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Nordic Everolimus (Certican) Trial in Heart and Lung Transplantation (NOCTET)

This study has been completed.

Sponsor:
Novartis Pharmaceuticals

Information provided by:
Novartis

ClinicalTrials.gov Identifier:
NCT00377962

First received: September 15, 2006
Last updated: May 12, 2011
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History of Changes

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Results First Received: March 23, 2011

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Prevention
Condition:	Disorder Related to Cardiac Transplantation
Interventions:	Drug: Everolimus Drug: Mycophenolic acid (MPA)/azathioprine (AZA) Drug: Calcineurin inhibitors (CNI) Drug: Steroids

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
This was a 12-month study in maintenance heart and lung transplant patients with a follow-up period of an additional 12 months. Results to 24 months are presented. Patients were randomized to continue their current calcineurin inhibitors (CNI) based regimen or to start everolimus with reduction of CNI blood levels.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Participant Flow for 2 periods

Period 1: Core Study: 0-12 Months

	Everolimus + CNI Reduction	Control
STARTED	**140**	**142**

COMPLETED	**112**	**133**
NOT COMPLETED	**28**	**9**
Adverse Event	**18**	**2**
Death	**3**	**0**
Withdrew Consent	**5**	**2**
Administrative Reason	**1**	**1**
Unspecified reasons	**1**	**4**

Period 2: Extension Study: 12-24 Months

	Everolimus + CNI Reduction	Control
STARTED	**108**	**127**
COMPLETED	**98**	**123**
NOT COMPLETED	**10**	**4**
Death	**1**	**1**
Adverse Event	**8**	**0**
Abnormal laboratory value	**1**	**0**
Unspecified reason	**0**	**3**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Total	Total of all reporting groups

Baseline Measures

	Everolimus + CNI Reduction	Control	Total
Number of Participants [units: participants]	**140**	**142**	**282**
Age [units: years] Mean (Standard Deviation)	**59.2 (9.5)**	**56.4 (10.7)**	**57.8 (9.96)**
Gender [units: participants]			
Female	**37**	**40**	**77**
Male	**103**	**102**	**205**

Outcome Measures

Hide All Outcome Measures

1. Primary: Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to Month 12 [Time Frame: Baseline to Month 12]

Measure Type	Primary
Measure Title	Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to Month 12
Measure Description	Renal function was assessed by determining the measured glomerular filtration rate (mGFR) using creatinine ethylenediamine tetraacetic acid (Cr-EDTA) clearance or an equivalent method. A positive change score indicates improved renal function.
Time Frame	Baseline to Month 12
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**
Number of Participants Analyzed [units: participants]	**114**	**132**
Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to Month 12 [units: mL/min] Mean (Standard Deviation)		
Baseline	**48.6 (15.1)**	**48.0 (13.2)**
Month 12	**53.2 (15.7)**	**47.5 (16.1)**
Change from Baseline	**4.6 (10.4)**	**-0.5 (9.0)**

No statistical analysis provided for Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to Month 12

2. Secondary: Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to End of Study (Month 24) [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to End of Study (Month 24)
Measure Description	Renal function was assessed by determining the measured glomerular filtration rate (mGFR) using creatinine ethylenediamine tetraacetic acid (Cr-EDTA) clearance or an equivalent method. A positive change score indicates improved renal function.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	Control
Number of Participants Analyzed [units: participants]	**103**	**119**
Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to End of Study (Month 24) [units: mL/min] Mean (Standard Deviation)		
Month 0	**49.3 (14.7)**	**49.1 (13.0)**
Month 24	**52.5 (16.4)**	**46.8 (15.2)**
Change	**3.2 (12.3)**	**-2.4 (9.0)**

No statistical analysis provided for Change in Measured Glomerular Filtration Rate (mGFR) From Baseline to End of Study (Month 24)

3. Secondary: Change in Serum Creatinine From Baseline to End of Study (Month 24) [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Change in Serum Creatinine From Baseline to End of Study (Month 24)
Measure Description	Renal function was assessed by determining serum creatinine using standard laboratory methods. A positive change score indicates improved renal function.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	Control
Number of Participants Analyzed [units: participants]	**114**	**132**
Change in Serum Creatinine From Baseline to End of Study (Month 24) [units: µmol/L] Mean (Standard Deviation)		
Month 0	**126 (30)**	**129 (29)**

Month 24	**126 (64)**	**132 (37)**
Change	**0 (53)**	**3 (23)**

No statistical analysis provided for Change in Serum Creatinine From Baseline to End of Study (Month 24)

4. Secondary: Number of Patients With Biopsy-proven Acute Rejection From Month 12 to End of Study (Month 24) [Time Frame: Month 12 to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Number of Patients With Biopsy-proven Acute Rejection From Month 12 to End of Study (Month 24)
Measure Description	Biopsy-proved acute rejection was defined as a treated acute rejection confirmed by biopsy, graded locally according to the International Society for Heart & Lung Transplantation (ISHLT) criteria. A treated acute rejection was defined as an acute rejection clinically suspected, whether biopsy-proven or not, which had been treated and confirmed by the investigator according to the response to therapy.
Time Frame	Month 12 to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**
Number of Participants Analyzed [units: participants]	**108**	**127**
Number of Patients With Biopsy-proven Acute Rejection From Month 12 to End of Study (Month 24) [units: Participants]	**6**	**5**

No statistical analysis provided for Number of Patients With Biopsy-proven Acute Rejection From Month 12 to End of Study (Month 24)

5. Secondary: Number of Patients Who Died and Number of Patients With Graft Loss From Month 12 to End of Study (Month 24) [Time Frame: Month 12 to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Number of Patients Who Died and Number of Patients With Graft Loss From Month 12 to End of Study (Month 24)
Measure Description	Number of patients not alive and number of patients with loss of their graft.
Time Frame	Month 12 to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	Control
Number of Participants Analyzed [units: participants]	**108**	**127**
Number of Patients Who Died and Number of Patients With Graft Loss From Month 12 to End of Study (Month 24) [units: Participants]		
Death	**3**	**0**
Graft Loss	**0**	**0**

No statistical analysis provided for Number of Patients Who Died and Number of Patients With Graft Loss From Month 12 to End of Study (Month 24)

6. Secondary: Number of Patients in Need of Dialysis From Month 12 to End of Study (Month 24) [Time Frame: Month 12 to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Number of Patients in Need of Dialysis From Month 12 to End of Study (Month 24)
Measure Description	No text entered.
Time Frame	Month 12 to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The intent-to-treat (ITT) population consisted of all patients as randomized, who were given at least one dose of study drug and had at least one post-baseline assessment. (Extension study)

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	Control
Number of Participants Analyzed [units: participants]	**108**	**127**
Number of Patients in Need of Dialysis From Month 12 to End of Study (Month 24) [units: Participants]	**0**	**2**

No statistical analysis provided for Number of Patients in Need of Dialysis From Month 12 to End of Study (Month 24)

7. Secondary: Change in Forced Expiratory Volume in 1 Second (FEV1) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Change in Forced Expiratory Volume in 1 Second (FEV1) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup
Measure Description	Forced expiratory volume in 1 second (FEV1) was measured by spirometry conducted according to internationally accepted standards. FEV1 is the volume delivered in the first second of a forced vital capacity (FVC) maneuver. A positive change score indicates improved lung function.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Patients in the lung transplant subgroup of the intent-to-treat (ITT) population which included all randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**
Number of Participants Analyzed [units: participants]	**36**	**40**
Change in Forced Expiratory Volume in 1 Second (FEV1) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup [units: Liters] Mean (Standard Deviation)	**-0.2 (0.2)**	**-0.1 (0.2)**

No statistical analysis provided for Change in Forced Expiratory Volume in 1 Second (FEV1) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup

8. Secondary: Change in Forced Vital Capacity (FVC) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Change in Forced Vital Capacity (FVC) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup
Measure Description	Forced vital capacity (FVC) was measured by spirometry conducted according to internationally accepted standards. FVC is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration. A positive change score indicates improved lung function.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another

method. Also provides relevant details such as imputation technique, as appropriate.
Patients in the lung transplant subgroup of the intent-to-treat (ITT) population which included all randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**
Number of Participants Analyzed [units: participants]	**36**	**40**
Change in Forced Vital Capacity (FVC) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup [units: Liters] Mean (Standard Deviation)	**-0.2 (0.3)**	**-0.1 (0.4)**

No statistical analysis provided for Change in Forced Vital Capacity (FVC) From Baseline to End of Study (Month 24) in the Lung Transplant Subgroup

9. Secondary: Change in Left Ventricular Function (Diameter and Thickness Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Change in Left Ventricular Function (Diameter and Thickness Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup
Measure Description	Left ventricular function was assessed by echocardiography which was performed according to local routine practice. Echocardiography parameters were left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), interventricular septal wall thickness (IVSTd), and posterior wall thickness (PWTd). A positive change score indicates improved left ventricular function.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Patients in the heart transplant subgroup of the intent-to-treat (ITT) population which included all randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**

Number of Participants Analyzed [units: participants]	**56**	**73**
Change in Left Ventricular Function (Diameter and Thickness Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup [units: cm] Mean (Standard Deviation)		
LVEDD (N = 56, 73)	**-0.1 (0.8)**	**-0.0 (0.4)**
LVESD (N = 42, 57)	**0.1 (0.7)**	**0.1 (0.6)**
IVSTd (N = 43, 57)	**-0.4 (2.4)**	**-0.1 (1.2)**
PWTd (N = 43, 56)	**-0.5 (2.1)**	**-0.1 (1.1)**

No statistical analysis provided for Change in Left Ventricular Function (Diameter and Thickness Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup

10. Secondary: Change in Left Ventricular Function (Filling and Ejection Fraction Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Change in Left Ventricular Function (Filling and Ejection Fraction Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup
Measure Description	Left ventricular function was assessed by echocardiography which was performed according to local routine practice. Echocardiography parameters were filling fraction (FF) and ejection fraction (EF). A positive change score indicates improved left ventricular function.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Patients in the heart transplant subgroup of the intent-to-treat (ITT) population which included all randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**
Number of Participants Analyzed [units: participants]	**59**	**71**
Change in Left Ventricular Function (Filling and Ejection Fraction Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup [units: %] Mean (Standard Deviation)		
		0.1

EF (N = 59, 71)	**-0.6 (8.5)**	**(7.9)**
FF (N = 42, 57)	**0 (1)**	**0 (1)**

No statistical analysis provided for Change in Left Ventricular Function (Filling and Ejection Fraction Parameters) From Baseline to End of Study (Month 24) in the Heart Transplant Subgroup

11. Secondary: Mean Days of Hospitalization From Baseline to End of Study (Month 24) [Time Frame: Baseline to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Mean Days of Hospitalization From Baseline to End of Study (Month 24)
Measure Description	No text entered.
Time Frame	Baseline to end of study (Month 24)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	**Control**
Number of Participants Analyzed [units: participants]	**108**	**127**
Mean Days of Hospitalization From Baseline to End of Study (Month 24) [units: Days] Mean (Standard Deviation)	**8.5 (7.4)**	**16.2 (19.3)**

No statistical analysis provided for Mean Days of Hospitalization From Baseline to End of Study (Month 24)

12. Secondary: Number of Patients Discontinued From the Study Due to Adverse Events From Month 12 to End of Study (Month 24) [Time Frame: Month 12 to end of study (Month 24)]

Measure Type	Secondary
Measure Title	Number of Patients Discontinued From the Study Due to Adverse Events From Month 12 to End of Study (Month 24)
Measure Description	No text entered.
Time Frame	Month 12 to end of study (Month 24)
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who were given at least 1 dose of study drug and had at least 1 post-baseline assessment.

Reporting Groups

	Description
Everolimus + CNI Reduction	Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%,upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice
Control	CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.

Measured Values

	Everolimus + CNI Reduction	Control
Number of Participants Analyzed [units: participants]	**108**	**127**
Number of Patients Discontinued From the Study Due to Adverse Events From Month 12 to End of Study (Month 24) [units: Participants]		
Total discontinued due to AE(s)	**8**	**0**
Pulmonary embolism	**2**	**0**
Skin problems	**1**	**0**
Hypercholesterolemia	**1**	**0**
Stroke	**1**	**0**
Muscular pain	**1**	**0**
Diarrhea	**1**	**0**
Edema	**1**	**0**

No statistical analysis provided for Number of Patients Discontinued From the Study Due to Adverse Events From Month 12 to End of Study (Month 24)

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	24 months
Additional Description	Safety population stratified by sub groups (heart patients and lung patients) and duration of core study and extension study.

Reporting Groups

	Description
Control: 12 Month Heart	Subgroup of "Control" group with heart patients at 12 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus + CNI Reduction: 12 Month Heart	Subgroup of "everolimus + CNI reduction" group with heart patients at 12 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.
Control: 12 Month Lung	Subgroup of "control" group with lung patients at 12 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus+CNI Reduction: 12 Month Lung	Subgroup of "everolimus + CNI reduction" group with lung patients at 12 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.

Control: 24 Month Heart	Subgroup of "Control" group with heart patients at 24 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus + CNI Reduction: 24 Month Heart	Subgroup of "everolimus + CNI reduction" group with heart patients at 24 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.
Control: 24 Month Lung	Subgroup of "Control" group with lung patients at 24 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus + CNI Reduction: 24 Month Lung	Subgroup of "everolimus + CNI reduction" group with lung patients at 24 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.

Serious Adverse Events

	Control: 12 Month Heart	Everolimus + CNI Reduction: 12 Month Heart	Control: 12 Month Lung	Everolimus+CNI Reduction: 12 Month Lung	Control: 24 Month Heart	Everolimus + CNI Reduction: 24 Month Heart	Control: 24 Month Lung	Everolimus + CNI Reduction: 24 Month Lung
Total, serious adverse events								
# participants affected / at risk	**23/96 (23.96%)**	**40/94 (42.55%)**	**17/46 (36.96%)**	**25/46 (54.35%)**	**31/86 (36.05%)**	**25/69 (36.23%)**	**21/41 (51.22%)**	**16/39 (41.03%)**
Blood and lymphatic system disorders								
Anaemia NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**1/46 (2.17%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Cardiac disorders								
Angina pectoris † 1								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Aortic valve stenosis † 1								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**1/69 (1.45%)**	**1/41 (2.44%)**	**0/39 (0.00%)**
Atrial fibrillation † 1								
# participants affected / at risk	**1/96 (1.04%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**1/69 (1.45%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Atrial flutter † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**1/46 (2.17%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**1/41 (2.44%)**	**0/39 (0.00%)**
Atrial tachycardia † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Cardiac failure NOS † 1								

# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Coronary artery atheroma haemorrhage † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Coronary artery disease NOS † 1								
# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Oedema NOS † 1								
# participants affected / at risk	0/96 (0.00%)	3/94 (3.19%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Pulmonary oedema NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Right ventricular failure † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Supraventricular tachycardia † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Endocrine disorders								
Hyperthyroidism † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Gastrointestinal disorders								
Abdominal pain NOS † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Acute abdomen † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Appendicitis † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Diarrhoea NOS † 1								
# participants affected / at risk	0/96 (0.00%)	2/94 (2.13%)	1/46 (2.17%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Diverticulitis								

NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Food poisoning NOS † [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Gastric ulcer † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Gastric ulcer perforation † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Gastrointestinal haemorrhage NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Ileus † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Inguinal hernia NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Nausea † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Pancreatitis NOS † [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Peptic ulcer † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Rectal disorder NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Vomiting NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	2/94 (2.13%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
General disorders								
Chest pain † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)

Compartment syndrome † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**1/69 (1.45%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Death NOS † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**1/39 (2.56%)**
Fatigue † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Haemorrhage NOS † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Malaise † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**1/41 (2.44%)**	**0/39 (0.00%)**
Pain NOS † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Pyrexia † [1]								
# participants affected / at risk	**1/96 (1.04%)**	**3/94 (3.19%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Hepatobiliary disorders								
Cholelithiasis † [1]								
# participants affected / at risk	**1/96 (1.04%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Immune system disorders								
Graft rejection † [1]								
# participants affected / at risk	**1/96 (1.04%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Heart transplant rejection † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Hypersensitivity NOS † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**1/46 (2.17%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Infections and infestations								
Brain abscess NOS † [1]								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**1/41 (2.44%)**	**0/39 (0.00%)**
Bronchitis NOS †								

[1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Bronchitis acute NOS [†] [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	2/46 (4.35%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	1/39 (2.56%)
Cholecystitis acute NOS [†] [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Cystitis NOS [†] [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Cytomegalovirus infection [†] [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Ear infection NOS [†] [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Epididymitis NOS [†] [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Erysipelas [†] [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Gastroenteritis NOS [†] [1]								
# participants affected / at risk	2/96 (2.08%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	2/86 (2.33%)	2/69 (2.90%)	0/41 (0.00%)	0/39 (0.00%)
Herpes simplex [†] [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Herpes zoster [†] [1]								
# participants affected / at risk	0/96 (0.00%)	2/94 (2.13%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	1/39 (2.56%)
Infection NOS [†] [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	1/46 (2.17%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Influenza [†] [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	1/41 (2.44%)	1/39 (2.56%)
Lobar pneumonia NOS [†] [1]								

# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Localised infection † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Lower respiratory tract infection NOS † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56%)
Nasopharyngitis † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Pneumonia NOS † 1								
# participants affected / at risk	3/96 (3.13%)	7/94 (7.45%)	3/46 (6.52%)	6/46 (13.04%)	2/86 (2.33%)	0/69 (0.00%)	7/41 (17.07%)	5/39 (12.82%)
Pneumonia aspergilla † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Pseudomonas aeruginosa infection NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	2/46 (4.35%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Pyelonephritis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Sepsis NOS † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Sinusitis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Upper respiratory tract infection NOS † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	1/46 (2.17%)	1/46 (2.17%)	2/86 (2.33%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Urinary tract infection NOS † 1								
# participants affected / at risk	1/96 (1.04%)	3/94 (3.19%)	1/46 (2.17%)	0/46 (0.00%)	1/86 (1.16%)	2/69 (2.90%)	0/41 (0.00%)	0/39 (0.00%)
Injury, poisoning and procedural complications								
Animal bite † 1								
# participants								

affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56%)
Forearm fracture † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Fracture NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Hand fracture † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Head injury † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Leg fracture † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Radius fracture † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Investigations								
Arteriogram coronary † 1								
# participants affected / at risk	2/96 (2.08%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Biopsy lung † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Blood creatinine increased † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Lung function abnormal † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Lung function decreased † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Lymphocyte morphology NOS abnormal † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Pericardial drainage † 1								

# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Weight decreased † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Metabolism and nutrition disorders								
Gout † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Malnutrition NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56%)
Musculoskeletal and connective tissue disorders								
Arthritis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Back pain † 1								
# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Bursitis † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Intervertebral disc prolapse † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Localised osteoarthritis † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Muscle atrophy † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Myalgia † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Neck pain † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Sciatica † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Basal cell carcinoma † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**1/69 (1.45%)**	**2/41 (4.88%)**	**0/39 (0.00%)**
Benign adrenal neoplasm NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**1/69 (1.45%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Bowen's disease † 1								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Breast cancer female NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**1/46 (2.17%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Carcinoma NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Lip neoplasm malignant stage unspecified † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**1/46 (2.17%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Lung cancer stage unspecified (exc metas † 1								
# participants affected / at risk	**1/96 (1.04%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**1/86 (1.16%)**	**0/69 (0.00%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Malignant melanoma stage IV † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**1/41 (2.44%)**	**0/39 (0.00%)**
Prostate cancer NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**1/94 (1.06%)**	**0/46 (0.00%)**	**0/46 (0.00%)**	**0/86 (0.00%)**	**1/69 (1.45%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Skin carcinoma NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**0/94 (0.00%)**	**1/46 (2.17%)**	**1/46 (2.17%)**	**0/86 (0.00%)**	**1/69 (1.45%)**	**0/41 (0.00%)**	**0/39 (0.00%)**
Squamous cell carcinoma † 1								
# participants affected / at risk	**3/96 (3.13%)**	**1/94 (1.06%)**	**1/46 (2.17%)**	**1/46 (2.17%)**	**0/86 (0.00%)**	**0/69 (0.00%)**	**1/41 (2.44%)**	**2/39 (5.13%)**
Squamous cell								

carcinoma of skin † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Nervous system disorders								
Burning sensation NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Cerebrovascular accident NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Dizziness (exc vertigo) † [1]								
# participants affected / at risk	0/96 (0.00%)	2/94 (2.13%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Epilepsy NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Haemorrhagic stroke † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Migraine NOS † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Monoparesis † [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Restless leg syndrome † [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Syncope † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Syncope aggravated † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Psychiatric disorders								
Confusion † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Renal and urinary disorders								

Fluid retention † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Nephropathy NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Oliguria † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Renal failure NOS † 1								
# participants affected / at risk	0/96 (0.00%)	2/94 (2.13%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Renal impairment NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56%)
Reproductive system and breast disorders								
Benign prostatic hyperplasia † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Ovarian cyst † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56%)
Uterine prolapse † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Respiratory, thoracic and mediastinal disorders								
Asthma NOS † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Bronchostenosis † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Cough † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Dyspnoea NOS † 1								

# participants affected / at risk	2/96 (2.08%)	2/94 (2.13%)	0/46 (0.00%)	1/46 (2.17%)	2/86 (2.33%)	1/69 (1.45%)	1/41 (2.44%)	0/39 (0.00%)
Epistaxis † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Excessive bronchial secretion † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	2/41 (4.88%)	0/39 (0.00%)
Haemoptysis † [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Mediastinal emphysema † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Obliterative bronchiolitis † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	2/46 (4.35%)	0/86 (0.00%)	0/69 (0.00%)	6/41 (14.63%)	1/39 (2.56%)
Pleuritic pain † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Pneumothorax NOS † [1]								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56%)
Pulmonary fibrosis † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Respiratory distress † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Respiratory failure (exc neonatal) † [1]								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Skin and subcutaneous tissue disorders								
Angioneurotic oedema † [1]								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Dermatitis NOS † [1]								
# participants								

affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Diabetic foot ulcer † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Surgical and medical procedures								
Angioplasty † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	2/69 (2.90%)	0/41 (0.00%)	0/39 (0.00%)
Cholecystectomy † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Facial lesion excision † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Hip arthroplasty † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Leg amputation † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Operation NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Suture removal † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Vascular disorders								
Arterial stenosis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Arteriosclerosis † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Cerebral artery thrombosis † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Hypertension aggravated † 1								

# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00%)
Intracranial haemorrhage NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Phlebitis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Postural hypotension † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00%)
Pulmonary embolism † 1								
# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	2/46 (4.35%)	2/46 (4.35%)	1/86 (1.16%)	2/69 (2.90%)	1/41 (2.44%)	1/39 (2.56%)
Pulmonary hypertension NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Subarachnoid haemorrhage NOS † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Transient ischaemic attack † 1								
# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	1/41 (2.44%)	0/39 (0.00%)
Venous thrombosis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00%)
Venous thrombosis deep limb † 1								
# participants affected / at risk	1/96 (1.04%)	2/94 (2.13%)	0/46 (0.00%)	0/46 (0.00%)	1/86 (1.16%)	1/69 (1.45%)	0/41 (0.00%)	1/39 (2.56%)

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

Other Adverse Events

Hide Other Adverse Events

Time Frame	24 months
Additional Description	Safety population stratified by sub groups (heart patients and lung patients) and duration of core study and extension study.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Control: 12 Month Heart	Subgroup of "Control" group with heart patients at 12 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus + CNI Reduction: 12 Month Heart	Subgroup of "everolimus + CNI reduction" group with heart patients at 12 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.
Control: 12 Month Lung	Subgroup of "control" group with lung patients at 12 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus+CNI Reduction: 12 Month Lung	Subgroup of "everolimus + CNI reduction" group with lung patients at 12 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.
Control: 24 Month Heart	Subgroup of "Control" group with heart patients at 24 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus + CNI Reduction: 24 Month Heart	Subgroup of "everolimus + CNI reduction" group with heart patients at 24 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.
Control: 24 Month Lung	Subgroup of "Control" group with lung patients at 24 months. CNI ± MPA/AZA ± steroids. In the standard CNI arm, all immunosuppressants including mycophenolic acid (MPA) and azathioprine (AZA) continued unchanged as per local practice. Steroid treatment was according to local practice.
Everolimus + CNI Reduction: 24 Month Lung	Subgroup of "everolimus + CNI reduction" group with lung patients at 24 months. Everolimus (3-8 ng/mL) + CNI reduction ± MPA/AZA ± steroids. Everolimus 0.75-1.5 mg twice daily. Dose adjusted to target blood concentration in the range 3-8 ng/mL. CNI reduction (reduced 50-70%): target of achieving a cyclosporine A (CsA) trough level < 75 ng/mL or a tacrolimus trough level < 4 ng/mL. MPA was reduced by 25%, upon CNI reduction. If participants were treated with AZA (alternative to MPA) no dose reduction was needed. Steroid treatment was according to local practice.

Other Adverse Events

	Control: 12 Month Heart	Everolimus + CNI Reduction: 12 Month Heart	Control: 12 Month Lung	Everolimus+CNI Reduction: 12 Month Lung	Control: 24 Month Heart	Everolimus + CNI Reduction: 24 Month Heart	Control: 24 Month Lung	Everolim + CNI Reduction Month Lu
Total, other (not including serious) adverse events								
# participants affected / at risk	**48/96 (50.00%)**	**75/94 (79.79%)**	**33/46 (71.74%)**	**42/46 (91.30%)**	**33/86 (38.37%)**	**29/69 (42.03%)**	**21/41 (51.22%)**	**27/39 (69.2**
Blood and lymphatic system disorders								
Leucopenia NOS † 1								
# participants affected / at risk	**0/96 (0.00%)**	**8/94 (8.51%)**	**0/46 (0.00%)**	**8/46 (17.39%)**	**1/86 (1.16%)**	**1/69 (1.45%)**	**0/41 (0.00%)**	**1/39 (2.56**
Cardiac disorders								
Oedema NOS † 1								
# participants	**10/96 (10.42%)**	**24/94 (25.53%)**			**9/86 (10.47%)**			**5/39 (12.8**

affected / at risk			3/46 (6.52%)	14/46 (30.43%)		4/69 (5.80%)	2/41 (4.88%)	
Congenital, familial and genetic disorders								
Epidermal naevus † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	2/39 (5.13
Gastrointestinal disorders								
Abdominal pain upper † 1								
# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	1/46 (2.17%)	3/46 (6.52%)	1/86 (1.16%)	0/69 (0.00%)	3/41 (7.32%)	0/39 (0.00
Diarrhoea NOS † 1								
# participants affected / at risk	4/96 (4.17%)	15/94 (15.96%)	3/46 (6.52%)	7/46 (15.22%)	0/86 (0.00%)	4/69 (5.80%)	1/41 (2.44%)	3/39 (7.69
Gastritis NOS † 1								
# participants affected / at risk	1/96 (1.04%)	1/94 (1.06%)	1/46 (2.17%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	2/39 (5.13
Mouth ulceration † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	0/46 (0.00%)	5/46 (10.87%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00
Nausea † 1								
# participants affected / at risk	1/96 (1.04%)	4/94 (4.26%)	1/46 (2.17%)	2/46 (4.35%)	2/86 (2.33%)	1/69 (1.45%)	1/41 (2.44%)	2/39 (5.13
General disorders								
Fall † 1								
# participants affected / at risk	2/96 (2.08%)	0/94 (0.00%)	0/46 (0.00%)	2/46 (4.35%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	2/39 (5.13
Fatigue † 1								
# participants affected / at risk	5/96 (5.21%)	6/94 (6.38%)	2/46 (4.35%)	2/46 (4.35%)	0/86 (0.00%)	0/69 (0.00%)	1/41 (2.44%)	0/39 (0.00
Pyrexia † 1								
# participants affected / at risk	6/96 (6.25%)	1/94 (1.06%)	2/46 (4.35%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	1/41 (2.44%)	0/39 (0.00
Infections and infestations								
Bronchitis NOS † 1								
# participants affected / at risk	0/96 (0.00%)	5/94 (5.32%)	3/46 (6.52%)	2/46 (4.35%)	0/86 (0.00%)	0/69 (0.00%)	2/41 (4.88%)	2/39 (5.13
Infection NOS † 1								
# participants affected / at risk	0/96 (0.00%)	3/94 (3.19%)	1/46 (2.17%)	0/46 (0.00%)	3/86 (3.49%)	2/69 (2.90%)	2/41 (4.88%)	2/39 (5.13
Influenza † 1								
# participants affected / at risk	5/96 (5.21%)	2/94 (2.13%)	2/46 (4.35%)	1/46 (2.17%)	1/86 (1.16%)	2/69 (2.90%)	0/41 (0.00%)	1/39 (2.56
Nasopharyngitis † 1								
# participants affected / at risk	15/96 (15.63%)	18/94 (19.15%)	12/46 (26.09%)	11/46 (23.91%)	12/86 (13.95%)	7/69 (10.14%)	7/41 (17.07%)	8/39 (20.5
Pneumonia NOS † 1								
# participants affected / at risk	5/96 (5.21%)	3/94 (3.19%)	2/46 (4.35%)	5/46 (10.87%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	3/39 (7.69
Upper respiratory tract infection NOS † 1								
# participants affected / at risk	1/96 (1.04%)	2/94 (2.13%)	6/46 (13.04%)	9/46 (19.57%)	2/86 (2.33%)	2/69 (2.90%)	4/41 (9.76%)	6/39 (15.3
Urinary tract infection								

NOS † 1								
# participants affected / at risk	0/96 (0.00%)	3/94 (3.19%)	3/46 (6.52%)	4/46 (8.70%)	1/86 (1.16%)	1/69 (1.45%)	2/41 (4.88%)	3/39 (7.69
Investigations								
Blood creatinine increased † 1								
# participants affected / at risk	2/96 (2.08%)	1/94 (1.06%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	2/39 (5.13
Metabolism and nutrition disorders								
Hypercholesterolaemia † 1								
# participants affected / at risk	4/96 (4.17%)	0/94 (0.00%)	3/46 (6.52%)	6/46 (13.04%)	1/86 (1.16%)	2/69 (2.90%)	0/41 (0.00%)	2/39 (5.13
Hypokalaemia † 1								
# participants affected / at risk	0/96 (0.00%)	1/94 (1.06%)	1/46 (2.17%)	4/46 (8.70%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	2/39 (5.13
Musculoskeletal and connective tissue disorders								
Arthralgia † 1								
# participants affected / at risk	5/96 (5.21%)	6/94 (6.38%)	2/46 (4.35%)	3/46 (6.52%)	0/86 (0.00%)	1/69 (1.45%)	1/41 (2.44%)	1/39 (2.56
Arthritis NOS † 1								
# participants affected / at risk	1/96 (1.04%)	0/94 (0.00%)	0/46 (0.00%)	3/46 (6.52%)	0/86 (0.00%)	1/69 (1.45%)	0/41 (0.00%)	1/39 (2.56
Myalgia † 1								
# participants affected / at risk	3/96 (3.13%)	7/94 (7.45%)	1/46 (2.17%)	1/46 (2.17%)	2/86 (2.33%)	0/69 (0.00%)	0/41 (0.00%)	0/39 (0.00
Pain in limb † 1								
# participants affected / at risk	1/96 (1.04%)	5/94 (5.32%)	0/46 (0.00%)	1/46 (2.17%)	2/86 (2.33%)	1/69 (1.45%)	0/41 (0.00%)	0/39 (0.00
Nervous system disorders								
Headache NOS † 1								
# participants affected / at risk	7/96 (7.29%)	7/94 (7.45%)	3/46 (6.52%)	5/46 (10.87%)	1/86 (1.16%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56
Respiratory, thoracic and mediastinal disorders								
Cough † 1								
# participants affected / at risk	3/96 (3.13%)	5/94 (5.32%)	3/46 (6.52%)	3/46 (6.52%)	0/86 (0.00%)	3/69 (4.35%)	1/41 (2.44%)	1/39 (2.56
Excessive bronchial secretion † 1								
# participants affected / at risk	0/96 (0.00%)	0/94 (0.00%)	0/46 (0.00%)	0/46 (0.00%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	2/39 (5.13
Skin and subcutaneous tissue disorders								
Acne NOS † 1								
# participants affected / at risk	0/96 (0.00%)	11/94 (11.70%)	0/46 (0.00%)	1/46 (2.17%)	0/86 (0.00%)	0/69 (0.00%)	0/41 (0.00%)	1/39 (2.56
Vascular disorders								
Hypertension NOS † 1								
# participants affected / at risk	5/96 (5.21%)	4/94 (4.26%)	4/46 (8.70%)	6/46 (13.04%)	0/86 (0.00%)	3/69 (4.35%)	2/41 (4.88%)	3/39 (7.69
Hypertension aggravated † 1								

# participants affected / at risk	**0/96 (0.00%)**	**5/94 (5.32%)**	**1/46 (2.17%)**	**1/46 (2.17%)**	**3/86 (3.49%)**	**1/69 (1.45%)**	**1/41 (2.44%)**	**1/39 (2.56**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☑ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Restriction Description: The terms and conditions of Novartis' agreements with its investigators may vary. However, Novartis does not prohibit any investigator from publishing. Any publications from a single-site are postponed until the publication of the pooled data (ie, data from all sites) in the clinical trial.

Results Point of Contact:

Name/Title: Study Director
Organization: Novartis Pharmaceuticals
phone: 862 778-8300

No publications provided by Novartis

Publications automatically indexed to this study:

Arora S, Erikstad I, Ueland T, Sigurdardottir V, Ekmehag B, Jansson K, Eiskjaer H, Bøtker HE, Mortensen SA, Saunamaki K, Gude E, Ragnarsson A, Solbu D, Aukrust P, Gullestad L. Virtual histology assessment of cardiac allograft vasculopathy following introduction of everolimus--results of a multicenter trial. Am J Transplant. 2012 Oct;12(10):2700-9. doi: 10.1111/j.1600-6143.2012.04234.x. Epub 2012 Sep 7.

Arora S, Gude E, Sigurdardottir V, Mortensen SA, Eiskjær H, Riise G, Mared L, Bjørtuft O, Ekmehag B, Jansson K, Simonsen S, Aukrust P, Solbu D, Iversen M, Gullestad L. Improvement in renal function after everolimus introduction and calcineurin inhibitor reduction in maintenance thoracic transplant recipients: the significance of baseline glomerular filtration rate. J Heart Lung Transplant. 2012 Mar;31(3):259-65. doi: 10.1016/j.healun.2011.12.010.

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ClinicalTrials.gov Identifier:	NCT00377962 History of Changes
Other Study ID Numbers:	**CRAD001AIC01**
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