



Clinical trial results:

A Single Dose Biocomparison Study to Assess Two Pediatric Formulations of MK-8669

to the Provisional Market Formulation in Healthy Subjects

Summary

EudraCT number	2011-003433-33
Trial protocol	Outside EU/EEA
Global end of trial date	28 January 2012

Results information

Result version number	v1 (current)
This version publication date	20 January 2017
First version publication date	20 January 2017

Trial information

Trial identification

Sponsor protocol code	8669-060
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp
Sponsor organisation address	One Merck Drive, Whitehouse Station, New Jersey, United States, 08889-0100
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000458-PIP01-08
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	28 January 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2012
Global end of trial reached?	Yes
Global end of trial date	28 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the whole blood pharmacokinetics and comparative bioavailability of ridaforolimus (MK-8669) administered as three different formulations in healthy male study participants. Pharmacokinetic measurements included area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}) and maximum concentration (C_{max}) of ridaforolimus. The pharmacokinetic data were compared between the provisional market 10 mg enteric-coated tablet (ECT), enteric-coated granules (ECG), and uncoated granules (UG) in the fasted state, and between ECG and UG in the fed state.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	21
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)	21

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Within approximately 2 to 4 weeks prior to administration of the initial dose of study drug, potential participants were evaluated to determine that they fulfilled the entry requirements.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Treated Participants
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Arm description:

In Periods 1 to 3, participants were randomized to receive 1 of 3 oral treatments in the fasted state: 40 mg ridaforolimus ECT (Treatment A); 40 mg ridaforolimus ECG (Treatment B); 40 mg ridaforolimus UG (Treatment C). In Period 4, participants were administered either ECG or UG following a high-fat meal. Each period was 14 days in duration; single-dose administration was followed by at least a 2 week washout period between doses.

Arm type	Experimental
Investigational medicinal product name	Ridaforolimus 40 mg ECT (Treatment A)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg (4 x 10 mg enteric-coated tablets) administered orally as a single dose

Investigational medicinal product name	Ridaforolimus 40 mg ECG (Treatment B)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

40 mg enteric-coated granules administered orally as a single dose

Investigational medicinal product name	Ridaforolimus 40 mg UG (Treatment C)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

40 mg uncoated granules administered orally as a single dose

Number of subjects in period 1	All Treated Participants
Started	21
Completed	17
Not completed	4
Missed treatment	1
Withdrawal	3

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
Reporting group description: -	

Reporting group values	Overall Study	Total	
Number of subjects	21	21	
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	34 ± 10	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	21	21	

Subject analysis sets

Subject analysis set title	Ridaforolimus ECT (Trt A): Fasted
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECT under fasting conditions and had available PK data

Subject analysis set title	Ridaforolimus ECG (Trt B): Fasted
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECG under fasting conditions and had available PK data

Subject analysis set title	Ridaforolimus UG (Trt C): Fasted
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus UG under fasting conditions and had available PK data

Subject analysis set title	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis]
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECG under fasting conditions, and had available PK data for both fasting and fed states.

Subject analysis set title	Ridaforolimus ECG (Trt B): Fed [Food effect analysis]
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECG under fed conditions, and had available PK data for both fasting and fed states.

Subject analysis set title	Ridaforolimus UG (Trt C): Fasted [Food effect analysis]
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus UG under fasting conditions, and had available PK data for both fasting and fed states.

Subject analysis set title	Ridaforomilus UG (Trt C): Fed [Food effect analysis]
Subject analysis set type	Per protocol

Subject analysis set description:

Healthy adult males who received a single 40 mg oral dose of ridaforolimus UG under fed conditions, and had available PK data for both fasting and fed states.

Reporting group values	Ridaforolimus ECT (Trt A): Fasted	Ridaforolimus ECG (Trt B): Fasted	Ridaforomilus UG (Trt C): Fasted
Number of subjects	19	19	19
Age Categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	19	19	19

Reporting group values	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis]	Ridaforolimus ECG (Trt B): Fed [Food effect analysis]	Ridaforolimus UG (Trt C): Fasted [Food effect analysis]
Number of subjects	7	7	10
Age Categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	7	7	10

Reporting group values	Ridaforomilus UG (Trt C): Fed [Food effect analysis]		
Number of subjects	10		
Age Categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±		

Gender Categorical			
Units: Subjects			
Female	0		
Male	10		

End points

End points reporting groups

Reporting group title	All Treated Participants
Reporting group description: In Periods 1 to 3, participants were randomized to receive 1 of 3 oral treatments in the fasted state: 40 mg ridaforolimus ECT (Treatment A); 40 mg ridaforolimus ECG (Treatment B); 40 mg ridaforolimus UG (Treatment C). In Period 4, participants were administered either ECG or UG following a high-fat meal. Each period was 14 days in duration; single-dose administration was followed by at least a 2 week washout period between doses.	
Subject analysis set title	Ridaforolimus ECT (Trt A): Fasted
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECT under fasting conditions and had available PK data	
Subject analysis set title	Ridaforolimus ECG (Trt B): Fasted
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECG under fasting conditions and had available PK data	
Subject analysis set title	Ridaforolimus UG (Trt C): Fasted
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus UG under fasting conditions and had available PK data	
Subject analysis set title	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis]
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECG under fasting conditions, and had available PK data for both fasting and fed states.	
Subject analysis set title	Ridaforolimus ECG (Trt B): Fed [Food effect analysis]
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus ECG under fed conditions, and had available PK data for both fasting and fed states.	
Subject analysis set title	Ridaforolimus UG (Trt C): Fasted [Food effect analysis]
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus UG under fasting conditions, and had available PK data for both fasting and fed states.	
Subject analysis set title	Ridaforolimus UG (Trt C): Fed [Food effect analysis]
Subject analysis set type	Per protocol
Subject analysis set description: Healthy adult males who received a single 40 mg oral dose of ridaforolimus UG under fed conditions, and had available PK data for both fasting and fed states.	

Primary: Area Under the Concentration-Time Curve of Single Dose (40 mg) Ridaforolimus from Time 0 to Infinity (AUC0-inf)

End point title	Area Under the Concentration-Time Curve of Single Dose (40 mg) Ridaforolimus from Time 0 to Infinity (AUC0-inf)
End point description: Whole blood samples for determination of ridaforolimus concentrations were collected at predose and specified time points over 168 hours following the ridaforolimus dose under fasting conditions in each treatment period.	
End point type	Primary

End point timeframe:

For Periods 1, 2, 3, and 4: Predose (0) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 168 hours postdose

End point values	Ridaforolimus ECT (Trt A): Fasted	Ridaforolimus ECG (Trt B): Fasted	Ridaforomilus UG (Trt C): Fasted	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	19	18 ^[1]	
Units: ng•hr/mL				
geometric mean (confidence interval 95%)	2387.05 (1850.18 to 3079.7)	1571.17 (1222.71 to 2018.94)	2075.12 (1857.33 to 2318.45)	

Notes:

[1] - One participant did not complete Period 1 and was excluded from statistical analysis for AUC0-inf.

Statistical analyses

Statistical analysis title	AUC 0-inf: ECG (Trt B) vs. ECT (Trt A), fasted
Statistical analysis description:	
Geometric mean (GM) values and variance components arising from a linear mixed-effects model were used to determine the geometric mean ratio (GMR) of AUC0-inf for ridaforolimus ECG versus ridaforolimus ECT under fasting conditions. The ECG and ECT formulations were considered comparable if the GMR was within pre-specified confidence-interval (CI) bounds (0.70, 1.43).	
Comparison groups	Ridaforolimus ECT (Trt A): Fasted v Ridaforolimus ECG (Trt B): Fasted
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
Parameter estimate	GMR
Point estimate	0.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.48
upper limit	0.9

Notes:

[2] - The same 19 participants were treated in the Trt A and Trt B groups. The analysis was based on 38 observations from 19 participants, not on 38 participants.

Statistical analysis title	AUC 0-inf: UG (Trt C) vs. ECT (Trt A), fasted
Statistical analysis description:	
GM values and variance components arising from a linear mixed-effects model were used to determine the GMR of AUC0-inf for ridaforolimus UG versus ridaforolimus ECT under fasting conditions. The UG and ECT formulations were considered comparable if the GMR was within pre-specified confidence-interval (CI) bounds (0.70, 1.43)	
Comparison groups	Ridaforolimus ECT (Trt A): Fasted v Ridaforomilus UG (Trt C): Fasted

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	equivalence ^[3]
Parameter estimate	GMR
Point estimate	0.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.04

Notes:

[3] - The same 18 to 19 participants were treated in the TrT A and TrT C groups. The analysis was based on 37 observations from 18 to 19 participants, not on 37 participants.

Secondary: AUC0-inf of Ridaforolimus ECG (Treatment B): Fasted versus Fed States

End point title	AUC0-inf of Ridaforolimus ECG (Treatment B): Fasted versus Fed States
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End point description:

Whole blood samples for determination of ridaforolimus concentrations were collected at predose and specified time points over 168 hours following the ridaforolimus dose in each treatment period. Area under the curve from time 0 to infinity (AUC0-inf) was analyzed following administration of a single 40 mg dose of ridaforolimus ECG under fasting conditions during Periods 1, 2, and 3, and under fed conditions during Period 4. ECT and UG formulations were not included in this analysis.

End point type	Secondary
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End point timeframe:

For Periods 1, 2, 3, and 4: Predose (0) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 168 hours postdose

End point values	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis]	Ridaforolimus ECG (Trt B): Fed [Food effect analysis]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: ng•hr/mL				
geometric mean (confidence interval 95%)	1949.56 (1505.06 to 2525.34)	1359.27 (1049.36 to 1760.71)		

Statistical analyses

Statistical analysis title	AUC 0-inf: ECG (TrT B), Fasted vs. Fed
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Statistical analysis description:

To estimate food effect on whole blood AUC0-inf of 40 mg ridaforolimus ECG, the least squares (LS) mean and corresponding 90% CI for difference in log-transformed AUC0-inf (Fed – Fasted) was calculated from the model using the mean square error and referencing a t-distribution. Mean difference on the log-scale and CI was exponentiated to obtain the AUC0-inf GMR and 90% CIs (Fed / Fasted).

Comparison groups	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis] v Ridaforolimus ECG (Trt B): Fed [Food effect analysis]
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Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence ^[4]
Parameter estimate	GMR
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	0.93

Notes:

[4] - The same 7 participants were treated in the TrT B fasted and fed groups. The analysis was based on 14 observations from 7 participants, not on 14 participants.

Secondary: Maximum Concentration (Cmax) of Ridaforolimus ECG (Treatment B): Fasted versus Fed States

End point title	Maximum Concentration (Cmax) of Ridaforolimus ECG (Treatment B): Fasted versus Fed States
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End point description:

Whole blood samples for determination of ridaforolimus concentrations were collected at predose and specified time points over 168 hours following the ridaforolimus dose in each treatment period. Maximum concentration (Cmax) was analysed following administration of ridaforolimus 40 mg ECG under fasting conditions during Periods 1, 2, and 3, and under fed conditions during Period 4.

End point type	Secondary
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End point timeframe:

For Periods 1, 2, 3, and 4: Predose (0) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 168 hours postdose

End point values	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis]	Ridaforolimus ECG (Trt B): Fed [Food effect analysis]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: ng/mL				
geometric mean (confidence interval 95%)	189.94 (130.14 to 277.22)	83.9 (57.48 to 122.45)		

Statistical analyses

Statistical analysis title	Cmax: ECG (TrT B), Fasted vs. Fed
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Statistical analysis description:

To estimate food effect on whole blood Cmax of 40 mg ridaforolimus ECG, the LS mean and corresponding 90% CI for difference in log-transformed Cmax (Fed – Fasted) was calculated from the model using the mean square error and referencing a t-distribution. Mean difference on the log-scale and CI was exponentiated to obtain the Cmax GMR and 90% CIs (Fed / Fasted).

Comparison groups	Ridaforolimus ECG (Trt B): Fasted [Food effect analysis] v Ridaforolimus ECG (Trt B): Fed [Food effect analysis]
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Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence ^[5]
Parameter estimate	GMR
Point estimate	0.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.31
upper limit	0.64

Notes:

[5] - The same 7 participants were treated in the TrT B fasted and fed groups. The analysis was based on 14 observations from 7 participants, not on 14 participants.

Secondary: AUC0-inf of Ridaforolimus UG (Treatment C): Fasted versus Fed States

End point title	AUC0-inf of Ridaforolimus UG (Treatment C): Fasted versus Fed States
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End point description:

Whole blood samples for determination of ridaforolimus concentrations were collected at predose and specified time points over 168 hours following the ridaforolimus dose in each treatment period. Area under the curve from time 0 to infinity (AUC0-inf) was analysed following administration of ridaforolimus 40 mg UG under fasting conditions during Periods 1, 2, and 3, and under fed conditions during Period 4.

End point type	Secondary
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End point timeframe:

For Periods 1, 2, 3, and 4: Predose (0) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 168 hours postdose

End point values	Ridaforolimus UG (Trt C): Fasted [Food effect analysis]	Ridaforolimus UG (Trt C): Fed [Food effect analysis]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: ng•hr/mL				
geometric mean (confidence interval 95%)	2211.29 (1814.93 to 2694.21)	1664.81 (1366.4 to 2028.38)		

Statistical analyses

Statistical analysis title	AUC 0-inf: UG (TrT C), Fasted vs. Fed
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Statistical analysis description:

To estimate food effect on whole blood C_{max} of 40 mg ridaforolimus ECG, the LS mean and corresponding 90% CI for difference in log-transformed C_{max} (Fed – Fasted) was calculated from the model using the mean square error and referencing a t-distribution. Mean difference on the log-scale and CI was exponentiated to obtain the C_{max} GMR and 90% CIs (Fed / Fasted).

Comparison groups	Ridaforolimus UG (Trt C): Fasted [Food effect analysis] v Ridaforolimus UG (Trt C): Fed [Food effect analysis]
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Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence ^[6]
Parameter estimate	GMR
Point estimate	0.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.68
upper limit	0.84

Notes:

[6] - The same 10 participants were treated in the TrT C fasted and fed groups. The analysis was based on 20 observations from 10 participants, not on 20 participants.

Secondary: Cmax of Ridaforolimus UG (Trt C): Fasted versus Fed States

End point title	Cmax of Ridaforolimus UG (Trt C): Fasted versus Fed States
End point description:	Whole blood samples for determination of ridaforolimus concentrations were collected at predose and specified time points over 168 hours following the ridaforolimus dose in each treatment period. Maximum concentration (Cmax) was analysed following administration of ridaforolimus 40 mg UG in under fasting conditions during Periods 1, 2, and 3, and under fed conditions during Period 4.
End point type	Secondary
End point timeframe:	For Periods 1, 2, 3, and 4: Predose (0) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 168 hours postdose.

End point values	Ridaforolimus UG (Trt C): Fasted [Food effect analysis]	Ridaforolimus UG (Trt C): Fed [Food effect analysis]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: ng/mL				
geometric mean (confidence interval 95%)	178.16 (146.12 to 217.23)	93.55 (76.73 to 114.07)		

Statistical analyses

Statistical analysis title	Cmax: UG (Trt C), Fasted vs. Fed
Statistical analysis description:	To estimate food effect on whole blood Cmax of 40 mg ridaforolimus UG, the LS mean and corresponding 90% CI for difference in log-transformed Cmax (Fed – Fasted) was calculated from the model using the mean square error and referencing a t-distribution. Mean difference on the log-scale and CI was exponentiated to obtain the Cmax GMR and 90% CIs (Fed / Fasted).
Comparison groups	Ridaforolimus UG (Trt C): Fasted [Food effect analysis] v Ridaforolimus UG (Trt C): Fed [Food effect analysis]

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence ^[7]
Parameter estimate	GMR
Point estimate	0.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.44
upper limit	0.62

Notes:

[7] - The same 10 participants were treated in the TrT C fasted and fed groups. The analysis was based on 20 observations from 10 participants, not on 20 participants.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From beginning of treatment (Day 1) to treatment Week 4 in Period 1, Period 2, Period 3, and Period 4, and for a poststudy evaluation before the end of approximately 10 weeks

Adverse event reporting additional description:

An adverse experience was any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	Ridaforolimus ECT (Trt A)-Fasted
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus ECT under fasting conditions

Reporting group title	Ridaforolimus ECG (Trt B)-Fasted
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus ECG under fasting conditions

Reporting group title	Ridaforolimus UG (Trt C)-Fasted
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus UG under fasting conditions

Reporting group title	Ridaforolimus ECG (Trt B)-Fed Light
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus ECG in Period 4 following a light breakfast

Reporting group title	Ridaforolimus UG (Trt C)-Fed Light
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus UG in Period 4 following a light breakfast

Reporting group title	Ridaforolimus ECG (Trt B)-Fed Full
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus ECG in Period 4 following a high-fat breakfast

Reporting group title	Ridaforolimus UG (Trt C)-Fed Full
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Reporting group description:

Healthy adult males that received a single 40 mg oral dose of ridaforolimus UG in Period 4 following a high-fat breakfast

Serious adverse events	Ridaforolimus ECT (Trt A)-Fasted	Ridaforolimus ECG (Trt B)-Fasted	Ridaforolimus UG (Trt C)-Fasted
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

Serious adverse events	Ridaforolimus ECG (Trt B)-Fed Light	Ridaforolimus UG (Trt C)-Fed Light	Ridaforolimus ECG (Trt B)-Fed Full
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Ridaforolimus UG (Trt C)-Fed Full		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Ridaforolimus ECT (Trt A)-Fasted	Ridaforolimus ECG (Trt B)-Fasted	Ridaforolimus UG (Trt C)-Fasted
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)	3 / 19 (15.79%)	3 / 19 (15.79%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	4 / 19 (21.05%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	4	0	0
Gastrointestinal disorders			
APHTHOUS STOMATITIS			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
DRY MOUTH			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
DYSPEPSIA			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
STOMATITIS			

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
TONGUE ULCERATION			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
NASAL CONGESTION			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
SINUS CONGESTION			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
THROAT IRRITATION			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
PAPULE			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
PRURITUS			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
RASH MACULAR			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Non-serious adverse events	Ridaforolimus ECG (Trt B)-Fed Light	Ridaforolimus UG (Trt C)-Fed Light	Ridaforolimus ECG (Trt B)-Fed Full
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	2 / 5 (40.00%)	1 / 7 (14.29%)

Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 5 (20.00%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
APHTHOUS STOMATITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
DRY MOUTH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
DYSPEPSIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
STOMATITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
TONGUE ULCERATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 2 (0.00%)	1 / 5 (20.00%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
NASAL CONGESTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
SINUS CONGESTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
THROAT IRRITATION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 5 (20.00%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Skin and subcutaneous tissue disorders			
PAPULE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
RASH MACULAR			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Ridaforolimus UG (Trt C)-Fed Full		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
APHTHOUS STOMATITIS			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
DRY MOUTH			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
DYSPEPSIA			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
STOMATITIS			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
TONGUE ULCERATION			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
COUGH			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
NASAL CONGESTION			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
SINUS CONGESTION			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
THROAT IRRITATION			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
PAPULE			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
PRURITUS			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
RASH MACULAR			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2011	Amendment 1 specified revised study eligibility criteria and clarified the study flow chart
09 January 2012	Amendment 2 incorporated flexibility to repeat a treatment period, if deemed necessary by the Sponsor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Caveat: 7 of 21 participants had a light breakfast rather than a protocol-defined high-fat breakfast prior to blood sampling in Period 4. However, these participants were re-dosed and repeated the period after the proper high-fat breakfast.

Notes: