



## 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 |
|-----------------------|----------|

#### 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<sub>0-inf</sub>) and maximum concentration (C<sub>max</sub>) 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 |
|-----------|--------------------------|

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

| <b>Number of subjects in period 1</b> | 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<br>Units: Subjects |               |       |  |

|   |            |    |  |
|---|------------|----|--|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 34<br>± 10 | -  |  |
| Gender Categorical<br>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 |  |  |

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## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | All Treated Participants                                 |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup>                |  |
| Units: ng•hr/mL                          |                                   |                                   |                                  |  |
| geometric mean (confidence interval 95%) | 2387.05<br>(1850.18 to 3079.7)    | 1571.17<br>(1222.71 to 2018.94)   | 2075.12<br>(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 <sup>[2]</sup>  |
| 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 <sup>[3]</sup> |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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<br>(1505.06 to 2525.34)                          | 1359.27<br>(1049.36 to 1760.71)                       |  |  |

### Statistical analyses

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

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<br>Ridaforolimus ECG (Trt B): Fed [Food effect analysis] |
|-------------------|---|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 14                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[4]</sup> |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|----------------------------|-----------------------------------|

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<br>Ridaforolimus ECG (Trt B): Fed [Food effect analysis] |
|-------------------|---|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 14                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[5]</sup> |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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<br>(1814.93 to 2694.21)                         | 1664.81<br>(1366.4 to 2028.38)                       |  |  |

### Statistical analyses

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

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 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 <sup>[6]</sup> |
| 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 <sup>[7]</sup> |
| 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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Ridaforolimus ECT (Trt A)-Fasted |
|-----------------------|----------------------------------|

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 |
|-----------------------|----------------------------------|

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 |
|-----------------------|---------------------------------|

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 |
|-----------------------|-------------------------------------|

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 |
|-----------------------|------------------------------------|

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 |
|-----------------------|------------------------------------|

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 |
|-----------------------|-----------------------------------|

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                               |



| <b>Serious adverse events</b>                     | Ridaforolimus ECG<br>(Trt B)-Fed Light | Ridaforolimus UG<br>(Trt C)-Fed Light | Ridaforolimus ECG<br>(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                                     |

| <b>Serious adverse events</b>                     | Ridaforolimus UG<br>(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 %

| <b>Non-serious adverse events</b>                     | Ridaforolimus ECT<br>(Trt A)-Fasted | Ridaforolimus ECG<br>(Trt B)-Fasted | Ridaforolimus UG<br>(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              |
| <b>TONGUE ULCERATION</b>                               |                |                |                |
| subjects affected / exposed                            | 1 / 19 (5.26%) | 1 / 19 (5.26%) | 1 / 19 (5.26%) |
| occurrences (all)                                      | 1              | 1              | 1              |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                |                |
| <b>COUGH</b>   |                |                |                |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 0 / 19 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all)                                      | 0              | 0              | 0              |
| <b>NASAL CONGESTION</b>                                |                |                |                |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 0 / 19 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all)                                      | 0              | 0              | 0              |
| <b>OROPHARYNGEAL PAIN</b>                              |                |                |                |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 1 / 19 (5.26%) | 1 / 19 (5.26%) |
| occurrences (all)                                      | 0              | 1              | 1              |
| <b>SINUS CONGESTION</b>                                |                |                |                |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 0 / 19 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all)                                      | 0              | 0              | 0              |
| <b>THROAT IRRITATION</b>                               |                |                |                |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 0 / 19 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all)                                      | 0              | 0              | 0              |
| <b>Skin and subcutaneous tissue disorders</b>          |                |                |                |
| <b>PAPULE</b>  |                |                |                |
| subjects affected / exposed                            | 1 / 19 (5.26%) | 0 / 19 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all)                                      | 1              | 0              | 0              |
| <b>PRURITUS</b>  |                |                |                |
| subjects affected / exposed                            | 1 / 19 (5.26%) | 0 / 19 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all)                                      | 1              | 0              | 0              |
| <b>RASH MACULAR</b>                                    |                |                |                |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 0 / 19 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all)                                      | 0              | 0              | 1              |

|   |                                     |                                    |                                    |
|---|-------------------------------------|------------------------------------|------------------------------------|
| <b>Non-serious adverse events</b>                     | 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             |

|   |                                   |  |  |
|---|-----------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | 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:

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### 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: