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Proof-of-Concept Randomized Trial of the Monoclonal Antibody GSK249320 Versus Placebo in Stroke Patients

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Background and Purpose—One class of poststroke restorative therapy focuses on promoting axon outgrowth by blocking myelin-based inhibitory proteins such as myelin-associated glycoprotein. The purpose of the current study was to extend preclinical and clinical findings of GSK249320, a humanized monoclonal antibody to myelin-associated glycoprotein with disabled Fc region, to explore effects on motor outcomes poststroke.

Methods—In this phase IIb double-blind, randomized, placebo-controlled study, patients at 30 centers with ischemic stroke 24 to 72 hours prior and gait deficits were randomized to 2 IV infusions of GSK249320 or placebo. Primary outcome measure was change in gait velocity from baseline to day 90.

Results—A total of 134 subjects were randomized between May 2013 and July 2014. The 2 groups were overall well matched at baseline. The study was stopped at the prespecified interim analysis because the treatment difference met the predefined futility criteria cutoff; change in gait velocity to day 90 was 0.55±0.46 (mean±SD) in the GSK249320 group and 0.56±0.50 for placebo. Secondary end points including upper extremity function were concordant. The 2 IV infusions of GSK249320 were well tolerated. No neutralizing antibodies to GSK249320 were detected.

Conclusions—GSK249320, within 72 hours of stroke, demonstrated no improvement on gait velocity compared with placebo. Possible reasons include challenges translating findings into humans and no direct evidence that the therapy reached the biological target. The antibody was well tolerated and showed low immunogenicity, findings potentially useful to future studies aiming to use a monoclonal antibody to modify activity in specific biological pathways to improve recovery from stroke.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01808261.

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Key Words: axon ■ brain ■ clinical trial ■ gait ■ stroke

After an injury from an acute stroke, numerous restorative events evolve within the brain. Targeting these events therapeutically may augment poststroke neural repair and favorably impact long-term outcome.[1] Numerous biological targets are under study to develop restorative therapies. One class of therapy focuses on promoting recovery after stroke by blocking myelin-based inhibitory proteins that inhibit axon outgrowth. Three major inhibitors of such growth have been identified, 1 being myelin-associated glycoprotein (MAG). After stroke, MAG levels spontaneously increase in penumbra,[2] suggesting that MAG may be a useful target to promote neural repair, an idea bolstered by previous observations that MAG blockade promotes axonal growth.[3–5]

The main objective of the current study was to determine whether a monoclonal antibody targeting MAG improves stroke recovery in patients with ischemic stroke. The specific therapy under study was GSK249320, an IgG1-type humanized monoclonal antibody to MAG with disabled Fc region. Anti-MAG antibodies have been shown to neutralize MAG-mediated inhibition in preclinical studies[6] and to promote regeneration after peripheral nerve injury.[7,8] Blocking the action of a related protein, Nogo, 7 days after ischemic stroke in rats improved behavioral recovery by promoting axonal growth.[9] The preclinical program for GSK249320 included rodent studies that found that the antibody penetrated the infarct site and had small but significant effects on behavioral outcomes when initiated 24 hours poststroke without affecting infarct volume,[10] and primate studies in which IV infusion of GSK249320 beginning 24 hours after experimental ischemic infarct facilitated behavioral recovery.[11] GSK249320 was found to be safe in healthy

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human subjects,[12] and a recent randomized, placebo-controlled phase II trial in patients 24 to 72 hours after ischemic stroke also found the antibody to be safe and suggested potential efficacy for improving recovery of gait.[13]

The current study built on these findings as a phase IIb double-blind, randomized, placebo-controlled, multicenter study. Patients with ischemic stroke 24 to 72 hours prior and deficits in gait were randomized to receive 2 IV infusions of GSK249320 or placebo. The primary outcome measure was change from baseline to day 90 in gait velocity, which is valid, reliable, and sensitive after stroke.[14,15] The study was stopped at the interim analysis because there was insufficient evidence to justify continuing the study given that the observed difference between treatment groups met the predefined futility cutoff.

Methods

Study Overview

Thirty centers across 4 countries enrolled subjects in the study, between May 2013 and July 2014. The study was approved by each site's institutional review board. All subjects, or surrogates, gave written informed consent. Participation spanned 6 visits from baseline to day 180. Key entry/exclusion criteria appear in Table 1. See also online-only Data Supplement.

Randomization

Subjects were centrally randomized to GSK249320 15 mg/kg or placebo in a 1:1 allocation ratio, using permuted blocks, with treatment stratified according to baseline gait velocity (0, >0–<0.4, or 0.4–0.8 m/s). See also online-only Data Supplement.

Study Assessments

At baseline, prior to first infusion and thus <72 hours poststroke, assessments included National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale, gait velocity, and Box and Blocks (no. blocks transferred during 1 minute). All study assessors were formally trained and certified in each of these outcome measures (see online-only Data Supplement). Patients and assessors were blinded at all times. These were serially evaluated during the remaining 5 visits, as was the amount of rehabilitation (physical and occupational) therapy that patients received. Safety assessments included vital signs, clinical laboratories, ECGs, suicidality, adverse events (AE), serious adverse events, and falls and were monitored by the internal Safety Review Committee. Blood samples were collected at baseline, pre- and post-dosing of IP at visit 2 (day 6), as well as at visits 3 and 6 (day 30 and 180, respectively), or at the time of study withdrawal if applicable, from which free serum MAG levels and GSK249320 levels were measured. See also online-only Data Supplement.

Data Analysis

The primary efficacy end point was the mean change in gait velocity from baseline to day 90. To test the hypothesis that treatment with GSK249320 leads to an improvement of change in gait velocity compared with placebo at day 90, a repeated-measures mixed-effects model was used in a Bayesian framework, including fixed effects for treatment, visit, age, sex, treatment by visit interaction, baseline mean gait velocity by visit interaction, and baseline NIHSS by visit interaction. For additional information, see online-only Data Supplement. At the end of study, a positive signal of efficacy was to be declared if the posterior probability that the true improvement over placebo (GSK249320-placebo) was greater than zero is >95%, and a negative signal of efficacy was to be declared if the posterior probability that the true improvement over placebo is greater than zero is <85%; otherwise the result was to be interpreted as indeterminate. If the true mean gait velocity improvement with GSK249320 is 0.25 m/s over placebo, assuming variance as in the earlier placebo-controlled phase II study of GSK249320,[13] enrolling 136 subjects with day 90 data would provide an 85% chance of observing a positive signal of efficacy. Assuming a 16% dropout rate to day 90, enrollment of 162 subjects was planned. Note that a change in gait velocity of 0.1 m/s has been suggested as clinically meaningful in populations with impaired walking speed,[16] and an increase of 0.16 m/s is linked to a meaningful improvement in disability.[17]

One interim and one headline data analysis were planned during the study. The interim analysis was planned for when ≈70 subjects completed the day 90 visit. At that time, the internal Safety Review Committee was to determine whether the estimated treatment effect of GSK249320 was likely to be futile based on a prespecified clinically meaningful treatment effect, that is, if the posterior probability that the true improvement over placebo is greater than zero is <70%. If the data hit the futility threshold, the internal Safety Review Committee would recommend discontinuation of the study.

The safety population was defined as subjects who received at least 1 infusion of IP. The intent-to-treat (ITT) population was defined as subjects in the safety population who underwent at least 1 post-baseline efficacy assessment, with subjects analyzed according to the treatment to which they were randomized. Intent to treat was the population used for the primary efficacy analysis. The per-protocol (PP) population was defined as all subjects in the intent-to-treat population, who were not protocol violators with regard to inclusion/exclusion criteria, unblinding, IP administration, or gait velocity assessments. Subjects who did not receive both infusions of IP were also excluded from the PP population.

Table 1. Key Entry and Exclusion Criteria

Entry criteria
Radiology confirmed supratentorial ischemic stroke; nonlacunar (either >15 mm diameter in 1 direction or >4 cc volume)
Stroke onset within 24–72 h of IP infusion
NIHSS score 3–21
Leg motor deficit: NIHSS Q6 score 1–4
Impaired walking ability: gait velocity ≤0.8 m/s
Aged 18–90 y
Expectation subject will receive standard physical, occupational, and speech rehabilitation therapies as indicated for poststroke deficits
Exclusion criteria
Ability to walk >0.8 m/s per gait velocity assessment
Symptomatic stroke <3 mo before study entry
Significant prestroke disability: Rankin score >2 before index stroke
Poorly responsive: NIHSS Q1a score 2 or 3
Significant aphasia
Preexisting significant gait deficit, chronic liver disease, or prolonged QTc interval
Preexisting active poorly controlled neurological or psychiatric disease
Expected death because of index stroke or other preexisting condition
Participation in another investigational study targeting stroke recovery during study
MRI contraindication
Pregnant/lactating

MRI indicates magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

Results

Study Conduct

Across all 4 participating countries, 134 subjects were randomized, including 64 who were enrolled during the 3 months it took for the 70th subject to reach day 90, the futility criteria interim analysis to be completed, and the internal Safety Review Committee to make and communicate the decision to stop the study. Of the 133 who received investigational product, 64 subjects (48%) completed the study, and 69 subjects (52%) withdrew from the study or were lost to follow-up (Figure 1). The primary reason for withdrawal was that the study was terminated at the interim analysis. A total of 100 subjects (75%) were in the study for >90 days. A total of 116 subjects (87%) received both infusions of IP; 1 subject received no IP infusions, 10 subjects received only 1 IP infusion, 2 subjects received an incorrect dose for 1 infusion because of incorrect preparation of the dose, and 3 subjects received less than the full 100 mL volume of IP for at least 1 infusion. Overall, protocol deviations were reported for 109 subjects (81%), most of which were minor and did not require exclusion from the PP population (Table I in the online-only Data Supplement); all protocol deviations were collected, for transparency, regardless as to whether or not they had an impact on outcome. Of the 134 subjects randomized into the study, 133 were included in the safety population (placebo: n=68; GSK249320: n=65), 120 were included in the intent-to-treat population (placebo: n=60; GSK249320: n=60), and 104 were included in the PP population.

Subjects

Baseline data (Table 2) were generally balanced across treatment groups. The majority of enrollees (91%) had stroke involving the middle cerebral artery territory. During study participation, the amount of rehabilitation therapy, in minutes, provided to enrollees was substantial and variable, with subjects randomized to GSK249320 receiving a greater amount of therapy (Table 3).

Analysis of Treatment Efficacy

The study was stopped at the interim analysis because the posterior mean treatment difference was 0.027 at day 90 (95% credible interval, −0.146 to 0.199) and the posterior probability that true treatment difference was greater than zero was 0.621, which was lower than the predefined futility cutoff of 0.70 (Figure 2). Analysis of the PP population and using the final database including subject data for those subjects with an early withdrawal visit because of study termination were concordant (online-only Data Supplement).

Gait velocity data described the proportion of subjects in each gait impairment category (0, >0–< 0.4, 0.4–0.8, and >0.8 m/s) over time. Most subjects were nonambulatory at baseline and progressed to some level of ambulation by day 180, but a review of summary statistics for the secondary end points

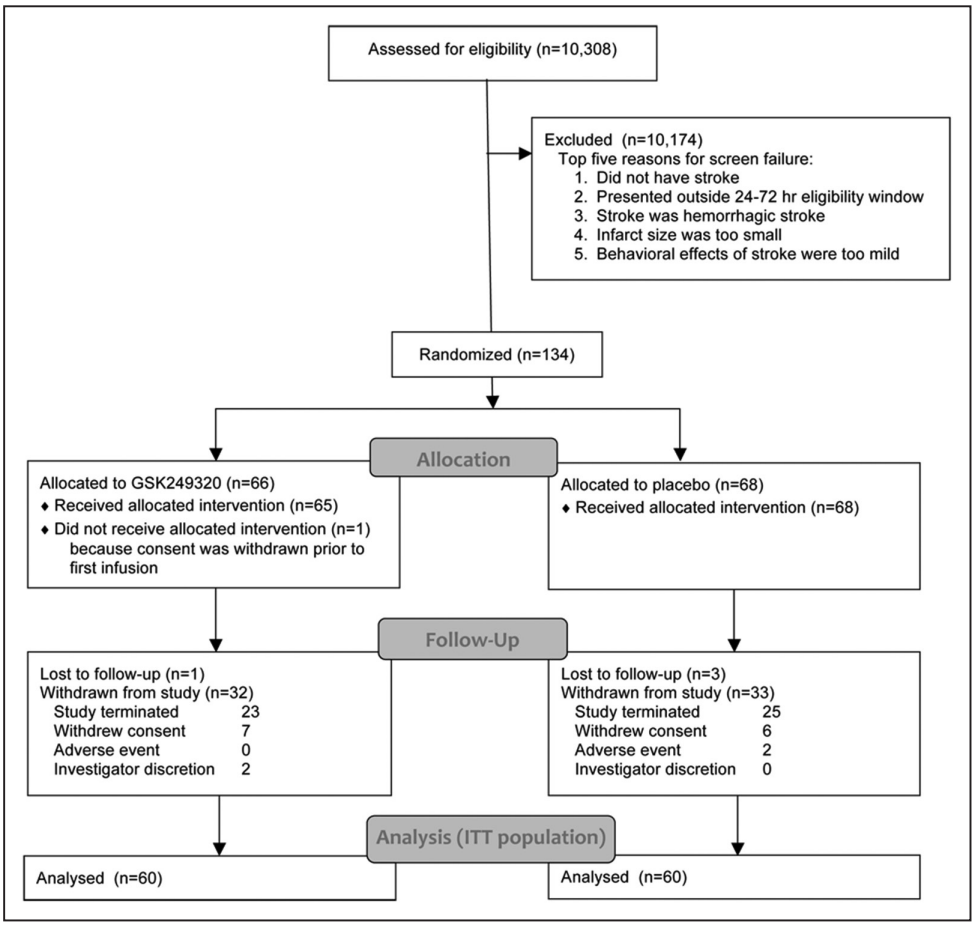

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. ITT indicates intent to treat.

Table 2. Baseline Clinical Measures and Demographics

	Placebo (n=68)	GSK249320 (n=65)
Age, y*	67.1±11.2	68.2±11.9
Sex (F/M)	29/39	31/34
Hypertension	51	47
Diabetes mellitus	22	18
Hyperlipidemia	36	28
Atrial fibrillation	18	17
History of angina pectoris/MI	1	1
History of stroke	0	0
Ethnicity		
Hispanic/Latino	0	1
Not Hispanic/Latino	68	64
Race		
White	62	62
Black/African Heritage	4	2
American Indian/Alaskan Native	1	0
Asian	1	1
Received IV tPA	29	25
Received IA reperfusion therapy	3	9
Stroke subtype		
Large-artery atherosclerosis	24	20
Cardioembolism	19	25
Small-vessel occlusion	10	9
Ischemic stroke other determined pathogenesis	2	2
Ischemic stroke undetermined pathogenesis	13	9
Gait impairment stratification		
0	55	53
>0–<0.4	5	5
0.4–0.8	8	6
>0.8	0	1
NIHSS total score at day 1, median (range)	9.5 (3–20)	10.0 (3–19)
NIHSS Q6 leg deficit at day 1*	2.4±1.20	2.1±1.09
NIHSS Q5 arm deficit at day 1*	2.7±1.29	2.4±1.34
Box and blocks score at day 1*		
Stroke-affected arm	3.2±7.7	4.2±8.4
Nonstroke arm	25.1±13.3	23.3±12.4
No. of hours between stroke onset and first IP infusion*	52.7±14.4	52.4±13.3

Values are for safety population, except for box and blocks score at day 1, which is for per-protocol population. MI indicates myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Values are represented in mean±SD.

(change in gait impairment category, change in box and blocks score, distribution of modified Rankin Scale scores, and total NIHSS score) suggests no obvious differences between treatment groups (Table 4).

Analysis of Safety

The 2 IV infusions of GSK249320 were well tolerated as evidenced by an AE rate comparable to placebo, the majority of AEs having been reported as mild or moderate in severity, and the low withdrawal rate because of AEs (Table II in the online-only Data Supplement). No clinically important safety trends were observed post-dosing with GSK249320. There was no difference in the proportion of subjects having a fall, or in the number of falls, between treatment groups. The overall incidence of events common to stroke was comparable across the treatment groups (Table III in the online-only Data Supplement). AEs were reported in 57 subjects (84%) in the placebo group and in 49 subjects (75%) in the GSK249320 group. The most common AEs were constipation, nausea, and headache. No AE reports suggested peripheral neuropathy, infusion site reaction, or hypersensitivity reaction with GSK249320. Withdrawal from the study because of an AE occurred in 2 subjects in the placebo group and in no subjects in the GSK249320 group.

Sixteen subjects (24%) in the placebo group experienced serious adverse events, compared with 9 subjects (14%) in the GSK249320 group. Five subjects (7%) died in the placebo group. Two subjects (3%) died in the GSK249320 group: respiratory failure in a 90-year-old subject 4 days after first infusion and cardiorespiratory arrest in a 76-year-old subject 22 days after first infusion, both considered unrelated to IP infusions.

Immunogenicity

Five subjects had preexisting antibodies at low titers that were not related to treatment. Six of the 64 subjects who received GSK249320 developed antidrug antibodies. Eight of the 68 subjects in the placebo treatment group had antidrug antibodies against GSK249320 that were also not related to treatment. No neutralizing antibodies were detected.

GSK249320 Reduced Free Serum MAG Levels

Before administration of IP, soluble, free MAG plasma levels were similar between placebo and GSK249320 groups (33.0±42.0 versus 30.0±30.7 pg/mL, mean±SD). A progressive slow decline in free MAG level was seen after day 6 for placebo subjects, whereas subjects receiving GSK249320 exhibited an abrupt decline in free MAG level between day

Table 3. Therapy Provided to Enrollees for the Duration of Study Participation

	Placebo (n=52)	GSK249320 (n=52)
Physical therapy	1422 (0–10 003)	1610 (92–11 285)
Occupational therapy	771 (0–10 003)	1312 (0–11 415)
Total therapy	2241 (0–20 006)	3264 (184–22 700)

Results are for per-protocol population given in median (range) and represent minutes of therapy.

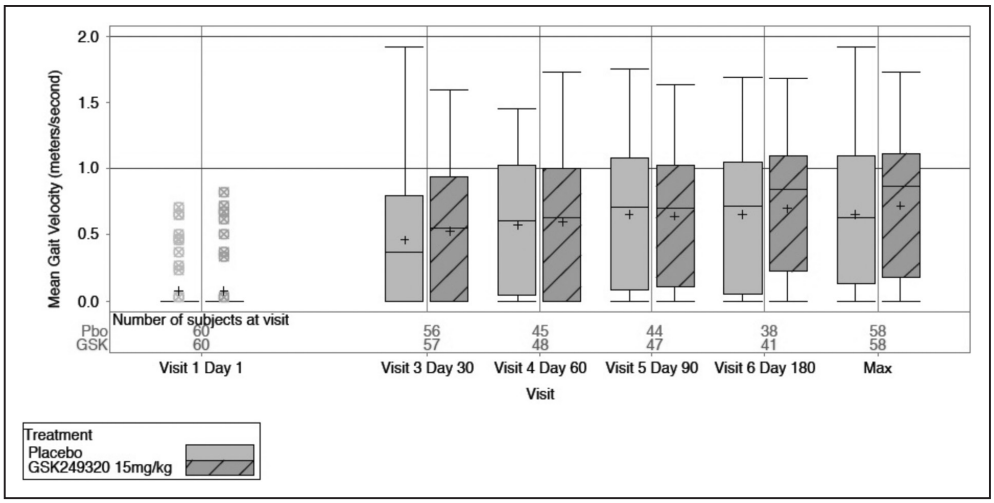

Figure 2. Box-and-whisker plots of gait velocity change over time and maximum value for the 2 treatment arms (intent-to-treat group).

1 and day 6 that was maintained until at least day 30: median inhibition of free MAG in plasma was 97.5% after the first infusion of GSK249320 on day 1 and was maintained after the second infusion on day 6 at 97% until at least day 30, with free MAG levels in GSK249320-treated subjects resuming to levels similar to placebo group subjects at day 180 (Figure I in the online-only Data Supplement). The median GSK249320 concentration at the end of the second IP infusion, which can be considered the maximum concentration, was 494.5 µg/mL, and the mean half-life of GSK249320 was 23.7±5.2 days (Figure II in the online-only Data Supplement).

Table 4. Study Outcomes

	Placebo	GSK249320
Change in gait velocity, baseline to day 90, mean±SD (ITT)	n=44 0.56±0.50	n=47 0.55±0.46
Change in gait velocity, baseline to day 180, mean±SD (ITT)	n=38 0.56±0.48	n=41 0.60±0.44
Change in box and blocks score, baseline to day 90, mean±SD (PP)	n=41	n=40
Stroke-affected arm	17.1±19.1	14.9±16.5
Nonstroke arm	18.6±15.2	14.6±16.4
Subjects falling to day 90 (safety)	15	12
Modified Rankin scale score, day 90 (PP)	n=46	n=45
0	0	2
1	7	6
2	13	11
3	10	11
4	14	14
5	2	1
NIHSS score, day 90, median (IQR) (PP)	4 (1.25–8.75)	4 (1–7)

Values are provided for the population indicated inside the parentheses. Gait velocity is in m/s. ITT was used for the primary efficacy analysis of the primary end point (gait velocity), PP was used for secondary end points, and the safety population was used for data on falls. IQR indicates interquartile range; ITT, intent to treat; NIHSS, National Institutes of Health Stroke Scale; and PP, per protocol.

Discussion

The current study hypothesized that GSK249320, administered as 2 IV infusions beginning 24 to 72 hours poststroke and spaced 5±2 days apart, would improve gait recovery over 90 days in subjects with ischemic stroke and leg weakness with impaired walking ability. The data do not support this, and the study was stopped at interim analysis because observed difference between treatment groups met the predefined futility threshold.

The primary outcome measure was gait velocity, a choice that in retrospect had both advantages and disadvantages. Gait velocity has an established record as a valid, reliable assessment sensitive to treatment effects.[14,15] Another advantage is that it measures function (ie, disability and activities limitations), rather than impairment, and can be directly linked with participation level (ie, handicap).[15,16,18,19] As a modality-specific outcome measure, gait velocity has potential advantages compared with global outcomes for understanding recovery such as granularity of assessment.[20] Furthermore, reduced gait velocity is common after stroke, gait improvements after stroke are linked to better quality of life, and in some studies gait recovery is ranked as the top priority by patients with hemiplegia after stroke.[16,21,22] The value of gait velocity as primary end point was also based in part on its direct link with entry criteria (Table 1), which required slow gait for study entry. However, at baseline, >80% of subjects were entirely unable to ambulate at all (gait velocity=0 m/s), masking accurate understanding of within-subject gait recovery. This produced a floor effect such that several different degrees of neural abnormality were scored identically, although the study did make the key distinction between patients with gait velocity=0 m/s and patients in whom gait velocity could not be assessed. Another potential disadvantage of gait as the primary end point is that it is a complex behavior influenced by activity at multiple nervous system levels. Many patients with severe hemiparesis learn to walk on their spasticity, further complicating interpretation of changes in gait velocity after stroke. Putting it in perspective, the current placebo group mean gait velocity change from baseline to day 90 (0.56 m/s) was >3-fold greater compared with placebo group of the

previous phase II GSK249320 trial (0.18 m/s),[13] a difference possibly because of play of chance but that reduced ability of the current study to detect a treatment group difference. Level of impairment also differed between studies, with median placebo group baseline total NIHSS score of 7 in the previous trial compared with 9.5 herein.

Other study design features may also be important for understanding results. Choice of patient population influences how hypotheses are tested. Patients with small-vessel infarcts, operationally <15 mm maximum diameter or 4 cc volume,[23] were excluded given their comparatively favorable prognosis.[24,25] Study entry required total NIHSS score of 3 to 21 and leg motor score of 1 to 4. This enrolled subjects with milder strokes, who might be expected to have a favorable prognosis regardless of treatment arm. The amount of IP infused could also be important. Median GSK249320 concentration at the end of the second infusion (maximum concentration) was lower herein as compared with subjects receiving the same dose in the previous study[20] in which the second infusion was administered 9±1 days apart (median 494.5 versus 723.0 μg/mL); conceivably infusing a higher amount of antibody might have increased its effect size.

It is useful to revisit assumptions that supported current study design. The antibody showed a favorable preclinical and clinical profile. It was well characterized and the progression of therapy development conformed to published recommendations.[17] Preclinical studies in rodents[10] and primates[11] suggested efficacy. The antibody was found to be safe in 37 healthy subjects, who received a single IV infusion ≤25 mg/kg,[12] and in a phase II study of 42 patients 24 to 72 hours after ischemic stroke, among whom 25 subjects received 2 IV infusions ≤15 mg/kg[13]; significant benefit compared with placebo was found over time for gait velocity, an end point well aligned with preclinical behavioral end points.

Other issues relevant to current results pertain to translation from animals to humans. Behavioral recovery[26,27] and neural plasticity[28–30] after stroke are accelerated in rodents compared with humans. On the basis of this, time of first infusion in animals (24 hours poststroke) was extended to 72 hours in humans, but this may not have been an appropriate extrapolation. The same concern might extend to presence of MAG, the biological target: in rats with experimental stroke, MAG levels start to increase by 3 days poststroke and peak at 2 weeks poststroke,[2] but it is uncertain whether this is true in humans. White matter constitutes 14% of rodent versus 50% of human brain volume[31,32]; axons might be more difficult for a large antibody to access in humans. Other limitations of animal models may also pertain, including that animal models incompletely capture the complex psychosocial issues that patients face after stroke, such as depression, caregiver support, and financial stressors.[33]

Direct evidence that substantial quantities of the therapy reached the biological target was not available. Indirect evidence of target binding in the current study was suggested by the substantial reduction in free MAG plasma levels with GSK249320 treatment. The half-life of GSK249320 in the current study was 23.7±5.2 days, similar to the value of 21 days found in healthy control subjects and typical of a monoclonal antibody.[12] Neutralizing antibodies were not detected and so did not contribute to current findings.

The experience of translating therapies targeting acute ischemic stroke has provided several lessons,[34] and in many cases, these inform translation of restorative stroke therapies to clinical trials. Examples include stepwise translation from preclinical to clinical studies, the need to standardize performance of assessments, careful selection of study sample size to insure adequate study power, and centralized data management. However, neuroprotection differs in many ways from restoration—restorative trials are not simply delayed neuroprotection trials. On the contrary, trials targeting brain restoration must address unique aspects of study design issues[33] within the context of topics such as end point selection, target population identification, and intervention timing because the optimal approach in these and other areas often does not directly extend from neuroprotection trials to restorative trials.[1,35]

This proof-of-concept study for GSK249320, a monoclonal antibody GSK249320 administered IV and initiated within 72 hours of stroke onset, demonstrated no improvement on gait outcomes compared with placebo. As mentioned above, many possible reasons might have contributed to these findings, including using an end point with too large a floor effect at baseline, enrolling patients with too severe a level deficit, using too low an antibody dose, interspecies differences in pharmacokinetics, lack of direct evidence that the therapy reached the biological target, or simply that GSK249320 does not work in human stroke. In the current study, the antibody was well tolerated and showed low immunogenicity, findings that may prove useful to future studies aiming to use a monoclonal antibody to modify activity in specific biological targets to promote improved stroke recovery.

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