AUTOIMMUNITY

The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study

Peter Kiessling,[1] Rocio Lledo-Garcia,[2]* Shikiko Watanabe,[3] Grant Langdon,[4] Diep Tran,[2] Muhammad Bari,[2] Louis Christodoulou,[2] Emma Jones,[5] Graham Price,[2] Bryan Smith,[2] Frank Brennan,[2] Ian White,[2] Stephen Jolles[6]

Pathogenic immunoglobulin G (IgG) autoantibodies characterize some human autoimmune diseases; their high concentration and long half-life are dependent on recycling by the neonatal Fc receptor (FcRn). Inhibition of FcRn is an attractive new treatment concept for IgG-mediated autoimmune diseases. Rozanolixizumab (UCB7665; CA170_01519.g57 IgG4P) is an anti-human FcRn monoclonal antibody. In cynomolgus monkeys, rozanolixizumab reduced IgG (maximum 75 to 90% by about day 10), was well tolerated, and did not increase risk of infection. We also report a first-in-human, randomized, double-blind, placebo-controlled, dose-escalating study of intravenous (IV) or subcutaneous (SC) rozanolixizumab in healthy subjects (NCT02220153). The primary objective was to evaluate safety and tolerability. Secondary objectives were assessment of rozanolixizumab pharmacokinetics and pharmacodynamics, including effects on circulating IgG concentrations. Forty-nine subjects were randomized to receive rozanolixizumab ($n = 36$) or placebo ($n = 13$) across six cohorts. The first three cohorts received IV doses, and the subsequent three cohorts received SC doses, of rozanolixizumab 1, 4, or 7 mg/kg ($n = 6$ for each cohort; plus $n = 7$ or 6 for placebo, respectively). The most frequent treatment-emergent adverse event [TEAE; headache, 14 of 36 (38.9%) subjects] was dose-dependent and more prominent after IV administration. Severe TEAEs occurred in four subjects, all in the highest-dose IV group [headache ($n = 3$) and back pain ($n = 1$)]. Rozanolixizumab pharmacokinetics demonstrated nonlinear increases with dose. There were sustained dose-dependent reductions in serum IgG concentrations (IV and SC rozanolixizumab). These data provide clinical evidence for the therapeutic potential of rozanolixizumab.

INTRODUCTION

Autoimmune and alloimmune diseases, such as anti–glomerular basement membrane antibody disease, immune thrombocytopenia (ITP), myasthenia gravis (MG), hemolytic anemia, and pemphigus vulgaris, are characterized by the presence of pathogenic autoantibodies, commonly of the immunoglobulin G (IgG) isotype. A number of strategies currently exist to reduce pathogenic autoantibodies; these include treatments aimed at reducing autoantibody production (immunosuppression with corticosteroids and second-line agents such as azathioprine, cyclophosphamide, mycophenolate mofetil, and B cell ablation) (1) or increasing autoantibody removal [plasma exchange, immunoadsorption, or immunomodulatory doses of intravenous immunoglobulin (IVIg)] (2). However, these treatments can be associated with side effects, accessibility issues, patient inconvenience, and overall time and cost implications (3–6).

Therapeutic plasma exchange involves the filtration of venous blood to remove high–molecular weight components, including immunoglobulins (both pathogenic and normal), albumin and proinflammatory factors that are involved in the pathogenesis of numerous autoimmune diseases (3). Although plasma exchange offers a potentially efficacious treatment option for autoimmune disorders, it is associated with numerous disadvantages including adverse reactions, exposure to blood products, and reduction of circulating plasma concentrations of all immunoglobulin isotypes (including IgM and IgA, not just IgG) (7). An alternative treatment option is immunoadsorption, which specifically removes IgG and no other plasma component, thus reducing the breadth of impact on the patient's humoral immune system; however, immunoadsorption is also associated with adverse reactions and the disadvantages associated with hospital-based therapies (8).

IVIg comprises human immunoglobulin (95 to 99% IgG and varying trace amounts of IgM, IgA, IgD, and IgE) prepared from large numbers of healthy donors (4). The mechanisms of action of IVIg are multiple and may include functional blockade of Fc receptors, autoantibody neutralization, inhibition of autoantibody production, complement inhibition, and modulation of cytokine and cytokine antagonist production (5). Administration of immunomodulatory doses of IVIg can reduce endogenous (including pathogenic) IgG concentrations as a result of saturation of the neonatal Fc receptor (FcRn) (9–11). Although IVIg is generally considered to have an acceptable safety profile, adverse systemic reactions are common, occurring in 20 to 50% of patients (12). In most chronic autoimmune diseases in which IVIg is used for immunomodulation (rather than replacement doses in antibody deficiency), a long-term dose (1 to 2 g/kg per cycle) may be required (13, 14).

Another common treatment option for many autoimmune diseases is corticosteroids, used either as stand-alone therapy or in combination with second-line immunosuppressive agents, plasma exchange, or IVIg (1). Corticosteroids are known to modestly reduce IgG concentrations in plasma (15); however, long-term steroid treatment is often limited by significant dose-dependent toxicities and lack of effect over time (6). Despite the universally accepted efficacy of corticosteroids in autoimmune conditions such as MG, the long-term adverse events (AEs) make the availability of other treatment options highly desirable (1).

IgG and albumin have half-lives of 3 to 4 weeks, the longest of any plasma proteins (16, 17). Their high concentrations (IgG, 7 to 17 g/liter in humans) and long half-lives are critically dependent on salvage and

[1]UCB Pharma, 40789 Monheim, Germany. [2]UCB Pharma, Slough SL1 3WE, UK. [3]UCB Pharma, Braine, 1420 Braine-l'Alleud, Belgium. [4]PTx Solutions Ltd., London, UK. [5]Veramed Ltd., Twickenham TW1 3QS, UK. [6]Department of Immunology, University Hospital of Wales, Cardiff CF14 4XW, UK.
*Corresponding author. Email: rocio.lledo-garcia@ucb.com

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recycling by the FcRn (18, 19). It has been estimated that the FcRn-mediated IgG recycling rate is 42% greater than the rate of IgG production, indicating that recycling of IgG, not its production, is the dominant process for maintaining the IgG plasma concentration in humans (18). Studies have shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling the proteins from the sorting endosome to the cell surface (20, 21). Salvage of IgG and albumin by FcRn extends their plasma half-life; in FcRn-deficient mice, the half-lives of both IgG and albumin are reduced from 6 to 8 days to around 1 day, plasma IgG concentrations are 20 to 30% of normal, and plasma albumin concentrations are 40% of normal (20). Anti-human and anti-murine FcRn antibodies have been shown to reduce plasma IgG concentrations in rodents (22–24); in nonhuman primates, administration of an anti-FcRn antibody reduced endogenous IgG by more than 60%, with no changes in albumin, IgM, or IgA (25).

It has been proposed that removal of pathogenic IgG autoantibodies by inhibiting FcRn and the associated IgG salvage pathway may constitute an attractive target in the treatment of autoantibody-mediated disease (20). Given the specificity of this approach, many of the side effects associated with immunosuppressive therapies could be avoided. Rozanolixizumab (UCB7665; CA170_01519.g57 IgG4P) is a humanized high-affinity anti-human FcRn monoclonal antibody (26). The antibody is an IgG4P, an inactive isotype with reduced likelihood of unwanted chain exchange (27, 28). This report presents data from a 4-week toxicology study of rozanolixizumab in cynomolgus monkeys and the results of a single-dose, dose-escalation study (NCT02220153), designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending IV or subcutaneous (SC) doses of rozanolixizumab in healthy human subjects.

RESULTS
Four-week toxicology study in cynomolgus monkeys
To evaluate the potential toxicity, toxicokinetics, and PD of high and repeated IV and SC doses of rozanolixizumab, we conducted a 4-week toxicology study in cynomolgus monkeys. Rozanolixizumab was shown to bind to, and inhibit the function of, human and cynomolgus monkey FcRn with comparable affinity and potency (26). SC (50 and 150 mg/kg) or IV (150 mg/kg) administration of rozanolixizumab every 3 days for 4 weeks was well tolerated in cynomolgus monkeys. Maximum concentrations of rozanolixizumab were achieved within 48 hours of the first SC administration. After dosing at 150 mg/kg every 3 days for 4 weeks, mean exposures to rozanolixizumab (AUC_τ) were similar to those after the first dose (Table 1), indicating absence of rozanolixizumab accumulation with repeated dosing. There were no sex-related differences in plasma concentrations or toxicokinetic parameters.

Marked decreases (75 to 90% from baseline) in plasma IgG concentrations were observed in all animals (50 and 150 mg/kg doses), with maximal effects achieved by about day 10 (fig. S1 and Fig. 1, respectively). Because the selected doses achieved a maximum FcRn-related PD effect, no clear dose dependency was observed.

There were neither rozanolixizumab-related mortalities nor adverse effects on the standard toxicology, clinical pathology, safety pharmacology, immunotoxicology, and pathology parameters, listed in Materials and Methods. There was no increase in infection rates, no effects on plasma concentrations of acute-phase proteins [for example, fibrinogen, haptoglobin, and C-reactive protein (CRP)], and no changes in IgM and IgA serum concentrations. Rozanolixizumab-related decreases in total protein and globulin were observed in all treatment groups (weeks 1 and 4) and were directly attributable to the decreased IgG concentrations. Although rozanolixizumab was specifically selected because it did not block albumin binding to FcRn, small albumin decreases were observed, possibly because of mild steric hindrance by the bound antibody. No corresponding effect on plasma calcium concentration was observed. All findings were within normal ranges (derived from historical values obtained from male and female control group animals) and returned to baseline by the end of the 8-week recovery phase.

Immunophenotyping did not reveal any treatment-related effect on relative or absolute numbers of lymphocytes and lymphocyte subpopulations in blood samples, nor on tissue samples at necropsy from bone marrow, spleen, or axillary lymph nodes.

Phase 1 clinical study
Subjects
In total, 184 subjects were screened, of whom 49 were randomized to receive rozanolixizumab ($n = 36$) or placebo ($n = 13$) across six cohorts: rozanolixizumab IV 1, 4, or 7 mg/kg ($n = 6$ in each dose group, plus $n = 7$ placebo in total) and rozanolixizumab SC 1, 4, or 7 mg/kg ($n = 6$ in each dose group, plus $n = 6$ placebo in total). Of these, 48 completed the study. One subject randomized to the placebo IV group permanently discontinued treatment because an incorrect dosage was prepared on the basis of body weight; this subject received a partial dose of placebo

Table 1. Cynomolgus monkey toxicology study design and toxicokinetic parameters of rozanolixizumab after repeated dosing. Rozanolixizumab/vehicle (drug formulation buffer) was dosed every 3 days. AUC_τ, area under the plasma concentration (for repeated dosing) versus time curve on day 1 or 28; C_{max}, maximum observed plasma concentration.

Dose and route of administration	Number of males (M)/females (F)	Necropsy at day 31	Necropsy at day 85	C_{max}, µg/ml Mean (SD)		AUC_τ, µg·day/ml Mean (SD)	
				Day 1	Day 28	Day 1	Day 28
Vehicle (SC)	5M/5F	3M/3F	2M/2F	—	—	—	—
50 mg/kg (SC)	3M/3F	3M/3F	0M/0F	437 (80)	131 (201)	1000 (177)	266 (362)
150 mg/kg (SC)	5M/5F	3M/3F	2M/2F	1950 (442)	1850 (1250)	3860 (893)	3560 (2850)
150 mg/kg (IV)	5M/5F	3M/3F	2M/2F	5430 (638)	5960 (1010)	6950 (593)	5940 (2620)
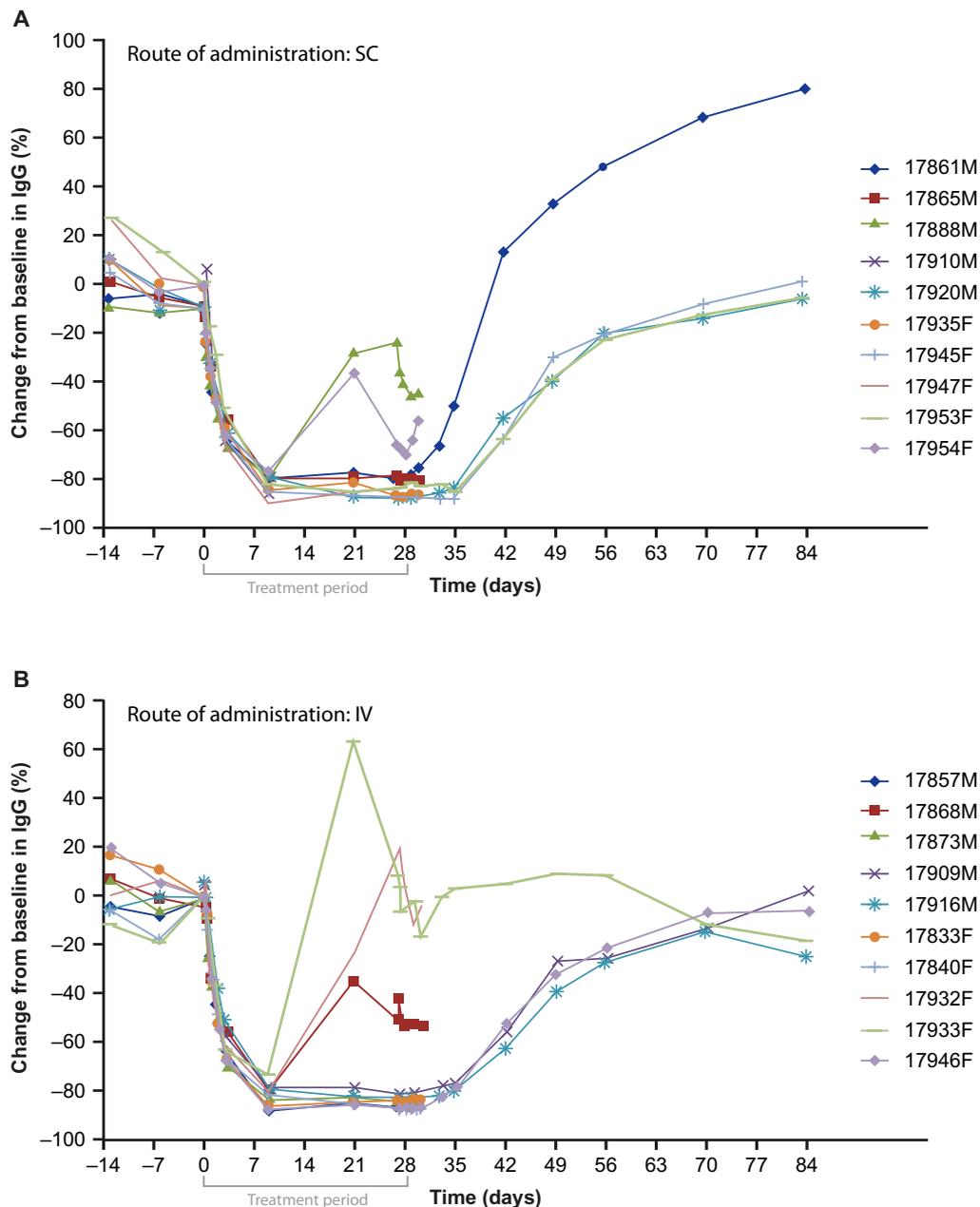
Fig. 1. The effect of high-dose rozanolixizumab on IgG concentration in cynomolgus monkeys. The effect of SC (**A**), or IV (**B**), high-dose rozanolixizumab (150 mg/kg) on plasma IgG concentration in individual cynomolgus monkeys. Change in plasma IgG concentration (before and after dosing) is given as percentage of concentration at time zero. From day 0, animals were dosed every 3 days for 4 weeks. Some animals (main study animals) were terminated at day 30, and the others were terminated at day 84 (recovery animals, after an 8-week treatment-free period); $n = 6$ to 10 in each group. F, female; M, male.

Safety

There were no deaths or serious AEs reported during the study. Most subjects in all IV and SC rozanolixizumab treatment groups (the rozanolixizumab Total group) and in all placebo IV and SC groups (the Placebo Total group) reported at least one TEAE: 27 of 36 (75.0%) for the rozanolixizumab Total group and 9 of 13 (69.2%) for the Placebo Total group. The incidences of TEAEs by route of administration and by individual treatment group are summarized in Table 2. Most TEAEs were mild or moderate in intensity. Severe TEAEs of headache ($n = 3$) and back pain ($n = 1$) were reported by four subjects, all in the rozanolixizumab 7 mg/kg IV group (Table 2). All of the severe TEAEs resolved within 4 days and did not lead to discontinuation from the study. The severe TEAEs of headache were judged by the investigator to be related to study treatment, and all three required medication with a combination of codeine, paracetamol, and ibuprofen. No severe TEAEs occurred after SC dosing of rozanolixizumab.

The most frequently reported TEAEs by route of administration and by individual treatment group are summarized in Table 3. No infusion or hypersensitivity reactions were reported, and the incidence of infections was similar in the placebo and rozanolixizumab groups. Nasopharyngitis was the most frequently reported infection across the treatment groups.

TEAEs considered related to study treatment by the investigator (TR-TEAEs) were reported by 24 of 36 subjects (66.7%) in the rozanolixizumab Total group and by 7 of 13 subjects (53.8%) in the Placebo Total group. The most common TR-TEAEs in the rozanolixizumab Total group were headache ($n = 14$ of 36, 38.9%), vomiting ($n = 9$ of 36, 25.0%), nausea ($n = 7$ of 36, 19.4%), and pyrexia ($n = 7$ of 36, 19.4%), and these all occurred more frequently in the IV groups than the SC groups. The only TR-TEAE reported by more than two subjects in the Placebo Total group was nasopharyngitis, which occurred in three subjects (23.1%) compared with four subjects (11.1%) in the rozanolixizumab Total group. The incidence of treatment-related infections and infestations was lower in the rozanolixizumab Total group than that in the placebo group (13.9% versus 23.1%, respectively).

Mean CRP increased from baseline in the rozanolixizumab 7 mg/kg IV group (from 1.27 to 10.18 mg/liter on day 3) and the rozanolixizumab

before being withdrawn by the sponsor. All randomized subjects ($n = 49$, including the subject who discontinued) were included in the full analysis set and in the PD per-protocol set (PPS). All subjects who received rozanolixizumab ($n = 36$) were included in the PK-PPS.

There were no notable differences in subject demographics between treatment groups. Mean age was 44 years (range, 22 to 65), most of the subjects (85.7%) were male, and most were white (69.4%) (Table 2). The mean total serum IgG concentration at screening was 10.6 g/liter (range, 7.4 to 14.7), and baseline concentrations were similar between treatment groups (Table 2).

Table 2. Subject demographics and summary of TEAEs (full analysis set). BMI, body mass index; TEAE, treatment-emergent AE; TR-TEAE, treatment-related TEAE.

	IV administration					SC administration				
	Placebo (n = 7)	Rozanolixizumab 1 mg/kg (n = 6)	Rozanolixizumab 4 mg/kg (n = 6)	Rozanolixizumab 7 mg/kg (n = 6)	Rozanolixizumab Total (n = 18)	Placebo (n = 6)	Rozanolixizumab 1 mg/kg (n = 6)	Rozanolixizumab 4 mg/kg (n = 6)	Rozanolixizumab 7 mg/kg (n = 6)	Rozanolixizumab Total (n = 18)
Age (years), mean (SD)	37.9 (10.8)	38.7 (12.2)	43.7 (9.6)	46.3 (10.0)	42.9 (10.5)	52.0 (10.8)	50.0 (13.0)	50.3 (13.5)	34.2 (11.6)	44.8 (14.3)
Sex (male), n (%)	6 (85.7)	5 (83.3)	5 (83.3)	6 (100)	16 (88.9)	5 (83.3)	5 (83.3)	4 (66.7)	6 (100)	15 (83.3)
BMI (kg/m^2), mean (SD)	23.6 (2.9)	25.4 (2.9)	24.8 (3.0)	26.8 (3.0)	25.6 (2.9)	24.6 (4.2)	25.9 (3.2)	26.2 (1.9)	23.7 (2.6)	25.3 (2.7)
Racial group, n (%)										
Asian	1 (14.3)	1 (16.7)	1 (16.7)	0	2 (11.1)	0	1 (16.7)	0	2 (33.3)	3 (16.7)
Black/ African American	0	1 (16.7)	0	2 (33.3)	3 (16.7)	0	0	1 (16.7)	1 (16.7)	2 (11.1)
White	4 (57.1)	3 (50.0)	5 (83.3)	3 (50.0)	11 (61.1)	6 (100)	5 (83.3)	5 (83.3)	3 (50.0)	13 (72.2)
Mixed, other	2 (28.6)	1 (16.7)	0	1 (16.7)	2 (11.1)	0	0	0	0	0
Total IgG (g/liter), mean (SD)	10.3 (1.6)	10.5 (2.4)	10.3 (1.2)	11.2 (2.1)	10.7 (1.9)	9.5 (1.4)	10.6 (2.2)	10.4 (2.5)	12.0 (2.0)	11.0 (2.2)
Any TEAE, n (%)	6 (85.7)	3 (50.0)	5 (83.3)	6 (100)	14 (77.8)	3 (50.0)	4 (66.7)	3 (50.0)	6 (100)	13 (72.2)
TR-TEAEs, n (%)	5 (71.4)	2 (33.3)	5 (83.3)	6 (100)	13 (72.2)	2 (33.3)	4 (66.7)	1 (16.7)	6 (100)	11 (61.1)
Mild TEAEs, n (%)	5 (71.4)	3 (50.0)	0	1 (16.7)	4 (22.2)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)	7 (38.9)
Moderate TEAEs, n (%)	1 (14.3)	0	5 (83.3)	1 (16.7)	6 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	3 (50.0)	6 (33.3)
Severe TEAEs, n (%)	0	0	0	4 (66.7)	4 (22.2)	0	0	0	0	0

7 mg/kg SC group (from 3.85 to 13.47 mg/liter on day 7), with both groups returning to normal CRP by day 17. The increases in CRP, beyond the normal range (0 to 5 mg/liter), were driven by three subjects in each group; however, two of these subjects in the rozanolixizumab 7 mg/kg SC group also had high predose CRP values (9.4 and 12.0 mg/liter). The increases in CRP were not associated with any AEs or changes in vital signs or laboratory parameters. Pyrexia of less than 39°C in the rozanolixizumab Total IV group was a TEAE related to abnormal vital signs, as reported in Table 3. All other mean hematology, clinical chemistry, urinalysis, vital signs, and electrocardiogram (ECG) results over time remained within normal ranges. No clinically relevant changes from baseline were observed after administration of IV or SC doses of rozanolixizumab.

Pharmacokinetics

Plasma concentration–time profiles for IV rozanolixizumab demonstrated nonlinear increases in plasma concentrations with dose (Table 4); elimination kinetics were characteristic of target-mediated disposition

(Fig. 2). The plasma concentration–time profile for SC rozanolixizumab was detectable only for the highest-dose group of 7 mg/kg. Comparison of the plasma concentration–time profiles and PK parameters of rozanolixizumab (7 mg/kg, administered IV and SC) demonstrated markedly lower rozanolixizumab concentrations after SC administration compared with IV administration. The variability in duration and extent of absorption observed after SC dosing was higher than with IV dosing. The nonlinear PK of rozanolixizumab precluded analyses of dose proportionality.

Pharmacodynamics

There were dose-dependent reductions in total serum IgG concentration over time with both IV and SC administration of rozanolixizumab (Fig. 3). Similar maximal reductions were observed for the rozanolixizumab IV and SC doses. The greatest mean reduction from baseline in IgG at maximum dose was normally reached by days 7 to 10, and IgG generally returned to baseline by day 57. The mean percentage reductions from baseline in total serum IgG concentration values on day 10 for the rozanolixizumab IV doses were 14.5, 33.4, and 47.6% for the

Table 3. Most common TEAEs and TR-TEAEs [≥10% of subjects receiving rozanolixizumab across all doses/routes (full analysis set)].

	IV administration					SC administration				
	Placebo (n = 7)	Rozanolixizumab 1 mg/kg (n = 6)	Rozanolixizumab 4 mg/kg (n = 6)	Rozanolixizumab 7 mg/kg (n = 6)	Rozanolixizumab Total (n = 18)	Placebo (n = 6)	Rozanolixizumab 1 mg/kg (n = 6)	Rozanolixizumab 4 mg/kg (n = 6)	Rozanolixizumab 7 mg/kg (n = 6)	Rozanolixizumab Total (n = 18)
TEAEs, n (%)	6 (85.7)	3 (50.0)	5 (83.3)	6 (100)	14 (77.8)	3 (50.0)	4 (66.7)	3 (50.0)	6 (100)	13 (72.2)
Headache	2 (28.6)	1 (16.7)	5 (83.3)	4 (66.7)	10 (55.6)	0	2 (33.3)	0	3 (50.0)	5 (27.8)
Vomiting	0	0	2 (33.3)	5 (83.3)	7 (38.9)	1 (16.7)	0	0	2 (33.3)	2 (11.1)
Nausea	0	0	2 (33.3)	5 (83.3)	7 (38.9)	1 (16.7)	0	0	0	0
Pyrexia	0	0	2 (33.3)	5 (83.3)	7 (38.9)	0	0	0	0	0
Nasopharyngitis	3 (42.9)	2 (33.3)	3 (50.0)	2 (33.3)	7 (38.9)	1 (16.7)	1 (16.7)	0	0	1 (5.6)
Cough	0	0	1 (16.7)	3 (50.0)	4 (22.2)	0	0	0	0	0
Abdominal pain	0	0	2 (33.3)	1 (16.7)	3 (16.7)	1 (16.7)	0	0	1 (16.7)	1 (5.6)
Diarrhea	0	0	1 (16.7)	2 (33.3)	3 (16.7)	1 (16.7)	1 (16.7)	0	2 (33.3)	3 (16.7)
Back pain	1 (14.3)	0	0	2 (33.3)	2 (11.1)	0	1 (16.7)	1 (16.7)	1 (16.7)	3 (16.7)
TR-TEAEs, n (%)	5 (71.4)	2 (33.3)	5 (83.3)	6 (100)	13 (72.2)	2 (33.3)	4 (66.7)	1 (16.7)	6 (100)	11 (61.1)
Headache	2 (28.6)	1 (16.7)	5 (83.3)	3 (50.0)	9 (50.0)	0	2 (33.3)	0	3 (50.0)	5 (27.8)
Vomiting	0	0	2 (33.3)	5 (83.3)	7 (38.9)	0	0	0	2 (33.3)	2 (11.1)
Nausea	0	0	2 (33.3)	5 (83.3)	7 (38.9)	0	0	0	0	0
Pyrexia	0	0	2 (33.3)	5 (83.3)	7 (38.9)	0	0	0	0	0
Cough	0	0	0	3 (50.0)	3 (16.7)	0	0	0	0	0
Nasopharyngitis	2 (28.6)	1 (16.7)	0	2 (33.3)	3 (16.7)	1 (16.7)	1 (16.7)	0	0	1 (5.6)
Abdominal pain	0	0	2 (33.3)	1 (16.7)	3 (16.7)	0	0	0	1 (16.7)	1 (5.6)
Diarrhea	0	0	1 (16.7)	2 (33.3)	3 (16.7)	0	1 (16.7)	0	2 (33.3)	3 (16.7)

1, 4, and 7 mg/kg doses, respectively, and 16.8, 25.9, and 43.4% for rozanolixizumab SC doses, respectively.

Statistically significant differences in total serum IgG concentration and AUC (IgG) were observed with rozanolixizumab 7 mg/kg (both IV and SC) when compared with placebo (pooled across all doses). The difference of effect between rozanolixizumab 7 mg/kg IV and placebo was −4.3 g/liter (95% CI, −4.8 to −3.8) for total serum IgG concentration and −110.1 g*day/liter (95% CI, −154.8 to −65.5) for AUC (IgG) ($P <$ 0.0001 for both comparisons). The difference of effect between rozanolixizumab 7 mg/kg SC and placebo was −4.2 g/liter (95% CI, −4.8 to −3.6) for total serum IgG concentration and −137.6 g*day/liter (95% CI, −192.1 to −83.2) for AUC (IgG) ($P <$ 0.0001 for both comparisons).

Dose-dependent reductions in each of the IgG subclasses (IgG1 to IgG4) were observed after both IV and SC administration of rozanolixizumab, with IgG3 serum concentrations demonstrating the most pronounced decrease (Fig. 4). The magnitude of reduction was similar across the dose groups, for both IV and SC dosing.

There was a modest decrease in mean albumin concentration over time after both IV and SC administration of rozanolixizumab (at day 10, −0.5 g/liter for rozanolixizumab 7 mg/kg IV and −2.0 g/liter for rozanolixizumab 7 mg/kg SC). However, there was no statistically significant difference from placebo-treated groups (−0.5 g/liter across pooled placebo groups), and values remained within the limits of the normal range in this study (34 to 50 g/liter). There were no significant or clinically relevant changes in any other exploratory PD variables or biomarkers of interest assessed in this study, including β2-microglobulin, a marker of inflammation and cell turnover.

Immunological analyses

After administration of rozanolixizumab, no significant changes over time were observed in concentrations of immunoglobulin isotypes (IgA, IgD, IgE, or IgM), complement proteins (C3, C4, C3d, or SC5b-9), or mononuclear cell subtypes [total T cells (CD3), T helper cells (CD3 and CD4), T cytotoxic cells (CD3 and CD8), B cells (CD19), and natural killer cells (CD16 and CD56)]. There were no changes in the titers of

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Table 4. PK parameters for rozanolixizumab (PK-PPS). $AUC_{(0-t)}$, area under the concentration–time curve between time 0 and time of the last detectable concentration; CV, coefficient of variation; GeoMean, geometric mean; max, maximum; min, minimum; NC, not calculated; t_{max}, time of observed C_{max}. GeoMeans and CVs were only calculated if at least two-thirds of the parameters were properly determined parameters (that is, not calculated and not flagged).

Parameter	Statistic	IV administration			SC administration		
		Rozanolixizumab 1 mg/kg ($n = 6$)	Rozanolixizumab 4 mg/kg ($n = 6$)	Rozanolixizumab 7 mg/kg ($n = 6$)	Rozanolixizumab 1 mg/kg ($n = 6$)	Rozanolixizumab 4 mg/kg ($n = 6$)	Rozanolixizumab 7 mg/kg ($n = 6$)
$AUC_{(0-t)}$ (hour*μg/ml)	GeoMean	55.21	2213	5753	NC	NC	643.3
	GeoCV (%)	54.8	21.3	20.5	NC	NC	75.6
C_{max} (μg/ml)	GeoMean	11.11	89.33	154.5	NC	NC	12.41
	GeoCV (%)	17.0	16.7	19.7	NC	NC	72.2
t_{max} (hour)	Median (min, max)	1.02 (0.98, 1.03)	2.52 (1.02, 4.12)	1.01 (1.00, 6.03)	NC	NC	48.15 (36.0, 71.9)

A

B
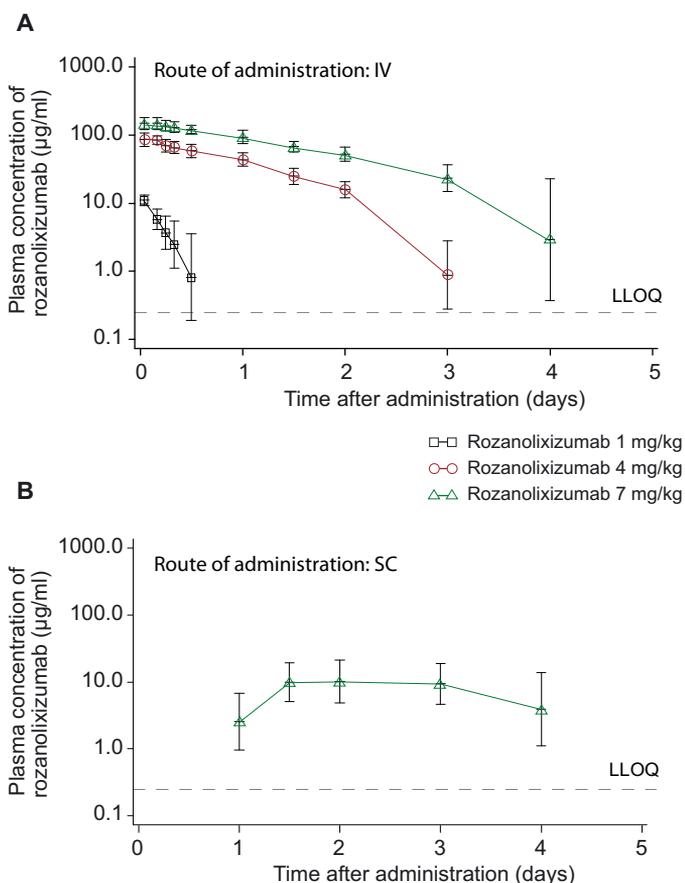
Fig. 2. PK of single-dose rozanolixizumab in healthy subjects. Plasma concentration–time profiles for rozanolixizumab by IV (**A**) or SC (**B**) administration. Geometric means and 95% confidence intervals (CIs) are shown; $n = 6$ in each group (PK-PPS analysis). Geometric mean and 95% CI were only calculated if at least two-thirds of the data were above lower limit of quantification (LLOQ) (0.25 μg/ml) at the respective time point. Time points at 12, 72, and 96 hours for IV administration contain one or more values below the limit of quantification replaced by LLOQ/2. The x axis was truncated to 5 days after administration because of concentrations being below the LLOQ.

specific antibodies, as determined by measurements of tetanus and influenza A–specific IgG antibodies after single administration of rozanolixizumab. There were no changes in serum cytokine analyses after SC doses of rozanolixizumab except for transient changes in some subjects; small increases that were considered insignificant in concentrations of IL-7 (interleukin-7), IL-8, TNFα (tumor necrosis factor–α), MCP-1 (monocyte chemotactic protein-1), and MIP-1β (macrophage inflammatory protein-1β) were observed after IV dosing with rozanolixizumab (7 mg/kg) (fig. S2).

Antidrug antibody (ADA)–positive subjects were detectable across all rozanolixizumab treatment groups: one, three, and five subjects in the IV 1, 4, and 7 mg/kg groups and three, three, and two subjects in the SC 1, 4, and 7 mg/kg groups, respectively. However, detectable ADAs (above the limit of quantification of the assay) were observed in only five subjects and were not related to dose (detectable between 0.256 and 1.303 units/ml). There was no apparent correlation between ADAs and observed reductions in IgG concentrations or between ADAs and the PK/exposure of rozanolixizumab.

DISCUSSION

We report results from a randomized, subject-blind, investigator-blind, placebo-controlled, single dose–escalating phase 1 clinical trial of rozanolixizumab in healthy subjects. Results indicate the potential of this approach as a new therapeutic concept for autoimmune diseases.

Before human testing, the safety, PK, and PD of rozanolixizumab were assessed in cynomolgus monkeys, a pharmacologically relevant toxicology species. Rozanolixizumab was well tolerated in cynomolgus monkeys; notably, there were no occurrences of infection despite a 75 to 90% reduction of IgG for 4 weeks. Rozanolixizumab demonstrated specificity to IgG alone, with no changes observed in circulating concentrations of IgM or IgA. This is in contrast to currently available therapies, which can affect a range of immune modulators (7). No effect was observed on B cells or T cells, suggesting that rozanolixizumab will not decrease the potential of the immune system to mount an antibody response to neoantigens. These results supported the progression of rozanolixizumab into a phase 1 study in healthy subjects.

In healthy subjects, rozanolixizumab demonstrated an acceptable safety profile after single administration of doses of up to 4 mg/kg IV
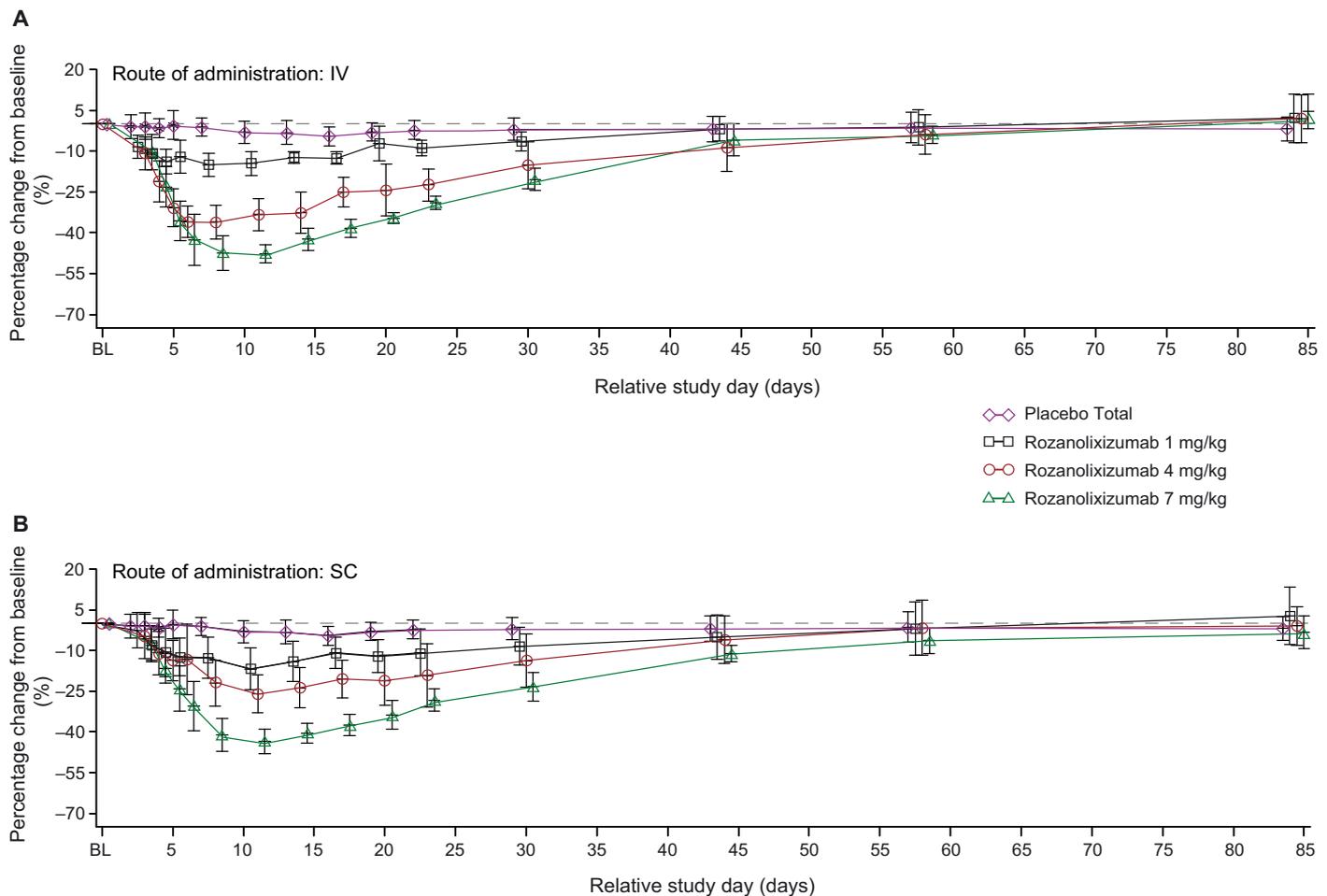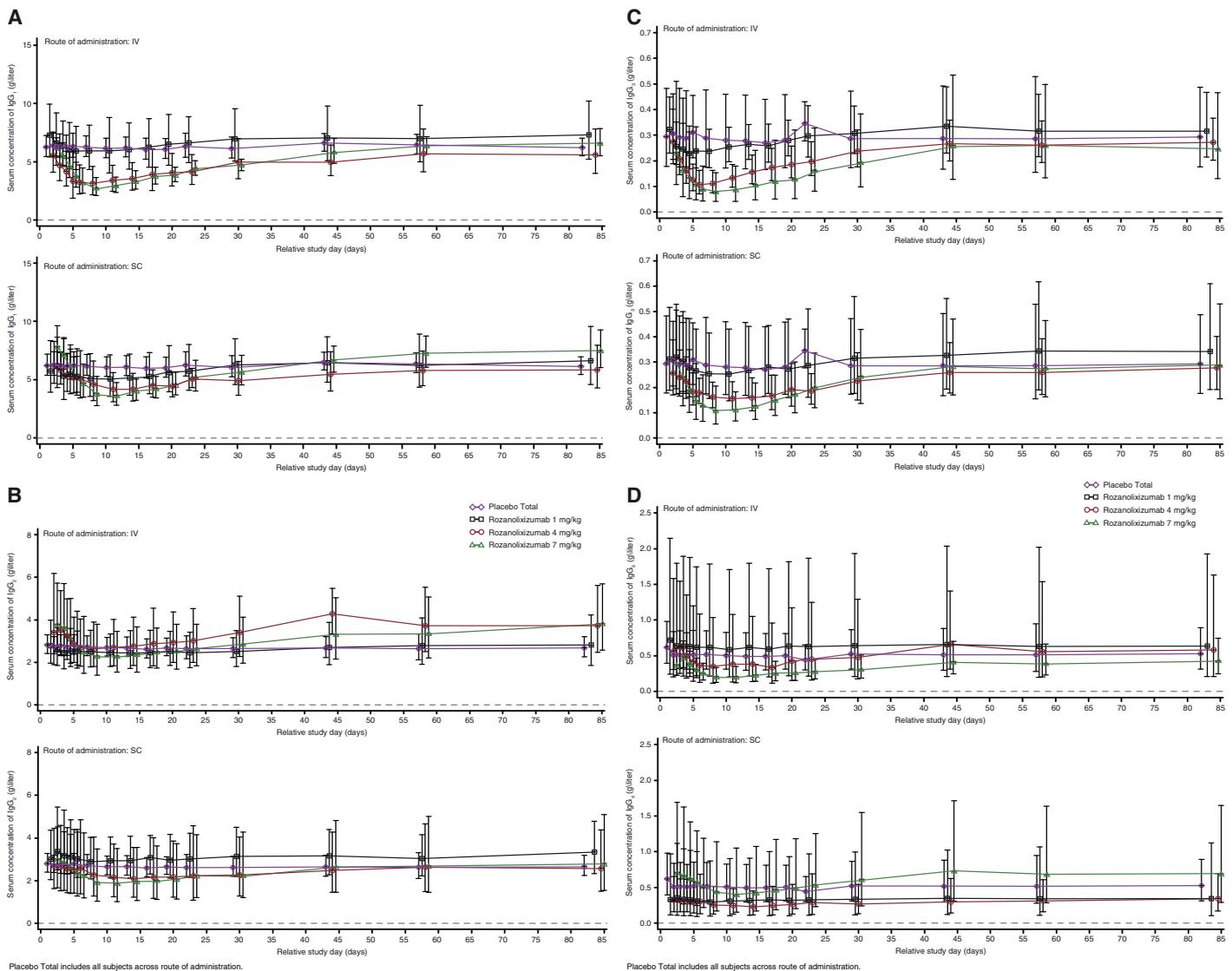
Fig. 3. The effect of single-dose rozanolixizumab on IgG concentration in healthy subjects. Mean percentage change from baseline in serum IgG concentrations over time, after a single dose of rozanolixizumab by IV (**A**) or SC (**B**) administration. Baseline is defined as the predose day 1 concentration. Mean percentage change and SD are shown; $n = 13$ for placebo and $n = 6$ in each rozanolixizumab group (full analysis set).

BL, baseline.
Placebo Total includes all subjects across route of administration.

and 7 mg/kg SC. At 7 mg/kg IV, severe TEAEs of headache and back pain were reported; all other reported TEAEs were mild or moderate in intensity. The rozanolixizumab dose escalation in this study was based on the safety and tolerability data, PK data, and the observed reduction of IgG concentrations in serum after the previous doses. Escalation was halted at the 7 mg/kg IV dose because the AE profile did not support higher exposures in healthy subjects. Instead, subsequent rozanolixizumab doses used in this study were SC administration of 1, 4, and 7 mg/kg. After review of the safety data from all rozanolixizumab treatment groups, it was concluded that the study had provided sufficient data on single doses of IV and SC rozanolixizumab to support progression into multiple-dose studies in patients.

The safety data reported here for rozanolixizumab in healthy subjects contrast with findings from the preclinical toxicology cynomolgus monkey study. No clinically related AEs were reported in cynomolgus monkeys (despite twice weekly doses of up to 150 mg/kg IV and SC resulting in up to 90% reduction in total IgG), so no (or a low) incidence of AEs as a result of decrease in IgG was anticipated in human subjects. The reasons for the different rozanolixizumab safety profiles between

cynomolgus monkeys and human subjects are not clear (because rozanolixizumab has equivalent potency in cynomolgus monkeys and humans). The SC route of administration of rozanolixizumab up to 7 mg/kg in humans demonstrated a more favorable safety and tolerability profile than the IV route, and there were no reports of infusion site or hypersensitivity reactions. The AEs commonly observed at the 7 mg/kg IV dose (headache, vomiting, nausea, and pyrexia) were similar in nature to those observed with immunomodulatory doses of IVIg (4) and were lower in severity and frequency in the 7 mg/kg SC dose group; nausea and pyrexia were not observed at all after SC dosing. It should be noted that no premedications or comedications were used in this study for prophylaxis of these AEs. Lower incidences of systemic AEs are well recognized for SCIg (SC immunoglobulin) versus IVIg (29, 30). Similarly, no severe TEAEs occurred after SC dosing of rozanolixizumab, in contrast to IV dosing.

The IgG subclasses (IgG1, IgG2, and IgG4) all have a similar half-life of ~21 days with a shorter half-life of ~7 days for IgG3 (31, 32). However, IgG half-lives may be prolonged in some immune disorders (33). After rozanolixizumab administration in healthy subjects, the

Fig. 4. The effect of single-dose rozanolixizumab on the concentration of IgG subtypes in healthy subjects. Serum concentrations of IgG1 (**A**), IgG2 (**B**), IgG3 (**C**), and IgG4 (**D**) after a single dose of placebo or rozanolixizumab by IV or SC administration. Geometric means and 95% CIs are shown; $n = 13$ for placebo and $n = 6$ in each rozanolixizumab group (full analysis set).

most pronounced decrease that we observed was for IgG3, but dose-dependent reductions in total IgG concentrations and IgG subclasses 1 to 4 were observed after both IV and SC administration. Pathogenic and nonpathogenic IgG have the same Fc domains (which define FcRn binding); the only difference between them are in the antigen specificity (that is, the Fab domain structure). Pathogenic and nonpathogenic IgG molecules are therefore expected to behave similarly, so it is possible that rozanolixizumab will induce remission by rapid clearance of pathogenic IgG in patients with autoantibody-mediated disease (7).

In healthy subjects, IgG concentrations in the serum were reduced by up to 50% in this study, which is similar to the 50 to 60% reductions observed after plasma exchange (34, 35). The safety profile of IV doses of 7 mg/kg precluded the use of higher doses in this study of healthy individuals; however, the effect of this treatment in patients with autoantibody-mediated disease is not yet known.

The observed reductions in serum IgG concentrations in the current study persisted for weeks, with maximal reductions achieved by days 7 to 10 and thereafter gradually returning to baseline by day 57. This prolonged decrease may be attributed to the rapid blockade of FcRn by rozanolixizumab, as well as the persistence of reduced recycling of IgG. The rate of IgG recovery after a single treatment compares favorably with plasma exchange, in which plasma IgG returns to pretreatment concentrations within 2 weeks after one single exchange (7). With plasma exchange, a rebound in plasma IgG and autoantibodies has been observed soon after the initial reduction, because of renewed synthesis of IgG, and relatively rapid redistribution from extravascular to intravascular compartments (34).

Blockade of the FcRn with rozanolixizumab selectively reduced serum IgG concentrations with no significant effect on IgA, IgD, IgE, IgM, complement, or other immune-related biomarkers. This contrasts

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with the reductions in IgA and IgM associated with standard plasma exchange, and also the many known side effects of steroids and conventional immunosuppression (3, 36–39). We saw no changes in the concentration of specific antibodies generated by immunization (tetanus and influenza A), so no concerns were raised about increased risk of infection through compromised vaccination status, although this will require confirmation in longer, multiple-dose studies.

ADAs were detected in subjects across all treatment groups, but concentrations were low and above the limit of quantification in only five subjects, with no apparent correlation with dose or route of administration. Although high ADAs can be associated with significant effects on PK profiles, this is not normally the case with low ADAs (40). It should be noted that only single doses of rozanolixizumab were administered in this study; therefore, ADA would not be expected to affect PK because it would take 7 to 10 days for ADA concentrations to rise. The ADA profile after multiple drug doses in planned phase 2 studies will provide a more comprehensive picture of ADA effects on rozanolixizumab PK and subsequent efficacy.

Rozanolixizumab has demonstrated therapeutic potential, exemplified by the long duration of IgG reduction observed after a single dose; however, the long-term clinical effects are as yet unknown. The number of participants in this study was small, and all subjects in this phase 1 study were healthy volunteers rather than patients, so these promising results must be interpreted carefully. The safety, PK, PD, and immunogenicity of rozanolixizumab will now be evaluated in phase 2 studies of patients with IgG autoantibody-related conditions, who may demonstrate different responses to the treatment.

FcRn blockade offers several potential advantages in treating autoimmune diseases, including the potential for an improved safety profile (compared with current standards of care such as therapeutic plasma exchange), lack of unwanted effects on non-IgG isotypes, avoidance of exposure to blood products, and an independence of the finite supply of IVIg. If shown to be effective in larger clinical studies, FcRn inhibition therapy may provide a more cost-effective long-term option, especially if given SC, because of the lower clinical costs associated with outpatient or at-home administration.

The data reported here provide clinical evidence for the humanized, high-affinity, monoclonal IgG antibody rozanolixizumab as a potential new treatment concept for autoimmune diseases. The antibody provides a means of selectively inhibiting IgG (but not albumin) binding to human FcRn, so reducing IgG recycling, and rapidly clearing potentially pathogenic IgG. Our study found SC administered rozanolixizumab to be better tolerated than IV administration, based on the safety, PK, and PD data obtained; planned phase 2 studies will therefore use SC dosing. A phase 2 study in patients with primary ITP (NCT02718716) and MG (NCT03052751) is now being undertaken to investigate this concept further.

MATERIALS AND METHODS
Four-week toxicity study in cynomolgus monkeys
Study design
Rozanolixizumab bound to, and inhibited the pharmacological activity of, cynomolgus monkey and human FcRn with similar affinity and potency (26), confirming the cynomolgus monkey as a pharmacologically relevant species for safety assessment.

Male and female cynomolgus monkeys were injected with rozanolixizumab (50 or 150 mg/kg SC or 150 mg/kg IV) every 3 days for 4 weeks (Table 1), followed by an 8-week treatment-free recovery period.

Clinical signs, body weight, estimated food consumption, blood pressure measurements, electrocardiography, respiratory rate and depth, neurobehavior (Functional Observational Battery, modified for nonhuman primates), clinical pathology including weekly albumin determination and urinalysis, as well as blood and tissue immunophenotyping (bone marrow, left axillary lymph node, and spleen) were assessed. Complete necropsies were performed on all animals with recordings of macroscopic abnormalities, organ weights, and microscopic examination. Blood was collected for intensive bioanalysis of rozanolixizumab, total plasma IgG concentration, and ADA.

This good laboratory practice (GLP)–compliant study was conducted at Covance Laboratories, in compliance with the German Chemical Law (GLP regulations, as outlined in Annex 1 to §19a Chemikaliengesetz) and with the Organisation for Economic Co-Operation and Development's Principles of GLP, ENV/MC/CHEM (98) 17 (revised in 1997, issued January 1998). All procedures in the study were in compliance with the German Animal Welfare Act, were approved by the local Institutional Animal Care and Use Committee, and were in consideration of European Commission Recommendation 2007/526/EC on guidelines for the accommodation and care of animals used for experimental and other scientific purposes (Appendix A of Convention ETS 123).

Assay methodology
To quantify total IgG in monkey plasma, samples (10 µl) were mixed with an internal standard (isotopically labeled unique IgG peptide; Eurogentec), denatured, and trypsin-digested. After digestion, the samples were diluted, and the resulting signature peptides [analyte: H2N-TTPPVLDSDGSYFLYSK-COOH; internal standard: H2N-TTPP(U-13C5, 15N)VLDSDGSYFLYSK-COOH] were analyzed by reversed-phase ultrahigh-pressure liquid chromatography coupled with tandem electrospray mass spectrometry detection. The assay had an LLOQ of 0.102 mg/ml and an upper limit of quantification of 15.345 mg/ml. The assay did not distinguish between endogenous IgG and administered rozanolixizumab; hence, a transient peak associated with rozanolixizumab was observed shortly after dosing.

Rozanolixizumab in cynomolgus monkey plasma was quantified using a validated Meso Scale Discovery (MSD) assay (41) at Quotient Bioresearch, now LGC, with an LLOQ of 0.31 µg/ml. Briefly, rozanolixizumab was captured by biotinylated FcRn immobilized on a streptavidin-coated MSD plate and revealed using commercially available goat anti-human κ antibody (NB7463, Novus Biologicals) that had been conjugated to SULFO-TAG in-house (qualified assay developed by UCB Pharma). The electrochemoluminescence signal was proportional to the amount of rozanolixizumab in the sample. Detection of ADA was undertaken using a similarly validated MSD assay run at LGC. Briefly, samples were premixed with biotinylated rozanolixizumab and rozanolixizumab conjugated to SULFO-TAG. Anti-rozanolixizumab forms complexes with the conjugated reagents, which were subsequently immobilized on a streptavidin MSD plate. After a wash step, the electrochemoluminescence reaction was completed using Read Buffer. The calibrator used in the assay was pooled ADA harvested from cynomolgus monkeys dosed with the V-region Fab′ of rozanolixizumab. Data were read from the calibrator curve to give a semiquantitative measure of units per milliliter.

Phase 1 study
Study design
This was a randomized, subject-blind, investigator-blind, placebo-controlled, single dose–escalating study of rozanolixizumab administered by IV or SC infusion to healthy subjects. A 4-week screening period (day −28 to day −2) was followed by a 6-day treatment period

(day −1 to day 5). Subjects received a single dose of placebo (0.9% sodium chloride aqueous solution) or rozanolixizumab as a 1-hour IV or SC infusion on day 1 of the treatment period and remained at the clinical site until day 5. The posttreatment safety follow-up period ran from day 6 until the end of the clinical study (day 85).

Subjects were planned to be randomized to seven cohorts to receive a single IV or SC dose of rozanolixizumab or placebo in a ratio of 3:1, with six subjects receiving rozanolixizumab and two subjects receiving placebo in each cohort. It was planned to randomize 56 subjects—8 to each of the seven cohorts. Within each cohort, a sentinel group of two subjects were randomized to receive rozanolixizumab or placebo in a 1:1 ratio. Once safety was confirmed for these two sentinel subjects over a 48-hour observation period, the remaining six subjects in the same cohort were randomized to receive rozanolixizumab or placebo in a ratio of 5:1.

Dose escalation between cohorts
In the first three cohorts, IV doses of placebo or rozanolixizumab (1, 4, and 7 mg/kg) were evaluated. The routes of administration (IV versus SC) and doses for the last four planned cohorts were to be adapted on the basis of safety, PK, and PD data from these first three cohorts.

The dosing options for subsequent cohorts were as follows: proceed to a higher dose, repeat the same dose (that is, expand the cohort), reduce the dose, or alter the route of administration (IV versus SC). All decisions on dose escalation between cohorts were made by the Safety Review Group. Because sufficient data on the emergent safety and tolerability profiles of rozanolixizumab were collected in the earlier cohorts, the planned dose escalation between the sixth and seventh cohorts did not occur. Therefore, the final study included six placebo-controlled treatment cohorts: rozanolixizumab 1, 4, or 7 mg/kg, each IV or SC.

Cohort discontinuation and maximum tolerated dose
A cohort would be discontinued if a clinically significant event occurred that contraindicated the dosing of any more subjects or if the Safety Review Group judged discontinuation necessary for any medical, safety, or regulatory reasons. Furthermore, no dose escalation was to occur if the maximum tolerated dose was reached, as defined by the following criteria: one or more subjects experiencing a serious infective episode requiring hospitalization and IV antibiotics; more than one subject experiencing absolute neutrophil count $<1.0 \times 10^9$/liter, absolute lymphocyte count $<0.5 \times 10^9$/liter, increase in alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal range, increase in serum creatinine >1.5 times the upper limit of normal or >3 times the baseline value, severe infusion reaction requiring corticosteroids/epinephrine, or change in QTcF >60 ms and QTcF absolute value of >500 ms.

Study subjects
Subjects were healthy male and female subjects aged between 18 and 65 years with a body mass index between 18 and 30 kg/m². All prescription and nonprescription medicines (except paracetamol and contraceptive methods) were prohibited from day −1 until the end of the posttreatment safety follow-up period (day 85), unless required to treat an AE. Prophylactic antimicrobial therapy and IV IgG could be considered in the case of prolonged hypogammaglobulinemia.

Study objectives
The primary study objective was to evaluate the safety and tolerability of single ascending doses of rozanolixizumab administered by IV or SC infusion in healthy subjects. Secondary objectives were to assess the PK of single doses of rozanolixizumab administered IV and SC and the effect of single doses of rozanolixizumab on total circulating IgG concentrations and IgG subclass concentrations in circulation. Exploratory analyses included immunologic investigations.

Safety
Safety measurements included reporting of AEs, physical examination, vital signs, 12-lead ECG, continuous ECG Holter recording, clinical chemistry, hematology, coagulation, and urinalysis. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. AEs were followed up until they resolved, had stable sequelae, were determined by the investigator to be no longer clinically significant, or until the subject was lost to follow-up.

PK analysis
Blood samples for PK analysis were taken before dosing, immediately after the end of infusion, at 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dose, and on days 7, 10, 13, 16, 19, 22, 29, 43, 57, and 85. A qualified MSD assay with an LLOQ of 0.25 μg/ml was used to determine unbound concentrations of rozanolixizumab in plasma. Briefly, rozanolixizumab was captured by biotinylated FcRn immobilized on an MSD plate and revealed using commercially available goat anti-human κ antibody that had been conjugated to SULFO-TAG in-house. The electrochemoluminescence signal was proportional to the amount of rozanolixizumab in the sample. The PK variables determined for rozanolixizumab were C_{max}, $AUC_{(0–t)}$, and t_{max}.

PD analysis
Blood samples for PD analyses were taken before dosing, at 24, 48, 72, and 96 hours after dose, and on days 7, 10, 13, 16, 19, 22, 29, 43, 57, and 85. PD measurements analyzed as secondary variables were concentrations of total serum IgG concentration, total endogenous IgG without ADA, and IgG subclasses (IgG1 to IgG4). Total serum IgG concentration was quantified using an immune turbidimetry method with an LLOQ of 0.3 mg/ml (Roche/Hitachi cobas c system). Exploratory PD variables were measures of total protein, albumin, α-globulin, β-globulin, and β2-microglobulin.

Immunologic measurements
The following immunogenicity/immunologic measurements were analyzed as exploratory variables: concentrations of immunoglobulin isotypes (IgA, IgD, IgE, and IgM), serum complement concentrations (C3, C3d, C4, and SC5b-9), mononuclear cell subtypes (CD3, CD4, CD8, CD16, CD19, CD45, and CD56), tetanus- and influenza A virus–specific IgG antibodies, cytokine concentrations, ADA status, anti-IgM antibody status, and other exploratory biomarkers. A qualified MSD assay with an LLOQ of 0.25 units/ml was used to determine ADA status. Briefly, ADA in samples was captured by biotin-conjugated rozanolixizumab (surface-bound) and revealed by rozanolixizumab conjugated to SULFO-TAG, during an overnight mixing step with an electrochemoluminescence readout. The assay featured a screening cut point, with ADAs reported as relative mass units.

Analysis sets
The full analysis set included all randomized subjects who received any dose of rozanolixizumab or placebo. The full analysis set was used for demographics, safety, PD summaries, and all data listings.

The PK-PPS included subjects who received any dose of rozanolixizumab or placebo and had no important protocol deviations affecting the PK variables. The evaluable population for the PK noncompartmental analysis consisted of the PK-PPS subjects for whom a sufficient number of samples were available to determine at least one PK variable (and therefore did not include subjects who received placebo). The PK and ADA analyses were carried out on the PK-PPS.

The PD-PPS included subjects who received any dose of rozanolixizumab or placebo and had no important protocol deviations affecting the PD variables. All PD end points were analyzed using the full analysis set.

Standard protocol approvals, registration, and patient consents

Informed consent was obtained from all study subjects. The study was conducted in accordance with the applicable regulatory and International Council for Harmonisation–Good Clinical Practice requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws and regulations of the study sites.

Statistical methods

On the basis of the planned seven-cohort study design, a sample size of at least 56 subjects (8 subjects per cohort) was expected to be appropriate to explore the safety and PK of rozanolixizumab while limiting exposure to a minimum number of subjects. Assuming a mean IgG concentration of 11.2 g/liter with placebo (19) and 2.8 g/liter after rozanolixizumab treatment, with common SD of 2.5, a sample size of 6 subjects at the highest rozanolixizumab dose and 14 placebo subjects (pooled across all cohorts) provided more than 90% power to detect a 75% reduction in IgG at 5% significance.

Data were summarized by treatment group and by nominal time point where appropriate. Treatment groups with different routes of administration were listed and summarized separately. For continuous variables, summary statistics included number of observations (n), mean, median, SD, minimum, maximum, and 95% CIs assuming a Student's t distribution. Coefficient of variation, geometric mean, and 95% CI of the geometric mean were also presented in the descriptive statistics for PK variables. Total serum IgG concentration and baseline-corrected AUC (IgG) were analyzed by analysis of covariance, with baseline data as a covariate and dose as a fixed effect for IV and SC cohorts, separately. A two-sided test at 5% significance was used to assess the difference between the highest rozanolixizumab dose and placebo. Categorical end points were summarized using n, frequency, and percentages. In general, missing data were not imputed.

Statistical evaluation was performed by PAREXEL. All analyses were performed using SAS version 9.3 (SAS Institute). The PK variables for rozanolixizumab were calculated by UCB with noncompartmental analysis methods using Phoenix WinNonlin version 6.4.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/9/414/eaan1208/DC1
Fig. S1. The effect of SC or IV dosing of rozanolixizumab (50 and 150 mg/kg every 3 days for 28 days) on mean plasma IgG concentrations in cynomolgus monkeys.
Fig. S2. Changes in selected plasma cytokine concentrations after single-dose rozanolixizumab in healthy subjects.

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Citation: P. Kiessling, R. Lledo-Garcia, S. Watanabe, G. Langdon, D. Tran, M. Bari, L. Christodoulou, E. Jones, G. Price, B. Smith, F. Brennan, I. White, S. Jolles, The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study. *Sci. Transl. Med.* **9**, eaan1208 (2017).

Kiessling *et al.*, *Sci. Transl. Med.* **9**, eaan1208 (2017)   1 November 2017

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Science Translational Medicine

The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study

Peter Kiessling, Rocio Lledo-Garcia, Shikiko Watanabe, Grant Langdon, Diep Tran, Muhammad Bari, Louis Christodoulou, Emma Jones, Graham Price, Bryan Smith, Frank Brennan, Ian White and Stephen Jolles

The benefits of not recycling

Autoimmune diseases mediated by pathogenic IgG can be treated by B cell–depleting therapies or IVIg, but such therapies are costly and not without side effects. IgG is recycled and kept in the circulation partially through the activity of the neonatal Fc receptor (FcRn). Kiessling *et al.* report the development of a monoclonal antibody to inhibit FcRn, which should lower IgG levels, thereby reducing pathogenic IgG. This antibody was tested for safety and efficacy in nonhuman primates as well as humans. The antibody was well-tolerated and substantially reduced circulating IgG. These promising results warrant further testing in autoimmune individuals.

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