



Clinical trial results:

A prospective, randomized, active controlled, parallel group, multi-center trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission in subjects with lupus nephritis.

The study was divided into two phases, the induction phase and the maintenance phase designed to compare MMF with azathioprine over a maximum 3 year period. Here only results for the induction phase are described.

Summary

EudraCT number	2004-004917-41
Trial protocol	DE GB HU CZ ES BE PT AT IT
Global end of trial date	16 March 2007

Results information

Result version number	v1 (current)
This version publication date	26 February 2017
First version publication date	26 February 2017
Summary attachment (see zip file)	WX17801_Vifor Pharma (WX17801 Vifor Pharma.pdf)

Trial information

Trial identification

Sponsor protocol code	WX17801
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aspreva Pharmaceuticals Corporation
Sponsor organisation address	1203-4464, Markham Street, Victoria, Canada, V8Z 7X8
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Scientific contact	Udo-Michael Göhring , Aspreva Pharmaceuticals Corporation, udo-michael.goehring@viforpharma.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	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 May 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2007
Global end of trial reached?	Yes
Global end of trial date	16 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective for Induction: To assess the efficacy of MMF compared to intravenous cyclophosphamide (IVC) in inducing response in subjects with lupus nephritis (LN).

Protection of trial subjects:

This study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments, or with local laws and regulations if these afforded greater protection to the individual. Additionally, the study was performed according to the principles of Good Clinical Practice (GCP). The protocol and all accompanying material provided to the subject (eg, subject information and informed consent forms) as well as any advertising or compensation given to the subjects were submitted by the investigators to an Independent Ethics Committee (IEC) or Institutional Review Board (IRB). Approval from the committee was obtained before starting the study.

In addition, a blinded Clinical Endpoints Committee (CEC) was formed comprising two physicians with proven expertise in LN and a biostatistician experienced in the conduct and data handling of large clinical trials. The CEC adjudicated the primary endpoint in the induction phase (response) for all enrolled subjects. The CEC had the responsibility for ensuring that defined clinical endpoints were substantiated by the evidence. The CEC's role included identifying protocol violations and adjudicating the appropriateness of withdrawals.

Background therapy:

All subjects received concomitant corticosteroid therapy consisting of oral prednisolone (or equivalent) starting at 0.75-1.0 mg/kg/day (maximum 60 mg/day). Prednisolone was tapered according to the following schedule:

- Decreased by 10 mg/day every two weeks to 40 mg/day, followed by
- Decreased by 5 mg/day every two weeks to 10 mg/day

Reductions below 10 mg/day were allowed after four weeks of stable response. Subjects with lack of response were allowed one 4-week interval without dose reduction or one dose escalation to the previous dose for two weeks, at any time up to Week 24. Lack of response was defined as no or minimal change per investigator judgment over three months or deterioration not meeting the criteria for withdrawal.

Evidence for comparator:

The active comparator during the induction phase was IVC plus corticosteroid. In the National Institutes of Health (NIH) series of trials, IVC was shown to be more effective than corticosteroid alone in preventing end stage renal disease and death. In a meta analysis, cyclophosphamide plus steroids reduced the risk of doubling of serum creatinine compared to steroids alone. In these studies, IVC was administered as six, monthly infusions, with an initial dose of 0.5 g/m², and subsequent infusions of 0.5 to 1.0 g/m², with a target dose 1.0 g/m². By consensus of the Steering Committee of the study and investigators, IVC was administered according to a modified NIH regimen, which differed from the NIH regimen in that the initial infusion dose was 0.75 g/m². IVC and MMF were given with concomitant corticosteroids.

Actual start date of recruitment	13 July 2005
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	Portugal: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Argentina: 52
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	China: 94
Country: Number of subjects enrolled	Costa Rica: 12
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Malaysia: 23
Country: Number of subjects enrolled	Mexico: 28
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	370
EEA total number of subjects	61

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)	24
Adults (18-64 years)	345
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted with an enrollment target of 358 subjects at 100 sites across the world.

Pre-assignment

Screening details:

At the Baseline visit prior to the induction phase, subjects were randomly assigned to a treatment group. The randomization was stratified according to key prognostic factors (race, biopsy class).

Period 1

Period 1 title	Induction phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blinding a study of this type was not practical for ethical and operational reasons. In order to reduce the risk of bladder toxicity and dehydration, subjects treated with IVC must be hydrated adequately before, during, and immediately after each infusion, including intravenous saline infusions prior to dosing and at least four liters of oral fluids for 24 h after dosing. Administration of this volume of fluid represented an unnecessary risk to subjects with renal dysfunction treated with MMF.

Arms

Are arms mutually exclusive?	Yes
Arm title	Mycophenolate mofetil (MMF)

Arm description:

Dosing of MMF started at 500 mg twice daily (BID) for the first week, increasing to 1 g BID for the second week and 1.5 g BID for the third and subsequent weeks. Subjects took 500 mg tablets BID (morning and evening), before meals with a glass of water. If a dose was missed, the subject took the next correct dose rather than "doubling up" at the next dosing time point.

Arm type	Experimental
Investigational medicinal product name	Mycophenolate mofetil (MMF)
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 g orally BID plus corticosteroid for 24 weeks.

Arm title	Intravenous cyclophosphamide (IVC)
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Arm description:

IVC doses were administered every four weeks (monthly) to a total of six infusions. Dosing was started at 0.75 g/m² of body surface area (BSA) for the first month, with subsequent doses at 0.5-1.0 g/m². The target dose was 1.0 g/m², but doses were titrated by 0.25 g/m² increments to maintain nadir leukocyte count between 2500-4000/mm³. A 25% reduction for age greater than 60 years and a 25% reduction for serum creatinine >300 µmol/L (3.4 mg/dL) was allowed.

Arm type	Active comparator
Investigational medicinal product name	Intravenous cyclophosphamide (IVC)
Investigational medicinal product code	
Other name	Endoxan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.5 to 1.0 g/m² BSA. Monthly infusions plus corticosteroid for 24 weeks.

Number of subjects in period 1	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)
Started	185	185
Completed	150	156
Not completed	35	29
Adverse event, serious fatal	3	1
Consent withdrawn by subject	6	5
Physician decision	1	3
Reason for withdrawal is not noted	-	2
Adverse event, non-fatal	21	12
Withdrawal criteria	1	2
Non-compliance	-	1
Lost to follow-up	1	2
Sponsor decision	2	1

Baseline characteristics

Reporting groups

Reporting group title	Mycophenolate mofetil (MMF)
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Reporting group description:

Dosing of MMF started at 500 mg twice daily (BID) for the first week, increasing to 1 g BID for the second week and 1.5 g BID for the third and subsequent weeks. Subjects took 500 mg tablets BID (morning and evening), before meals with a glass of water. If a dose was missed, the subject took the next correct dose rather than "doubling up" at the next dosing time point.

Reporting group title	Intravenous cyclophosphamide (IVC)
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Reporting group description:

IVC doses were administered every four weeks (monthly) to a total of six infusions. Dosing was started at 0.75 g/m² of body surface area (BSA) for the first month, with subsequent doses at 0.5-1.0 g/m². The target dose was 1.0 g/m², but doses were titrated by 0.25 g/m² increments to maintain nadir leukocyte count between 2500-4000/mm³. A 25% reduction for age greater than 60 years and a 25% reduction for serum creatinine >300 µmol/L (3.4 mg/dL) was allowed.

Reporting group values	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)	Total
Number of subjects	185	185	370
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	10	14	24
Adults (18-64 years)	174	171	345
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	32.4	31.3	
standard deviation	± 11.17	± 10.25	-
Gender categorical			
Units: Subjects			
Female	157	156	313
Male	28	29	57

End points

End points reporting groups

Reporting group title	Mycophenolate mofetil (MMF)
Reporting group description:	
Dosing of MMF started at 500 mg twice daily (BID) for the first week, increasing to 1 g BID for the second week and 1.5 g BID for the third and subsequent weeks. Subjects took 500 mg tablets BID (morning and evening), before meals with a glass of water. If a dose was missed, the subject took the next correct dose rather than "doubling up" at the next dosing time point.	
Reporting group title	Intravenous cyclophosphamide (IVC)
Reporting group description:	
IVC doses were administered every four weeks (monthly) to a total of six infusions. Dosing was started at 0.75 g/m ² of body surface area (BSA) for the first month, with subsequent doses at 0.5-1.0 g/m ² . The target dose was 1.0 g/m ² , but doses were titrated by 0.25 g/m ² increments to maintain nadir leukocyte count between 2500-4000/mm ³ . A 25% reduction for age greater than 60 years and a 25% reduction for serum creatinine >300 µmol/L (3.4 mg/dL) was allowed.	
Subject analysis set title	Asia - MMF
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in MMF group from Asia region.	
Subject analysis set title	Asia - IVC
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in IVC group from Asia region.	
Subject analysis set title	Latin America - MMF
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in MMF group from Latin America region.	
Subject analysis set title	Latin America - IVC
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in IVC group from Latin America region.	
Subject analysis set title	US/Canada - MMF
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in MMF group from US/Canada region.	
Subject analysis set title	US/Canada -IVC
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in IVC group from US/Canada region.	
Subject analysis set title	Rest of World - MMF
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in MMF group from Rest of World region.	
Subject analysis set title	Rest of World - IVC
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included in IVC group from Rest of World region.	

Primary: Number (percentage) of subjects showing treatment response at 24 weeks

End point title	Number (percentage) of subjects showing treatment response at 24 weeks
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End point description:

Treatment response was defined as follows:

a) Decrease in proteinuria, defined as a decrease in the urine protein to creatinine ratio to <3 in subjects with baseline nephrotic range proteinuria (≥ 3 urine protein to creatinine ratio) or a decrease in the urine protein to creatinine ratio by $\geq 50\%$ in subjects with subnephrotic proteinuria (<3 urine protein to creatinine ratio at Baseline). Urine protein to creatinine ratios were derived from the 24 hour urine collection.

b) Stabilization of serum creatinine (ie, at Week 24 serum creatinine level $\pm 25\%$ of baseline), or improvement.

The results are described for the intent-to-treat (ITT) population consisting of all subjects who were randomized to the study and had at least one post-Baseline efficacy assessment (the subject was assessed for response by the CEC).

The primary efficacy objective of demonstrating that MMF was statistically significantly superior to IVC was not met because of multifactorial reasons.

End point type	Primary
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End point timeframe:

From Baseline to 24 weeks.

End point values	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)	Asia - MMF	Asia - IVC
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	185	185	57	60
Units: percent				
number (not applicable)	56.2	53	52.6	65

End point values	Latin America - MMF	Latin America - IVC	US/Canada - MMF	US/Canada - IVC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	50	37	38
Units: percent				
number (not applicable)	60.7	32	56.8	47.4

End point values	Rest of World - MMF	Rest of World - IVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	37		
Units: percent				
number (not applicable)	54.3	67.6		

Statistical analyses

Statistical analysis title	Comparison between treatment groups
Statistical analysis description:	
OR = (Odds of response in MMF)/(Odds of response in IVC).	
OR >1.0 indicated that MMF was associated with a higher response rate than IVC.	
p-value for between-group comparison of MMF versus IVC was based on logistic regression.	
The primary analysis (logistic regression) had a significant interaction between treatment and region that showed that the differences in response between the MMF and IVC groups depended on the region of the world.	
Comparison groups	Intravenous cyclophosphamide (IVC) v Mycophenolate mofetil (MMF)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.478
Method	Regression, Logistic
Parameter estimate	Odds response MMF/Odds response IVC
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.8

Statistical analysis title	Comparison between treatment groups - Asia
Statistical analysis description:	
OR = (Odds of response in MMF)/(Odds of response in IVC).	
OR >1.0 indicated that MMF was associated with a higher response rate than IVC.	
p-value for between-group comparison of MMF versus IVC was based on logistic regression.	
Comparison groups	Asia - MMF v Asia - IVC
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.176
Method	Regression, Logistic
Parameter estimate	Odds response MMF/Odds response IVC
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.3

Statistical analysis title	Comparison between treatment groups -Latin America
Statistical analysis description:	
OR = (Odds of response in MMF)/(Odds of response in IVC).	
OR >1.0 indicated that MMF was associated with a higher response rate than IVC.	
p-value for between-group comparison of MMF versus IVC was based on logistic regression.	
Comparison groups	Latin America - MMF v Latin America - IVC

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Logistic
Parameter estimate	Odds response MMF/Odds response IVC
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	7.7

Statistical analysis title	Comparison between treatment groups - US/Canada
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Statistical analysis description:

OR = (Odds of response in MMF)/(Odds of response in IVC).

OR >1.0 indicated that MMF was associated with a higher response rate than IVC.

p-value for between-group comparison of MMF versus IVC was based on logistic regression.

Comparison groups	US/Canada - MMF v US/Canada -IVC
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363
Method	Regression, Logistic
Parameter estimate	Odds response MMF/Odds response IVC
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.9

Statistical analysis title	Comparison between treatment groups -Rest of World
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Statistical analysis description:

OR = (Odds of response in MMF)/(Odds of response in IVC).

OR >1.0 indicated that MMF was associated with a higher response rate than IVC.

p-value for between-group comparison of MMF versus IVC was based on logistic regression.

Comparison groups	Rest of World - MMF v Rest of World - IVC
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.256
Method	Regression, Logistic
Parameter estimate	Odds response MMF/Odds response IVC
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.5

Secondary: Complete remission as defined by return to normal serum creatinine, proteinuria ≤500 mg/24 hours, and an inactive urinary sediment

End point title	Complete remission as defined by return to normal serum creatinine, proteinuria ≤500 mg/24 hours, and an inactive urinary sediment
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End point description:

Number (%) of subjects achieving complete remission. Complete remission was defined as return to normal serum creatinine, proteinuria ≤500 mg/24 hours and an inactive urinary sediment (absence of red blood cells, white blood cells or cellular or granular casts) after 24 weeks. Subjects who did not show complete remission at Week 24 or who had insufficient information (including missing values) were considered as not achieving complete remission.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24.

End point values	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	185		
Units: percent				
number (not applicable)	8.6	8.1		

Statistical analyses

Statistical analysis title	Complete remission for serum creatinine
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Statistical analysis description:

Complete remission was defined by return to normal serum creatinine.

Comparison groups	Mycophenolate mofetil (MMF) v Intravenous cyclophosphamide (IVC)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	12.1

Statistical analysis title	Complete remission for urine protein
Statistical analysis description: Complete remission was defined by return to proteinuria ≤ 500 mg/24 hours.	
Comparison groups	Mycophenolate mofetil (MMF) v Intravenous cyclophosphamide (IVC)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	5.6

Statistical analysis title	Complete remission for urine microscopy
Statistical analysis description: Complete remission was defined by return to inactive urinary sediment (absence of red blood cells, white blood cells or cellular or granular casts) after 24 weeks.	
Comparison groups	Mycophenolate mofetil (MMF) v Intravenous cyclophosphamide (IVC)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	16.6

Secondary: Proportion of subjects meeting complete remission criteria in at least one of the individual parameters (serum creatinine, urine protein, urine microscopy)

End point title	Proportion of subjects meeting complete remission criteria in at least one of the individual parameters (serum creatinine, urine protein, urine microscopy)
End point description: At least one complete remission criteria was defined as a subject who met any one of the three criteria : return to normal serum creatinine, return to proteinuria ≤ 500 mg/24 hours or return to inactive urinary sediment after 24 weeks. Subjects who did not meet at least one criteria for complete remission at Week 24, or who withdrew earlier than Week 24 or who did not have sufficient information (including missing values) were considered as "No".	
End point type	Secondary

End point timeframe:

From Baseline to Week 24.

End point values	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	185		
Units: percent				
number (not applicable)	76.2	75.7		

Statistical analyses

Statistical analysis title	Comparison between groups at Week 24
Comparison groups	Mycophenolate mofetil (MMF) v Intravenous cyclophosphamide (IVC)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	9.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were monitored from the time of informed consent throughout the course of the study, at every visit (including screening). A follow-up phone call was made 2 weeks after the last study visit (last dosing of study medication).

Adverse event reporting additional description:

The Safety population (364 subjects) was considered for AEs. It comprised all subjects who were randomized, received at least one dose of study medication during the 24 week induction phase of the study, and had at least one post-Baseline safety assessment during this phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Mycophenolate mofetil (MMF)
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Reporting group description: -

Reporting group title	Intravenous cyclophosphamide (IVC)
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Reporting group description: -

Serious adverse events	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 184 (27.72%)	41 / 180 (22.78%)	
number of deaths (all causes)	9	5	
number of deaths resulting from adverse events	7	2	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Venous stenosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	2 / 184 (1.09%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 20	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 184 (0.54%)	3 / 180 (1.67%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus pneumonitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy kidney			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			

subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (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	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus encephalitis			
subjects affected / exposed	0 / 184 (0.00%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 184 (0.00%)	3 / 180 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 184 (1.09%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 184 (0.54%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			

subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 184 (1.63%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 184 (1.09%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			

subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	3 / 184 (1.63%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure chronic			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	2 / 184 (1.09%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 184 (0.00%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	2 / 184 (1.09%)	4 / 180 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Arthralgia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 184 (2.72%)	3 / 180 (1.67%)	
occurrences causally related to treatment / all	4 / 5	2 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Bronchitis			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	5 / 184 (2.72%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 184 (0.54%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	2 / 184 (1.09%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis tuberculous			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis gastrointestinal			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 184 (0.54%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infection			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Meningitis streptococcal			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 184 (0.00%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subacute endocarditis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 184 (0.00%)	4 / 180 (2.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 184 (1.09%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 184 (0.54%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Mycophenolate mofetil (MMF)	Intravenous cyclophosphamide (IVC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	176 / 184 (95.65%)	171 / 180 (95.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 184 (13.59%)	24 / 180 (13.33%)	
occurrences (all)	25	27	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	35 / 184 (19.02%)	30 / 180 (16.67%)	
occurrences (all)	46	37	
Fatigue			
subjects affected / exposed	18 / 184 (9.78%)	18 / 180 (10.00%)	
occurrences (all)	20	29	
Pyrexia			
subjects affected / exposed	12 / 184 (6.52%)	30 / 180 (16.67%)	
occurrences (all)	13	37	
Oedema			
subjects affected / exposed	11 / 184 (5.98%)	16 / 180 (8.89%)	
occurrences (all)	11	17	

Asthenia subjects affected / exposed occurrences (all)	9 / 184 (4.89%) 11	15 / 180 (8.33%) 19	
Chest pain subjects affected / exposed occurrences (all)	8 / 184 (4.35%) 9	10 / 180 (5.56%) 15	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	24 / 184 (13.04%) 25	16 / 180 (8.89%) 20	
Dyspnoea subjects affected / exposed occurrences (all)	10 / 184 (5.43%) 10	6 / 180 (3.33%) 6	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	10 / 184 (5.43%) 10	11 / 180 (6.11%) 18	
Investigations White blood cell count decreased subjects affected / exposed occurrences (all)	5 / 184 (2.72%) 7	15 / 180 (8.33%) 26	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	11 / 184 (5.98%) 11	6 / 180 (3.33%) 9	
Tachycardia subjects affected / exposed occurrences (all)	10 / 184 (5.43%) 10	6 / 180 (3.33%) 6	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	38 / 184 (20.65%) 53	47 / 180 (26.11%) 106	
Dizziness subjects affected / exposed occurrences (all)	8 / 184 (4.35%) 8	10 / 180 (5.56%) 13	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	23 / 184 (12.50%)	11 / 180 (6.11%)	
occurrences (all)	25	11	
Leukopenia			
subjects affected / exposed	10 / 184 (5.43%)	36 / 180 (20.00%)	
occurrences (all)	13	52	
Neutropenia			
subjects affected / exposed	2 / 184 (1.09%)	12 / 180 (6.67%)	
occurrences (all)	2	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	52 / 184 (28.26%)	23 / 180 (12.78%)	
occurrences (all)	72	30	
Nausea			
subjects affected / exposed	27 / 184 (14.67%)	82 / 180 (45.56%)	
occurrences (all)	37	167	
Vomiting			
subjects affected / exposed	25 / 184 (13.59%)	67 / 180 (37.22%)	
occurrences (all)	29	143	
Abdominal pain			
subjects affected / exposed	19 / 184 (10.33%)	13 / 180 (7.22%)	
occurrences (all)	23	21	
Abdominal pain upper			
subjects affected / exposed	15 / 184 (8.15%)	18 / 180 (10.00%)	
occurrences (all)	19	25	
Constipation			
subjects affected / exposed	12 / 184 (6.52%)	9 / 180 (5.00%)	
occurrences (all)	14	11	
Dyspepsia			
subjects affected / exposed	10 / 184 (5.43%)	5 / 180 (2.78%)	
occurrences (all)	14	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	20 / 184 (10.87%)	64 / 180 (35.56%)	
occurrences (all)	22	75	
Rash			

subjects affected / exposed occurrences (all)	19 / 184 (10.33%) 24	21 / 180 (11.67%) 23	
Acne subjects affected / exposed occurrences (all)	9 / 184 (4.89%) 11	9 / 180 (5.00%) 10	
Erythema subjects affected / exposed occurrences (all)	5 / 184 (2.72%) 5	10 / 180 (5.56%) 10	
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	9 / 184 (4.89%) 9	11 / 180 (6.11%) 12	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	29 / 184 (15.76%) 48	43 / 180 (23.89%) 66	
Back pain subjects affected / exposed occurrences (all)	19 / 184 (10.33%) 24	16 / 180 (8.89%) 24	
Muscle spasms subjects affected / exposed occurrences (all)	19 / 184 (10.33%) 25	17 / 180 (9.44%) 29	
Pain in extremity subjects affected / exposed occurrences (all)	6 / 184 (3.26%) 10	9 / 180 (5.00%) 14	
Arthritis subjects affected / exposed occurrences (all)	4 / 184 (2.17%) 4	10 / 180 (5.56%) 16	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	25 / 184 (13.59%) 37	29 / 180 (16.11%) 42	
Urinary tract infection subjects affected / exposed occurrences (all)	19 / 184 (10.33%) 21	17 / 180 (9.44%) 22	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	17 / 184 (9.24%) 23	28 / 180 (15.56%) 37	
Herpes zoster subjects affected / exposed occurrences (all)	14 / 184 (7.61%) 15	5 / 180 (2.78%) 6	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	11 / 184 (5.98%) 11	3 / 180 (1.67%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2005	<p>PROTOCOL AMENDMENT 1</p> <ul style="list-style-type: none">• Added statistical analysis of efficacy and safety of induction phase. • Reorganized sections on analysis of maintenance phase• Removed secondary analysis of response in induction• Replaced randomization by minimization algorithm with randomization by stratification• Clarified number of subjects required for induction phase• Added description of Steering Committee, Clinical Endpoints CEC, and Publications Committee• Added sparse sampling population pharmacokinetics analysis• Clarified preparation of IV cyclophosphamide• Clarified calculation of azathioprine dosing• Rationalized and clarified allowed and prohibited medications• Clarified instructions on contraception• Clarified criteria for use of IV prednisone• Amended Screening Visit -7 days to -1 days prior to Baseline to -10 days to -1 day prior to Baseline• Clarified Visit 9 (end of induction phase) requirements• Clarified requirements for hematology laboratory monitoring per label requirements for induction and maintenance phases• Added hormone tests• Corrected overlap of requirements for urinary protein• Amended reference to registry study• Amended number and location of centers from 50 to 100 worldwide• Added rationale for including patients with Class V lupus nephritis• Revised schedule of assessments for usability and to reflect protocol revisions• Clarified instructions for reporting of serious adverse events• Replaced lower case Roman numeral page numbers in synopsis with continuous numeric page numbers• Renumbered references• Amended clinical phase of study from Phase III /IV to Phase III• Changed Project Leader and Project Statistician• Correction of minor typographic errors

26 April 2005	<p>PROTOCOL AMENDMENT 2</p> <ul style="list-style-type: none"> • Study title and overall study objectives were updated • Duration of induction phase treatment has been fixed at 24 weeks for all patients • The description of the primary efficacy analysis for the end of induction phase was clarified • Maintenance phase will continue until sufficient subjects have experienced treatment failure to maintain the power of the study, or until the last subject has been followed for 36 months, whichever is earlier • Treatment with pulse IV corticosteroids, plasmapheresis, or intravenous immunoglobulin, formerly permitted within the protocol, is now prohibited • Requirement for discussions with medical monitor were clarified • Required follow-up of subjects withdrawn was added • Inclusion and exclusion criteria were clarified. • Text was added regarding dosing of subjects aged 12-18 years • Low dose aspirin is added as an allowed medication • Serum pregnancy test must be completed within 7 days of Baseline • Description of pharmacokinetic sampling and analysis was expanded • Frequency of the SELENA-SLEDAI was reduced to 3-month intervals • Frequency of some laboratory tests were reduced • ECGs will be determined at Baseline, end of induction/beginning of maintenance, and end of maintenance • GFR will be determined at screening and all visits for which a 24-hour urine will be collected • Conversion of value for serum creatinine >300 umol/l was corrected in suggested dose adjustments for IVC dosing in renal insufficiency • Determination of urine protein:creatinine ratio was clarified • Urinalysis and urine microscopy were added to Schedule of Assessments • Schedule of CBCs was amended during the induction phase to create a consensus schedule fulfilling monitoring requirements for both study treatments, so that timing of CBCs would not reveal treatment assignments to blinded reviewers • Instructions for preparation of IV cyclophosphamide were clarified • Justification for sample size
30 June 2005	<p>PROTOCOL AMENDMENT 3</p> <ul style="list-style-type: none"> • Amended sample size and statistical analysis according to FDA Special Protocol Assessment requirement that primary efficacy analysis be for superiority rather than non-inferiority • Amended long title to reflect induction phase being unblinded • Clarified definition of treatment response (primary endpoint of induction phase and required for entry into maintenance) • Clarified IVC dosing, number of doses, target dose, and adjustment of doses • Clarified that secondary efficacy endpoints during the induction phase would be analysed descriptively • Corrected footnote in Table of Assessments for induction regarding frequency of pregnancy tests • Amended reference to BILAG from 'organ' to 'system' in secondary endpoints • Corrected glossary of abbreviations • Corrected typographic error in Appendix 3 • Corrected arithmetic error in conversion of serum creatinine units
23 August 2006	<p>PROTOCOL AMENDMENT 4</p> <ul style="list-style-type: none"> • A full pharmacokinetic (PK) profiling for a subset of subjects was added.

22 February 2007	<p>PROTOCOL AMENDMENT 5</p> <ul style="list-style-type: none"> • Temporary dose stoppage of IVC was allowed for no more than 7 days in total. • Urine protein to creatinine ratio was clarified to specify that the ratio was derived from the 24 hour urine protein and creatinine measurements. • Hierarchical testing for the key secondary endpoints in the induction phase was included in the statistical analysis following feedback from the FDA. • The interpretation of what constitutes high dose phenobarbital was clarified to reflect that it was the judgment of the investigators. • The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) flare instrument was removed and the procedure for calculating the total for the SLEDAI was corrected. The flare instrument that was part of the Safety of Exogenous Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI scale, which appeared in Appendix 7 of the protocol but was not used for the study, was deleted due to the potential for confusion with study flare definitions. • The visit window at the beginning of induction was increased. Due to practical difficulties regarding the availability of laboratory results required for randomization, the window for the beginning of the induction visit (Visit 2) was increased from 10 to 14 days from Screening and the end of induction (Visit 9) was increased from 7 to 10 days. • The BILAG worksheet in Appendix 5 of the protocol was updated to conform to the latest version that was used in the clinical study.
16 March 2007	<p>PROTOCOL AMENDMENT 6</p> <p>Protocol Amendment 6, dated April 12, 2007 was approved by the IECs/IRBs before implementation. Last subject, last visit on March 16, 2007 was completed but the database had not been locked prior to implementation of this amendment.</p> <ul style="list-style-type: none"> • The primary analysis for the induction phase of protocol was changed from a Fisher's Exact Test comparing the proportion of responders in the two treatment groups, to a logistic regression comparing the proportion of responders in the two treatment groups. The rationale for this change in statistical test was that the logistic regression included the covariates race (Caucasian/Asian/Other), and World Health Organization (WHO) LN Class (V only, others) (the stratification variables used for the randomization), and geographical region (US/Canada, Latin America, Asia and Rest of the World). Analysis with these covariates is common in LN trials and provided a more meaningful analysis of the response to treatment than the Fisher's Exact Test. Fisher's Exact Test is used primarily when the expected number of subjects in a treatment by response cell is less than five, which was unlikely to be the case in this study. • Partial remission was one of the secondary efficacy parameters for efficacy assessments at the end of the induction phase. This parameter of partial remission was removed from the protocol, since it was felt that the primary endpoint of response was more clinically meaningful and more robust. • For the purpose of clarification, the complete remission criteria were amended to "proportion of subjects meeting remission criteria for each individual parameter AND proportion of subjects meeting at least one criterion for complete remission". The secondary efficacy parameter was changed from the "number of" subjects to the "proportion of" subjects. • Clarification of the hierarchical testing of the secondary efficacy variables in the induction phase was added to the synopsis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported