

**Clinical trial results:****A Phase 2, Placebo Controlled, Randomized, Double-Blind, Parallel-Arm Study to Evaluate Efficacy and Safety of BMS- 986141 For the Prevention of Recurrent Brain Infarction in Subjects Receiving Acetylsalicylic Acid (ASA) Following Acute Ischemic Stroke or Transient Ischemic Attack Summary**

EudraCT number	2015-003959-22
Trial protocol	ES
Global end of trial date	31 March 2017

Results information

Result version number	v2 (current)
This version publication date	27 October 2018
First version publication date	15 April 2018
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	CV006-004
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02671461
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

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	31 March 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the dose-response relationship of BMS-986141 on the recurrence of brain infarction at 28 days as assessed by a composite of symptomatic ischemic stroke and unrecognized brain infarction as assessed by MRI in subjects with ischemic stroke or TIA treated with ASA.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2016
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 States: 16
Worldwide total number of subjects	16
EEA total number of subjects	0

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)	10
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

16 subjects were enrolled; 15 were randomized, and 14 subjects were treated and included in final data analysis. 1 subject was not randomized because the interactive voice response system did not work at the time of enrollment; 1 consent withdrawn by subject

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo was taken once daily. Administration was exactly the same as for BMS-986141

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching Placebo for BMS-986141 QD for up to 28 days

Arm title	BMS-986141 0.8 mg
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Arm description:

BMS-986141 0.8 mg QD for up to 28 days

Arm type	Experimental
Investigational medicinal product name	BMS-986141
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.8 mg BMS-986141 QD for up to 28 days

Arm title	BMS-986141 4.8 mg
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Arm description:

BMS-986141 4.8 mg QD for up to 28 days

Arm type	Experimental
Investigational medicinal product name	BMS-986141
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4.8 mg BMS-986141 QD for up to 28 days

Number of subjects in period 1^[1]	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg
Started	2	5	7
Completed Treatment Period	1	2 ^[2]	2 ^[3]
Completed	1	4	6
Not completed	1	1	1
Consent withdrawn by subject	1	-	-
Lost to follow-up	-	-	1
Administrative Reason by Sponsor	-	1	-

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: 16 subjects were enrolled; 15 were randomized, and 14 subjects were treated and included in final data analysis. 1 subject was not randomized because the interactive voice response system did not work at the time of enrollment; 1 consent withdrawn by subject.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 16 subjects were enrolled; 15 were randomized, and 14 subjects were treated and included in final data analysis. 1 subject was not randomized because the interactive voice response system did not work at the time of enrollment; 1 consent withdrawn by subject.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 16 subjects were enrolled; 15 were randomized, and 14 subjects were treated and included in final data analysis. 1 subject was not randomized because the interactive voice response system did not work at the time of enrollment; 1 consent withdrawn by subject.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Matching placebo was taken once daily. Administration was exactly the same as for BMS-986141	
Reporting group title	BMS-986141 0.8 mg
Reporting group description: BMS-986141 0.8 mg QD for up to 28 days	
Reporting group title	BMS-986141 4.8 mg
Reporting group description: BMS-986141 4.8 mg QD for up to 28 days	

Reporting group values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg
Number of subjects	2	5	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	3	3
From 65-84 years	1	2	4
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	63.3	64.8	66.7
standard deviation	± 9.2	± 12.2	± 7.6
Sex: Female, Male			
Units: Subjects			
Female	1	1	3
Male	1	4	4
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	1
White	2	3	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	2	5	7

Unknown or Not Reported	0	0	0
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Reporting group values	Total		
Number of subjects	14		
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)	7		
From 65-84 years	7		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	5		
Male	9		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	10		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	14		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Matching placebo was taken once daily. Administration was exactly the same as for BMS-986141	
Reporting group title	BMS-986141 0.8 mg
Reporting group description: BMS-986141 0.8 mg QD for up to 28 days	
Reporting group title	BMS-986141 4.8 mg
Reporting group description: BMS-986141 4.8 mg QD for up to 28 days	

Primary: Number of subjects with composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28

End point title	Number of subjects with composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28 ^[1]
End point description: The incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28 was to be reported by arm in all treated subjects.	
End point type	Primary
End point timeframe: 28 Days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics were planned for this end point.

End point values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	0 ^[4]	
Units: subjects				

Notes:

[2] - Insufficient data available to perform analysis due to study termination

[3] - Insufficient data available to perform analysis due to study termination

[4] - Insufficient data available to perform analysis due to study termination

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with composite of adjudicated major bleeding and adjudicated clinically relevant non-major (CRNM) bleeding during the treatment period

End point title	Percentage of subjects with composite of adjudicated major bleeding and adjudicated clinically relevant non-major (CRNM) bleeding during the treatment period ^[5]
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End point description:

The proportion of subjects with composite of major bleeding and CRNM bleeding was to be reported. Point estimates and 95% CIs for event rates were to be presented by treatment, together with point

estimates and 95% CIs for the difference of event rates between each BMS-986141 arm and placebo.

End point type	Primary
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End point timeframe:

Up to 90 days

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics were planned for this end point.

End point values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[6]	0 ^[7]	0 ^[8]	
Units: Percentage of subjects				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[6] - Insufficient data available to perform analysis due to study termination

[7] - Insufficient data available to perform analysis due to study termination

[8] - Insufficient data available to perform analysis due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with major adverse cardiovascular events (MACE)

End point title	Percentage of subjects with major adverse cardiovascular events (MACE)
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End point description:

MACE was defined as a composite of adjudicated recurrent stroke, myocardial infarction, or cardiovascular death. The percentage of treated subjects experiencing these events at Day 90 was to be reported by arm.

End point type	Secondary
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End point timeframe:

90 days

End point values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[9]	0 ^[10]	0 ^[11]	
Units: Percentage of subjects				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[9] - Insufficient data available to perform analysis due to study termination

[10] - Insufficient data available to perform analysis due to study termination

[11] - Insufficient data available to perform analysis due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with adjudicated symptomatic recurrent stroke (including fatal and non-fatal)

End point title	Percentage of subjects with adjudicated symptomatic recurrent stroke (including fatal and non-fatal)
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End point description:

The percentage of subjects with adjudicated symptomatic recurrent stroke at Day 28 was to be reported by arm for all treated subjects.

End point type	Secondary
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End point timeframe:

Day 28

End point values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[12]	0 ^[13]	0 ^[14]	
Units: Percentage of subjects				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[12] - Insufficient data available to perform analysis due to study termination

[13] - Insufficient data available to perform analysis due to study termination

[14] - Insufficient data available to perform analysis due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with composite of unrecognized brain infarction assessed by MRI at Day 28 and MACE at Day 90

End point title	Percentage of subjects with composite of unrecognized brain infarction assessed by MRI at Day 28 and MACE at Day 90
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End point description:

The percentage of subjects with unrecognized brain infarction at Day 28 and MACE at Day 90 was to be reported by arm for all treated subjects.

End point type	Secondary
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End point timeframe:

Day 90

End point values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[15]	0 ^[16]	0 ^[17]	
Units: Percentage of subjects				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[15] - Insufficient data available to perform analysis due to study termination

[16] - Insufficient data available to perform analysis due to study termination

[17] - Insufficient data available to perform analysis due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects composite of adjudicated recurrent ischemic stroke, myocardial infarction, or cardiovascular death

End point title	Percentage of subjects composite of adjudicated recurrent ischemic stroke, myocardial infarction, or cardiovascular death
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End point description:

The percentage of treated subjects with composite of adjudicated recurrent ischemic stroke, myocardial infarction, or cardiovascular death was reported by arm.

End point type	Secondary
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End point timeframe:

Day 90

End point values	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[18]	0 ^[19]	0 ^[20]	
Units: Percentage of subjects				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[18] - Insufficient data available to perform analysis due to study termination

[19] - Insufficient data available to perform analysis due to study termination

[20] - Insufficient data available to perform analysis due to study termination

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until 30 days following last dose (assessed up to March 2017, approximately 6 months)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Matching placebo was taken once daily. Administration was exactly the same as for BMS-986141

Reporting group title	BMS-986141 0.8 mg
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Reporting group description:

BMS-986141 0.8 mg QD for up to 28 days

Reporting group title	BMS-986141 4.8 mg
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Reporting group description:

BMS-986141 4.8 mg QD for up to 28 days

Serious adverse events	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	BMS-986141 0.8 mg	BMS-986141 4.8 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	4 / 5 (80.00%)	3 / 7 (42.86%)
Investigations			
Blood Potassium Increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 5 (20.00%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

General disorders and administration site conditions Oedema Peripheral subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0
Reproductive system and breast disorders Vaginal Discharge subjects affected / exposed occurrences (all) Vulvovaginal Pruritis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	2 / 5 (40.00%) 2	0 / 7 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0
Renal and urinary disorders Micturation Urgency subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscle Spasms subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 2	3 / 5 (60.00%) 3	0 / 7 (0.00%) 0
Infections and infestations Tinea Pedis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Viral Upper Respiratory Tract Infection	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2016	Changed top dose to be studied from 16 mg QD to 8 mg QD. Initiation of the 8 mg dose group will only begin following DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of total planned subjects. Changes were made to some exclusion criteria to minimize subject risk. Guidance around the use of CYP3A4 inhibitors and inducers has been further clarified. The statistical sections and sample size calculations have been updated to correspond to these changes. PK sampling windows were expanded; changed requirements for contraception to be the use of one highly effective method of contraception or one less effective method of contraception; added statement to Appendix 1 that local laws and regulations may require use of alternative and/or additional contraception methods; clarified genotyping testing; provided further clarifications to assist with study implementation; updated text per new BMS protocol model document template; corrected typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported