



Clinical trial results:

A Randomised, Placebo Controlled, Double-Blinded Comparative Study Evaluating the Effect of Ramipril on Urinary Protein Excretion in Maintenance Renal Transplant Patients Converted to Sirolimus Summary

EudraCT number	2007-001675-11
Trial protocol	FR ES BE AT DE IT HU PL
Global end of trial date	09 September 2013

Results information

Result version number	v2 (current)
This version publication date	03 August 2016
First version publication date	05 August 2015
Version creation reason	• Correction of full data set correct of data set required

Trial information

Trial identification

Sponsor protocol code	0468E5-4439
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00502242
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B1741001

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021 , ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021 , ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2013
Global end of trial reached?	Yes
Global end of trial date	09 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of ramipril in preventing a urinary protein to creatinine ratio (U p/c) of 0.5 or greater following conversion to sirolimus (SRL) from a calcineurin inhibitor (CNI) (either tacrolimus [TAC] or cyclosporine [CsA]) in maintenance renal transplant patients.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Background therapy:

In addition to SRL, all participants, at the discretion of the investigator, received background medication of corticosteroids and/or one of the following: mycophenolate mofetil (MMF), mycophenolate sodium (MPS), or azathioprine (AZA). Participants were permitted to switch between MMF, MPS, and AZA. Participants not receiving MMF, MPS, or AZA or who discontinued these agents received corticosteroids at a minimum of 2.5 milligrams (mg) per (/) day. Participants receiving corticosteroids were not permitted to undergo corticosteroid withdrawal following randomisation.

Evidence for comparator: -

Actual start date of recruitment	14 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Argentina: 26
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Brazil: 49
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Mexico: 28
Country: Number of subjects enrolled	South Africa: 21
Country: Number of subjects enrolled	United States: 130

Worldwide total number of subjects	295
EEA total number of subjects	17

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)	271
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was completed within 3 weeks before randomisation (from time informed consent form was signed to Day of Randomisation).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramipril

Arm description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received ramipril, 5 or 10 mg/day orally (PO). 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 nanograms per millilitre [ng/mL] less than [$<$]1 year post-transplant [PT], 5-15 ng/mL greater than or equal to [$\geq$]1 year PT) for up to 52 weeks. Ramipril was increased to 10-20 mg if U p/c was ≥ 0.5 . If U p/c ≥ 0.5 persisted, losartan 50 mg/day was added; if U p/c ≥ 0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c < 0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Arm type	Experimental
Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

After randomisation, ramipril or placebo administration was initiated. For participants enrolled prior to implementation of Amendment 3, ramipril or placebo was initiated at 10 mg/day. For participants enrolled after implementation of Amendment 3, ramipril or placebo was initiated at 5 mg/day. If ramipril or placebo needed to be temporarily withheld but was resumed within the 4-week pre-SRL conversion phase, and the participant received a minimum of 10 consecutive days of ramipril or placebo therapy prior to SRL conversion the participant was permitted to be converted. If a participant was not able to resume ramipril or placebo therapy, the participant was dropped from the study and no further data was collected. Losartan rescue therapy was initiated at 50 mg/day and may have been titrated to 100 mg/day if the Up/c ratio was not maintained at < 0.5 on 50 mg/day. All study medication doses given, were adjusted throughout the study based on the maintenance of targeted Up/c levels.

Arm title	Placebo
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Arm description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received double-blinded placebo, 1 capsule (5 or 10 mg/day), PO. 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 ng/mL < 1 year PT, 5-15 ng/mL ≥ 1 year PT) for up to 52 weeks. Placebo dose was doubled if U p/c was ≥ 0.5 . If U p/c ≥ 0.5 persisted, losartan 50 mg/day was added; if U p/c ≥ 0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c < 0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

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

Dosage and administration details:

After randomisation, ramipril or placebo administration was initiated. For participants enrolled prior to implementation of Amendment 3, ramipril (or placebo) was initiated at 10 mg/day. For participants enrolled following implementation of Amendment 3, ramipril or placebo was initiated at 5 mg/day. If ramipril or placebo needed to be temporarily withheld but was resumed within the 4-week pre-SRL conversion phase, and the participant received a minimum of 10 consecutive days of ramipril or placebo therapy prior to SRL conversion the participant was permitted to be converted. If a participant was not able to resume ramipril or placebo therapy, the participant was dropped from the study and no further data was collected. Losartan rescue therapy was initiated at 50 mg/day and may have been titrated to 100 mg/day if the Up/c ratio was not maintained at <0.5 on 50 mg/day. All study medication doses given, were adjusted throughout the study based on the maintenance of targeted Up/c level

Number of subjects in period 1	Ramipril	Placebo
Started	155	140
Completed	104	84
Not completed	51	56
Adverse event, serious fatal	1	1
Consent withdrawn by subject	6	7
Physician decision	2	3
Adverse event, non-fatal	30	19
Other	8	14
Lack of efficacy	1	11
Protocol deviation	3	1

Baseline characteristics

Reporting groups

Reporting group title	Ramipril
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Reporting group description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received ramipril, 5 or 10 mg/day orally (PO). 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 nanograms per millilitre [ng/mL] less than [$<$]1 year post-transplant [PT], 5-15 ng/mL greater than or equal to [$\geq$]1 year PT) for up to 52 weeks. Ramipril was increased to 10-20 mg if U p/c was ≥ 0.5 . If U p/c ≥ 0.5 persisted, losartan 50 mg/day was added; if U p/c ≥ 0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c < 0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Reporting group title	Placebo
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Reporting group description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received double-blinded placebo, 1 capsule (5 or 10 mg/day), PO. 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 ng/mL < 1 year PT, 5-15 ng/mL ≥ 1 year PT) for up to 52 weeks. Placebo dose was doubled if U p/c was ≥ 0.5 . If U p/c ≥ 0.5 persisted, losartan 50 mg/day was added; if U p/c ≥ 0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c < 0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Reporting group values	Ramipril	Placebo	Total
Number of subjects	155	140	295
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	46.8 ± 12.7	47.5 ± 12.9	-
Gender categorical Units: Subjects			
Female	48	50	98
Male	107	90	197

End points

End points reporting groups

Reporting group title	Ramipril
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Reporting group description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received ramipril, 5 or 10 mg/day orally (PO). 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 nanograms per millilitre [ng/mL] less than [$<$] 1 year post-transplant [PT], 5-15 ng/mL greater than or equal to [$\geq$] 1 year PT) for up to 52 weeks. Ramipril was increased to 10-20 mg if U p/c was ≥ 0.5 . If U p/c ≥ 0.5 persisted, losartan 50 mg/day was added; if U p/c ≥ 0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c < 0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Reporting group title	Placebo
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Reporting group description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received double-blinded placebo, 1 capsule (5 or 10 mg/day), PO. 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 ng/mL < 1 year PT, 5-15 ng/mL ≥ 1 year PT) for up to 52 weeks. Placebo dose was doubled if U p/c was ≥ 0.5 . If U p/c ≥ 0.5 persisted, losartan 50 mg/day was added; if U p/c ≥ 0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c < 0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Subject analysis set title	Pharmacokinetic analysis set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

C_{min,TN} was determined for SRL using the area method for the intervals: 0-2 weeks, >2-4 weeks, >4-12 weeks, >12-24 weeks, >24-36 weeks and >36-52 weeks using the equation $C_{min,TN} = AUC_{i-j}/(t_{j-i} - t_{i-i})$, where AUC was the area under the concentration-time curve, i was the beginning of the interval and j was the end of the interval. C_{min,TN} was calculated for participants who did not dropout of studies, but were missing concentrations at the interval endpoints by carrying the last observed concentration forward to the interval endpoint.

Primary: Percentage of Participants who had Initiated Losartan Therapy at 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants who had Initiated Losartan Therapy at 52 Weeks Following Conversion to SRL
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End point description:

The event for each participant was defined as the initiation of losartan while on SRL and ramipril/placebo combination therapy. Participants who started losartan prior to SRL administration were not counted as events. Percentage was estimated using Kaplan-Meier method for time to event data. Modified Intent to Treat (mITT) population: all participants in the safety population who took at least one dose of SRL.

End point type	Primary
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End point timeframe:

From Day 1 of SRL conversion to 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: Percentage of Participants				
number (confidence interval 95%)	6.2 (2.7 to 11.6)	23.2 (15.7 to 31.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis Ramipril, Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002 ^[1]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.528

Notes:

[1] - 2-sided p-value; alpha equals (=) 0.05

Stratified log-rank test with region and race strata

Secondary: Percentage of Participants who had a Dose Escalation in Randomised Test Article (Ramipril or Placebo) by 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants who had a Dose Escalation in Randomised Test Article (Ramipril or Placebo) by 52 Weeks Following Conversion to SRL
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End point description:

Defined as the time from the first dose of SRL administration to the first dose escalation of randomised test article (ramipril or placebo; in weeks), or censored on the day that a participant stopped the combination of SRL and randomised test article (ramipril or placebo) if the participants did not experience any ramipril/placebo dose escalation following conversion to SRL. Dose-escalation was defined as an increase in total daily dose of ramipril/placebo compared to Day 1 post conversion. Percentage was estimated using Kaplan-Meier method for time to event data. mITT population.

End point type	Secondary
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End point timeframe:

From Day 1 of SRL conversion to 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: Percentage of Participants				
number (confidence interval 95%)	14.4 (8.7 to 21.3)	29.2 (21.2 to 37.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)	
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0031
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.237
upper limit	0.763

Secondary: Percentage of Participants With U p/c <0.5 at 24 and 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants With U p/c <0.5 at 24 and 52 Weeks Following Conversion to SRL
End point description: Spot urine sample of protein and creatinine concentrations were obtained during the pre-SRL conversion period and after conversion. mITT population; includes assessments from On-Therapy and Off-Therapy Periods.	
End point type	Secondary
End point timeframe: 24 weeks and 52 weeks after conversion	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: Percentage of Participants				
number (not applicable)				
Up to 24 weeks post-conversion	92	77.8		
Up to 52 weeks post-conversion	82.6	73		

Statistical analyses

Statistical analysis title	Up to 24 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 ^[2]
Method	Fisher exact

Notes:

[2] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Up to 52 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.074 ^[3]
Method	Fisher exact

Notes:

[3] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants With Urinary Albumin to Creatinine Ratio (U alb/c) <0.5 at 24 and 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants With Urinary Albumin to Creatinine Ratio (U alb/c) <0.5 at 24 and 52 Weeks Following Conversion to SRL
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End point description:

Spot urine sample of albumin and creatinine concentrations were obtained during the pre-SRL conversion period and after conversion. mITT population; includes assessments from On-Therapy and Off-Therapy Periods.

End point type	Secondary
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End point timeframe:

24 weeks and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: Percentage of Participants				
number (not applicable)				
Up to 24 weeks post-conversion	95.7	89.7		
Up to 52 weeks post-conversion	88.4	82.5		

Statistical analyses

Statistical analysis title	Up to 24 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.093 ^[4]
Method	Fisher exact

Notes:

[4] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Up to 52 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.219 ^[5]
Method	Fisher exact

Notes:

[5] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants with Both U alb/c <0.5 and U p/c <0.5 at 24 and 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants with Both U alb/c <0.5 and U p/c <0.5 at 24 and 52 Weeks Following Conversion to SRL
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End point description:

The U alb/c and U p/c must have been collected on the same day to be counted as the numerator. mITT population; includes assessments from On-Therapy and Off-Therapy Periods.

End point type	Secondary
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End point timeframe:

24 weeks and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: Percentage of Participants				
number (not applicable)				
Up to 24 weeks post-conversion	91.3	77		
Up to 52 weeks post-conversion	79	70.6		

Statistical analyses

Statistical analysis title	Up to 24 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 ^[6]
Method	Fisher exact

Notes:

[6] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Up to 52 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.121 ^[7]
Method	Fisher exact

Notes:

[7] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: U p/c at Baseline and Weeks 3, 4, 8, 12, 24, 30, 36, and 52 Following Conversion to SRL

End point title	U p/c at Baseline and Weeks 3, 4, 8, 12, 24, 30, 36, and 52 Following Conversion to SRL
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End point description:

U p/c was measured in milligrams per milligram (mg/mg). The baseline U p/c values were the last values of the pre-SRL conversion period. mITT population; n (number) = number of participants assessed for the specified parameter at a given visit; only participants with non-missing records of U p/c were included in the analysis. Includes measures collected from On-Therapy and Off-Therapy Periods. CFB = change from baseline.

End point type	Secondary
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End point timeframe:

Baseline and 3, 4, 8, 12, 24, 30, 36, and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: mg /mg				
arithmetic mean (standard deviation)				
Baseline (n=138,126)	0.17 (± 0.37)	0.15 (± 0.07)		

Week 3 (n=130,117)	0.18 (± 0.11)	0.23 (± 0.19)		
Week 4 (n=136,124)	0.18 (± 0.09)	0.28 (± 0.27)		
Week 8 (n=130,119)	0.23 (± 0.39)	0.31 (± 0.37)		
Week 12 (n=124,121)	0.23 (± 0.3)	0.38 (± 1.18)		
Week 24 (n=121,122)	0.26 (± 0.4)	0.31 (± 0.39)		
Week 30 (n=111,108)	0.23 (± 0.23)	0.32 (± 0.37)		
Week 36 (n=109,92)	0.22 (± 0.13)	0.29 (± 0.3)		
Week 52 (n=126,111)	0.27 (± 0.31)	0.35 (± 0.43)		

Attachments (see zip file)	Adjusted Geometric Mean Fold Change/U pc at Baseline and
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Statistical analyses

Statistical analysis title	CFB at Week 3, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	= 0.0098 ^[9]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	0.96

Notes:

[8] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[9] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). Analysis of covariance (ANCOVA) model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 4, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	= 0.0003 ^[11]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.89

Notes:

[10] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[11] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 8, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	= 0.0016 ^[13]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.91

Notes:

[12] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[13] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 12, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	= 0.0165 ^[15]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.96

Notes:

[14] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[15] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 24, Ramipril v Placebo
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[16]
P-value	= 0.0264 ^[17]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.98

Notes:

[16] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[17] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 30, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 0.0062 ^[19]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.93

Notes:

[18] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[19] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 36, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[20]
P-value	= 0.0341 ^[21]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.99

Notes:

[20] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[21] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 52, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[22]
P-value	= 0.06 ^[23]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.01

Notes:

[22] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[23] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic Up/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Secondary: U alb/c at Baseline and Weeks 3, 4, 8, 12, 24, 30, 36, and 52 Following Conversion to SRL

End point title	U alb/c at Baseline and Weeks 3, 4, 8, 12, 24, 30, 36, and 52 Following Conversion to SRL
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End point description:

U alb/c was measured in mg/mg. Baseline U alb/c values were the last values of the pre-SRL conversion period. mITT population; n=number of participants assessed for the specified parameter at a given visit; only participants with non-missing records of U alb/c were included in the analysis. Includes measures collected from On-Therapy and Off-Therapy Periods. CFB = change from baseline.

End point type	Secondary
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End point timeframe:

Baseline and 3, 4, 8, 12, 24, 30, 36, and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: mg /mg				
arithmetic mean (standard deviation)				
Baseline (n=138,126)	0.04 (± 0.26)	0.02 (± 0.02)		
Week 3 (n=129,117)	0.03 (± 0.05)	0.06 (± 0.11)		
Week 4 (n=136,124)	0.03 (± 0.04)	0.09 (± 0.16)		
Week 8 (n=129,119)	0.06 (± 0.31)	0.11 (± 0.24)		
Week 12 (n=124,121)	0.05 (± 0.09)	0.17 (± 0.84)		
Week 24 (n=121,122)	0.08 (± 0.24)	0.11 (± 0.28)		
Week 30 (n=111,108)	0.06 (± 0.13)	0.11 (± 0.21)		

Week 36 (n=109,92)	0.05 ($\pm$ 0.08)	0.1 ($\pm$ 0.21)		
Week 52 (n=126,111)	0.09 ($\pm$ 0.21)	0.15 ($\pm$ 0.31)		

Attachments (see zip file)	Adjusted Geometric Mean Fold Change/U alb/c at Baseline and
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Statistical analyses

Statistical analysis title	CFB at Week 3, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[24]
P-value	= 0.0034 ^[25]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.89

Notes:

[24] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[25] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 4, Ramipril v Placebo
Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[26]
P-value	< 0.0001 ^[27]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.76

Notes:

[26] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[27] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 8, Ramipril v Placebo
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[28]
P-value	= 0.0002 ^[29]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.79

Notes:

[28] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[29] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 12, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[30]
P-value	= 0.0032 ^[31]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.87

Notes:

[30] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[31] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 24, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[32]
P-value	= 0.013 ^[33]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.92

Notes:

[32] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[33] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 30, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[34]
P-value	= 0.0577 ^[35]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.01

Notes:

[34] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[35] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 36, Ramipril v Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[36]
P-value	= 0.1146 ^[37]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.07

Notes:

[36] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[37] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Statistical analysis title	CFB at Week 52, Ramipril v Placebo
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[38]
P-value	= 0.3496 ^[39]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.2

Notes:

[38] - Treatment ratio (Ramipril/Placebo) in the geometric mean fold-change.

[39] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA model with change in the logarithmic U alb/c as dependent variable, treatment and region/race as factors, and logarithmic baseline as covariate.

Secondary: Percentage of Participants Who Discontinued SRL Therapy at 24 and 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants Who Discontinued SRL Therapy at 24 and 52 Weeks Following Conversion to SRL
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End point description:

Defined as the percentage of participants who stop SRL (as test article) between the first day of SRL and either Week 24 or Week 52 following conversion to SRL. If a participant had a >14 day gap in SRL use, the stop date of SRL was the date of the last SRL use before it was re-initiated. Participants who early terminate SRL at Week 24 were defined as having SRL stop day less than or equal to ($\leq$) Day 190 (selected as the midpoint between Weeks 24 and 30). Participants who early terminate SRL at Week 52 were defined as having SRL stop day $\leq$ Day 337 (selected as the midpoint between Weeks 44 and 52). mITT population.

End point type	Secondary
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End point timeframe:

24 weeks and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: p e r c e n t a g e o f participants				
number (not applicable)				
Up to 24 weeks post-conversion	15.2	15.9		
Up to 52 weeks post-conversion	19.6	28.6		

Statistical analyses

Statistical analysis title	Up to 24 weeks post-conversion
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[40]
P-value	= 1
Method	Fisher exact

Notes:

[40] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Up to 52 weeks post-conversion
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[41]
P-value	= 0.1115
Method	Fisher exact

Notes:

[41] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Abbreviated Modified Diet in Renal Disease (MDRD) Glomerular Filtration Rate (GFR) at Weeks 12, 24, and 52 Following Conversion to SRL

End point title	Abbreviated Modified Diet in Renal Disease (MDRD) Glomerular Filtration Rate (GFR) at Weeks 12, 24, and 52 Following Conversion to SRL
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End point description:

Calculated in millimetres per minute per 1.73 square meters (mL/min/1.73m²). Age and corresponding creatinine at each visit (Weeks 12, 24, and 52) were used to calculate GFR. mITT population; n=number of participants assessed for the specified parameter at a given visit. Includes measures collected from On-Therapy and Off-Therapy Periods.

End point type	Secondary
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End point timeframe:

12, 24, and 52 weeks following conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)				
Baseline (n=138,126)	62.06 (± 14.08)	63.3 (± 15.64)		
Week 12 (n=125,122)	64.91 (± 16.54)	66.58 (± 15.26)		
Week 24 (n=123,122)	65.18 (± 17.99)	63.85 (± 16.49)		
Week 52 (n=128,115)	64.17 (± 16.79)	63.41 (± 15.54)		

Statistical analyses

Statistical analysis title	Change from Baseline at Week 12
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[42]
P-value	= 0.4933 ^[43]
Method	ANCOVA
Parameter estimate	Adjusted LS Mean Difference
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	1.61
Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[42] - Adjusted Least Squares (LS) Mean Difference Adjusted for baseline

[43] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) ANCOVA model with MDRD change as dependent variable, treatment and region/race as factors, and baseline as covariate.

Statistical analysis title	Change from Baseline at Week 24
Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[44]
P-value	= 0.0888 ^[45]
Method	ANCOVA
Parameter estimate	Adjusted LS Mean Difference
Point estimate	2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	5.33
Variability estimate	Standard error of the mean
Dispersion value	1.45

Notes:

[44] - Adjusted LS Mean Difference Adjusted for baseline

[45] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) ANCOVA model with MDRD change as dependent variable, treatment and region/race as factors, and baseline as covariate.

Statistical analysis title	Change from Baseline at Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other ^[46]
P-value	= 0.1475 ^[47]
Method	ANCOVA
Parameter estimate	Adjusted LS Mean Difference
Point estimate	2.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	4.99
Variability estimate	Standard error of the mean
Dispersion value	1.46

Notes:

[46] - Adjusted LS Mean Difference Adjusted for baseline

[47] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) ANCOVA model with MDRD change as dependent variable, treatment and region/race as factors, and baseline as covariate.

Secondary: Fraction of Albumin (milligrams per decilitre [mg/dL]) to Protein (mg/dL) in Urine at 24 and 52 Weeks After Conversion to SRL

End point title	Fraction of Albumin (milligrams per decilitre [mg/dL]) to Protein (mg/dL) in Urine at 24 and 52 Weeks After Conversion to SRL
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End point description:

Baseline fraction was the last value of the pre-SRL conversion period. Only the last value of U p/c or U alb/c was used for analysis if multiple measurements occurred in the same data analysis interval. Fraction of albumin and protein was calculated only when urine protein was 6.2 mg/dL or higher. For urine albumin, if the value was reported as '<xx.x', the numerical portion of the value was used in the calculation of fraction of albumin and protein. mITT population; n=number of participants assessed for the specified parameter at a given visit. Includes measures collected from On-Therapy and Off-Therapy Periods.

End point type	Secondary
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End point timeframe:

24 weeks and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	110		
Units: (mg /dL) /(mg / d L)				
arithmetic mean (standard deviation)				
Week 24 (n=104,110)	0.19 (± 0.17)	0.25 (± 0.19)		
Week 52 (n=111,105)	0.22 (± 0.18)	0.25 (± 0.2)		

Statistical analyses

Statistical analysis title	Week 24
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other ^[48]
P-value	= 0.1167 ^[49]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.04

Notes:

[48] - Treatment ratio (Ramipril/Placebo) in the geometric mean.

[49] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) Log (Fraction of albumin to protein in urine) as dependent variable, treatment and region/race as factor, and Log (baseline) as covariate.

Statistical analysis title	Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other ^[50]
P-value	= 0.7519 ^[51]
Method	ANCOVA
Parameter estimate	Treatment Ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.31

Notes:

[50] - Treatment ratio (Ramipril/Placebo) in the geometric mean.

[51] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) Log (Fraction of albumin to protein in urine) as dependent variable, treatment and region/race as factor, and Log (baseline) as covariate.

Secondary: Percentage of Participants with Potentially Clinically Important Blood Pressure (BP) Values by Diastolic and Systolic BP Category

End point title	Percentage of Participants with Potentially Clinically Important Blood Pressure (BP) Values by Diastolic and Systolic BP Category
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End point description:

BP values of potential clinical importance were recorded and categorised as follows: diastolic BP (DBP) ≤50 millimetres of mercury (mmHg) or ≥110 mmHg and systolic BP (SBP) ≤90 mmHg and ≥180 mmHg. Data were summarised for the on-therapy period and the off-therapy period and for the pre-SRL period. Safety population.

End point type	Secondary
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End point timeframe:

Baseline, Pre-SRL (from first dose of ramipril/placebo up to SRL conversion), On-Therapy (up to 52 weeks after SRL conversion), and Off-Therapy Period (up to 56 weeks after SRL conversion)

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Baseline, Low DBP ≤50 mmHg (n=155,140)	0	0.7		

Baseline, Low SBP: ≤ 90 mmHg (n=155,140)	0	0.7		
Pre-SRL, Low DBP: ≤ 50 mmHg (n=152,135)	0	0.7		
Pre-SRL, High DBP: ≥ 110 mmHg (n=152,135)	0	1.5		
Pre-SRL, Low SBP: ≤ 90 mmHg (n=152,135)	0	0.7		
Pre-SRL, High SBP: ≥ 180 mmHg (n=152,135)	0.7	0.7		
On Therapy, Low DBP: ≤ 50 mmHg (n=138,126)	3.6	2.4		
On Therapy, High DBP: ≥ 110 mmHg (n=138,126)	0	1.6		
On Therapy, Low SBP: ≤ 90 mmHg (n=138,126)	3.6	4		
On Therapy, High SBP: ≥ 180 mmHg (n=138,126)	0.7	4		
Off Therapy, High DBP ≥ 110 mmHg (n=35,69)	2.9	1.4		
Off Therapy, Low SBP: ≤ 90 mmHg (n=35,69)	2.9	1.4		

Statistical analyses

Statistical analysis title	Pre-SRL, Low DBP ≤ 50 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47 ^[52]
Method	Fisher exact

Notes:

[52] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL, High DBP ≥ 110 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.22 ^[53]
Method	Fisher exact

Notes:

[53] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL, Low SBP: ≤ 90 mmHg
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47 ^[54]
Method	Fisher exact

Notes:

[54] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL, High SBP: ≥ 180 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 ^[55]
Method	Fisher exact

Notes:

[55] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On Therapy, Low DBP ≤ 50 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.725 ^[56]
Method	Fisher exact

Notes:

[56] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On Therapy, High DBP ≥ 110 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.227 ^[57]
Method	Fisher exact

Notes:

[57] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On Therapy, Low SBP: ≤ 90 mmHg
Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1 ^[58]
Method	Fisher exact

Notes:

[58] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On Therapy, High SBP: ≥ 180 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106 ^[59]
Method	Fisher exact

Notes:

[59] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Off Therapy, High DBP ≥ 110 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 ^[60]
Method	Fisher exact

Notes:

[60] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Off Therapy, Low SBP: ≤ 90 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 ^[61]
Method	Fisher exact

Notes:

[61] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Baseline, Low DBP ≤ 50 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.475 ^[62]
Method	Fisher exact

Notes:

[62] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Baseline, Low SBP: ≤ 90 mmHg
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.475 ^[63]
Method	Fisher exact

Notes:

[63] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: SRL Time Normalised Trough Concentration (Cmin,TN) by Time Interval

End point title	SRL Time Normalised Trough Concentration (Cmin,TN) by Time Interval
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End point description:

Cmin,TN was determined for SRL using the area method for the intervals: 0–2 weeks, >2–4 weeks, >4–12 weeks, >12–24 weeks, >24–36 weeks and >36–52 weeks using the equation $C_{min,TN} = AUC_{i-j}/(t_{i-j} - t_{i-1})$, where AUC was the area under the concentration-time curve, i was the beginning of the interval and j was the end of the interval. Cmin,TN was calculated for participants who did not dropout of studies, but were missing concentrations at the interval endpoints by carrying the last observed concentration forward to the interval endpoint. Safety population; n=number of participants assessed for the specified parameter for the given time interval; only participants dosed throughout the interval were included.

End point type	Secondary
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End point timeframe:

From Day 1 of SRL conversion to 52 weeks after conversion

End point values	Pharmacokinetic analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	258			
Units: ng/mL				
arithmetic mean (standard deviation)				
0-2 weeks (n=258)	9.853 (± 6.025)			
>2-4 weeks (n=257)	9.872 (± 4.1408)			
>4-12 weeks (n=256)	9.273 (± 3.1763)			
>12-24 weeks (n=244)	9.274 (± 2.8944)			
>24-36 weeks (n=226)	9.316 (± 3.1535)			
>36-52 weeks (n=193)	8.961 (± 2.9031)			
0-52 weeks (n=264)	9.3 (± 2.2678)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Haemoglobin Levels ≤100 grams per litre (g/L)

End point title	Percentage of Participants with Haemoglobin Levels ≤100 grams per litre (g/L)
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End point description:

Safety population

End point type	Secondary
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End point timeframe:

Baseline, Pre-SRL (from first dose of ramipril/placebo up to SRL conversion), On-Therapy (up to 52 weeks after SRL conversion), and Off-Therapy Period (up to 56 weeks after SRL conversion)

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Baseline (n=155,140)	1.3	1.4		
Pre-SRL (n=148,129)	2	0.8		
On-Therapy (n=138,124)	17.4	12.1		
Off-Therapy (n=33,34)	9.1	2.9		

Statistical analyses

Statistical analysis title	Baseline
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [64]
Method	Fisher exact

Notes:

[64] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.626 [65]
Method	Fisher exact

Notes:

[65] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.297 [66]
Method	Fisher exact

Notes:

[66] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Off-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.356 ^[67]
Method	Fisher exact

Notes:

[67] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants Using Red Blood Cell Production Stimulants (Erythropoiesis Stimulating Agents [ESAs])

End point title	Percentage of Participants Using Red Blood Cell Production Stimulants (Erythropoiesis Stimulating Agents [ESAs])
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End point description:

Safety population; n=number of participants analysed for the specified parameter at a given visit.

End point type	Secondary
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End point timeframe:

Baseline, Pre-SRL (from first dose of ramipril/placebo up to SRL conversion), On-Therapy (up to 52 weeks after SRL conversion), and Off-Therapy Period (up to 56 weeks after SRL conversion)

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Baseline (n=155,140)	5.8	1.4		
Pre-SRL (n=155,140)	4.5	0.7		
On-Therapy (n=138,126)	4.3	3.2		
Off-Therapy (n=136,122)	1.5	4.1		

Statistical analyses

Statistical analysis title	Baseline
Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.064 ^[68]
Method	Fisher exact

Notes:

[68] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.069 ^[69]
Method	Fisher exact

Notes:

[69] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.752 ^[70]
Method	Fisher exact

Notes:

[70] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Off-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.261 ^[71]
Method	Fisher exact

Notes:

[71] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Change from Baseline in Fasting Lipid Parameters (millimoles per litre [mmol/L]) at 4, 12, 24, and 52 Weeks Following Conversion to SRL

End point title	Change from Baseline in Fasting Lipid Parameters (millimoles per litre [mmol/L]) at 4, 12, 24, and 52 Weeks Following Conversion to SRL
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End point description:

Parameters assessed included (all fasting) total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C). Safety population; n=number of participants assessed for the specified parameter at a given visit.

End point type	Secondary
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End point timeframe:

4, 12, 24, and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	109		
Units: mmol/L				
arithmetic mean (standard error)				
TC, Week 4 (n=128,109)	0.83 (± 0.06)	0.91 (± 0.09)		
TC, Week 12 (n=115,108)	0.94 (± 0.09)	0.92 (± 0.1)		
TC, Week 24 (n=105,102)	0.91 (± 0.12)	0.87 (± 0.09)		
TC, Week 52 (n=94,79)	0.84 (± 0.11)	0.69 (± 0.12)		
HDL-C, Week 4 (n=125,107)	0.06 (± 0.02)	0.09 (± 0.03)		
HDL-C, Week 12 (n=114,104)	0.03 (± 0.02)	0.03 (± 0.02)		
HDL-C, Week 24 (n=102,100)	0.07 (± 0.03)	0.04 (± 0.03)		
HDL-C, Week 52 (n=92,78)	0.12 (± 0.03)	0.06 (± 0.04)		
LDL-C, Week 4 (n=123,100)	0.59 (± 0.06)	0.56 (± 0.07)		
LDL-C, Week 12 (n=109,96)	0.66 (± 0.08)	0.53 (± 0.08)		
LDL-C, Week 24 (n=96,95)	0.66 (± 0.1)	0.56 (± 0.08)		
LDL-C, Week 52 (n=90,73)	0.56 (± 0.1)	0.27 (± 0.09)		
Triglycerides, Week 4 (n=127,108)	0.41 (± 0.07)	0.65 (± 0.1)		
Triglycerides, Week 12 (n=114,107)	0.59 (± 0.1)	0.79 (± 0.11)		
Triglycerides, Week 24 (n=104,102)	0.54 (± 0.11)	0.72 (± 0.13)		
Triglycerides, Week 52 (n=93,77)	0.44 (± 0.1)	0.58 (± 0.14)		

Statistical analyses

Statistical analysis title	TC, Week 4
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.381 ^[72]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[72] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	TC, Week 12
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.956 ^[73]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[73] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	TC, Week 24
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.903 ^[74]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[74] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	TC, Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.503 ^[75]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.1

Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[75] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	HDL-C, Week 4
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.451 ^[76]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[76] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	HDL-C, Week 12
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.919 ^[77]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[77] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	HDL-C, Week 24
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.637 ^[78]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[78] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	HDL-C, Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.229 ^[79]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[79] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	LDL-C, Week 4
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.766 ^[80]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.03

Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[80] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	LDL-C, Week 12
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.217 ^[81]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[81] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	LDL-C, Week 24
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.457 ^[82]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[82] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	LDL-C, Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041 ^[83]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[83] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	Triglycerides, Week 4
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.044 ^[84]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[84] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	Triglycerides, Week 12
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.18 ^[85]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.2

Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[85] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	Triglycerides, Week 24
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.264 ^[86]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[86] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Statistical analysis title	Triglycerides, Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.408 ^[87]
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[87] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity). ANCOVA with treatment as a factor and baseline as a covariate.

-9999/9999 = data not available (no CI generated).

Secondary: Biopsy-Confirmed Acute Rejection (BCAR) - Number of Participants with an Event

End point title	Biopsy-Confirmed Acute Rejection (BCAR) - Number of Participants with an Event
End point description: BCAR was defined according to updated Banff criteria (1997) for renal allograft rejection. The time to the first BCAR was defined as the date of first BCAR to the date of the first dose of SRL (in weeks). Participants without BCAR were censored at the time of withdrawal from the study. mITT population; includes BCAR occurring in On-Therapy and Off-Therapy Periods.	
End point type	Secondary
End point timeframe: From Day 1 of SRL conversion to 52 weeks after conversion	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: Number of Participants with an Event				
Biopsy-Confirmed Acute Rejection (BCAR)	13	5		

Statistical analyses

Statistical analysis title	Ramipril, Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0732 ^[88]
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	2.487
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.887
upper limit	6.978

Notes:

[88] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) Hazard ratio was based on the Cox proportional hazards model.

Secondary: Percentage of Participants with First BCAR at 24 and 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants with First BCAR at 24 and 52 Weeks Following Conversion to SRL
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End point description:

BCAR was defined according to updated Banff criteria (1997) for renal allograft rejection. Participants without BCAR were censored at the time of withdrawal from the study. Defined as the first BCAR occurring on therapy following conversion to SRL based on the mITT population. Time to first BCAR was defined as the date of first BCAR to date of the first dose of SRL (in weeks). Percentages were estimated

using the Kaplan-Meier method for time to event data. mITT population; includes BCAR occurring in the On-Therapy and Off-Therapy Periods

End point type	Secondary
End point timeframe:	
24 weeks and 52 weeks after conversion	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: percentage of participants				
number (confidence interval 95%)				
24 weeks postconversion	8 (4.2 to 13.3)	0.8 (0.1 to 4)		
52 weeks postconversion	9.5 (5.3 to 15.1)	3.2 (1.1 to 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with BCAR by Severity of First BCAR

End point title	Number of Participants with BCAR by Severity of First BCAR
End point description:	
Severity was summarised by type (antibody versus T-cell) and by phase: post-SRL (where both on-therapy and off-therapy events are included) and post-SRL (on-therapy). BCAR was categorised using Banff criteria as antibody-mediated (AM) or T-cell. AM BCAR severity was graded as Grade I (mild), Grade II (moderate [mod]), and Grade III (severe). T-cell BCAR severity was graded as 'Grade Ia, Ib (mild), Grade IIa, IIb (mod), and Grade III (severe). If a participant had both T-cell BCAR and AM BCAR on the first rejection, the participant was counted in each category. For participants with T-cell BCAR (post-SRL and post-SRL On -Therapy) the p-value could not be calculated and all events were mild in severity. mITT population; only participants with BCAR were included in the analysis.	
End point type	Secondary
End point timeframe:	
From Day 1 of SRL conversion to 52 weeks after conversion	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: Number of participants				
Post-SRL, AM BCAR, Grade I (mild)	1	2		
Post-SRL, AM BCAR, Grade II (mod)	0	1		
Post-SRL, AM BCAR, Grade III (severe)	0	1		
Post-SRL, T-Cell BCAR, Grade I (mild)	12	4		
Post-SRL (On-Therapy), AM BCAR, Grade I (mild)	1	1		
Post-SRL (On-Therapy), AM BCAR, Grade II (mod)	0	1		

Post-SRL (On-Therapy), T-Cell BCAR, Grade I (mild)	10	3		
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Statistical analyses

Statistical analysis title	Post-SRL, AM BCAR
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7165 ^[89]
Method	Cochran-Mantel-Haenszel

Notes:

[89] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) Cochran-Mantel-Haenszel row mean test

Statistical analysis title	Post-SRL (On-Therapy), AM BCAR
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4795 ^[90]
Method	Cochran-Mantel-Haenszel

Notes:

[90] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity) Cochran-Mantel-Haenszel row mean test

Secondary: Percentage of Participants with Graft Loss at 24 and 52 Weeks Following Conversion to SRL

End point title	Percentage of Participants with Graft Loss at 24 and 52 Weeks Following Conversion to SRL
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End point description:

Graft loss was defined as physical loss (nephrectomy or re-transplantation), functional loss (requiring dialysis for ≥56 days with no return of graft function), or death. mITT population

End point type	Secondary
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End point timeframe:

24 weeks and 52 weeks after conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	126		
Units: percentage of participants				
number (not applicable)				
Week 24	0	0		
Week 52	0	0.8		

Statistical analyses

Statistical analysis title	Week 52
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4773 ^[91]
Method	Fisher exact

Notes:

[91] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants using Statins

End point title	Percentage of Participants using Statins
End point description:	
Safety population; n=number of participants analysed for the specified parameter at a given visit.	
End point type	Secondary

End point timeframe:

Baseline, Pre-SRL (from first dose of ramipril/placebo up to SRL conversion), On-Therapy (up to 52 weeks after SRL conversion), and Off-Therapy Period (up to 56 weeks after SRL conversion)

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Baseline (n=155,140)	45.8	36.4		
Pre-SRL (n=155,140)	45.2	40		
On-Therapy (n=138,126)	67.4	72.2		
Off-Therapy (n=136,122)	62.5	68.9		

Statistical analyses

Statistical analysis title	Baseline
Comparison groups	Ramipril v Placebo

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.124 ^[92]
Method	Fisher exact

Notes:

[92] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.41 ^[93]
Method	Fisher exact

Notes:

[93] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.423 ^[94]
Method	Fisher exact

Notes:

[94] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Off-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.297 ^[95]
Method	Fisher exact

Notes:

[95] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants with an Infection

End point title	Percentage of Participants with an Infection
End point description: Includes treatment-emergent adverse events based on categorisation by the investigator as 'infection', regardless of the event preferred term in Medical Dictionary for Regulatory Activities (MedDRA.) Safety population	
End point type	Secondary
End point timeframe: From Day 1 of Ramipril/Placebo to 52 weeks after SRL conversion	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Percentage of Participants with	54.2	56.4		

Statistical analyses

Statistical analysis title	Ramipril, Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.726 ^[96]
Method	Fisher exact

Notes:

[96] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants with Angioedema

End point title	Percentage of Participants with Angioedema
End point description:	Includes treatment-emergent adverse events based on categorisation by the investigator as angioedema, regardless of the event preferred term in MedDRA. Safety population
End point type	Secondary
End point timeframe:	From Day 1 of Ramipril/Placebo to 52 weeks after SRL conversion

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Percentage of Participants with Angioedema	1.3	1.4		

Statistical analyses

Statistical analysis title	Ramipril, Placebo
Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [97]
Method	Fisher exact

Notes:

[97] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants with Malignancy

End point title	Percentage of Participants with Malignancy
End point description: Includes treatment-emergent adverse events based on categorisation by the investigator as 'malignancy', regardless of the event preferred term in MedDRA. Safety population	
End point type	Secondary
End point timeframe: From Day 1 of Ramipril/Placebo to 52 weeks after SRL conversion	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percentage of participants				
number (not applicable)				
Percentage of Participants with	3.9	2.9		

Statistical analyses

Statistical analysis title	Ramipril, Placebo
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.753 [98]
Method	Fisher exact

Notes:

[98] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Secondary: Percentage of Participants with Hyperkalaemia

End point title	Percentage of Participants with Hyperkalaemia
End point description: Hyperkalaemia defined as serum potassium >5.6 millimoles per litre (mmol/L) Safety population; n=number of participants assessed for the specified parameter at a given visit.	
End point type	Secondary

End point timeframe:

Baseline, Pre-SRL (from first dose of ramipril/placebo up to SRL conversion), On-Therapy (up to 52 weeks after SRL conversion), and Off-Therapy Period (up to 56 weeks after SRL conversion)

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	140		
Units: percent of participants				
number (not applicable)				
Baseline (n=155,140)	0	1.4		
Pre-SRL (n=151,135)	4.6	1.5		
On-Therapy (n=138,124)	0.7	1.6		
Off-Therapy (n=34,36)	2.9	0		

Statistical analyses

Statistical analysis title	Baseline
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.224 ^[99]
Method	Fisher exact

Notes:

[99] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Pre-SRL
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.179 ^[100]
Method	Fisher exact

Notes:

[100] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	On-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.604 ^[101]
Method	Fisher exact

Notes:

[101] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Statistical analysis title	Off-Therapy
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.486 ^[102]
Method	Fisher exact

Notes:

[102] - 2-sided p-value; alpha=0.05 (unadjusted for multiplicity)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomisation through Week 52 following conversion to SRL

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious AE (SAE). However, what is presented are distinct events. An event may be categorised as serious in one participant and as non-serious in another participant, or one participant may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants were receiving CsA or TAC and either MMF, MPS, or AZA or steroids dosed per centre's standard of care. Participants received double-blinded placebo, 1 capsule (5 or 10 mg/day), PO. 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 ng/mL <1 year PT, 5-15 ng/mL ≥1 year PT) for up to 52 weeks. Placebo dose was doubled if U p/c was ≥0.5. If U p/c ≥0.5 persisted, losartan 50 mg/day was added; if U p/c ≥0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c <0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Reporting group title	Ramipril
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Reporting group description:

Participants were receiving CsA or TAC and either mycophenolate mofetil (MMF), mycophenolate sodium (MPS), or azathioprine (AZA) or steroids dosed per centre's standard of care. Participants received ramipril, 5 or 10 milligrams (mg) per (/) day orally (PO). 2-6 weeks after randomisation, participants stopped TAC or CsA (within 21 days of SRL initiation) and received SRL, PO, 2-4 mg/day (6-12 mg on Day 1 if TAC or CsA withdrawn abruptly) to achieve target trough levels (7-15 nanograms per millilitre [ng/mL] less than [$<$]1 year post-transplant [PT], 5-15 ng/mL greater than or equal to [$\geq$]1 year PT) for up to 52 weeks. Ramipril was increased to 10-20 mg if U p/c was ≥0.5. If U p/c ≥0.5 persisted, losartan 50 mg/day was added; if U p/c ≥0.5 still persisted, losartan was increased to 100 mg/day. If then U p/c <0.5 was not maintained, study medication was discontinued and participant entered off-therapy phase of study.

Serious adverse events	Placebo	Ramipril	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 140 (27.86%)	50 / 155 (32.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 140 (1.43%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemangioblastoma			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 140 (0.71%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 140 (1.43%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena caval stenosis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Generalised oedema			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 140 (0.00%)	4 / 155 (2.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	3 / 140 (2.14%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	1 / 140 (0.71%)	11 / 155 (7.10%)	
occurrences causally related to treatment / all	1 / 1	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed ^[1]	1 / 90 (1.11%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 140 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 140 (0.71%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium test positive			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus test positive			

subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level increased			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Complications of transplanted kidney			
subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft complication			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	0 / 140 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 140 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 140 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 140 (1.43%)	4 / 155 (2.58%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileus			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 140 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Obstructive uropathy			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 140 (0.71%)	4 / 155 (2.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 140 (0.71%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			

subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral bacterial infection			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 140 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 140 (0.71%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 140 (0.71%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 140 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This adverse event of benign prostatic hyperplasia is only applicable to males and therefore the total number of subjects exposed is only the male participants and not the total number of participants in the reporting group.

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

Non-serious adverse events	Placebo	Ramipril	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 140 (87.86%)	133 / 155 (85.81%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 140 (10.00%)	10 / 155 (6.45%)	
occurrences (all)	16	10	
Hypotension			
subjects affected / exposed	7 / 140 (5.00%)	14 / 155 (9.03%)	
occurrences (all)	8	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 140 (5.00%)	12 / 155 (7.74%)	
occurrences (all)	8	12	
Local swelling			
subjects affected / exposed	9 / 140 (6.43%)	3 / 155 (1.94%)	
occurrences (all)	10	3	
Oedema peripheral			
subjects affected / exposed	30 / 140 (21.43%)	27 / 155 (17.42%)	
occurrences (all)	35	30	
Pyrexia			
subjects affected / exposed	9 / 140 (6.43%)	11 / 155 (7.10%)	
occurrences (all)	9	16	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed ^[2]	6 / 90 (6.67%)	4 / 107 (3.74%)	
occurrences (all)	8	4	
Menorrhagia			
subjects affected / exposed ^[3]	1 / 50 (2.00%)	4 / 48 (8.33%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	14 / 140 (10.00%) 19	24 / 155 (15.48%) 26	
Oropharyngeal pain subjects affected / exposed occurrences (all)	12 / 140 (8.57%) 15	7 / 155 (4.52%) 7	
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	11 / 140 (7.86%) 13	24 / 155 (15.48%) 28	
Weight increased subjects affected / exposed occurrences (all)	5 / 140 (3.57%) 5	8 / 155 (5.16%) 9	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	10 / 140 (7.14%) 11	12 / 155 (7.74%) 16	
Headache subjects affected / exposed occurrences (all)	16 / 140 (11.43%) 22	19 / 155 (12.26%) 22	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	10 / 140 (7.14%) 11	18 / 155 (11.61%) 19	
Leukopenia subjects affected / exposed occurrences (all)	6 / 140 (4.29%) 6	19 / 155 (12.26%) 24	
Gastrointestinal disorders Aphthous stomatitis subjects affected / exposed occurrences (all)	14 / 140 (10.00%) 18	12 / 155 (7.74%) 21	
Diarrhoea subjects affected / exposed occurrences (all)	37 / 140 (26.43%) 44	40 / 155 (25.81%) 52	
Mouth ulceration subjects affected / exposed occurrences (all)	17 / 140 (12.14%) 21	12 / 155 (7.74%) 18	

Nausea subjects affected / exposed occurrences (all)	9 / 140 (6.43%) 10	8 / 155 (5.16%) 9	
Stomatitis subjects affected / exposed occurrences (all)	11 / 140 (7.86%) 14	7 / 155 (4.52%) 7	
Vomiting subjects affected / exposed occurrences (all)	8 / 140 (5.71%) 9	10 / 155 (6.45%) 13	
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	25 / 140 (17.86%) 26	18 / 155 (11.61%) 21	
Rash subjects affected / exposed occurrences (all)	13 / 140 (9.29%) 15	5 / 155 (3.23%) 6	
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	15 / 140 (10.71%) 17	8 / 155 (5.16%) 8	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	13 / 140 (9.29%) 16	15 / 155 (9.68%) 21	
Back pain subjects affected / exposed occurrences (all)	6 / 140 (4.29%) 6	10 / 155 (6.45%) 10	
Pain in extremity subjects affected / exposed occurrences (all)	12 / 140 (8.57%) 14	6 / 155 (3.87%) 9	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 140 (5.00%) 7	8 / 155 (5.16%) 10	
Upper respiratory tract infection			

subjects affected / exposed	16 / 140 (11.43%)	27 / 155 (17.42%)	
occurrences (all)	18	30	
Urinary tract infection			
subjects affected / exposed	13 / 140 (9.29%)	12 / 155 (7.74%)	
occurrences (all)	22	26	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	19 / 140 (13.57%)	14 / 155 (9.03%)	
occurrences (all)	20	15	
Hypercholesterolaemia			
subjects affected / exposed	14 / 140 (10.00%)	17 / 155 (10.97%)	
occurrences (all)	17	23	
Hyperlipidaemia			
subjects affected / exposed	9 / 140 (6.43%)	15 / 155 (9.68%)	
occurrences (all)	9	15	
Hypertriglyceridaemia			
subjects affected / exposed	15 / 140 (10.71%)	16 / 155 (10.32%)	
occurrences (all)	25	18	
Hypokalaemia			
subjects affected / exposed	9 / 140 (6.43%)	3 / 155 (1.94%)	
occurrences (all)	10	3	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This adverse event of erectile dysfunction is only applicable to males and therefore the total number of subjects exposed is only the male participants and not the total number of participants in the reporting group.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This adverse event of menorrhagia is only applicable to females and therefore the total number of subjects exposed is only the female participants and not the total number of participants in the reporting group.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2007	• Phase 1 (Pre-SRL conversion): 2 to 4 weeks of therapy with ramipril or placebo (2 weeks were added). • Revised the total duration of the study to be approximately 160 (from 164) weeks.
03 September 2008	• Phase 1 Pre-SRL conversion was shortened to a minimum of 2 weeks up to a maximum of 4 weeks to decrease the amount of required in-clinic visits and allow participants to convert to SRL earlier while still performing all safety assessments. • Phase 2: added in MPS and editorial changes. • Formatting was changed and dosage amount of MMF, MPS, and AZA was clarified. • Time after transplant was changed from 6 to 60 months to 3 to 60 months. • The 4-weeks post randomisation period before SRL conversion was shortened to 2 to 4 weeks. Investigators then had the option to convert participants, if eligible for SRL conversion, at 2 weeks post randomisation rather than waiting until 4 weeks. The 4-week post-randomisation visit remained as an optional visit in the protocol. • Inclusion criteria number 4 was modified to include participants as early as 3 months post-transplant. • Ualb/c ratios stated in the exclusion criteria and relating to dose changes were removed from the protocol. • Target blood pressure was clarified to state <140/90 mm Hg throughout the protocol. • Angioedema was added as a safety endpoint and was considered an AE with special circumstances and was to be reported as a SAE for the duration of the study. • Day of randomisation and Day 1 of conversion may not have been required in centre visits if approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and if appropriate arrangements were made for data collection and supply of study drug to participants. • Visits at Weeks 4, 8, and 12 post-discontinuation (off-therapy) had the option to be performed locally as approved by the IEC/IRB. • Ualb/c ratios for purposes of participant eligibility as well as dosage adjustments were removed from the protocol (all eligibility and dose adjustment decisions were based on the urine protein to creatinine ratios). The Ualb/c data were collected and analysed but not reported back to the centre.

10 December 2008	• Starting dose for ramipril and matching placebo lowered from 10 mg/day to 5 mg/day. • Enrolment period extended to 104 weeks. • Clarified participants can initiate conversion to SRL as late as 6 weeks following randomisation. • Participants who discontinued from assigned therapy once conversion to SRL began were followed for 52 weeks after initiation of conversion. • Clarified only women of child bearing potential required two methods of contraception when using MMF or MPS. • Updated Exclusion Criteria regarding prohibition of renin-angiotensin-aldosterone system blockade and of participants with Grade C Child-Pugh score. • Clarified dose reduction instructions regarding elevated serum creatinine, hyperkalaemia, hypotension, and hypertension applied to all participants. Hypertension was separated in its own section for clarity. • New SRL target trough levels determined by high-performance liquid chromatography. Notation that dose changes for the participants other immunosuppressive medications were based upon the new target SRL trough levels. • Changed study drug administration for off-therapy participants. • Clarified concomitant treatment for anaemia. • Changed information on concomitant use of insulin. • Clarified the definition of hypotension. • Updated definition of "off-therapy" participants. • Evaluation of hepatic impairment at screening was added. • Clarified utilisation of urine albumin to creatinine ratios. • Clarified timing for Day 1. • Added Week 24 and Week 52 post-SRL conversion visit. • Clarified AE follow-up for off-therapy participants and dropped participants; clarification of concomitant medication collection for off-therapy participants • Updated unblinding procedures. • Updated safety reporting. • Clarification of statistical methods. • Addition of secondary endpoint for evaluation of albumin to protein. • Addition of information on interim analysis. • Correction to statement of statistical power from 90% to 84%.
26 October 2009	• Updates to duration of participant participation and duration of study. • Updated exclusion criteria: Clarification to exclude planned systemic treatments with voriconazole, cisapride, or ketoconazole; haemoglobin criterion added to align with safety endpoint. • Clarification that participants with the following condition or characteristic at the visit immediately prior to the start of SRL were excluded from SRL conversion: Less than 10 consecutive days of treatment with ramipril or placebo therapy. • Based on feedback from the Food and Drug Administration, the interim analysis was removed. • Clarification regarding planned systemic treatment with voriconazole, cisapride, or ketoconazole. If a participant was receiving any of these medications before enrolment, use of the medication must have been discontinued before randomisation. If unplanned or unexpected use was deemed necessary by the investigator, further participation of the participant was discussed with the Medical Monitor. • Clarifications to: definitions of screen failures, dropped participants, and unblinding of participants. • Change in target SRL trough levels. • Clarifications to dose adjustments made for urine protein-to-creatinine ratio >0.5; and U p/c testing between protocol required visits. • Clarification that the decreasing the dose or holding/discontinuing/withdrawing of losartan was considered a dose reduction and that there was a time limit to this dose reduction consistent with ramipril or placebo dose reductions. • Clarifications to the treatment of elevated serum creatinine, the recording and reporting of AEs and SAEs, and to medication error versus overdose.

26 April 2010	• The enrolment period was extended until the end of December 2010 (time from first participant enrolled to last participant enrolled). • Clarifications added: - If treatment with SRL continued after a participant was discontinued from study treatment, this was collected in the case report form (CRF) on the immunosuppression off-therapy CRF page. - Ramipril or placebo and losartan dose adjustments due to a urine protein-to-creatinine ratio ≥ 0.5. Wording added to help clarify the timing of when repeat U p/c testing was required. • Previously Performed Biopsies (Data Safety Monitoring Board [DSMB] request): - All kidney biopsies that were performed on participants prior to 22 Mar 2010, including those for suspected rejection, for other indications at the discretion of the investigator, or for site protocol biopsies, were collected upon obtaining participant consent. - These biopsies were read by a central pathologist who was blinded to treatment assignment. • Mandatory Biopsies (DSMB request): - Performed at selected centres only. - Read locally according to the updated Banff 1997 criteria. - All participants enrolled at the participating centres after the implementation of Amendment 5 were required to have biopsies. - Biopsies were required for all newly enrolled participants prior to the day of randomisation (performed prior to the first dose of ramipril or placebo). - Data from a biopsy performed within 12 weeks of randomisation was permitted to be used as the baseline except for biopsies performed at the time of implantation. - A repeat biopsy was also required at Week 8 post-SRL conversion (± 4 weeks).
18 May 2010	• A new visit was added at Week 44 Post-Conversion based on a recommendation made by the DSMB for an additional creatinine evaluation at 44 weeks post-SRL conversion. • The total volume of blood collected was increased from approximately 183 mL, to approximately 189 mL, dependent on the amount of time the participant on study.
28 February 2011	• Updated the number of participants to be enrolled; the screen failure rate and the pre conversion withdrawal rates were underestimated. Based on the current rate, approximately 440 participants were to be screened to achieve conversion targets. • Clarification that all participants, regardless if they are receiving lipid-lowering therapy, must have had fasting lipid levels below the exclusion criteria. • Enrolment timelines extended to allow complete enrolment of the study. • Addition of Hy's Law language. Changes included additional tests. • Revisions to the AE reporting section (replaced Wyeth AE and reporting sections with Pfizer sections). • There were 3 main changes for sites and study personnel: - SAEs with a causal relationship to SRL were to be collected after participants discontinued early from assigned therapy. - Criteria were provided for assessing and reporting potential drug-induced liver toxicity (Hy's Law). - Criterion was provided for reporting exposure to SRL during pregnancy (exposure in-utero).

29 February 2012	• Randomisation process for the study changed from the Wyeth randomisation system, CORE, to the Pfizer system, IMPALA. • For Turkey only, the study was changed to a Phase 3B study in order to address the Health Authority in Turkey's request that the phase of the protocol be changed. • Added exclusion criteria: Participants who were either pregnant or lactating at the time of screening. This change was made at the request of the Health Authority in Poland. • Changed the study procedure for the protocol: Per the request of the Ethics Committee in Israel, additional blood chemistry testing (for potassium) was added for the Week 1 post randomisation visit. • Per the Pfizer template for protocols, the change in terminology of events previously described as "Adverse Events with Special Circumstance" was changed to Medically Important Adverse Events. This change did not impact the reporting requirements; these events were viewed and defined in the protocol as medically important events and hence fell within the requirements for SAE reporting. • Changed as required per Pfizer template for protocol, including the addition of required specific text regarding exposure in utero, and additional clarification pertaining to cases that met or did not meet the criteria for Hy's law. • A new section was added to the protocol for medication error reporting. All medication errors events were to be reported regardless of whether or not they were accompanied by an AE and must have been documented accordingly on the medication error CRF. • A new section was added to the protocol for the DSMB; the operation of the Data Monitoring Committee and its interaction with the sponsor in terms of recommendations was stated in the protocol. • A new section was added to the protocol for the reporting of safety issue and serious breaches of the protocol or ICH GCP. • Extended study timelines to 5 years.
14 February 2013	• To reflect Pfizer's updated policy requirements, the following change/clarification to the protocol was provided to all participating sites: SAEs occurring to a participant after the active reporting period had ended should have been reported to the sponsor if the investigator became aware of them. At a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to study drug were to be reported to the sponsor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported