

**Clinical trial results:****Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-neutrophil Cytoplasm Antibody Associated Vasculitis: an International Randomised Controlled Trial****Summary**

EudraCT number	2009-013220-24
Trial protocol	GB IT SE DK CZ ES PL
Global end of trial date	31 July 2017

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018
Summary attachment (see zip file)	PEXIVAS Cumulative SAE report (SAE Cumulative Report_EudraCT_Jun2018.pdf)

Trial information**Trial identification**

Sponsor protocol code	A091637
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Additional study identifiers

ISRCTN number	ISRCTN07757494
ClinicalTrials.gov id (NCT number)	NCT00987389
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
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Sponsor organisation name	University of Pennsylvania; Division of Rheumatology
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Sponsor organisation name	Okayama University
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2017
Global end of trial reached?	Yes
Global end of trial date	31 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

There are 2 principal questions for this research:

- 1) Does the addition of 7 plasma exchange procedures to usual therapy early in the treatment of patients with severe ANCA associated vasculitis significantly reduce their risk of death or kidney failure?
- 2) Does a reduced-dose regimen of steroids compared to a standard-dose regimen in the first 6 months of treatment of patients with ANCA associated vasculitis significantly reduce their risk of death or kidney failure?

Protection of trial subjects:

This clinical trial involved over 700 participants with systemic vasculitis. The inclusion criteria consists of an ANCA-associated vasculitis diagnosis (AAV) with at least one severe manifestation, either nephritis or lung haemorrhage. Patients with anti-glomerular basement membrane disease; other forms of vasculitis; or who are pregnant were excluded. Any participants becoming pregnant whilst are permitted to remain on study provided that consent remains valid and all teratogenic medications are switched to safer alternatives.

Informed consent was sought from all potentially eligible patients, or deferred consent from a surrogate decision maker if the patient was unable to consent. Subsequent patient consent was sought once the patient regained capacity.

Strict patient confidentiality was observed throughout all aspects of the study. Medical records were reviewed by members of the local research team only. No patient identifiable data was distributed beyond the local team as all patient data was anonymised prior to transmitting to the data and coordination teams.

Overall supervision of the trial is provided by a Trial Steering Committee to ensure safe conduct of the trial and compliance with GCP and the trial protocol.

Background therapy:

Once enrolled, participants were randomised to receive either a low- or standard-dose glucocorticoid regime; and to receive adjunctive plasma exchange or not. Alongside this, patients received standard immunosuppressive therapy in the form of either Rituximab or Cyclophosphamide. All patients received between 1-3g of IV Methylprednisolone over 1 to 3 days before beginning their oral Glucocorticoid regime.

The standard immunosuppressive therapy was decided by preference of the site investigator/patient. Participants may have received either intravenous (15mg/kg/pulse) or oral (2mg/kg/day)

Cyclophosphamide according to local preferences. Cyclophosphamide doses were reduced according to advanced age, poor baseline renal function or cytopenias.

Participants receiving Rituximab were given 4 weekly intravenous infusions (375mg/m²). The first dose was received within 14 days of participation and subsequent doses should follow 7 days later, with a 5-10 day window to allow for practical considerations. All doses of Rituximab were given within 42 days of enrolment and Rituximab was not given within 48 hours prior to receiving a PLEX treatment.

Randomisation was stratified according to background immunosuppressant.

Evidence for comparator:

Plasma exchange (PLEX), a method of rapidly removing potentially pathogenic ANCA and other mediators of inflammation and coagulation, has shown promise as an adjunctive therapy in AAV to improve early disease control and improve rates of renal recovery in severe disease. Glucocorticoids (GC) are a standard of care in the treatment of AAV. High doses of GC early in disease although undeniably reduce disease activity due to their anti-inflammatory and immunosuppressive properties also increase the risk of infection particularly in the elderly and in the presence of uremia. There are no randomized trial data to guide GC dosing.

Evidence summarised in Walsh et. al., Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. Am J Kidney Dis 2011; 57(4) 566-574

Actual start date of recruitment	08 June 2010
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	Norway: 8
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 179
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Denmark: 57
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Canada: 191
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Australia: 94
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Belgium: 1
Worldwide total number of subjects	704
EEA total number of subjects	351

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)	1
Adults (18-64 years)	339
From 65 to 84 years	337
85 years and over	27

Subject disposition

Recruitment

Recruitment details:

704 patients were recruited. The first patient was recruited on 8th June 2010 and the last patient recruited on 30th September 2016.

Pre-assignment

Screening details:

During screening, patient's eligibility was assessed based on a diagnosis of new or relapsing severe ANCA-associated vasculitis (AAV). Any previous vasculitis treatment was also considered and patients would not have been eligible to participate if they had recently received Cyclophosphamide; Rituximab; dialysis or a prior renal transplant.

Period 1

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

Blinding implementation details:

Not blinded.

Arms

Are arms mutually exclusive?	No
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Arm title	Plasma Exchange
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Arm description:

7 x Plasma Exchange procedures within 14 days of randomisation.

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

Dosage and administration details:

Glucocorticoids administered as per randomisation allocation: low or standard dose Glucocorticoids.

Arm title	No Plasma Exchange
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Arm description:

No Plasma Exchange received.

Arm type	No Intervention
Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Glucocorticoids administered as per randomisation allocation: low or standard dose Glucocorticoids.

Arm title	Reduced Glucocorticoids
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Arm description:

Glucocorticoid dose according to patient weight. Patients weighing less than 50kg will receive the following: 50mg at Week 1, 25mg at Week 2, 20mg at Weeks 3-4, 15mg at Weeks 5-6, 12.5mg at Weeks 7-8, 10mg at Weeks 9-10, 7.5mg at Weeks 11-12, 6mg at Weeks 13-14, 5mg from Week 15-52.

Patients weighing between 50-75kg will receive the following: 60mg at Week 1, 30mg at Week 2, 25mg

at Weeks 3-4, 20mg at Weeks 5-6, 15mg at Weeks 7-8, 12.5mg at Weeks 9-10, 10mg at Weeks 11-12, 7.5mg at Weeks 13-14, 5mg from Week 15-52.

Patients weighing between 50-75kg will receive the following: 75mg at Week 1, 40mg at Week 2, 30mg at Weeks 3-4, 25mg at Weeks 5-6, 20mg at Weeks 7-8, 15mg at Weeks 9-10, 12.5mg at Weeks 11-12, 10mg at Weeks 13-14, 7.5mg at Weeks 15-18, 5mg from Week 19-52.

Arm type	Experimental
Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Glucocorticoids administered as per randomisation allocation: low or standard dose Glucocorticoids.	
Arm title	Standard Glucocorticoids

Arm description:

Glucocorticoid dose according to patient weight. Patients weighing less than 50kg will receive the following: 50mg at Weeks 1-2, 40mg at Weeks 3-4, 30mg at Weeks 5-6, 25mg at Weeks 7-8, 20mg at Weeks 9-10, 15mg at Weeks 11-12, 12.5mg at Weeks 13-14, 10mg at Weeks 15-18, 7.5mg from Week 19-22, 5mg from Week 23-52.

Patients weighing between 50-75kg will receive the following: 60mg at Weeks 1-2, 50mg at Weeks 3-4, 40mg at Weeks 5-6, 30mg at Weeks 7-8, 25mg at Weeks 9-10, 20mg at Weeks 11-12, 15mg at Weeks 13-14, 10mg at Weeks 15-18, 7.5mg from Week 19-22, 5mg from Week 23-52.

Patients weighing over 75kg will receive the following: 75mg at Weeks 1-2, 60mg at Weeks 3-4, 50mg at Weeks 5-6, 40mg at Weeks 7-8, 30mg at Weeks 9-10, 25mg at Weeks 11-12, 20mg at Weeks 13-14, 15mg at Weeks 15-18, 10mg from Week 19-20, 7.5mg at Week 21-22 and 5mg from Week 23-52.

Arm type	Active comparator
Investigational medicinal product name	Glucocorticoids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Glucocorticoids administered as per randomisation allocation: low or standard dose Glucocorticoids.

Number of subjects in period 1	Plasma Exchange	No Plasma Exchange	Reduced Glucocorticoids
Started	352	352	353
Completed	352	352	353

Number of subjects in period 1	Standard Glucocorticoids
Started	351
Completed	351

Baseline characteristics

Reporting groups

Reporting group title	Plasma Exchange
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Reporting group description:

7 x Plasma Exchange procedures within 14 days of randomisation.

Reporting group title	No Plasma Exchange
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Reporting group description:

No Plasma Exchange received.

Reporting group title	Reduced Glucocorticoids
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Reporting group description:

Glucocorticoid dose according to patient weight. Patients weighing less than 50kg will receive the following: 50mg at Week 1, 25mg at Week 2, 20mg at Weeks 3-4, 15mg at Weeks 5-6, 12.5mg at Weeks 7-8, 10mg at Weeks 9-10, 7.5mg at Weeks 11-12, 6mg at Weeks 13-14, 5mg from Week 15-52.

Patients weighing between 50-75kg will receive the following: 60mg at Week 1, 30mg at Week 2, 25mg at Weeks 3-4, 20mg at Weeks 5-6, 15mg at Weeks 7-8, 12.5mg at Weeks 9-10, 10mg at Weeks 11-12, 7.5mg at Weeks 13-14, 5mg from Week 15-52.

Patients weighing between 50-75kg will receive the following: 75mg at Week 1, 40mg at Week 2, 30mg at Weeks 3-4, 25mg at Weeks 5-6, 20mg at Weeks 7-8, 15mg at Weeks 9-10, 12.5mg at Weeks 11-12, 10mg at Weeks 13-14, 7.5mg at Weeks 15-18, 5mg from Week 19-52.

Reporting group title	Standard Glucocorticoids
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Reporting group description:

Glucocorticoid dose according to patient weight. Patients weighing less than 50kg will receive the following: 50mg at Weeks 1-2, 40mg at Weeks 3-4, 30mg at Weeks 5-6, 25mg at Weeks 7-8, 20mg at Weeks 9-10, 15mg at Weeks 11-12, 12.5mg at Weeks 13-14, 10mg at Weeks 15-18, 7.5mg from Week 19-22, 5mg from Week 23-52.

Patients weighing between 50-75kg will receive the following: 60mg at Weeks 1-2, 50mg at Weeks 3-4, 40mg at Weeks 5-6, 30mg at Weeks 7-8, 25mg at Weeks 9-10, 20mg at Weeks 11-12, 15mg at Weeks 13-14, 10mg at Weeks 15-18, 7.5mg from Week 19-22, 5mg from Week 23-52.

Patients weighing over 75kg will receive the following: 75mg at Weeks 1-2, 60mg at Weeks 3-4, 50mg at Weeks 5-6, 40mg at Weeks 7-8, 30mg at Weeks 9-10, 25mg at Weeks 11-12, 20mg at Weeks 13-14, 15mg at Weeks 15-18, 10mg from Week 19-20, 7.5mg at Week 21-22 and 5mg from Week 23-52.

Reporting group values	Plasma Exchange	No Plasma Exchange	Reduced Glucocorticoids
Number of subjects	352	352	353
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	171	168	164
From 65-84 years	169	168	173
85 years and over	11	16	16
Age continuous Units: years			
arithmetic mean	62.8	63.5	63.3
standard deviation	± 14.4	± 13.7	± 14.2
Gender categorical Units: Subjects			
Female	149	158	156
Male	203	194	197

Prior history of AAV Units: Subjects			
Yes	35	28	34
No	317	324	319
ANCA Units: Subjects			
PR3+	143	143	143
MPO+	209	209	210
Lung Haemorrhage Units: Subjects			
No haemorrhage	257	256	257
Not severe	64	66	65
Severe	31	30	31
Creatinine at randomisation Units: µmol/L			
median	327	335.9	320
inter-quartile range (Q1-Q3)	206 to 491	209 to 495	190 to 480

Reporting group values	Standard Glucocorticoids	Total	
Number of subjects	351	704	
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	175	339	
From 65-84 years	164	337	
85 years and over	11	27	
Age continuous Units: years			
arithmetic mean	63.1	-	
standard deviation	± 13.9		
Gender categorical Units: Subjects			
Female	151	307	
Male	200	397	
Prior history of AAV Units: Subjects			
Yes	29	63	
No	322	641	
ANCA Units: Subjects			
PR3+	143	286	
MPO+	208	418	
Lung Haemorrhage Units: Subjects			
No haemorrhage	256	513	
Not severe	65	130	
Severe	30	61	
Creatinine at randomisation Units: µmol/L			
median	335	-	
inter-quartile range (Q1-Q3)	219 to 502		

End points

End points reporting groups

Reporting group title	Plasma Exchange
Reporting group description: 7 x Plasma Exchange procedures within 14 days of randomisation.	
Reporting group title	No Plasma Exchange
Reporting group description: No Plasma Exchange received.	
Reporting group title	Reduced Glucocorticoids
Reporting group description: Glucocorticoid dose according to patient weight. Patients weighing less than 50kg will receive the following: 50mg at Week 1, 25mg at Week 2, 20mg at Weeks 3-4, 15mg at Weeks 5-6, 12.5mg at Weeks 7-8, 10mg at Weeks 9-10, 7.5mg at Weeks 11-12, 6mg at Weeks 13-14, 5mg from Week 15-52. Patients weighing between 50-75kg will receive the following: 60mg at Week 1, 30mg at Week 2, 25mg at Weeks 3-4, 20mg at Weeks 5-6, 15mg at Weeks 7-8, 12.5mg at Weeks 9-10, 10mg at Weeks 11-12, 7.5mg at Weeks 13-14, 5mg from Week 15-52. Patients weighing between 50-75kg will receive the following: 75mg at Week 1, 40mg at Week 2, 30mg at Weeks 3-4, 25mg at Weeks 5-6, 20mg at Weeks 7-8, 15mg at Weeks 9-10, 12.5mg at Weeks 11-12, 10mg at Weeks 13-14, 7.5mg at Weeks 15-18, 5mg from Week 19-52.	
Reporting group title	Standard Glucocorticoids
Reporting group description: Glucocorticoid dose according to patient weight. Patients weighing less than 50kg will receive the following: 50mg at Weeks 1-2, 40mg at Weeks 3-4, 30mg at Weeks 5-6, 25mg at Weeks 7-8, 20mg at Weeks 9-10, 15mg at Weeks 11-12, 12.5mg at Weeks 13-14, 10mg at Weeks 15-18, 7.5mg from Week 19-22, 5mg from Week 23-52. Patients weighing between 50-75kg will receive the following: 60mg at Weeks 1-2, 50mg at Weeks 3-4, 40mg at Weeks 5-6, 30mg at Weeks 7-8, 25mg at Weeks 9-10, 20mg at Weeks 11-12, 15mg at Weeks 13-14, 10mg at Weeks 15-18, 7.5mg from Week 19-22, 5mg from Week 23-52. Patients weighing over 75kg will receive the following: 75mg at Weeks 1-2, 60mg at Weeks 3-4, 50mg at Weeks 5-6, 40mg at Weeks 7-8, 30mg at Weeks 9-10, 25mg at Weeks 11-12, 20mg at Weeks 13-14, 15mg at Weeks 15-18, 10mg from Week 19-20, 7.5mg at Week 21-22 and 5mg from Week 23-52.	

Primary: Composite of time to death and/or ESRD

End point title	Composite of time to death and/or ESRD
End point description: Time to event (ESRD and Death)	
End point type	Primary
End point timeframe: Whole trial	

End point values	Plasma Exchange	No Plasma Exchange	Reduced Glucocorticoids	Standard Glucocorticoids
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	352	352	353	351
Units: Events				
No	252	243	246	249
Yes	100	109	107	102

Statistical analyses

Statistical analysis title	PLEX ITT (Partially Adjusted)
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Statistical analysis description:

The primary outcome is a composite of all-cause mortality or ESRD. The comparison of PLEX vs. no PLEX is based on the ITT analysis population using a time to event analysis (time from randomisation to death or ESRD). A Cox proportional hazards model was fitted to obtain an adjusted hazard ratio and 95% confidence interval. No PLEX and Standard GC were used as the reference groups in the Cox regression model.

Comparison groups	Plasma Exchange v No Plasma Exchange
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.422
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.17

Notes:

[1] - Adjusted for treatment arm as part of the factorial design.

Statistical analysis title	PLEX ITT (Adjusted)
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Statistical analysis description:

The primary outcome is a composite of all-cause mortality or ESRD. The comparison of PLEX vs. no PLEX is based on the ITT analysis population using a time to event analysis (time from randomisation to death or ESRD). A Cox proportional hazards model was fitted to obtain an adjusted hazard ratio and 95% confidence interval. No PLEX and Standard GC were used as the reference groups in the Cox regression model.

No PLEX and Standard GC were used as the reference groups in the Cox regression mo

Comparison groups	Plasma Exchange v No Plasma Exchange
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.268
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.13

Notes:

[2] - Adjusted for all minimisation variables.

Statistical analysis title	Glucocorticoids ITT (Partially Adjusted)
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Statistical analysis description:

The primary outcome is a composite of all-cause mortality or ESRD. The comparison of PLEX vs. no PLEX is based on the ITT analysis population using a time to event analysis (time from randomisation to death or ESRD). A Cox proportional hazards model was fitted to obtain an adjusted hazard ratio and 95% confidence interval.

No PLEX and Standard GC were used as the reference groups in the Cox regression model.

Comparison groups	Reduced Glucocorticoids v Standard Glucocorticoids
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	= 0.863
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.34

Notes:

[3] - Adjusted for treatment arm as part of factorial design.

Statistical analysis title	Glucocorticoids ITT (Adjusted)
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Statistical analysis description:

The primary outcome is a composite of all-cause mortality or ESRD. The comparison of PLEX vs. no PLEX is based on the ITT analysis population using a time to event analysis (time from randomisation to death or ESRD). A Cox proportional hazards model was fitted to obtain an adjusted hazard ratio and 95% confidence interval. No PLEX and Standard GC were used as the reference groups in the Cox regression model.

No PLEX and Standard GC were used as the reference groups in the Cox regression model.

Comparison groups	Reduced Glucocorticoids v Standard Glucocorticoids
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	= 0.998
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.31

Notes:

[4] - Adjusted for all minimisation variables.

Primary: Per-Protocol Analysis

End point title	Per-Protocol Analysis
End point description:	
End point type	Primary
End point timeframe:	
Whole trial	

End point values	Plasma Exchange	No Plasma Exchange	Reduced Glucocorticoids	Standard Glucocorticoids
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	338	322	330	325
Units: Events				
No	243	223	238	242
Yes	95	99	92	83

Statistical analyses

Statistical analysis title	Glucocorticoids (Partially Adjusted)
Statistical analysis description:	
<p>The comparison of Reduced GC to Standard dose GC is a non-inferiority hypothesis with a non-inferiority margin of an 11% absolute risk increase expressed as the reduced dose GC group relative to the standard dose GC group. Since an intention to treat analysis can increase the risk of falsely claiming non-inferiority, this analysis was conducted for participant's adherent to the assigned GC regimen (the per-protocol population). Standard GC was used as the reference groups in the Binomial model.</p>	
Comparison groups	Reduced Glucocorticoids v Standard Glucocorticoids
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.507
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.023
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.034
upper limit	0.08

Notes:

[5] - The GC dose per-protocol analysis population will consist of:

- Participants randomised to reduced dose GC who receive $\leq 130\%$ of the cumulative oral dose of the reduced dose regimen in the first 6 months of therapy.
- Participants randomised to standard dose GC who receive $\geq 70\%$ of the cumulative oral dose of the standard regimen in the first 6 months of therapy.

Statistical analysis title	PLEX (Partially Adjusted)
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Statistical analysis description:

As part of the sensitivity analysis, we have also analysed the primary outcome for the PLEX arm as per-protocol. Per-Protocol set for the PLEX arms was defined as any patients randomised in the PLEX arm to have received at least one PLEX treatment within 14 days of randomisation or any patients randomised to PLEX arm to not have received any PLEX but died within 14 days of randomisation. No PLEX was used as the reference groups in the Cox regression model.

Comparison groups	Plasma Exchange v No Plasma Exchange
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.352
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.16

Notes:

[6] - T

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Serious Adverse Events (SAEs) were required to be reported to the Sponsor within 24 hours of site awareness. SAEs continued to be reported until completion of all patient follow-up on 31 July 2017. The only non-SAEs collected were infections.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: All SAEs are captured in the attached cumulative SAE report.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2012	Protocol Version 2, patient medication diary and patient card were introduced. The patient medication diary enabled better drug accountability. The exclusion criteria were updated to clarify any patients that had received plasma exchange within 3 months prior to randomisation would not be eligible. The Patient Information Sheet/ Informed Consent Form were also updated to clarify which staff member was taking consent.
12 December 2014	Amendment 7 introduced Protocol Version 3.0 and included an increase in target recruitment from 500 to 700 participants due to a lower than expected event rate. The increased sample size allowed us to address the primary outcome measure: death and end stage renal disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23497590>