MSJ Experimental Translational Clinical

Original Research Paper

A double-blind, placebo-controlled, single ascending-dose study of remyelinating antibody rHIgM22 in people with multiple sclerosis

Multiple Sclerosis Journal—Experimental, Translational and Clinical

October-December 2017, 1–11

DOI: 10.1177/2055217317743097

Andrew Eisen, Benjamin M Greenberg*, James D Bowen*, Douglas L Arnold* and Anthony O Caggiano

Abstract

Objective: The objective of this paper is to assess, in individuals with clinically stable multiple sclerosis (MS), the safety, tolerability, pharmacokinetics (PK) and exploratory pharmacodynamics of the monoclonal recombinant human antibody IgM22 (rHIgM22).

Methods: Seventy-two adults with stable MS were enrolled in a double-blind, randomized, placebo-controlled, single ascending-dose, Phase 1 trial examining rHIgM22 from 0.025 to 2.0 mg/kg. Assessments included MRI, MR spectroscopy, plasma PK, and changes in clinical status, laboratory values and adverse events for three months. The final cohort had additional clinical, ophthalmologic, CSF collection and exploratory biomarker evaluations. Participants were monitored for six months.

Results: rHIgM22 was well tolerated with no clinically significant safety signals. Noncompartmental PK modeling demonstrated linear dose-proportionality both of C_{max} and $AUC_{0–Last}$. The steady-state apparent volume of distribution of approximately 58 ml/kg suggested primarily vascular compartmentalization. CSF:plasma rHIgM22 concentration increased from 0.003% on Day 2 for both 1.0 and 2.0 mg/kg to 0.056% and 0.586% for 1.0 and 2.0 mg/kg, respectively, on Day 29. No statistically significant treatment-related changes were observed in exploratory pharmacodynamic outcome measures included for the 21 participants of the extension cohort.

Conclusions: Single doses of rHIgM22 were well tolerated and exhibited linear PK, and antibody was detected in the CSF.

Keywords: Clinical trial, demyelination, disease-modifying therapies, multiple sclerosis

Date received: 28 June 2017; revised 12 September 2017; accepted: 9 October 2017

Introduction

The mainstay of current treatments for relapsing–remitting multiple sclerosis (MS) is the use of immunomodulatory and immunosuppressive drugs. These drugs have reduced the annualized relapse rate but the disease can continue to progress and disabilities accumulate. Even in extreme cases of immunoablation with reconstitution of the immune system by autologous hematopoietic stem cell transplantation, repair of pre-existing damage is limited.[1]

Therefore, attention in drug development for MS has been drawn to the potential for reparative, remyelinating therapies.[2–4] A number of small-molecule drugs that are approved for other indications have been identified, using preclinical screening techniques, that appear to promote remyelination in animal models and some of these have completed early-stage clinical trials[5] (see also NCT02040298). In addition, a monoclonal antibody that neutralizes the myelination inhibitory factor LINGO-1 has been advanced through Phase 2 clinical trials in optic neuritis and MS[6,7] (see also NCT01721161 and NCT01864148).

Another monoclonal antibody that has been shown to promote remyelination in animal models is recombinant human immunoglobulin (Ig)M22 (rHIgM22).[8–10] This antibody was identified and cloned from a patient with Waldenstrom's

Correspondence to:
Anthony O Caggiano
Acorda Therapeutics Inc, 420 Saw Mill River Rd., Ardsley, NY, New York 10502-2605, USA.
tcaggiano@acorda.com

Andrew Eisen
Acorda Therapeutics Inc, Ardsley, NY, USA

Benjamin M Greenberg*
University of Texas SW Medical Center, Dallas, TX, USA

James D Bowen*
Swedish Hospital Medical Center, Seattle, WA, USA

Douglas L Arnold*
NeuroRx Research, Montreal, QC, Canada

Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Anthony O Caggiano
Acorda Therapeutics Inc, Ardsley, NY, USA

*On behalf of the IM22-MS-1004 Study Team

macroglobulinemia. It binds to a prevalent antigen expressed only in the central nervous system (CNS) white matter. Although the complex, proteo-lipid antigen recognized by this antibody and the pathways modulated by its binding have not been fully defined, it has been shown capable of promoting remyelinating activity in cellular systems and several animal models of demyelination.[11] Herein we report on the safety, tolerability, pharmacokinetics (PK) and CNS penetration of rHIgM22 in a first-in-human, randomized, placebo-controlled, Phase 1, single ascending-dose clinical trial in individuals with clinically stable MS.

Methods

Study design, consent and approvals. This was a Phase 1, multicenter, double-blind, randomized, placebo-controlled, dose-escalation study designed to evaluate safety, tolerability, PK, immunogenicity (reported elsewhere), and exploratory pharmacodynamics of single intravenous (IV) administrations of rHIgM22 in patients with clinically stable MS. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements. The protocol was approved by the institutional review boards and all participants gave written informed consent. The Trial Registration Identifier is NCT01803867 (www.clinicaltrials.gov).

Eligibility, enrollment, dosing and follow-up. Following informed consent, individuals with a diagnosis of MS (McDonald 2010 criteria[12]) and between the ages of 18 and 70 years, inclusive, with no evidence of active disease or medication changes within the preceding three months, were enrolled at one of 17 centers in the United States (US). Key exclusion criteria were various medical conditions or medication usage that would potentially impair safe participation or interpretation of trial results or initiation of various disease-modulating therapies within prespecified intervals, a history of infusion reactions to biologics or any contraindication to brain magnetic resonance imaging (MRI). Patients were enrolled and completed all visits between April 2013 and October 2014. See https://clinicaltrials.gov/ct2/show/NCT01803867.

Initially, individuals were enrolled in one of five successive dose-escalation cohorts in which the first two patients in each cohort were randomized, one to receive placebo and one to receive active drug. Following a review of clinical and radiologic safety findings at two weeks, in the absence of any dose-limiting toxicity, the next eight individuals were randomized to placebo (one) or active drug (seven). Following a review of all preceding safety data, in the absence of any dose-limiting toxicity, the next higher-dose cohort was similarly enrolled. In this fashion, 51 patients were enrolled in the five dose levels spanning 0.025 to 2.0 mg/kg rHIgM22 (Table 1). One patient was replaced after receiving the study drug and withdrawing consent before completing the requisite evaluations.

Antibody or placebo was administered in a volume of 200 ml over one hour. Treatment was blinded to participants and non-pharmacy site personnel. The starting dose of rHIgM22 was based on the no-observed-adverse-effect-level (NOAEL) in the most sensitive non-clinical species with a scaling factor for species size and an additional safety factor of 12.8. The maximum dose was the human equivalent of approximately 15 times the maximally effective dose observed for rHIgM22 in the Theiler's murine encephalomyelitis virus (TMEV) mouse model of MS.[13] Participants were followed, with periodic assessments, for three months.

Following completion of these initial five cohorts, a further 21 individuals were enrolled in a sixth cohort and randomly assigned to receive placebo or rHIgM22 at 1.0 or 2.0 mg/kg (1:1:1). The patients in this cohort were evaluated with additional clinical assessments (noted below) and exploratory biomarkers, with follow-up extending to six months from study drug administration as noted in Figure 1. The individuals in this sixth cohort also consumed 50 ml of 70% non-radioactive heavy water (D_2O) twice daily for two, two-week intervals (Study Day –14 to Day 1 and Day 15 to Day 29) to label newly synthesized exploratory biomarkers related to myelin synthesis.[13–16] Participants in the sixth cohort also had lumbar punctures to obtain CSF for PK and exploratory biomarker evaluations on Day 2 and Day 29.

Imaging

Participants were evaluated by MRI of the brain on either 1.5 or 3 T clinical scanners at screening, Day 15 and Day 60 of the study. These evaluations included a proton density (PD)-weighted scan, T2-weighted scan, a single-voxel proton magnetic resonance spectroscopy (MRS), and a T1-weighted scan, all prior to gadolinium (Gd) injection. This was followed by a fluid-attenuated inversion recovery (FLAIR) scan immediately after Gd injection

Table 1. Baseline demographics and clinical status of participants.

		Five-dose escalation cohorts rHIgM22 dose (mg/kg)						Sixth cohort rHIgM22 dose (mg/kg)		
Variable	All participants	Placebo	0.025	0.125	0.5	1.0	2.0	Placebo	1.0	2.0
n	72	10	8	8	8	9	8	7	7	7
Age										
Mean years	51.3	50.1	52.8	54.1	52.1	50.7	47.5	50.0	51.0	54.4
(SD)	(9.88)	(11.45)	(10.43)	(14.19)	(8.87)	(7.97)	(9.77)	(7.87)	(11.05)	(8.60)
Gender										
Female	46	6	1	7	4	5	6	6	6	5
Male	26	4	7	1	4	4	2	1	1	2
MS diagnosis										
RR	38	6	4	3	4	4	5	5	4	3
SP	25	2	3	4	3	3	2	2	2	4
PP	7	2	1	1	1	2	0	0	0	0
PR	2	0	0	0	0	0	1	0	1	0
Race										
White	65	8	8	8	7	8	6	7	6	7
Black	6	2	0	0	1	1	1	0	1	0
Mixed	1	0	0	0	0	0	1	0	0	0
EDSS score										
Mean	4.9	4.1	5.3	5.2	5.2	5.3	5.4	4.0	5.1	4.5
(SD) or (range)	(2.1)	(1.5–6.5)	(1.5–8.5)	(2.5–8.0)	(2.0–9.0)	(2.5–8.0)	(2.5–8.0)	(1.0–6.5)	(2.5–6.5)	(2.0–6.5)
MS duration										
Mean years	14.2	7.4	19.1	9.1	16.1	13.2	13.5	7.6	12.9	16.4
(SD)	(9.6)	(5.13)	(12.10)	(7.40)	(10.56)	(6.92)	(9.84)	(7.00)	(9.63)	(9.80)

This was a small, Phase 1, randomized controlled trial that did not attempt to balance the distribution of participants in the placebo and treatment groups with regard to various demographic characteristics. The individuals randomized to placebo tended to have less severe MS (lower EDSS) of shorter duration than the individuals randomized to treatment with rHIgM22.
rHIgM22: monoclonal recombinant human antibody IgM22; MS: multiple sclerosis; RR: relapsing–remitting; SP: secondary progressive; PP: primary progressive; PR: progressive relapsing; EDSS: Expanded Disability Status Scale.

during a 10-minute wait period and a T1-weighted scan post-Gd injection.

Clinical and laboratory evaluations

Standard clinical and laboratory safety measures were evaluated at every visit. Clinical assessments included physical examination, vital signs, assessment of suicidality (Columbia-Suicide Severity Rating Scale (C-SSRS)), recording of AEs and determination of the Expanded Disability Status Scale (EDSS) in all participants. Laboratory evaluations included hematology, liver function, metabolic and urinalysis. The Timed 25-Foot Walk (T25FW), low-contrast visual acuity (LCVA, 1.25% and 2.5%), high-contrast visual acuity (HCVA), optical coherence tomography (OCT; Heidelberg Spectralis), pupillometry (NeurOptics DP 2000), and the Patient Global Impression of Change (PGIC) were added for all individuals in the sixth cohort.

PK

Standard PK parameters of rHIgM22 were derived from plasma concentration versus time data. PK samples were obtained 10 times during the first 24 hours then at each visit on study Days 3, 5, 8, 15, 29 and 60. A validated PK assay was used, based on immunoprecipitation capture with antihuman-IgM antibodies bound to magnetic beads to isolate the IgM in the matrix. The captured material was subjected to proteolysis with trypsin to produce a characteristic peptide (LLIYDITK) measured as a surrogate for intact rHIgM22 via high-performance liquid chromatography and mass spectrometry/mass spectrometry detection using positive ion electrospray (unpublished). The concentration of the

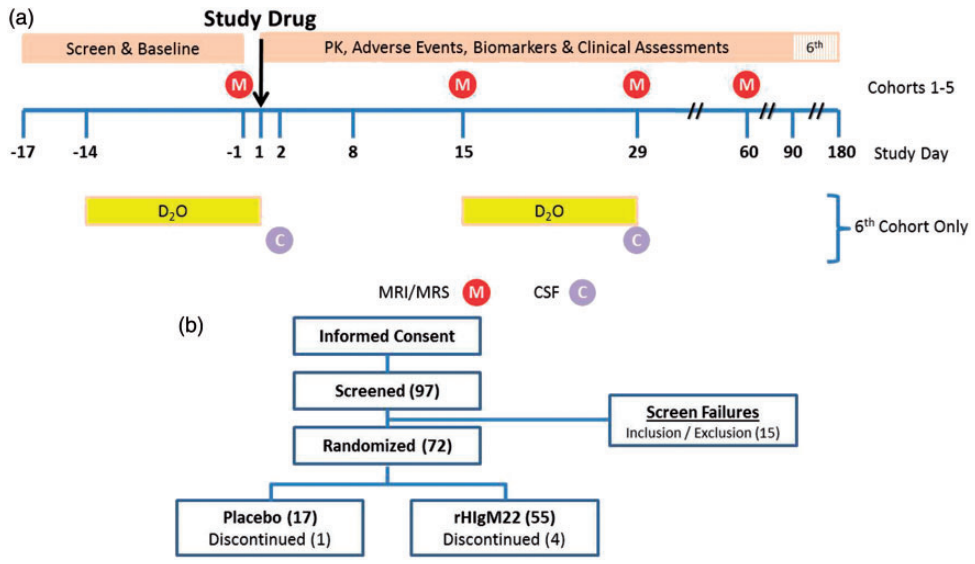

Figure 1. Study timeline, evaluations and enrollment. Panel (a) is a schematic of study design, and evaluations conducted in the first five dose-escalation cohorts are noted above the timeline. Additional procedures added to the sixth cohort included the consumption of heavy water and two lumbar punctures to obtain cerebrospinal fluid (CSF) as noted below the timeline. Panel (b) depicts the enrollment and disposition of the participants. In the five dose-escalation cohorts, individuals received single doses of monoclonal recombinant human antibody immunoglobulin (Ig)M22 (rHIgM22) ranging from 0.025 to 2.000 mg/kg. Each cohort planned for eight active rHIgM22 and two placebo patients. The sixth cohort included three groups of seven patients each, who received placebo, 1.0 mg/kg or 2.0 mg/kg rHIgM22.
PK: pharmacokinetics; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; D2O: non-radioactive heavy water.

intact rHIgM22 was imputed from the measure of the peptide surrogate. The single-dose PK parameters derived included: $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, CL and V_{ss}. The CSF rHIgM22 concentration and ratio of CSF to plasma concentration were determined for the individuals in the sixth cohort from lumbar puncture samples obtained on Day 2 and Day 29.

Exploratory biomarkers

Cytokine profiles, complement levels, antitherapeutic antibody titers, and neutralizing antibody titers were obtained from all individuals. Fractional synthesis rates of specific myelin biomarkers were determined by mass spectroscopic methods from blood and CSF samples of patients in the sixth cohort and will be described elsewhere.

Analyses and statistics

All non-PK summary statistics and statistical analyses were performed using SAS® (SAS Institute Inc) version 9.1.3 or higher. The PK parameters were estimated using non-compartmental methods with WinNonlin® Professional version 5.1 or higher (Pharsight Corp, Mountain View, CA). Descriptive summaries are presented separately for the initial five dose-escalation cohorts and for the sixth cohort.

Results

Participant demographics

From March 2013 through January 2015, 97 patients from 18 sites were screened and 72 were randomized in this Phase 1, single ascending-dose trial. The characteristics of the participants by cohort are noted in Table 1. Given the small size of each cohort, there was considerable imbalance in a number of demographic characteristics, particularly in the severity and duration of disease and the gender distribution in individual groups. Of particular note, the placebo-treated patients overall were less severely impaired (EDSS) and had a much shorter duration of disease (Table 1). There were also differences between individual cohorts of drug-treated patients, though overall the demographic characteristics were broadly consistent with the population affected by MS in the US.

Safety and tolerability

In general, infusions of rHIgM22 were well tolerated by these participants. Among the 55 individuals receiving the antibody, there were no significant infusion reactions, no alterations in vital signs, laboratory findings or unanticipated events as noted in Table 2. There were no discontinuations due to

Table 2. Treatment-emergent adverse events (TEAEs).

Description	All rHIgM22 ($N = 55$)	All placebo ($N = 17$)
Any TEAE	47 (86%)	16 (94%)
Any serious TEAE	0	1 (6%) Recurrent skin cancer
Any TEAE leading to discontinuation	0	0
Headache		
n	15	5
(unique % of participants)	(27%)	(29%)
(range or specific post-infusion day onset)	(0–30)	(–1, 0, 0, 1, 166)
Contact dermatitis	5 (9%) (1, 1, 2, 2, 3)	2 (12%) (2, 9)
Infusion-site hematoma	4 (7%) [1,4,4,16]	1 (6%) [3]
MS relapse	4 (7%) (3, 7, 24, 33)	0a
Arthralgia	3 (6%) (27, 53, 67, 143)	0
Back pain	3 (6%) (9, 31, 53)	0
Contusion	3 (6%) (4, 5, 8)	0
Fatigue	3 (6%) (13, 42, 90)	0
Flushing	3 (6%) (1, 1, 1)	0
Muscular weakness	3 (6%) (8, 23, 32)	0
Neck pain	3 (6%) (4, 31, 90)	1 (6%) (3)
Pain in extremity	3 (6%) (1, 17, 26)	1 (6%) (61)
Pruritus	3 (6%) (1, 1, 41)	0

[a]One placebo-treated individual had a "pseudo exacerbation" starting on study day 13 characterized by Uhthoff's phenomenon for 45 days coincident with onset of a urinary tract infection for two weeks and an overlapping period of blurred vision from study Days 29 to 169.

All adverse events occurring in 4% or more of the study participants are listed. The one serious adverse event (a recurrent skin cancer) was experienced by an individual who received placebo. Within each box the top entry is the number of events, the middle entry is the percentage of participants and the bottom entry represents either the range in or the specific study days of onset for the TEAE.

rHIgM22: monoclonal recombinant human antibody IgM22; MS: multiple sclerosis.

Table 3. Radiologic findings.

		Dose-escalation cohorts Placebo or rHIgM22 dose (mg/kg)						Sixth cohort Placebo or rHIgM22 dose (mg/kg)		
Variable		Placebo	0.025	0.125	0.5	1.0	2.0	Placebo	1.0	2.0
Gd-enhancing lesions Mean (SD)	n	10	8	8	8	9	8	7	7	7
	Baseline	0.0 (0.0)	0.1 (0.4)	0.1 (0.4)	0.5 (1.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.4)	0.0 (0.0)
	Day 60	0.0 (0.0)	0.4 (0.7)	0.0 (0.0)[b] –0.1 (0.4)	0.0 (0.0)	0.0 (0.0)[c]	0.0 (0.0)[b]	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)[d]
	Change to Day 60	0.0 (0.0)	0.3 (0.7)		–0.5 (1.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	–0.1 (0.4)	0.0 (0.0)
Brain-volume Change (%) Mean (SD)	*n*	3	0	0	0	8	7	7	6	7
	Change to Day 60	0.09 (0.47)	ND	ND	ND	0.04 (0.35)	0.00 (0.36)	–0.06 (0.36)	0.05 (0.34)	–0.07 (0.58)
NAA:Cr ratio Mean (SD)	*n*	10	8	8	7	9	8	7	7	7
	Baseline	1.38 (0.19)	1.51 (0.32)	1.41 (0.24)	1.40 (0.19)	1.53 (0.23)	1.41 (0.19)	1.38 (0.20)	1.33 (0.21)	1.52 (0.24)
	Day 60	1.41 (0.21)	1.51 (0.30)	1.36 (0.35)	1.45 (0.11)	1.52 (0.17)	1.44 (0.16)	1.44 (0.28)	1.33 (0.23)	1.65 (0.51)
	Change to Day 60	0.02 (0.10)	–0.05 (0.10)	–0.02 (0.12)	0.05 (0.13)	–0.03 (0.13)	0.06 (0.16)	0.06 (0.20)	–0.01 (0.09)	0.20 (0.28)

The table indicates that there were no meaningful differences in changes from baseline to Day 60 in radiologic findings between the placebo and any treatment group.
rHIgM22: monoclonal recombinant human antibody IgM22; Gd: gadolinium; NAA: *N*-acetylaspartate; Cr: creatine.

treatment-emergent adverse events (TEAEs). A total of 47 out of 55 (86%) participants treated with rHIgM22 experienced a total of 186 TEAEs compared with 16 out of 17 (94%) individuals treated with placebo who experienced 54 TEAEs. Among the 55 participants receiving rHIgM22, there were four individuals who experienced an MS relapse during the course of their participation in the trial, while none were recorded among the 17 patients who received placebo. However, one placebo-treated individual had a "pseudo-exacerbation" starting on study Day 13 characterized by Uhthoff's phenomenon lasting 45 days, coincident with onset of a urinary tract infection for two weeks and an overlapping period of blurred vison from study Days 29–169. None of the relapses were considered atypical or related to the study drug by the investigators and the occurrences were not dose related.

There were three participants who had hemispheric Gd+ lesions upon entry but who were not the individuals who subsequently developed symptoms consistent with a clinical relapse. Overall, there were no meaningful changes or differences in the number of Gd+ lesions over the 60 days from administration of placebo or rHIgM22 across any of the dose levels examined in this trial. These values are found in Table 3.

PK

rHIgM22 exhibited a dose-proportional C_{max} and $AUC_{0-\infty}$ over the range of doses tested in this trial. The calculated PK values are typical for human IgMs reported in the literature with a half-life of approximately four days at the highest dose. The half-life increased from 39 to 100 hours as the dose increased from 0.025 to 2.0 mg/kg and probably reflects saturation of clearance mechanisms (Table 4).

rHIgM22 was measurable in the CSF of individuals enrolled in the sixth cohorts who all consented to having lumbar punctures performed on Day 2 and Day 29 after receiving the study drug at 1 or 2 mg/kg. The rHIgM22 peptide-specific mass spectroscopic concentration analysis developed for plasma (with a lower limit of quantitation of 10 ng/ml) was extended to CSF with a lower limit of quantitation (0.05 ng/ml). While PK parameters for CSF or white matter in the brain cannot be extrapolated from these two measurements, CSF concentrations and the ratio

Table 4. Pharmacokinetic parameters.

		Dose-escalation cohorts rHIgM22 dose (mg/kg)					Sixth cohort rHIgM22 Dose (mg/kg)	
Parameter	Statistic	0.025 ($N=8$)	0.125 ($N=8$)	0.500 ($N=8$)	1.000 ($N=9$)	2.000 ($N=8$)	1.000 ($N=7$)	2.000 ($N=7$)
$AUC_{0-\infty}$ (ng·h/ml)	*n*	6	8	6	8	8	7	6
	Mean	26,441.15	158,433.02	819,052.93	1,803,988.71	4,669,342.02	2,245,010.46	3,644,755.42
	(SD)	(9,344.117)	(32,726.064)	(124584.919)	(743599.033)	(1115533.415)	(772724.725)	(1002106.887)
C_{max} (ng/ml)	*n*	7	8	8	9	8	7	7
	Mean	572.43	2932.50	10,935.00	22,466.67	45,512.50	23,471.43	45,000.00
	(SD)	(105.236)	(522.268)	(1989.853)	(4804.165)	(6836.130)	(4053.276)	(9578.796)
T_{max} (h)	*n*	7	8	8	9	8	7	7
	Mean	0.376	0.544	0.265	0.568	0.348	0.483	0.174
	(SD)	(0.4336)	(0.4855)	(0.1794)	(0.5521)	(0.3115)	(0.3899)	(0.1514)
$T_{1/2}$ (h)	*n*	7	8	8	9	8	7	7
	Mean	39.32	50.04	72.02	80.43	99.90	86.03	79.83
	(SD)	(14.762)	(14.248)	(5.762)	(37.492)	(20.500)	(19.927)	(27.404)
V_{ss} (ml/kg)	*n*	7	8	8	9	8	7	7
	Mean	54.70	52.48	57.51	58.81	56.06	52.15	56.60
	(SD)	(13.420)	(14.305)	(7.136)	(17.181)	(6.756)	(10.238)	(18.719)
CL (ml/h/kg)	*N*	6	8	6	8	8	7	6
	Mean	1.050	0.817	0.614	0.650	0.446	1.050	0.817
	(SD)	(0.3692)	(0.1609)	(0.1110)	(0.2851)	(0.1081)	(0.3692)	(0.1609)

Key plasma pharmacokinetic parameters are listed for rHIgM22 doses between 0.025 and 2.0 mg/kg. There is dose proportionality in C_{max} and $AUC_{0-\infty}$ and the other measurements are in accord with typical values reported for human IgMs.
rHIgM22: monoclonal recombinant human antibody IgM22; AUC: area under the curve; Ig: immunoglobulin.

of CSF:plasma are reported in Table 5. On study Day 2, 24 hours after the rHIgM22 infusion, the concentration of the antibody in CSF was between 10^{-4}- and 10^{-5}-fold of that found in the plasma. However, while the concentration of rHIgM22 dropped dramatically over the ensuing month both in plasma and CSF, the ratio of the antibody in CSF: plasma at Day 29 was between 10^{-2} and 10^{-3}.

Exploratory clinical and pharmacodynamic measures

MRS revealed no changes in central voxel *N*-acetylaspartate (NAA):creatine (Cr) from the single administered dose of rHIgM22. These results are noted in Table 3.

No statistically significant change was noted in any of the various clinical and potential pharmacodynamic assessments tested. However, there was a trend toward improvement in the PGIC (Figures 2).

Exploratory analyses were conducted on blood and CSF samples collected for biomarker studies.[17] These analyses were designed to examine the rate of synthesis of myelin components that naturally turn over and can be detected in the blood and/or CSF from the incorporation of deuterium from the heavy water (D_2O) ingested by the participants. Molecules examined included 24-hydroxy-cholesterol in blood, galactocerebrosides in CSF and several myelin proteins in CSF (myelin basic protein (MBP), myelin proteolipid protein (PLP), oligodendrocyte myelin glycoprotein (OMG), myelin oligodendrocyte glycoprotein (MOG) and myelin-associated glycoprotein (MAG)). There were no evident trends associated with treatment or time period in any of the CSF analytes. There was a nonsignificant increase in the fractional synthetic rate for 24-hydroxy-cholesterol in blood with rHIgM22 treatment at 2 mg/kg in the interval between study Visit 5 (Day 15) and Visit 6 (Day 29). Methodologic details, results and other considerations of this isotopomer analysis will be reported separately.

Table 5. CSF rHIgM22 concentration.

Parameter	Study day	Statistic	Placebo ($n = 7$)	rHIgM22 1.0 mg/kg ($n = 7$)	rHIgM22 2.0 mg/kg ($n = 7$)
CSF concentration (ng/ml)	Day 2	*n*	7	7	7
		Mean	0.000	0.5403	1.1300
		(SD)	(0.000)	(0.6825)	(1.0288)
	Day 29	*n*	7	6	6
		Mean	0.000	0.0440	0.1157
		(SD)	(0.000)	(0.077687)	(0.1844)
Ratio CSF:plasma	Day 2	*n*	0	7	6
		Mean	–	0.00003	0.00003
		(SD)		(0.00003)	(0.00003)
	Day 29	*n*	0	4	3
		Mean	–	0.00056	0.00586
		(SD)		(0.0008745)	(0.00924)

The concentration of rHigM22 in the CSF collected from the 14 participants receiving drug in the sixth cohort of the trial are noted in the above table. The partition between the blood and CSF on Day 2 of ~ 10,000:1 is in accord with reported values for IgM in general. However, while the concentration of rHIgM22 both in blood and CSF declines over time, by Day 29 of the study the ratio of CSF to blood, where both were measurable, shows an increase of roughly 100-fold, implying a delayed clearance from the CSF.
rHIgM22: monoclonal recombinant human antibody IgM22; CSF: cerebrospinal fluid; Ig: immunoglobulin.

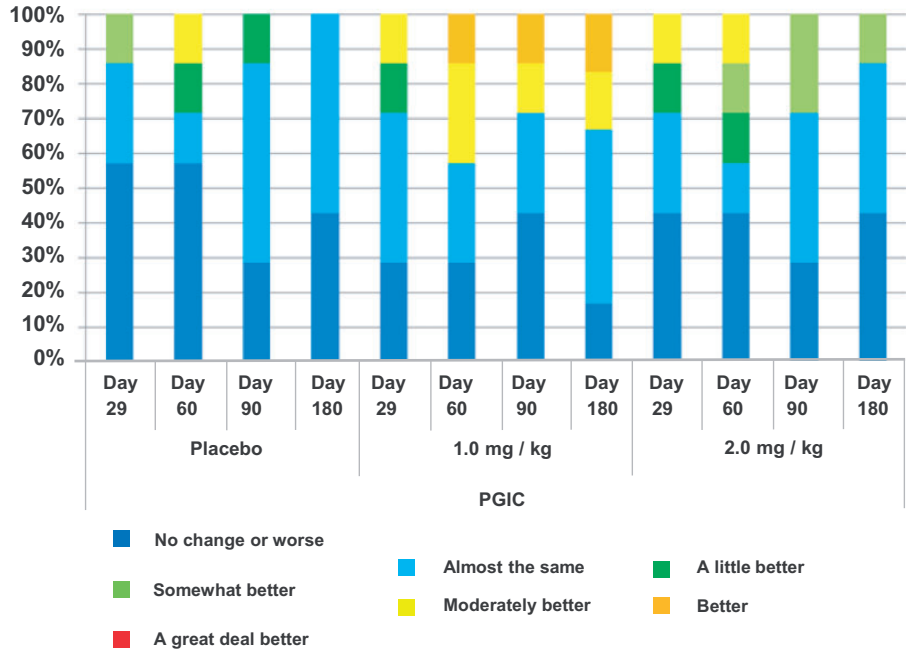

Figure 2. Patient Global Impression of Change (PGIC) trend toward improvement. The 21 participants in the sixth cohort were administered this questionnaire to assess the change (if any) in activity limitations, symptoms, emotions and overall quality of life, related to their condition since baseline. More individuals receiving monoclonal recombinant human antibody IgM22 (rHIgM22) reported improvements in their status than did individuals receiving placebo throughout the study.

Discussion

This was a first-in-human, double-blind, randomized, placebo-controlled, single ascending-dose study designed to assess the safety, tolerability, PK, immunogenicity, and exploratory pharmacodynamics of IV administrations of rHIgM22 in patients with stable MS. A double-blind, placebo-controlled design for this study was adopted to help evaluate

the potential treatment relatedness of any EAEs or changes in clinical measures in this patient population, particularly given the long period of follow-up. The utility of the placebo control was ultimately limited by the relatively small size of the group and the somewhat unbalanced demographics.

Of note, the duration of disease, on average, was half as long for placebo-treated versus rHIgM22-treated individuals (7.5 years and 14.3 years, respectively). Consistent with this difference, the mean EDSS for the placebo-treated participants was lower than the individuals treated with rHIgM22. This may have particularly limited the ability to compare the exploratory outcome measures between groups.

TEAEs were reported in 94% of placebo- and 86% of rHIgM22-treated patients. Common AEs (frequency $> 5\%$) in rHIgM22-treated individuals that were not observed in placebo-treated patients were MS relapse, fatigue, arthralgia, back pain, muscular weakness, pruritus, contusion, and flushing. None of these events occurred in more than 7% of antibody-treated patients, so that an equivalent frequency for any of these events in the 17-person placebo group would have been represented by one individual or less. Most TEAEs were mild or moderate in severity, and the occurrences of these events did not appear to be dose dependent.

The incidence of MS relapse observed in this study was consistent with the estimated annualized relapse rate extrapolated from the literature for the time period in which this study was conducted.[18,19] Based on a relapse rate of 0.3 relapses per year, approximately four relapses would be expected in a group of 55 MS patients treated with rHIgM22 and one relapse in the 17 placebo-treated individuals. This is not inconsistent with the finding of four acute relapses in rHIgM22-treated participants and no relapse among the placebo-treated individuals found in this study (although one placebo-treated patient was reported to have a "pseudo-exacerbation"). There was no evidence of association between relapse and dose of rHIgM22. The majority of reported AEs were events often associated with MS.

Non-compartmental modeling of plasma concentrations of rHIgM22 demonstrated linear dose-proportionality of both C_{max} and AUC_{0-Last}. Clearance and other rHIgM22 PK parameters were typical for a human IgM. Comparisons of drug plasma concentrations to concentrations in the CSF within cohort 6 suggest the amount of rHIgM22 that crossed the blood-brain/blood-CSF barriers was dose dependent and consistent with other antibody studies.[20–22] The increasing CSF:plasma concentration ratio over time is not readily interpretable, particularly given that the concentration gradient from plasma to CSF remains very high, which means that antibody could continue to accumulate within the CNS. The antibody is expected to bind to white matter in the CNS, which further complicates the interpretation of CSF levels.[23–25]

This was primarily a safety and tolerability study and not powered to detect significant differences for any specific clinical or exploratory outcome measure. The single-dose, low sample size for each dose level and the high level of variability in exploratory outcome measures between and within participants, compounded by baseline differences between groups, made it impossible to adequately evaluate the significance of any differences observed. For example, a single dose of rHIgM22 can promote remyelination and increases the brainstem level of total NAA detected by MRS in the TMEV model.[10] The increased NAA probably reflects the effects of remyelination that lead to healthier axons. However, in this single-dose clinical trial the NAA/CR ratio was not similarly affected and the study was not powered to see such an effect.

Finally, this study confirms, based on plasma and CSF concentrations of rHIgM22, that the blood-brain barrier (BBB) may be largely intact in these stable MS patients, in accord with a previous dynamic contrast-enhanced MRI study.[26] Yet, despite an intact BBB, this IgM molecule was able to penetrate the CNS. An ongoing Phase 1, single ascending-dose study in people with MS immediately following a relapse (NCT02398461) may determine whether the BBB in that setting is more permeable to rHIgM22 and whether the presence of the antibody in the CNS in that setting will be associated with clinical or radiologic (MRS and magnetization transfer ratio) evidence consistent with effects on remyelination. In aggregate, the two studies will guide development of future studies of rHIgM22 designed to determine if it is possible to promote remyelination in people with MS.

Acknowledgments

The authors wish to thank the patients and their caregivers for their participation in this study.
Author contributions are as follows: AE, BMG and AOC contributed to the design of the study and analysis of results. AE drafted the manuscript. BMG, JDB and AOC

edited the manuscript on behalf of the principal investigators. DLA design imaging plan and interpreted MRI data. Principal investigators on the IM22-MS-1004 Study Team who enrolled and evaluated participants (listed alphabetically) are:

Principal investigator	Institution
Mark Agius	University of California Davis Medical Center
Angela Applebee	Fletcher Allen Health Care
James Bowen	Swedish Neuroscience Institute
Bruce Cree	University of California San Francisco
Richard Gibson	New Orleans Center for Clinical Research-Knoxville
Andrew Goodman	University of Rochester Medical Center
Alexandra Goodyear	Stanford University Medical Center
Benjamin Greenberg	University Southwestern Medical Center
Azra Hussaini	Parexel
Mariko Kita	Virginia Mason Medical Center
Sharon Lynch	University of Kansas Medical Center
David Mattson	Indiana University
Ronald Murray	IMMUNOe International Research Centers
Nirav Patel	Collaborative NeuroScience Network Inc
Syed Rizvi	The Neurology Foundation Inc
Mark Tullman	MS Center for Innovations in Care
Timothy Vollmer	University of Colorado

We also wish to thank Ron Tashjian from Acorda Therapeutics as well as Brendan Putz, Jessica Schiller and Dr Paola Moya from PAR International, who were instrumental in the conduct of the trial.
Finally, we wish to acknowledge Drs Moses Rodriguez and Arthur Warrington and their colleagues at the Mayo Clinic for their discovery and evaluation of rHIgM22 as a potential remyelinating therapy for MS.

Conflicts of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: At the time of this study, AE and AOC were full-time employees of Acorda Therapeutics Inc. BMG, JDB and DLA have served as consultants to Acorda Therapeutics Inc.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by Acorda Therapeutics Inc (Ardsley, NY).

References

1. Muraro PA, Pasquini M, Atkins HL, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. *JAMA Neurol* 2017; 74: 459–469.
2. Munzel EJ and Williams A. Promoting remyelination in multiple sclerosis—recent advances. *Drugs* 2013; 73: 2017–2029.
3. Harlow DE, Honce JM and Miravalle AA. Remyelination therapy in multiple sclerosis. *Front Neurol* 2015; 6: 257.
4. Keough MB and Yong VW. Remyelination therapy for multiple sclerosis. *Neurotherapeutics* 2013; 10: 44–54.
5. Schwartzbach CJ, Grove RA, Brown R, et al. Lesion remyelinating activity of GSK239512 versus placebo in patients with relapsing–remitting multiple sclerosis: A randomised, single-blind, phase II study. *J Neurol* 2017; 264: 304–315.
6. Tran JQ, Rana J, Barkhof F, et al. Randomized phase I trials of the safety/tolerability of anti-LINGO-1 monoclonal antibody BIIB033. *Neurol Neuroimmunol Neuroinflamm* 2014; 1: e18.
7. Pepinsky RB, Arndt JW, Quan C, et al. Structure of the LINGO-1-anti-LINGO-1 Li81 antibody complex provides insights into the biology of LINGO-1 and the mechanism of action of the antibody therapy. *J Pharmacol Exp Ther* 2014; 350: 110–123.
8. Mitsunaga Y, Ciric B, Van Keulen V, et al. Direct evidence that a human antibody derived from patient serum can promote myelin repair in a mouse model of chronic-progressive demyelinating disease. *FASEB J* 2002; 16: 1325-1327.
9. Warrington AE, Bieber AJ, Ciric B, et al. A recombinant human IgM promotes myelin repair after a single, very low dose. *J Neurosci Res* 2007; 85: 967–976.
10. Wootla B, Denic A, Watzlawik JO, et al. Antibody-mediated oligodendrocyte remyelination promotes axon health in progressive demyelinating disease. *Mol Neurobiol* 2016; 53: 5217–5228.
11. Pirko I, Ciric B, Gamez J, et al. A human antibody that promotes remyelination enters the CNS and decreases lesion load as detected by T2-weighted spinal cord MRI in a virus-induced murine model of MS. *FASEB J*. 2004; 18: 1577–1579.
12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.

13. Schellekens RC, Stellaard F, Woerdenbag HJ, et al. Applications of stable isotopes in clinical pharmacology. *Br J Clin Pharmacol* 2011; 72: 879–897.
14. Muse ED, Jurevics H, Toews AD, et al. Parameters related to lipid metabolism as markers of myelination in mouse brain. *J Neurochem* 2001; 76: 77–86.
15. Dufner D and Previs SF. Measuring in vivo metabolism using heavy water. *Curr Opin Clin Nutr Metab Care*. 2003; 6: 511–517.
16. Price JC, Holmes WE, Li KW, et al. Measurement of human plasma proteome dynamics with (2)H(2)O and liquid chromatography tandem mass spectrometry. *Anal Biochem* 2012; 420: 73–83.
17. Fanara P, Wong PY, Husted KH, et al. Cerebrospinal fluid-based kinetic biomarkers of axonal transport in monitoring neurodegeneration. *J Clin Invest* 2012; 122: 3159–3169.
18. Fahrbach K, Huelin R, Martin AL, et al. Relating relapse and T2 lesion changes to disability progression in multiple sclerosis: A systematic literature review and regression analysis. *BMC Neurol* 2013; 13: 180.
19. Freedman MS, Montalban X, Miller AE, et al. Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: Assessing absolute differences using a number needed to treat analysis. *Mult Scler Relat Disord* 2016; 10: 204-212.
20. Prasad R. Immunoglobulins in certain CNS disorders: A study of CSF Ig classes G, A, M, D, and E concentrations. *Am J Clin Pathol* 1985; 83: 190–195.
21. Forsberg P, Henriksson A, Link H, et al. Reference values for CSF-IgM, CSF-IgM/S-IgM ratio and IgM index, and its application to patients with multiple sclerosis and aseptic meningoencephalitis. *Scand J Clin Lab Invest* 1984; 44: 7–12.
22. Blennow K, Skoog I, Wallin A, et al. Immunoglobulin M in cerebrospinal fluid: Reference values derived from 111 healthy individuals 18–88 years of age. *Eur Neurol* 1996; 36: 201–205.
23. de Lange EC. Utility of CSF in translational neuroscience. *J Pharmacokinet Pharmacodyn* 2013; 40: 315–326.
24. Gaohua L, Neuhoff S, Johnson TN, et al. Development of a permeability-limited model of the human brain and cerebrospinal fluid (CSF) to integrate known physiological and biological knowledge: Estimating time varying CSF drug concentrations and their variability using in vitro data. *Drug Metab Pharmacokinet* 2016; 31: 224–233.
25. Pardridge WM. CSF, blood-brain barrier, and brain drug delivery. *Expert Opin Drug Deliv* 2016; 13: 963–975.
26. Cramer SP, Simonsen H, Frederiksen JL, et al. Abnormal blood-brain barrier permeability in normal appearing white matter in multiple sclerosis investigated by MRI. *Neuroimage Clin* 2014; 4: 182–189.