A Randomized, Double-Blind, Placebo-Controlled Phase 1 Study of the Pharmacokinetics and Pharmacodynamics of REGN3918, a Human Antibody Against Complement Factor C5, in Healthy Volunteers

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Background

Dysregulation of complement activity has a driving role in several diseases, in which complement factor C5 is a clinically validated target: paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome and a subset of patients with myasthenia gravis. Although eculizumab has been demonstrated to be an effective therapy for these conditions, treatment is burdensome as the drug must be administered by intravenous (IV) infusion every 2 weeks to maintain efficacy. Moreover, it is now recognized that as many as 20% of PNH patients on treatment at the approved maintenance dose (900 mg IV every 2 weeks) require significant increases in dose or dose frequency due to breakthrough hemolysis secondary to incomplete inhibition of C5.[1,2] Additionally, in rare instances eculizumab is ineffective due to polymorphic variation at Arg885 such that the C5 protein is not bound by eculizumab.[3] Thus, there is a need to provide more durable inhibition of hemolysis, and to improve the dosing regimen, either by development of a convenient subcutaneous (SC) formulation, or by prolonging the IV dosing interval. Currently, a fully human monoclonal antibody to C5 is under development, selected to address the unmet needs in PNH and other diseases in which tissue damage is mediated by terminal complement pathway activity.

Introduction

REGN3918, or pozelimab (International Nonproprietary Name), is a fully human monoclonal immunoglobulin G4P antibody directed against the terminal complement protein C5 which inhibits terminal complement activation by blocking C5 cleavage, thereby blocking the formation of the membrane attack complex (MAC; C5b-9). REGN3918 binds with high affinity to wild-type and variant (R885H/C) human C5. REGN3918 was well-tolerated in monkey toxicology studies with up to 26 weeks of dosing at up to 100 mg/kg/wk.[4] This finding was supportive of conducting this first-in-human study of REGN3918 in healthy volunteers.

Objective

- The primary objective of this study (Clinicaltrials.gov Identifier: NCT03115996) was to evaluate the safety and tolerability of REGN3918 administered in healthy volunteers, using both single ascending IV and SC doses and a multiple dose regimen consisting of an IV loading dose plus multiple weekly SC doses.
- The secondary objectives of this study were to assess the pharmacokinetic and pharmacodynamic profile of REGN3918.

Methods

A total of 57 subjects were randomized (56 received study treatment) to 4 sequential ascending IV dose cohorts plus 2 sequential ascending SC cohorts, followed by 1 multiple dose cohort (consisting of an IV loading dose and weekly SC doses). Each cohort consisted of 8 subjects randomized to receive REGN3918 or placebo (6 active: 2 placebo). REGN3918 was administered as follows:

- Cohort 1: 1 mg/kg IV, single dose
- Cohort 2a: 3 mg/kg IV, single dose
- Cohort 2b: 300 mg SC, single dose
- Cohort 3a: 10 mg/kg IV, single dose
- Cohort 3b: 600 mg SC, single dose
- Cohort 4: 30 mg/kg IV, single dose
- Cohort 5: Loading dose of 15 mg/kg IV followed by 4 repeat SC doses of 400 mg administered once weekly for 4 weeks.

An adaptive design was implemented to allow for dose level and dosing interval adjustment utilizing in-study pharmacokinetic and pharmacodynamic measures. The pharmacodynamic profile of REGN3918 was assessed utilizing a sheep red blood cell complement activity assay (CH50 assay) as well as serum concentrations of total C5.

Results

Baseline Characteristics

Baseline characteristics of subjects are summarized in **Table 1** according to treatment group.

Table 1. Summary of demographic and baseline characteristics of subjects by REGN3918 dose regimen and route of administration (safety analysis set)

		REGN3918						
	Placebo[a] (n=14)	1 mg/kg IV (n=6)	3 mg/kg IV (n=6)	10 mg/kg IV (n=6)	30 mg/kg IV (n=6)	300 mg SC (n=6)	600 mg SC (n=6)	15 mg/kg IV + 400 mg SC[b] (n=6)
Age, years, mean (SD)	36.5 (8.9)	35.5 (7.1)	36.7 (10.7)	39.3 (12.1)	35.3 (12.3)	24.5 (4.1)	32.5 (9.1)	40.0 (6.8)
Sex, male, n (%)	9 (64.3)	2 (33.3)	3 (50.0)	3 (50.0)	1 (16.7)	3 (50.0)	2 (33.3)	2 (33.3)
Race, n (%)								
White	12 (85.7)	4 (66.7)	4 (66.7)	5 (83.3)	6 (100)	5 (83.3)	4 (66.7)	5 (83.3)
Black or African American	2 (14.3)	1 (16.7)	1 (16.7)	1 (16.7)	0	0	1 (16.7)	0
Asian	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)
Other	0	1 (16.7)	1 (16.7)	0	0	0	0	0
Weight, kg, mean (SD)	73.9 (10.7)	69.9 (16.8)	67.8 (8.6)	68.8 (12.7)	64.5 (3.1)	74.7 (11.6)	75.5 (21.1)	71.2 (6.7)

[a]Pool of all administration types.
[b]Multiple dose study drug administration given as single dose of 15 mg/kg IV + 400 mg SC once weekly for 4 weeks.
IV, intravenous; n, number of dosed subjects; SC, subcutaneous; SD, standard deviation.

Pharmacokinetics and Pharmacodynamics

Figure 1. Mean (± SE) serum concentrations of total REGN3918 versus nominal time by treatment group

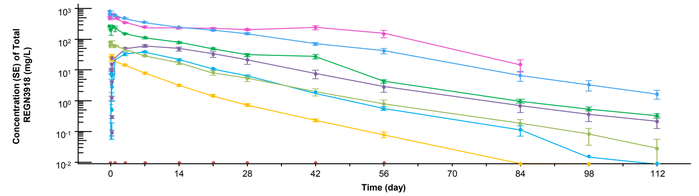
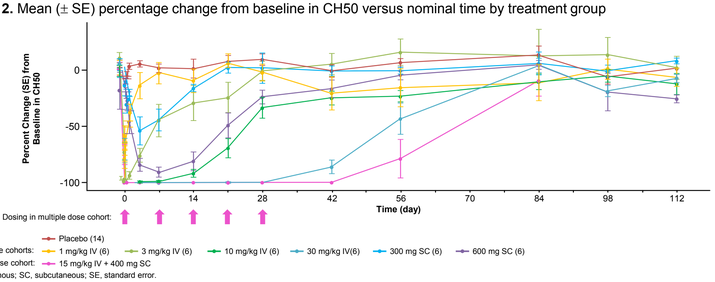


Figure 2. Mean (± SE) percentage change from baseline in CH50 versus nominal time by treatment group



REGN3918 exhibited dose-dependent increases in exposure in serum, with a trend toward prolonged serum concentrations at IV doses ≥10 mg/kg (**Figure 1**). Following SC administration, concentrations of REGN3918 in serum peaked at 4–8 days post-dose, and bioavailability was estimated as approximately 70%. REGN3918 exposure led to dose-dependent inhibition of CH50. In all 4 IV dosing cohorts, suppression of hemolysis was observed at 15 minutes post-injection. Maximal suppression of hemolysis was achieved with ≥3 mg/kg dosing. At 30 mg/kg, maximal suppression of hemolysis was maintained for ≥4 weeks, consistent with observed prolonged REGN3918 concentrations following this dose. In the 2 SC cohorts, peak suppression of hemolysis was observed 3–7 days post dosing, again consistent with observed peak concentrations of REGN3918 in serum. In the multiple dose Cohort 5, complete suppression of CH50 was observed over the 4-week dosing period and 2 weeks post the last dosing (**Figure 2**).

Safety

REGN3918 was found to be well tolerated in single doses of up to 30 mg/kg IV and 600 mg SC (**Table 2**). The multiple dose Cohort 5 has completed dosing in all subjects and has completed all safety follow-up. A single serious adverse event, salpingitis, occurred in 1 subject in Cohort 5; the serious adverse event occurred after completion of dosing and completely resolved after treatment with a short course of antibiotics.

Table 2. Overview of treatment-emergent adverse events (safety analysis set)

		REGN3918						
n (%) of subjects	Placebo[a] (n=14)	1 mg/kg IV (n=6)	3 mg/kg IV (n=6)	10 mg/kg IV (n=6)	30 mg/kg IV (n=6)	300 mg SC (n=6)	600 mg SC (n=6)	15 mg/kg IV + 400 mg SC[b] (n=6)
Any TEAE	13 (92.9)	5 (83.3)	4 (66.7)	5 (83.3)	6 (100)	4 (66.7)	6 (100)	3 (50.0)
Any serious TEAE	0	0	0	0	0	0	0	1 (16.7)
Any severe TEAE	0	0	0	0	0	0	0	1 (16.7)
Any TEAE leading to study withdrawal, discontinuation or death	0	0	0	0	0	0	0	0
TEAEs occurring in ≥20% of subjects in any treatment group by preferred term[c]								
Diarrhea	4 (28.6)	0	1 (16.7)	0	1 (16.7)	0	1 (16.7)	0
Dizziness	3 (21.4)	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (16.7)	0	0
Nasopharyngitis	3 (21.4)	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)	1 (16.7)	0
Nausea	3 (21.4)	0	0	1 (16.7)	0	1 (16.7)	2 (33.3)	0
Vomiting	3 (21.4)	0	0	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	0
Headache	2 (14.3)	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)
Oropharyngeal pain	1 (7.1)	0	0	0	2 (33.3)	0	0	1 (16.7)
Candida infection	0	0	0	0	2 (33.3)	0	0	0
Pollakiuria	0	0	0	0	0	0	0	2 (33.3)

[a]Pool of all administration types.
[b]Multiple dose study drug administration given as single dose of 15 mg/kg IV + 400 mg SC once weekly for 4 weeks.
[c]MedDRA (Version 21.0) coding dictionary applied.
IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Conclusion

- REGN3918 was generally well tolerated in both single ascending IV and SC dose administration as well as in a single IV loading dose followed by 4 consecutive weekly dose administrations.
- Rapid and maximal suppression of complement activity as measured by the sheep red blood cell CH50 assay was demonstrated for IV doses with ≥3 mg/kg dosing. At 30 mg/kg, maximal suppression of hemolysis was maintained for ≥4 weeks.
- A regimen of 15 mg/kg IV loading dose followed by 4 consecutive weekly 400 mg SC doses maintained suppression of CH50 throughout the dosing period and 2 weeks post the last dosing.

References

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Disclosures

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