		1
	Paresthesia oral		1	1
	Vomiting		1	1
General disorders and administration site conditions		3	6	9
	Chest pain		1	1
	Chills	1	4	5
	Discomfort		1	1
	Feeling cold	1		1
	Edema peripheral	1		1
Infections and infestations		1		1
	Klebsiella sepsis	1		1
Investigations		3	2	5
	Body temperature increased		1	1
	Hepatic enzyme increased	1		1
	Platelet count decreased	1		1
	Staphylococcus test positive		1	1
	Urine output decreased	1		1
Musculoskeletal and connective tissue disorders			1	1
	Muscle spasms		1	1
Renal and urinary disorders		1		1
	Oliguria	1		1
Respiratory, thoracic, and mediastinal disorders		1		1
	Respiratory failure	1		1
Vascular disorders		1		1
	Venous thrombosis limb	1		1

MedDRA, Medical dictionary for regulatory activities; TEAE, treatment-emergent adverse event.

TABLE 6.

Serious adverse events

Cohort	Subject	Type	MedDRA term	Start day	Stop day	Severity	Related to study drug	Action taken with study drug	AE caused early termination
Cohort 1	003	TEAE	Resp failure	5	5	Grade 5—Death	Not Related	Drug withdrawn	Yes
	004	PTAE	Postop wound infection	26	40	Grade 2—Moderate	Not Related	Not applicable	No
		PTAE	Chest pain	40	55	Grade 2—Moderate	Not Related	Npt applicable	No
Cohort 2	006	PTAE	COVID-19	20	24	Grade 1—Mild	Not Related	Not applicable	No
		PTAE	COVID-19	83	86	Grade 1—Mild	Not Related	Not applicable	No
	007	PTAE	Post procedural urine leak	10	15	Grade 2—Moderate	Not Related	Not applicable	No

AE, adverse event; F, female; M, male; MedDRA, Medical dictionary for regulatory activities; Resp, respiratory; Postop, postoperative; PTAE, post-treatment adverse event; TEAE, treatment-emergent adverse event.

profile was in line with expectations and that RMC-035 has predictable pharmacokinetics in this study group of 8 living donor kidney transplant recipients.

IRI and DGF are 2 common factors that may occur after kidney transplantation and can significantly affect its long-term success. Additionally, IRI can have long-term consequences such as chronic allograft dysfunction and reduced graft survival rates. These complications can cause an increase in healthcare costs as well as a decreased quality of life for transplant recipients.[7,8] Reducing IRI and the risk of DGF can bring several benefits to the patient, including improved long-term kidney function and reduced risk of rejection.[9] The risk of IRI in living-donor kidney transplantation is lower than that in deceased-donor kidney transplantation.[23] In general, kidneys from donors after circulatory death (DCD) experience greater ischemic injury than those from brain-dead donors, resulting in a higher risk of DGF.[6] Consequently, treatments that reduce the occurrence of IRI and DGF are important for kidney transplantations from deceased donors, particularly after DCD.

To the best of our knowledge, no pharmaceutical drug can prevent or decrease IRI, DGF, or their long-term consequences after kidney transplantation. Whether RMC-035 has the potential to improve outcomes by preventing IRI and DGF remains unknown, and requires further investigation in future clinical trials. However, RMC-035 possesses intrinsic properties and biological effects that may influence key elements of the pathological processes underlying IRI and DGF.

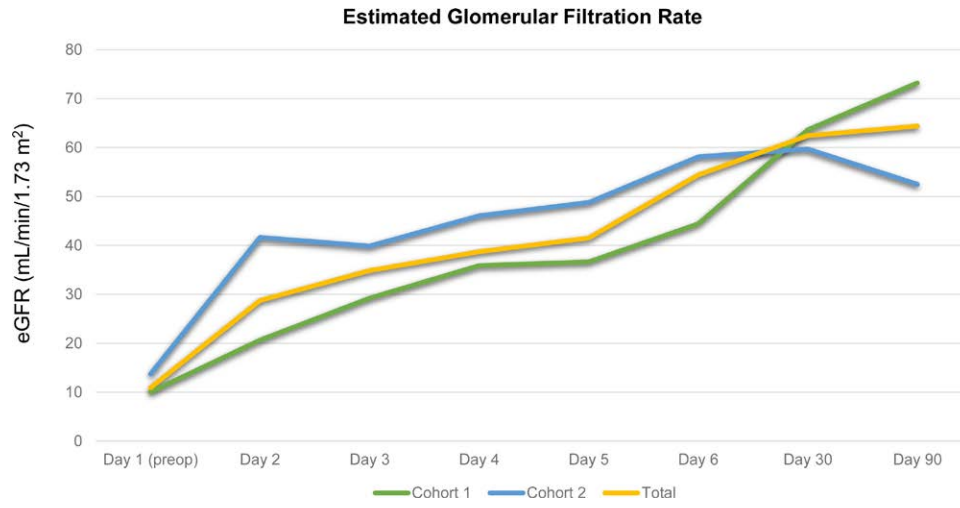

FIGURE 4. CKD-EPI estimated glomerular filtration rate based on serum creatinine + Cystatin C2[2] (mL/min/1.73 m[2]). All data are presented as median values from eligible subjects at each time point. eGFR, estimated glomerular filtration rate.

Therefore, RMC-035 has the potential to mitigate IRI in the transplanted kidneys. Given its potential kidney protective properties, it is plausible to speculate about its applicability in other organ transplantations, such as liver, heart, and lung transplantation, as these procedures commonly have a negative impact on kidney function.[25-27]

In conclusion, reducing IRI and DGF can have significant benefits for kidney transplant patients, including improved graft survival, improved kidney function, and a reduced risk of rejection. Controlled clinical studies should evaluate whether RMC-035 can prevent or reduce IRI and DGF in kidney transplantation. In this study, the treatment of living-donor kidney transplant recipients with RMC-035 displayed predictable pharmacokinetic properties.

ACKNOWLEDGMENTS

We thank all the patients who participated in this trial as well as the trial site staff and research nurses involved. We thank the Biobank and Study Support at the Karolinska University Hospital for their services, which contributed to this study. The MedDRA trademark was registered by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

REFERENCES

1. Lewis A, Koukoura A, Tsianos GI, et al. Organ donation in the US and Europe: The supply vs demand imbalance. *Transplant Rev (Orlando)*. 2021;35:100585.
2. Veras de Sandes-Freitas T, Abbud-Filho M, Garcia VD. Reasons for disparities in access to kidney transplantation. *Contrib Nephrol*. 2021;199:297–306.
3. Aiyegbusi O, McGregor E, McManus SK, et al. Immunosuppression therapy in kidney transplantation. *Urol Clin North Am*. 2022;49:345–360.
4. Zhang Y, Gerdtham UG, Rydell H, et al. Healthcare costs after kidney transplantation compared to dialysis based on propensity score methods and real world longitudinal register data from Sweden. *Sci Rep*. 2023;13:10730.
5. Swanson KJ, Bhattarai M, Parajuli S. Delayed graft function: current status and future directions. *Curr Opin Organ Transplant*. 2023;28:1–7.
6. Bahl D, Haddad Z, Datoo A, et al. Delayed graft function in kidney transplantation. *Curr Opin Organ Transplant*. 2019;24:82–86.
7. Li MT, Ramakrishnan A, Yu M, et al. Effects of delayed graft function on transplant outcomes: A meta-analysis. *Transplant Direct*. 2023;9:e1433.
8. Salazar Meira F, Zemiacki J, Figueiredo AE, et al. Factors associated with delayed graft function and their influence on outcomes of kidney transplantation. *Transplant Proc*. 2016;48:2267–2271.
9. Melih KV, Boynuegri B, Mustafa C, et al. Incidence, risk factors, and outcomes of delayed graft function in deceased donor kidney transplantation. *Transplant Proc*. 2019;51:1096–1100.
10. Massoth C, Zarbock A, Meersch M. Acute kidney injury in cardiac surgery. *Crit Care Clin*. 2021;37:267–278.
11. Wu MY, Yiang GT, Liao WT, et al. Current mechanistic concepts in ischemia and reperfusion injury. *Cell Physiol Biochem*. 2018;46:1650–1667.
12. Lim MA, Bloom RD. Medical therapies to reduce delayed graft function and improve long-term graft survival: Are we making progress? *Clin J Am Soc Nephrol*. 2020;15:13–15.
13. Ekström B, Berggård I. Human α1-microglobulin. Purification procedure, chemical and physiochemical properties. *J Biol Chem*. 1977;252:8048–8057.
14. Takagi T, Takagi K, Kawai T. Complete amino acid sequence of human α1-microglobulin. *Biochem Biophys Res Commun*. 1981;98:997–1001.
15. Kaumeyer JF, Polazzi JO, Kotick MP. The mRNA for a proteinase inhibitor related to the HI-30 domain of inter-alpha-trypsin inhibitor also encodes α-1-microglobulin (protein HC). *Nucleic Acids Res*. 1986;14:7839–7850.
16. Åkerström B, Gram M. A1M, an extravascular tissue cleaning and housekeeping protein. *Free Rad. Biol. Med.* 2014;74:274–282.
17. Olsson MG, Olofsson T, Tapper H, et al. The lipocalin 1-microglobulin protects erythroid K562 cells against oxidative damage induced by heme and reactive oxygen species. *Free Radic Res*. 2008;42:725–736.
18. Olsson MG, Nilsson EJ, Rutardottir S, et al. Bystander cell death and stress response is inhibited by the radical scavenger α1-microglobulin in irradiated cell cultures. *Radiat Res*. 2010;174:590–600.
19. May K, Rosenlöf L, Olsson MG, et al. Perfusion of human placenta with hemoglobin introduces preeclampsia-like injuries that are prevented by α1-microglobulin. *Placenta*. 2011;32:323–332.
20. Olsson MG, Allhorn M, Larsson J, et al. Up-regulation of A1M/α1-microglobulin in skin by heme and reactive oxygen species gives protection from oxidative damage. *PLoS One*. 2011;6:e27505.
21. Weiss R, Meersch M, Wempe C, et al. Recombinant alpha-1-microglobulin (RMC-035) to prevent acute kidney injury in cardiac surgery patients: phase 1b evaluation of safety and pharmacokinetics. *Kidney Int Rep*. 2023;8:980–988.
22. MedDRA Version 24.0 March 2021.
23. Araújo AM, Santos F, Guimarães J, et al. Living-donor kidney transplantation: predictive factors and impact on post-transplant outcome. *Transplant Proc*. 2015;47:938–941.

24. Carvalho JA, Nunes P, Antunes H, et al. Surgical complications in kidney transplantation: An overview of a Portuguese reference center. *Transplant Proc*. 2019;51:1590–1596.
25. Zhou J, Zhang X, Lyu L, et al. Modifiable risk factors of acute kidney injury after liver transplantation: A systematic review and meta-analysis. *BMC Nephrol*. 2021;22:149.
26. Thongprayoon C, Lertjitbanjong P, Hansrivijit P, et al. Acute kidney injury in patients undergoing cardiac transplantation: A meta-analysis. *Medicines (Basel, Switzerland)*. 2019;6:108.
27. Lertjitbanjong P, Thongprayoon C, Cheungpasitporn W, et al. acute kidney injury after lung transplantation: A systematic review and meta-analysis. *J Clin Med*. 2019;8:1713.