Clinical trial results:
Study MAG104615, a Proof of Concept Study for GSK249320 versus placebo in Stroke Patients

Summary

EudraCT number	2012-004494-23
Trial protocol	GB DE
Global end of trial date	28 July 2014

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	26 March 2015

Trial information

Trial identification

Sponsor protocol code	MAG104615

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01808261
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline , 1 8664357343, GSKClinicalSupportHD@gsk.com
Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of GSK249320 versus placebo on lower limb motor recovery, specifically locomotion, in ischemic stroke patients

Protection of trial subjects:

n/a

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Canada: 25
Worldwide total number of subjects	134
EEA total number of subjects	83

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	47
From 65 to 84 years	83
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study consisted of a 6 month Core Study Period and an Extended Follow Up Period, if required. The study was terminated early at the time of Interim Analysis for reasons of futility. At the time of early study termination, a total of 134 participants were randomized, of which 133 participants had received at least one dose of study medication.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo administered as two intravenous (IV) infusions, the first on Study Day 1 which is 24-72 hours post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 milliliters (mL) IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).

Arm type	Placebo
Investigational medicinal product name	Placebo for GSK249320
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

administered as 2 intravenous infusions; the first on study day 1 and the second on study day 6

Arm title	GSK249320 15 mg/kg

Arm description:

Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).

Arm type	Experimental
Investigational medicinal product name	GSK249320
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15mg/kg administered as 2 intravenous infusions; the first on study day 1 and the second on study day 6

Number of subjects in period 1[1]	Placebo	GSK249320 15 mg/kg
Started	68	65
Completed	32	32
Not completed	36	33
Consent withdrawn by subject	6	7
Physician decision	-	2
Adverse event, non-fatal	2	-
Lost to follow-up	3	1
Study Closed/Terminated	25	23

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant was randomized but did not receive treatment and so is not included in the baseline characteristic data.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo administered as two intravenous (IV) infusions, the first on Study Day 1 which is 24-72 hours post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 milliliters (mL) IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).	
Reporting group title	GSK249320 15 mg/kg
Reporting group description:	
Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).	

Reporting group values	Placebo	GSK249320 15 mg/kg	Total
Number of subjects	68	65	133
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	67.1	68.2	
standard deviation	± 11.2	± 11.92	-
Gender categorical Units: Subjects			
Female	29	31	60
Male	39	34	73
Race, Customized Units: Subjects			
African American/African Heritage	4	2	6
American Indian or Alaska Native	1	0	1
Asian - South East Asian Heritage	1	1	2
White - White/Caucasian/European	62	62	124

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo administered as two intravenous (IV) infusions, the first on Study Day 1 which is 24-72 hours post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 milliliters (mL) IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).

Reporting group title	GSK249320 15 mg/kg

Reporting group description:

Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received placebo administered as two intravenous (IV) infusions, the first on Study Day 1 which is 24-72 hours post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 milliliters (mL) IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush). Placebo - Per Protocol (PP) Population consisted of all participants who were included in the ITT population and did not violate protocol with regards to inclusion/exclusion criteria, unblinding, investigational product administration and gait velocity assessments.

Subject analysis set title	GSK249320 15 mg/kg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush). The GSK249320 15 mg/kg - Per Protocol (PP) Population consisted of all participants who were included in the ITT population and did not violate protocol with regards to inclusion/exclusion criteria, unblinding, investigational product administration and gait velocity assessments.

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo administered as two intravenous (IV) infusions, the first on Study Day 1 which is 24-72 hours post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 milliliters (mL) IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush). The Safety Population include all participants who received at least one infusion of investigational product.

Subject analysis set title	GSK249320 15 mg/kg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush). The Safety Population included all participants who received at least one infusion of investigational product.

Subject analysis set title	GSK249320 15 mg/kg - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush). The Pharmacokinetic (PK) Population included all participants in the Safety Population who had at least one PK sample with a concentration above the non-quantifiable limit.

Primary: Change from Baseline (BL) in gait velocity at Month 3/Day 90

End point title	Change from Baseline (BL) in gait velocity at Month 3/Day 90

End point description:

Gait is the way or manner in which a person walks. Gait velocity (walking speed) is an objective, quantitative measure of lower extremity motor recovery in individuals who have had a stroke. Participants were asked to walk at their usual pace over a level, indoor 10 meter(m) distance and were allowed to use their normal assistive devices. The time (seconds[s]) taken by the participants to travel the 10 m distance was recorded. Gait velocity (meters/second [m/s]) as assessed by study personnel was derived as: 10 divided by time to walk 10 meters. Two trials of gait velocity were conducted at each time point. Change from BL was calculated as the mean Month 3/Day 90 value minus the mean BL value. Analysis was done for Intent-To-Treat (ITT) population comprised of participants who received at least 1 infusion of investigational product and had at least 1 post-BL efficacy assessment. The measure type displayed are posterior means.

End point type	Primary

End point timeframe:

Baseline and Month 3/Day 90

End point values	Placebo	GSK249320 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[1]	60[2]		
Units: meters per second (m/s)				
arithmetic mean (standard deviation)	0.5417 (± 0.062)	0.5859 (± 0.0535)		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Credible intervals are displayed as confidence intervals. Posterior means, standard deviations, and credible intervals are provided in the table.

Comparison groups	Placebo v GSK249320 15 mg/kg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.713 [3]
Method	Bayesian method
Parameter estimate	Mean difference (final values)
Point estimate	0.0443
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.2

Notes:

[3] - P-value presented is the posterior probability that the treatment difference (GSK249320 15mg/kg – placebo) is greater than 0 m/s at Month 3/Day 90.

Secondary: Change from Baseline in gait velocity at Month 6/Day 180

End point title	Change from Baseline in gait velocity at Month 6/Day 180

End point description:

Gait is the way or manner in which a person walks. Gait velocity (walking speed) is an objective, quantitative measure of lower extremity motor recovery in individuals who have had a stroke. Participants were asked to walk at their usual pace over a level, indoor 10 meter(m) distance and were allowed to use their normal assistive devices. The time (seconds[s]) taken by the participants to travel the 10 m distance was recorded. Gait velocity (meters/second [m/s]) as assessed by study personnel was derived as: 10 divided by time to walk 10 metrers. Two trials of gait velocity were conducted at each time point. Change from BL was calculated as the mean Month 3/Day 90 value minus the mean BL value. Analysis was done for Intent-To-Treat (ITT) population comprised of participants who received at least 1 infusion of investigational product and had at least 1 post-BL efficacy assessment. The measure type displayed are posterior means.

End point type	Secondary

End point timeframe:

Baseline and Month 6/Day 180

End point values	Placebo	GSK249320 15 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[4]	60[5]		
Units: m/s				
arithmetic mean (standard deviation)	0.5442 (± 0.0665)	0.6236 (± 0.0556)		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Credible intervals are displayed as confidence intervals. Posterior means, standard deviations, and credible intervals are provided in the table.

Comparison groups	GSK249320 15 mg/kg v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.828 [6]
Method	Bayesian method
Parameter estimate	Mean difference (final values)
Point estimate	0.0794
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.093
upper limit	0.247

Notes:

[6] - P-value presented is the posterior probability that the treatment difference (GSK249320 15mg/kg – placebo) is greater than 0 m/s at Month 6/Day 180.

Secondary: Number of participants with indicated transition from one gait velocity category to another category at the indicated timepoints

End point title	Number of participants with indicated transition from one gait velocity category to another category at the indicated timepoints

End point description:

Participants were categorized at each visit into the following gait velocity categories: 0 m/s, >0 to <0.4 m/s, >=0.4 m/s to 0.8 m/s and >0.8m/s. The number of participants transitioning from one gait velocity category to another category was assessed at each post-Baseline visit and was presented in terms of the following transition categories: worsened, no change, improved 1 level, improved 2 levels and improved 3 levels. Analysis was done for Per Protocol(PP) Population that consisted of all participants who were included in the ITT population and did not violate protocol with regards to inclusion/exclusion criteria, unblinding, investigational product administration and gait velocity assessments. Only participants with data available at the specified time points were analyzed(represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study, missing data was not imputed.

End point type	Secondary

End point timeframe:

Baseline, Month 1/Day 30, Month 2/Day 60, Month 3/Day 90 and Month 6/Day 180.

End point values	Placebo - PP	GSK249320 15 mg/kg - PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52[7]	52[8]		
Units: Participants				
number (not applicable)				
Day 30, Worsened, n=48, 49	1	0		
Day 30, No Change, n=48, 49	19	18		
Day 30, Improved 1 Level, n=48, 49	11	11		
Day 30, Improved 2 Levels, n=48, 49	9	9		
Day 30, Improved 3 Levels, n=48, 49	8	11		
Day 60, Worsened, n=42, 42	0	0		
Day 60, No Change, n=42, 42	13	14		
Day 60, Improved 1 Level, n=42, 42	14	11		
Day 60, Improved 2 Levels, n=42, 42	6	7		
Day 60, Improved 3 Levels, n=42, 42	9	10		
Day 90, Worsened, n=42, 41	1	0		
Day 90, No Change, n=42, 41	9	8		
Day 90, Improved 1 Level, n=42, 41	12	14		
Day 90, Improved 2 Levels, n=42, 41	10	7		
Day 90, Improved 3 Levels, n=42, 41	10	12		
Day 180, Worsened, n=36, 39	1	0		
Day 180, No Change, n=36, 39	7	6		
Day 180, Improved 1 Level, n=36, 39	9	14		
Day 180, Improved 2 Levels, n=36, 39	11	5		
Day 180, Improved 3 Levels, n=36, 39	8	14		

Notes:

[7] - PP Population

[8] - PP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline (BL) in dexterity as measured by Box and Blocks test

End point title	Change from Baseline (BL) in dexterity as measured by Box

	and Blocks test

End point description:

Dexterity is the ability of a person to use the hands skillfully in performing a task. The Box and Blocks test is an objective, gross manual dexterity test in individuals with upper limb impairments. Participants were asked to move small wooden blocks from one side of a partitioned box to other. The score was determined by the number of blocks transferred within a 60 second time period. Both affected and unaffected arms were tested, starting with the unaffected arm. Change from BL was calculated as the individual post-BL value minus the BL value. Change from BL in the number of blocks transferred for the affected arm was analyzed using a Mixed Model Repeated Measures analysis with fixed effects for treatment, visit, treatment by visit interaction, sex, age, BL National Institute of Health stroke scale total score, BL number of blocks transferred by the affected and unaffected arms, country and presence of concomitant medications that potentially impact recovery.

End point type	Secondary

End point timeframe:

Baseline, Month 1/Day 30, Month 2/Day 60, Month 3/Day 90 and Month 6/Day 180

End point values	Placebo - PP	GSK249320 15 mg/kg - PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52[9]	52[10]		
Units: Number of blocks				
least squares mean (standard error)				
Day 30	10.13 (± 2.195)	12.538 (± 1.587)		
Day 60	11.469 (± 2.345)	14.484 (± 1.6)		
Day 90	15.196 (± 2.962)	17.631 (± 1.926)		
Day 180	14.869 (± 2.839)	18.813 (± 2.11)		

Notes:

[9] - PP Population

[10] - PP Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical data for Day 30. The point estimate and confidence interval are for the adjusted mean difference based on least square estimates.

Comparison groups	Placebo - PP v GSK249320 15 mg/kg - PP
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.408
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.067
upper limit	7.883

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Statistical data for Day 60. The point estimate and confidence interval are for the adjusted mean difference based on least square estimates.	
Comparison groups	Placebo - PP v GSK249320 15 mg/kg - PP
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	3.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.704
upper limit	8.735

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Statistical data for Day 90. The point estimate and confidence interval are for the adjusted mean difference based on least square estimates.	
Comparison groups	Placebo - PP v GSK249320 15 mg/kg - PP
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.668
upper limit	9.538

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Statistical data for Day 180. The point estimate and confidence interval are for the adjusted mean difference based on least square estimates.	
Comparison groups	Placebo - PP v GSK249320 15 mg/kg - PP
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	3.944

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	11.037

Secondary: Number of participants who experienced at least one fall

End point title	Number of participants who experienced at least one fall

End point description:

The number of participants who experienced at least one fall between Baseline to Day 90 and Baseline to Day 180 is summarized.

End point type	Secondary

End point timeframe:

Baseline to Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[11]	65[12]		
Units: Participants				
number (not applicable)				
Baseline to Day 90	15	12		
Baseline to Day 180	18	16		

Notes:

[11] - Safety Population

[12] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who experienced indicated number of falls

End point title	Number of participants who experienced indicated number of falls

End point description:

The number of participants who experienced 1, 2, 3 or >=4 falls between Baseline to Day 90 and Baseline to Day 180 is summarized. Only those participants who experienced at least one fall at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline to Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[13]	65[14]		
Units: Participants				
number (not applicable)				
Baseline to Day 90, 1 Fall, n=15, 12	8	6		
Baseline to Day 90, 2 Falls, n=15, 12	3	3		
Baseline to Day 90, 3 Falls, n=15, 12	0	2		
Baseline to Day 90, >=4 Falls, n=15, 12	4	1		
Baseline to Day 180, 1 Fall, n=18, 16	7	9		
Baseline to Day 180, 2 Falls, n=18, 16	6	2		
Baseline to Day 180, 3 Falls, n=18, 16	1	2		
Baseline to Day 180, >=4 Falls, n=18, 16	4	3		

Notes:

[13] - Safety Population

[14] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE) and any serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) and any serious adverse event (SAE)

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any dose: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect or all events of possible drug-induced liver injury with hyperbilirubinaemia. Medical or scientific judgement is exercised in other situations.

End point type	Secondary

End point timeframe:

From Day 1 until early withdrawal, death, Month 6/Day 180, or Extended Follow-Up visit

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[15]	65[16]		
Units: Participants				
number (not applicable)				
Any AE	57	49		
Any SAE	16	9		

Notes:

[15] - Safety Population: all participants who received at least one infusion of investigational product

[16] - Safety Population: all participants who received at least one infusion of investigational product

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with events common to stroke

End point title	Number of participants with events common to stroke

End point description:

Events common to stroke were those AEs that commonly occur after a stroke and are generally associated with the underlying stroke or the progression of stroke. These include Joint or soft tissue pain, Bladder Incontinence, Depression/Mood Disorder, Urinary tract infection, Dysphagia, Bowel Incontinence, Dysarthia, Confusion, Spasticity, Limb Edema, Aspiration Pneumonia, Hemorrhagic Transformation (symptomatic or asymptomatic), Pressure Ulcers, Progression of Stroke, Malnutrition, Deep vein thrombosis, Brain Herniation, Pulmonary embolism, Seizures, and Falls.

End point type	Secondary

End point timeframe:

From Day 1 until early withdrawal, death, Month 6/Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	65		
Units: Participants				
number (not applicable)				
Joint or soft tissue pain	19	22		
Bladder Incontinence	11	23		
Depression/Mood Disorder	17	16		
Urinary tract infection	17	13		
Dysphagia	12	12		
Bowel Incontinence	11	12		
Dysarthia	11	11		
Confusion	8	13		
Spasticity	9	9		
Limb Edema	5	12		
Aspiration Pneumonia	5	3		
Hemorrhagic Transformation	4	4		
Pressure Ulcers	3	2		
Progression of Stroke	2	2		
Malnutrition	1	2		
Deep vein thrombosis	2	0		
Brain Herniation	0	1		
Pulmonary embolism	1	0		
Seizures	0	1		
Falls	18	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in diastolic blood pressure (DBP) and systolic blood pressure (SBP) at Day 1 Post-dose, Day 6, Day 180 and Early Withdrawal

(EW) visit

End point title	Change from Baseline in diastolic blood pressure (DBP) and systolic blood pressure (SBP) at Day 1 Post-dose, Day 6, Day 180 and Early Withdrawal (EW) visit

End point description:

Safety was measured by monitoring vital signs including blood pressure. The Baseline for DBP and SBP was the value of pre-dose assessment on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Day 6, Day 180 and EW visit

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[17]	65[18]		
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
DBP, Day 1 Post-dose, n=68, 65	1.7 (± 10.58)	0.5 (± 10.14)		
DBP, Day 6 Pre-dose, n=60, 59	0.2 (± 16.52)	-1.1 (± 11.98)		
DBP, Day 6 Post-dose, n=58, 57	2.4 (± 15.06)	1.9 (± 16.36)		
DBP, Day 180, n=27, 28	8.1 (± 13.97)	5 (± 14.6)		
DBP, EW visit, n=24, 22	-5 (± 15.55)	1.8 (± 15.05)		
SBP, Day 1 Post-dose, n=68, 65	3.1 (± 16.15)	0.7 (± 11.81)		
SBP, Day 6 Pre-dose, n=60, 59	-3.5 (± 26.46)	-6 (± 20.13)		
SBP, Day 6 Post-dose, n=58, 57	-0.9 (± 24.59)	-2 (± 20.14)		
SBP, Day 180, n=27, 28	-6.4 (± 22.96)	-6.4 (± 27.79)		
SBP, EW visit, n=24, 22	-15.2 (± 29.08)	0 (± 25.42)		

Notes:

[17] - Safety Population

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate at Day 1 Post-dose, Day 6, Day 180 and EW visit

End point title	Change from Baseline in heart rate at Day 1 Post-dose, Day 6, Day 180 and EW visit

End point description:

Safety was measured by monitoring vital signs including heart rate. The Baseline for heart rate was the value of pre-dose assessment on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Day 1, Day 6, Day 180 and EW visit

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[19]	65[20]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 1 Post-dose, n=67, 65	0.9 (± 8.68)	0.7 (± 7.98)		
Day 6 Pre-dose, n=60, 59	-1.8 (± 13.03)	-0.4 (± 17.47)		
Day 6 Post-dose, n=58, 57	-3.9 (± 12.09)	-3.1 (± 15.3)		
Day 180, n=27, 28	-0.3 (± 17.5)	-3 (± 15.48)		
EW visit, n=24, 22	3.3 (± 15.47)	-2.1 (± 15.4)		

Notes:

[19] - Safety Population

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the indicated electrocardiogram (ECG) parameters at Day 6, Day 30 and EW visit

End point title	Change from Baseline in the indicated electrocardiogram (ECG) parameters at Day 6, Day 30 and EW visit

End point description:

A single 12-lead ECG was obtained at each time point and the following ECG intervals were determined: PR, QRS, QT, RR and corrected QT (QTc), QT interval corrected by Bazett's formula (QTcB), QT interval corrected by Fridericia's formula (QTcF). Baseline for ECG parameters was the value of Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30 and EW visit

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[21]	65[22]		
Units: Milliseconds				
arithmetic mean (standard deviation)				
PR, Day 6, n=50, 46	-1 (± 30.47)	-0.8 (± 20.02)		
PR, Day 30, n=38, 40	-5.9 (± 36.05)	-3.5 (± 42.08)		
PR, EW Visit, n=10, 14	-0.4 (± 21.01)	3.1 (± 33.96)		
QRS, Day 6, n=60, 57	4.9 (± 15.75)	-4 (± 44.11)		
QRS, Day 30, n=46, 50	3.4 (± 10.97)	1.1 (± 17.74)		
QRS, EW Visit, n=16, 16	2.6 (± 27.47)	-23.7 (± 81.24)		

RR, Day 6, n=53, 53	61.1 (± 246.84)	12.9 (± 154.09)		
RR, Day 30, n=40, 45	80.5 (± 245.31)	-21.8 (± 181.99)		
RR, EW Visit, n=13, 16	-21.6 (± 164.19)	85.6 (± 349.82)		
QT, Day 6, n=60, 57	10.4 (± 40.86)	9.4 (± 36.46)		
QT, Day 30, n=46, 49	4.1 (± 43.59)	-12.1 (± 42.06)		
QT, EW Visit, n=16, 15	20.8 (± 37.16)	43.7 (± 93.85)		
QTc, Day 6, n=58, 58	2.9 (± 30.7)	6.8 (± 43.87)		
QTc, Day 30, n=45, 50	-1.3 (± 32.92)	-2.2 (± 39.49)		
QTc, EW Visit, n=16, 16	7.1 (± 27.75)	8.9 (± 69.58)		
QTcB, Day 6, n=53, 51	2.2 (± 124.73)	4.5 (± 46.49)		
QTcB, Day 30, n=40, 44	-31.9 (± 120.26)	-13.9 (± 79.33)		
QTcB, EW Visit, n=13, 14	28.2 (± 37.06)	6.9 (± 52.02)		
QTcF, Day 6, n=53, 51	4.3 (± 74.12)	5.7 (± 33.25)		
QTcF, Day 30, n=40, 44	-16.9 (± 75.41)	-12 (± 58.16)		
QTcF, EW Visit, n=13, 14	26 (± 31.85)	18.3 (± 62.78)		

Notes:

[21] - Safety Population

[22] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate measured by ECG at Day 6, Day 30 and EW visit

End point title	Change from Baseline in heart rate measured by ECG at Day 6, Day 30 and EW visit

End point description:

A single 12-lead ECG was obtained at each time point that measured heart rate. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30 and EW visit

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[23]	65[24]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 6, n=60, 58	-3.4 (± 17.57)	-4.9 (± 15.37)		
Day 30, n=46, 50	-3.4 (± 19.81)	0.9 (± 16)		
EW Visit, n=16, 16	-5.4 (± 16.82)	-10.3 (± 29.58)		

Notes:

[23] - Safety Population

[24] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin (ALB) and total protein (TP)

End point title	Change from Baseline in albumin (ALB) and total protein (TP)

End point description:

ALB and TP were measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[25]	65[26]		
Units: Grams per liter				
arithmetic mean (standard deviation)				
ALB, Day 6, n=56, 57	0 (± 3.02)	-0.2 (± 3.67)		
ALB, Day 30, n=44, 47	1 (± 3.44)	3 (± 5.5)		
ALB, Day 90, n=32,38	2.3 (± 3.23)	4.4 (± 5.14)		
ALB, Day 180, n=23, 24	2.3 (± 3.8)	5.3 (± 3.86)		
TP, Day 6, n=56, 57	1 (± 4.64)	0.9 (± 5.9)		
TP, Day 30, n=44, 47	2.7 (± 5.13)	5.6 (± 8.11)		
TP, Day 90, n=32,38	3.1 (± 4.92)	6.5 (± 7.34)		
TP, Day 180, n=23, 24	4.4 (± 5.07)	7.6 (± 5.89)		

Notes:

[25] - Safety Population

[26] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

End point title	Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

End point description:

ALP, ALT and AST were measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value

minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[27]	65[28]		
Units: International units per liter				
arithmetic mean (standard deviation)				
ALP, Day 6, n=56, 57	7.7 (± 20.05)	6.2 (± 16.4)		
ALP, Day 30, n=44, 47	11.7 (± 21.47)	19.5 (± 35.87)		
ALP, Day 90, n=32,38	8.6 (± 27.18)	6.7 (± 18.01)		
ALP, Day 180, n=23, 24	8.9 (± 12.73)	4 (± 17.63)		
ALT, Day 6, n=56, 57	11.4 (± 25.92)	10.7 (± 16.22)		
ALT, Day 30, n=44, 47	7.9 (± 19.02)	10.6 (± 27.84)		
ALT, Day 90, n=32,38	-0.8 (± 16.14)	3.2 (± 11.21)		
ALT, Day 180, n=23, 24	-2 (± 12.83)	1.4 (± 10.66)		
AST, Day 6, n=56, 54	7.9 (± 26.39)	2.5 (± 15.52)		
AST, Day 30, n=44, 46	0.2 (± 14.24)	-0.9 (± 13.18)		
AST, Day 90, n=32,37	-6.1 (± 11.78)	-5.2 (± 13.33)		
AST, Day 180, n=23, 23	-3.2 (± 7.13)	-5 (± 9.7)		

Notes:

[27] - Safety Population

[28] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in direct bilirubin, total bilirubin, and creatinine

End point title	Change from Baseline in direct bilirubin, total bilirubin, and creatinine

End point description:

Direct bilirubin, total bilirubin and creatinine were measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[29]	65[30]		
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
direct bilirubin, Day 6, n=56, 57	0.3 (± 3.81)	0 (± 1.58)		
direct bilirubin, Day 30, n=44, 47	-1 (± 1.93)	-0.4 (± 1.48)		
direct bilirubin, Day 90, n=32,38	-1.5 (± 1.92)	-0.5 (± 1.62)		
direct bilirubin, Day 180, n=23, 24	-1.2 (± 1.59)	-0.1 (± 1.38)		
total bilirubin, Day 6, n=56, 57	-1.5 (± 3.76)	-1.8 (± 5.9)		
total bilirubin, Day 30, n=44, 47	-4.6 (± 4.9)	-3 (± 4.85)		
total bilirubin, Day 90, n=32,38	-4.9 (± 4.75)	-3.5 (± 5.59)		
total bilirubin, Day 180, n=23, 24	-4.6 (± 4.83)	-3.8 (± 5.28)		
creatinine, Day 6, n=56, 57	2.35 (± 20.52)	3.48 (± 16.778)		
creatinine, Day 30, n=44, 47	4.94 (± 31.767)	9.79 (± 28.329)		
creatinine, Day 90, n=32,38	6.69 (± 18.98)	3.09 (± 15.387)		
creatinine, Day 180, n=23, 24	5.07 (± 12.925)	0.24 (± 13.857)		

Notes:

[29] - Safety Population

[30] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in calcium (Ca), chloride (Cl), glucose (Gluc), potassium (K), sodium (Na) and urea/blood urea nitrogen (BUN)

End point title	Change from Baseline in calcium (Ca), chloride (Cl), glucose (Gluc), potassium (K), sodium (Na) and urea/blood urea nitrogen (BUN)

End point description:

Ca, Cl, Gluc, K, Na and urea/BUN were measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[31]	65[32]		
Units: Millimoles per liter				
arithmetic mean (standard deviation)				
Ca, Day 6, n=56, 54	0.042 (± 0.1163)	0.059 (± 0.1564)		

Ca, Day 30, n=44, 46	0.091 (± 0.1254)	0.158 (± 0.1985)		
Ca, Day 90, n=32,37	0.093 (± 0.1092)	0.186 (± 0.196)		
Ca, Day 180, n=23, 23	0.087 (± 0.1053)	0.182 (± 0.1315)		
Cl, Day 6, n=56, 57	-0.9 (± 3.13)	-1.4 (± 4.08)		
Cl, Day 30, n=44, 47	-1.6 (± 3.72)	-3.1 (± 5.01)		
Cl, Day 90, n=32,38	-1.3 (± 3.02)	-2.7 (± 4.67)		
Cl, Day 180, n=23, 24	-1.4 (± 2.48)	-3.4 (± 3.93)		
Gluc, Day 6, n=56, 57	0.21 (± 3.123)	-0.35 (± 2.619)		
Gluc, Day 30, n=44, 47	-0.93 (± 2.611)	-0.45 (± 2.476)		
Gluc, Day 90, n=32,38	-1.12 (± 2.075)	-0.38 (± 2.17)		
Gluc, Day 180, n=23, 24	-1.09 (± 3.045)	-1.02 (± 2.136)		
K, Day 6, n=55, 54	0.17 (± 0.384)	0.21 (± 0.452)		
K, Day 30, n=43, 46	0.37 (± 0.487)	0.3 (± 0.429)		
K, Day 90, n=31,37	0.36 (± 0.477)	0.39 (± 0.404)		
K, Day 180, n=22, 23	0.33 (± 0.517)	0.54 (± 0.472)		
Na, Day 6, n=56, 57	0.1 (± 2.82)	0 (± 2.83)		
Na, Day 30, n=44, 47	-0.3 (± 2.64)	-0.8 (± 3.21)		
Na, Day 90, n=32,38	0.4 (± 1.87)	-0.7 (± 2.91)		
Na, Day 180, n=23, 24	0.5 (± 2.04)	-1.2 (± 2.9)		
Urea/BUN, Day 6, n=56, 57	1.57 (± 2.392)	1.61 (± 2.541)		
Urea/BUN, Day 30, n=44, 47	1.09 (± 2.673)	2.19 (± 5.436)		
Urea/BUN, Day 90, n=32,38	1.02 (± 2.31)	1.04 (± 2.655)		
Urea/BUN, Day 180, n=23, 24	0.51 (± 2.364)	1.04 (± 3.502)		

Notes:

[31] - Safety Population

[32] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin

End point title	Change from Baseline in hemoglobin

End point description:

Hemoglobin was measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[33]	65[34]		
Units: Grams per liter				
arithmetic mean (standard deviation)				
Day 6, n=48, 51	-0.1 (± 9.55)	2.4 (± 10.21)		
Day 30, n=38, 44	-1 (± 13.19)	3.8 (± 14.84)		
Day 90, n=28, 35	-4.1 (± 16.61)	4.7 (± 15.91)		
Day 180, n=20, 22	-6.2 (± 17.7)	7.6 (± 13.45)		

Notes:

[33] - Safety Population

[34] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit

End point title	Change from Baseline in hematocrit

End point description:

Hematocrit was measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[35]	65[36]		
Units: percentage				
arithmetic mean (standard deviation)				
Day 6, n=48, 51	0.00096 (± 0.032094)	0.00896 (± 0.032858)		
Day 30, n=38, 44	-0.0035 (± 0.040669)	0.01116 (± 0.046146)		
Day 90, n=28, 35	-0.01446 (± 0.053418)	0.01329 (± 0.049054)		
Day 180, n=20, 22	-0.02455 (± 0.056181)	0.01909 (± 0.043139)		

Notes:

[35] - Safety Population

[36] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in eosinophils (EOS), lymphocytes (LYM), total absolute neutrophil count (ANC), platelet (PLT) count, white blood cell (WBC) count

End point title	Change from Baseline in eosinophils (EOS), lymphocytes (LYM), total absolute neutrophil count (ANC), platelet (PLT) count, white blood cell (WBC) count

End point description:

EOS, LYM, Total ANC, PLT count and WBC count were measured at Baseline, Day 6, Day 30, Day 90 and Day 180. Baseline was the value obtained on Day 1. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline, Day 6, Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[37]	65[38]		
Units: Giga (10^9 cells) per liter				
arithmetic mean (standard deviation)				
EOS, Day 6, n=48, 51	0.049 (± 0.1153)	0.082 (± 0.1692)		
EOS, Day 30, n=38, 44	0.058 (± 0.2207)	0.086 (± 0.1318)		
EOS, Day 90, n=28 ,35	0.058 (± 0.1175)	0.058 (± 0.1149)		
EOS, Day 180, n=20, 22	0.045 (± 0.1314)	0.048 (± 0.1206)		
LYM, Day 6, n=48, 51	-0.046 (± 0.3904)	-0.03 (± 0.675)		
LYM, Day 30, n=38, 44	0.026 (± 0.4666)	-0.002 (± 0.5728)		
LYM, Day 90, n=28, 35	0.066 (± 0.411)	0.236 (± 0.5854)		
LYM, Day 180, n=20, 22	0.017 (± 0.5005)	0.075 (± 0.5919)		
Total ANC, Day 6, n=48, 51	-0.375 (± 2.2795)	-0.756 (± 2.5842)		
Total ANC, Day 30, n=38, 44	-1.486 (± 2.4578)	-0.581 (± 4.7282)		
Total ANC, Day 90, n=28, 35	-1.469 (± 2.1498)	-1.455 (± 2.3515)		
Total ANC, Day 180, n=20, 22	-2.202 (± 2.7396)	-0.579 (± 1.6956)		
PLT Count, Day 6, n=47, 48	17.4 (± 37.57)	32.4 (± 41.01)		
PLT Count, Day 30, n=37, 42	40.5 (± 62.89)	47.6 (± 44.23)		
PLT Count, Day 90, n=28, 34	33.2 (± 53.36)	60.4 (± 56.3)		
PLT Count, Day 180, n=20, 22	19.9 (± 35.91)	35.9 (± 39.15)		
WBC Count,Day 6, n=48, 51	-0.4 (± 2.294)	-0.78 (± 2.288)		
WBC Count, Day 30, n=38, 44	-1.46 (± 2.524)	-0.54 (± 4.819)		
WBC Count, Day 90, n=28, 35	-1.45 (± 2.017)	-1.28 (± 2.119)		

WBC Count, Day 180, n=20, 22	-2.15 (± 2.496)	-0.55 (± 1.943)		

Notes:

[37] - Safety Population

[38] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: National Institute of Health Stroke Scale (NIHSS) total score at the indicated timepoints

End point title	National Institute of Health Stroke Scale (NIHSS) total score at the indicated timepoints

End point description:

The NIHSS is a 15 item, standardized, disease-specific, deficit scale which measures neurological impairment and is used to quantify participant status by measuring the severity of the stroke as assessed by NIHSS certified study personnel. The total NIHSS score is calculated as the sum of responses to the 15 items. The total NIHSS score ranges from 0-42, with a higher score indicative of a more severe impairment. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 30, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[39]	65[40]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Day 1, n=68, 65	10 (± 4.4)	9.8 (± 3.79)		
Day 30, n=52, 55	6.4 (± 4.4)	5.7 (± 4.66)		
Day 90, n=40, 45	5 (± 3.83)	4.8 (± 4.89)		
Day 180, n=27, 30	3.9 (± 3.22)	4.2 (± 3.87)		

Notes:

[39] - Safety Population

[40] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with suicidal ideation or behavior during treatment based on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of participants with suicidal ideation or behavior during treatment based on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

Prospective assessment of treatment-emergent suicidality was performed by the investigator via the C-SSRS. The C-SSRS is a questionnaire designed to assess severity of suicidality. C-SSRS has 10

questions (5 suicidal ideation questions and 5 suicidal behavior questions) and each question has a binary response (Yes/No). Suicidality during treatment was assessed by integrating both behavior and ideation categories of C-SSRS. Only participants with at least one on-treatment C-SSRS assessment were included in the analysis.

End point type	Secondary

End point timeframe:

Day 1, Day 6, Day 30, Day 60, Day 90 and Day 180

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63[41]	63[42]		
Units: Participants				
number (not applicable)	10	3		

Notes:

[41] - Safety Population

[42] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve from 0 to 5 days [AUC(0-5d)] and area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-inf)] for GSK249320

End point title	Area under the concentration-time curve from 0 to 5 days [AUC(0-5d)] and area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-inf)] for GSK249320

End point description:

Blood samples were collected for determination of plasma concentrations of GSK249320. AUC (0-5d) and AUC (0-inf) were derived from the plasma concentration-time data. Analysis was performed for Pharmacokinetic (PK) Population that comprised of all participants in the Safety Population who had at least one PK sample with a concentration above the non-quantifiable limit. Only participants in the GSK249320 15 mg/kg group were analyzed.

End point type	Secondary

End point timeframe:

Day 6, Day 30 and Day 180

End point values	GSK249320 15 mg/kg - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	62[43]			
Units: Milligrams/milliliter*hour				
geometric mean (geometric coefficient of variation)				
AUC(0-5d)	28.2273 (± 10.9)			
AUC(0-inf)	120.6895 (± 20.4)			

Notes:

[43] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax) for GSK249320

End point title	Maximum observed plasma concentration (Cmax) for GSK249320

End point description:

Cmax is the maximum observed concentration of GSK249320 obtained at the end of infusion post dose on day 6. Only those participants who provided a PK sample at the indicated time point were included in the analysis (as indicated by n=X in the category title).

End point type	Secondary

End point timeframe:

Day 6, Day 30 and Day 180

End point values	GSK249320 15 mg/kg - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	62[44]			
Units: Nanograms/milliliter				
arithmetic mean (standard deviation)				
Day 6, n=52	494523.4 (± 172671)			
Day 30, n=50	111067 (± 42801.2)			
Day 180, n=24	2180.47 (± 2245.78)			

Notes:

[44] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (tmax) for GSK249320

End point title	Time to Cmax (tmax) for GSK249320

End point description:

Cmax is defined as the maximum observed concentration of GSK249320 obtained at the end of infusion post dose on day 6. Tmax is the time of the occurrence of Cmax. Tmax was not calculated therefore there is no data to present for this outcome measure.

End point type	Secondary

End point timeframe:

Day 6, Day 30 and Day 180

End point values	GSK249320 15 mg/kg - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	0[45]			
Units: Hours				
arithmetic mean (standard deviation)	()			

Notes:

[45] - PK Population. Tmax was not calculated therefore there is no data to present here.

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal phase half-life for GSK249320

End point title	Terminal phase half-life for GSK249320

End point description:

Blood samples were collected for determination of plasma concentrations of GSK249320. Terminal phase half-life was derived from the plasma concentration-time data. Analysis was performed for PK Population that comprised of all participants in the Safety Population who had at least one PK sample with a concentration above the non-quantifiable limit. Only participants in the GSK249320 15 mg/kg group were analyzed.

End point type	Secondary

End point timeframe:

Day 6, Day 30 and Day 180

End point values	GSK249320 15 mg/kg - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	62[46]			
Units: Days				
median (full range (min-max))	23.09 (13.5 to 42.9)			

Notes:

[46] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) for GSK249320

End point title	Clearance (CL) for GSK249320

End point description:

Blood samples were collected for determination of plasma concentrations of GSK249320. CL was derived from the plasma concentration-time data. Analysis was performed for PK Population that comprised of all participants in the Safety Population who had at least one PK sample with a concentration above the non-quantifiable limit. Only participants in the GSK249320 15 mg/kg group were analyzed.

End point type	Secondary

End point timeframe:

Day 6, Day 30 and Day 180

End point values	GSK249320 15 mg/kg - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	62[47]			
Units: Milligrams/kilograms/hour				
geometric mean (geometric coefficient of variation)	0.1243 (± 20.4)			

Notes:

[47] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of distribution (V1 and V2) and Volume at steady state (Vss) for GSK249320

End point title	Volume of distribution (V1 and V2) and Volume at steady state (Vss) for GSK249320

End point description:

Blood samples were collected for determination of plasma concentrations of GSK249320. V1, V2 and Vss were derived from the plasma concentration-time data. Analysis was performed for PK Population that comprised of all participants in the Safety Population who had at least one PK sample with a concentration above the non-quantifiable limit. Only participants in the GSK249320 15 mg/kg group were analyzed.

End point type	Secondary

End point timeframe:

Day 6, Day 30 and Day 180

End point values	GSK249320 15 mg/kg - PK			
Subject group type	Subject analysis set			
Number of subjects analysed	62[48]			
Units: milliliters/kilogram				
geometric mean (geometric coefficient of variation)				
V1	43.6992 (± 6.7)			
V2	41.4193 (± 17.8)			
Vss	85.2892 (± 11.5)			

Notes:

[48] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with positive or negative results for antibodies against GSK249320

End point title	Number of participants with positive or negative results for antibodies against GSK249320

End point description:

Blood samples were collected and the presence of antibodies against GSK249320 was assessed using immunoelectrochemiluminescent assays for antibodies against GSK249320. Positive result indicated presence of antibodies and negative result indicated absence of antibodies. Confirmed samples with presence of antibodies were further characterized for neutralizing activity as binding antibody (BAb) and neutralising antibody (NAb) by a neutralization assay. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles). By-visit sample sizes vary due to missing data or early termination of the study.

End point type	Secondary

End point timeframe:

Day 1, Day 30, Day 180, EW visit and Follow-up visit

End point values	Placebo - Safety	GSK249320 15 mg/kg - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68[49]	65[50]		
Units: Participants				
number (not applicable)				
Day 1, BAb Positive, n=68, 65	7	5		
Day 1, BAb Negative, n=68, 65	60	59		
Day 1, NAb Positive, n=7, 5	0	0		
Day 1, NAb Negative, n=7, 5	0	2		
Day 30, BAb Positive, n=59, 60	4	4		
Day 30, BAb Negative, n=59, 60	44	46		
Day 30, NAb Positive, n=4, 4	0	0		
Day 30, NAb Negative, n=4, 4	1	1		
Day 180, BAb Positive, n=42, 41	0	5		
Day 180, BAb Negative, n=42, 41	24	19		
Day 180, NAb Positive, n=0, 5	0	0		
Day 180, NAb Negative, n=0, 5	0	0		
EW visit, BAb Positive, n=23, 23	1	4		
EW visit, BAb Negative, n=23, 23	22	18		
EW visit, NAb Positive, n=1, 4	0	0		
EW visit, NAb Negative, n=1, 4	1	4		
FU visit, BAb Positive, n=0, 1	0	1		
FU visit, BAb Negative, n=0, 1	0	0		
FU visit, NAb Positive, n=0, 1	0	0		
FU visit, NAb Negative, n=0, 1	0	1		

Notes:

[49] - Safety Population

[50] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study at constent to treatement until the end of study or follow up visit (6 months).

Adverse event reporting additional description:

SAEs and non-serious AEs were reported for members of the Safety Population, comprised of all participants who were randomized and took at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo administered as two intravenous (IV) infusions, the first on Study Day 1 which is 24-72 hours post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 milliliters (mL) IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).

Reporting group title	GSK249320 15 mg/kg

Reporting group description:

Participants received GSK249320 15 milligrams (mg)/kilogram (kg) administered as two IV infusions, the first on Study Day 1 which is 24-72 post-stroke onset, and the second on Study Day 6 (+/- 2 days). Each 100 mL IV infusion was delivered over a period of 75 minutes (a 60 minute infusion followed by a 10 to 15 minute flush).

Serious adverse events	Placebo	GSK249320 15 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 68 (23.53%)	9 / 65 (13.85%)	
number of deaths (all causes)	5	2	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Joint injury			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	

Neck injury			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Atrial fibrillation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Atrial flutter			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Atrioventricular block complete			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Bradyarrhythmia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cardiac arrest			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	

Cardiac failure congestive			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Sick sinus syndrome			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cerebral haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cerebrovascular accident			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Stroke in evolution			

subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Gastrointestinal disorders			
Anal ulcer			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Diarrhoea			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Rectal haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	2 / 68 (2.94%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Respiratory failure			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	

Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 68 (1.47%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 2	
Sepsis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 2	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	GSK249320 15 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 68 (36.76%)	32 / 65 (49.23%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 68 (5.88%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
Hypotension			
subjects affected / exposed	4 / 68 (5.88%)	2 / 65 (3.08%)	
occurrences (all)	4	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 68 (0.00%)	4 / 65 (6.15%)	
occurrences (all)	0	5	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 68 (10.29%)	12 / 65 (18.46%)	
occurrences (all)	7	14	
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 7 3 / 68 (4.41%) 3	13 / 65 (20.00%) 13 5 / 65 (7.69%) 5	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 3	4 / 65 (6.15%) 4	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4	5 / 65 (7.69%) 5	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5	0 / 65 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2013	Addition of actigraphy endpoint, change to membership and remit of the iSRC, change to the medical monitor, further clarification around certain study aspects and correction of typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported