Clinical trial results:
A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Voclosporin (23.7 mg BID, or 39.5 mg BID) with Placebo in Achieving Remission in Patients with Active Lupus Nephritis

Summary

EudraCT number	2012-003364-51
Trial protocol	ES BG PL
Global end of trial date	06 January 2017

Results information

Result version number	v1 (current)
This version publication date	12 May 2021
First version publication date	12 May 2021

Trial information

Trial identification

Sponsor protocol code	AUR-VCS-2012-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02141672
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 114577

Notes:

Sponsors

Sponsor organisation name	Aurinia Pharmaceuticals Inc.
Sponsor organisation address	1203-4464 Markham St, Victoria, Canada,
Public contact	Clinical Trial Information, Aurinia Pharmaceuticals Inc., clinicaltrials@auriniapharma.com
Scientific contact	Clinical Trial Information, Aurinia Pharmaceuticals Inc., clinicaltrials@auriniapharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2016
Global end of trial reached?	Yes
Global end of trial date	06 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of 2 doses of voclosporin compared to placebo in achieving complete remission after 24 weeks of therapy in subjects with active Lupus Nephritis (LN).

Protection of trial subjects:

A Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee was involved in study conduct and oversight. The DSMB evaluated the progress of the study, assessed data quality and timeliness, participant recruitment, accrual and retention, and participant benefit versus risk. All safety data, including deaths which occurred during the study, were reviewed by the DSMB.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Bangladesh: 46
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Belarus: 13
Country: Number of subjects enrolled	Ecuador: 5
Country: Number of subjects enrolled	Georgia: 5
Country: Number of subjects enrolled	Guatemala: 11
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Philippines: 43
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Sri Lanka: 14
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Thailand: 13

Country: Number of subjects enrolled	Ukraine: 12
Worldwide total number of subjects	265
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	262
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening will include provision of informed consent, physical examination including weight and height, medical history (including SLE and LN history), vital signs measurements, 12-lead ECG, and review of prior and concomitant medications and entry criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Voclosporin Low Dose

Arm description:

Voclosporin 23.7 mg (3 capsules) twice a day

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

Dosage and administration details:

Voclosporin 23.7 mg (3 capsules) twice daily

Arm title	Voclosporin High Dose

Arm description:

Voclosporin 39.5 mg (5 capsules) twice a day

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

Dosage and administration details:

Voclosporin 39.5 mg (5 capsules) twice daily

Arm title	Placebo

Arm description:

Matching placebo soft gel capsules

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

Dosage and administration details:

Matching placebo soft gel capsules; doses of 3 capsules twice a day (matching 23.7 mg voclosporin twice a day) or 5 capsules twice a day (matching 39.5 mg voclosporin twice a day)

Number of subjects in period 1	Voclosporin Low Dose	Voclosporin High Dose	Placebo
Started	89	88	88
Completed	73	80	70
Not completed	16	8	18
Adverse event, serious fatal	10	2	1
Physician decision	1	2	5
Consent withdrawn by subject	3	2	5
Adverse event, non-fatal	-	1	-
Lost to follow-up	1	1	3
Refused follow-up	1	-	1
Lack of efficacy	-	-	2
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Voclosporin Low Dose
Reporting group description:	
Voclosporin 23.7 mg (3 capsules) twice a day	
Reporting group title	Voclosporin High Dose
Reporting group description:	
Voclosporin 39.5 mg (5 capsules) twice a day	
Reporting group title	Placebo
Reporting group description:	
Matching placebo soft gel capsules	

Reporting group values	Voclosporin Low Dose	Voclosporin High Dose	Placebo
Number of subjects	89	88	88
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)	0	0	0
Adults (18-64 years)	87	88	87
From 65-84 years	2	0	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	31.4	30.6	33.1
standard deviation	± 11.78	± 9.59	± 10.03
Gender categorical Units: Subjects			
Female	76	81	73
Male	13	7	15
Race Units: Subjects			
American Indian or Alaska Native	4	2	3
Asian	52	44	36
Native Hawaiian or Pacific Islander	0	0	1
Black or African American	3	6	5
White	30	36	42
Unknown or Not Reported	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	9	13	13
Not Hispanic or Latino	80	75	75

Years Since Diagnosis of LN			
Units: Years			
arithmetic mean	4.2	3.2	3.5
standard deviation	± 5.14	± 4.36	± 4.03
Years Since First Significant Proteinuria			
Units: Years			
arithmetic mean	4.5	3.3	3.6
standard deviation	± 5.53	± 4.22	± 4.06
Baseline UPCR			
Units: mg/mg			
arithmetic mean	5.16	4.48	4.43
standard deviation	± 4.15	± 3.03	± 3.58
Baseline eGFR			
Units: mL/min/1.73 m2			
arithmetic mean	95.3	104	100.2
standard deviation	± 28.4	± 27.3	± 27.05

Reporting group values	Total		
Number of subjects	265		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	262		
From 65-84 years	3		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	230		
Male	35		
Race			
Units: Subjects			
American Indian or Alaska Native	9		
Asian	132		
Native Hawaiian or Pacific Islander	1		
Black or African American	14		
White	108		
Unknown or Not Reported	1		
Ethnicity			
Units: Subjects			
Hispanic or Latino	35		
Not Hispanic or Latino	230		

Years Since Diagnosis of LN Units: Years arithmetic mean standard deviation	- -		
Years Since First Significant Proteinuria Units: Years arithmetic mean standard deviation	- -		
Baseline UPCR Units: mg/mg arithmetic mean standard deviation	- -		
Baseline eGFR Units: mL/min/1.73 m2 arithmetic mean standard deviation	- -		

End points

End points reporting groups	
Reporting group title	Voclosporin Low Dose
Reporting group description:	
Voclosporin 23.7 mg (3 capsules) twice a day	
Reporting group title	Voclosporin High Dose
Reporting group description:	
Voclosporin 39.5 mg (5 capsules) twice a day	
Reporting group title	Placebo
Reporting group description:	
Matching placebo soft gel capsules	

Primary: Number of Subjects Achieving Complete Renal Remission at 24 Weeks	
End point title	Number of Subjects Achieving Complete Renal Remission at 24 Weeks
End point description:	
Complete remission is defined as: • Confirmed protein/creatinine ratio of ≤0.5 mg/mg and • eGFR ≥60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ≥20%. Subjects who received rescue medication for lupus nephritis or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to remission assessment until the time of the remission assessment were considered not achieving complete remission.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants	29	24	17	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Number of Subjects Achieving Complete Renal Remission at 24 Weeks	
Comparison groups	Voclosporin Low Dose v Placebo

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	4.05

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Number of Subjects Achieving Complete Renal Remission at 24 Weeks	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.204
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	3.27

Secondary: Number of Subjects Achieving Complete Renal Remission at 48 Weeks

End point title	Number of Subjects Achieving Complete Renal Remission at 48 Weeks

End point description:

Complete remission is defined as:
• Confirmed protein/creatinine ratio of ≤0.5 mg/mg and
• eGFR ≥60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ≥20%. Subjects who received rescue medication for lupus nephritis or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to remission assessment until the time of the remission assessment were considered not achieving complete remission.

End point type	Secondary

End point timeframe:

Week 48

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants	44	35	21	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Number of Subjects Achieving Complete Renal Remission at 48 Weeks	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.68
upper limit	6.13

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Number of Subjects Achieving Complete Renal Remission at 48 Weeks	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	4.02

Secondary: Number of Subjects Achieving Complete Renal Remission at 24 and 48 Weeks in the Presence of Low Dose Steroids

End point title	Number of Subjects Achieving Complete Renal Remission at 24

	and 48 Weeks in the Presence of Low Dose Steroids

End point description:

Complete Remission in presence of low-dose steroids is defined as complete remission with use of ≤5 mg prednisone for 8 weeks leading up to the Week 24 visit date or for 12 weeks leading up to the Week 48 visit date.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants				
Week 24	26	23	17	
Week 48	29	26	18	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Number of Subjects Achieving Complete Renal Remission at 24 Weeks in the Presence of Low Dose Steroids

Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	3.46

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Number of Subjects Achieving Complete Renal Remission at 24 Weeks in the Presence of Low Dose Steroids

Comparison groups	Voclosporin High Dose v Placebo

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.278
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	3.06

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Number of Subjects Achieving Complete Renal Remission at 48 Weeks in the Presence of Low Dose Steroids	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	3.78

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Number of Subjects Achieving Complete Renal Remission at 48 Weeks in the Presence of Low Dose Steroids	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	3.28

Secondary: Number of Subjects Achieving Sustained Early Complete Remission

End point title	Number of Subjects Achieving Sustained Early Complete Remission

End point description:

Sustained Early Complete Remission is defined as achieving UPCR ≤ 0.5mg at Week 24 or earlier which is sustained until Week 48 in the absence of rescue medication.

End point type	Secondary

End point timeframe:

Week 48

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants	36	22	15	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Sustained Early Complete Remission is defined as complete remission prior to Week 24 which is sustained through the Week 48 visit.

Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	6.85

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Sustained Early Complete Remission is defined as complete remission prior to Week 24 which is sustained through the Week 48 visit.

Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	3.37

Secondary: Time to Partial Remission (Number of Weeks)

End point title	Time to Partial Remission (Number of Weeks)

End point description:

Time to partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction sustained until week 48 in the absence of rescue medication.

End point type	Secondary

End point timeframe:

Week 48

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Weeks				
median (confidence interval 95%)	4.3 (2.6 to 5.9)	4.4 (4.1 to 6.1)	6.6 (4.6 to 8.6)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Time to Partial Remission (Number of Weeks)

Comparison groups	Voclosporin Low Dose v Placebo

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	2.27

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Time to Partial Remission (Number of Weeks)	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	2.43

Secondary: Duration of Complete Remission

End point title	Duration of Complete Remission
End point description:	
Duration of Complete Remission is defined as time of first occurrence of UPCR ≤ 0.5 mg/mg until the second increase above 0.5 mg/mg (i.e. a single occurrence above 0.5 is permitted) or use of rescue medication.	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants				
Number achieving complete remission	57	61	32	
Number remaining in complete remission	38	33	22	
Number with second increase in UPCR >0.5 mg/mg	19	28	10	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Hazard ratios and log-rank tests were calculated from a Cox proportional hazards model.	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	2.15

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Hazard ratios and log-rank tests were calculated from a Cox proportional hazards model.	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.118
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	4.16

Secondary: Number of Subjects Achieving Partial Renal Remission at 24 and 48 Weeks

End point title	Number of Subjects Achieving Partial Renal Remission at 24 and 48 Weeks

End point description:

Number of patients with partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction at week 24 or week 48 in the absence of rescue medication.

End point type	Secondary

End point timeframe:

Week 24 and 48

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants				
Week 24	62	58	43	
Week 48	61	63	42	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Number of Subjects Achieving Partial Renal Remission at Week 24

Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	4.33

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Number of Subjects Achieving Partial Renal Remission at Week 24

Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.76

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Number of Subjects Achieving Partial Renal Remission at Week 48	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	4.33

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Number of Subjects Achieving Partial Renal Remission at Week 48	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	5.02

Secondary: Number of Subjects Achieving Sustained Partial Remission

End point title	Number of Subjects Achieving Sustained Partial Remission

End point description:

Sustained partial remission is defined as achieving 50% UPCR reduction sustained until week 48 in the absence of rescue medication.

End point type	Secondary

End point timeframe:

Week 48

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants	61	63	42	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds Ratios were generated from a logistic regression model.

Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	4.33

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:	
Odds Ratios were generated from a logistic regression model.	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	5.02

Secondary: Number of Subjects Achieving Sustained Early Partial Remission

End point title	Number of Subjects Achieving Sustained Early Partial Remission
End point description:	
Sustained early partial Remission is defined as achieving 50% UPCR reduction at week 24 or earlier which is sustained until week 48 in the absence of rescue medication.	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: Participants	60	58	36	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Odds Ratios were generated from a logistic regression model.	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	5.43

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Odds Ratios were generated from a logistic regression model.	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	5.07

Secondary: Change From Baseline in Urine Protein Creatinine Ratio at Weeks 24 and 48

End point title	Change From Baseline in Urine Protein Creatinine Ratio at Weeks 24 and 48
End point description:	
Change from baseline in urine protein creatinine ratio at weeks 24 and 48	
End point type	Secondary
End point timeframe:	
Week 24 and Week 48	

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: mg/mg				
arithmetic mean (standard deviation)				
Baseline UPCR	5.161 (± 4.151)	4.476 (± 3.029)	4.433 (± 3.58)	
Week 24 UPCR	1.021 (± 1.2369)	1.356 (± 1.5204)	2.266 (± 2.8534)	
Change from Baseline at Week 24	-3.769 (± 3.351)	-2.792 (± 2.6207)	-2.216 (± 3.9284)	

Week 48 UPCR	0.689 (± 0.9172)	1.101 (± 1.3835)	1.763 (± 1.9927)	
Change from Baseline at Week 48	-3.998 (± 3.4208)	-2.993 (± 2.6608)	-2.384 (± 3.454)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
P-values were derived using an ANCOVA model. Week 24	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	-0.67

Secondary: Change From Baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Score

End point title	Change From Baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Score
End point description:	
The SELENA-SLEDAI assesses disease activity within the last 10 days. Twenty-four items are scored for nine organ systems, and summed to a maximum of 105 points. A score of 6 is considered clinically significant and indicates active disease. For analysis purposes, a score ≥6 was categorized as "high". The 24 items are as follows: seizure, psychosis, organic brain syndrome, visual disturbance, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24 and Week 48	

End point values	Voclosporin Low Dose	Voclosporin High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	88	
Units: mg/mg				
arithmetic mean (standard deviation)				
Score at Baseline	12.7 (± 6.37)	13.9 (± 6.51)	12.9 (± 6.57)	
Score at Week 24	6.2 (± 4.53)	6.5 (± 5.42)	8.8 (± 5.43)	
Change from Baseline at Week 24	-6.3 (± 5.86)	-7.1 (± 7.41)	-4.5 (± 7.09)	
Score at Week 48	4.7 (± 5.06)	5.3 (± 3.97)	7.8 (± 5.93)	
Change from Baseline at Week 48	-7.9 (± 6.39)	-8.3 (± 6.93)	-5.3 (± 6.85)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change in Baseline at Week 24	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.95
upper limit	-0.8

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change from Baseline at Week 24	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	-0.82

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change from Baseline at Week 48	
Comparison groups	Voclosporin Low Dose v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.44
upper limit	-1.45

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Change from Baseline at Week 48	
Comparison groups	Voclosporin High Dose v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.05
upper limit	-1.11

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 50. Treatment emergent AEs. Reporting period is from first dose up to 30 days after study completion or withdrawal

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Voclosporin Low Dose

Reporting group description:

Voclosporin 23.7 mg (3 capsules) twice a day

Reporting group title	Voclosporin High Dose

Reporting group description:

Voclosporin 39.5 mg (5 capsules) twice a day

Reporting group title	Placebo

Reporting group description:

Matching placebo soft gel capsules

Serious adverse events	Voclosporin Low Dose	Voclosporin High Dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 89 (28.09%)	22 / 88 (25.00%)	14 / 88 (15.91%)
number of deaths (all causes)	10	2	1
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 89 (2.25%)	2 / 88 (2.27%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 89 (2.25%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 89 (2.25%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Procedural pain			

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Convulsion			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	2 / 89 (2.25%)	2 / 88 (2.27%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	4 / 89 (4.49%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal impairment			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Strangury			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	1 / 89 (1.12%)	2 / 88 (2.27%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial pyelonephritis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body tinea			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 89 (1.12%)	2 / 88 (2.27%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	0 / 89 (0.00%)	0 / 88 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis tuberculous			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 89 (5.62%)	3 / 88 (3.41%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	1 / 6	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 89 (1.12%)	2 / 88 (2.27%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Skin infection			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis of genitourinary system			

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 89 (2.25%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Voclosporin Low Dose	Voclosporin High Dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 89 (92.13%)	83 / 88 (94.32%)	74 / 88 (84.09%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 89 (16.85%)	14 / 88 (15.91%)	8 / 88 (9.09%)
occurrences (all)	15	18	11
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 89 (6.74%)	9 / 88 (10.23%)	1 / 88 (1.14%)
occurrences (all)	7	9	1
Oedema peripheral			
subjects affected / exposed	9 / 89 (10.11%)	7 / 88 (7.95%)	8 / 88 (9.09%)
occurrences (all)	12	8	9
Oedema			

subjects affected / exposed	2 / 89 (2.25%)	5 / 88 (5.68%)	1 / 88 (1.14%)
occurrences (all)	3	6	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 89 (17.98%)	5 / 88 (5.68%)	3 / 88 (3.41%)
occurrences (all)	16	7	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 89 (4.49%)	5 / 88 (5.68%)	4 / 88 (4.55%)
occurrences (all)	4	5	4
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	27 / 89 (30.34%)	27 / 88 (30.68%)	12 / 88 (13.64%)
occurrences (all)	50	40	14
Blood pressure increased			
subjects affected / exposed	3 / 89 (3.37%)	5 / 88 (5.68%)	1 / 88 (1.14%)
occurrences (all)	4	6	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 89 (2.25%)	5 / 88 (5.68%)	1 / 88 (1.14%)
occurrences (all)	2	6	1
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 89 (11.24%)	15 / 88 (17.05%)	11 / 88 (12.50%)
occurrences (all)	12	21	14
Dizziness			
subjects affected / exposed	5 / 89 (5.62%)	2 / 88 (2.27%)	1 / 88 (1.14%)
occurrences (all)	5	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 89 (14.61%)	14 / 88 (15.91%)	7 / 88 (7.95%)
occurrences (all)	14	16	7
Leukopenia			
subjects affected / exposed	1 / 89 (1.12%)	3 / 88 (3.41%)	6 / 88 (6.82%)
occurrences (all)	1	4	6
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	16 / 89 (17.98%)	14 / 88 (15.91%)	14 / 88 (15.91%)
occurrences (all)	19	18	14
Nausea			
subjects affected / exposed	16 / 89 (17.98%)	11 / 88 (12.50%)	7 / 88 (7.95%)
occurrences (all)	21	16	7
Vomiting			
subjects affected / exposed	15 / 89 (16.85%)	9 / 88 (10.23%)	10 / 88 (11.36%)
occurrences (all)	18	13	11
Gingival hypertrophy			
subjects affected / exposed	3 / 89 (3.37%)	6 / 88 (6.82%)	0 / 88 (0.00%)
occurrences (all)	4	8	0
Dyspepsia			
subjects affected / exposed	6 / 89 (6.74%)	6 / 88 (6.82%)	4 / 88 (4.55%)
occurrences (all)	6	7	4
Abdominal pain upper			
subjects affected / exposed	5 / 89 (5.62%)	7 / 88 (7.95%)	5 / 88 (5.68%)
occurrences (all)	5	7	5
Skin and subcutaneous tissue disorders			
Hypertrichosis			
subjects affected / exposed	3 / 89 (3.37%)	7 / 88 (7.95%)	0 / 88 (0.00%)
occurrences (all)	3	9	0
Alopecia			
subjects affected / exposed	7 / 89 (7.87%)	4 / 88 (4.55%)	2 / 88 (2.27%)
occurrences (all)	7	4	2
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 89 (1.12%)	7 / 88 (7.95%)	0 / 88 (0.00%)
occurrences (all)	1	8	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 89 (10.11%)	7 / 88 (7.95%)	7 / 88 (7.95%)
occurrences (all)	13	8	13
Back pain			
subjects affected / exposed	8 / 89 (8.99%)	5 / 88 (5.68%)	3 / 88 (3.41%)
occurrences (all)	9	5	4

Muscle spasms			
subjects affected / exposed	5 / 89 (5.62%)	2 / 88 (2.27%)	3 / 88 (3.41%)
occurrences (all)	5	3	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 89 (13.48%)	18 / 88 (20.45%)	14 / 88 (15.91%)
occurrences (all)	21	30	22
Urinary tract infection			
subjects affected / exposed	6 / 89 (6.74%)	6 / 88 (6.82%)	5 / 88 (5.68%)
occurrences (all)	7	7	7
Nasopharyngitis			
subjects affected / exposed	5 / 89 (5.62%)	4 / 88 (4.55%)	3 / 88 (3.41%)
occurrences (all)	7	7	4
Herpes zoster			
subjects affected / exposed	5 / 89 (5.62%)	6 / 88 (6.82%)	5 / 88 (5.68%)
occurrences (all)	5	6	5
Bronchitis			
subjects affected / exposed	2 / 89 (2.25%)	5 / 88 (5.68%)	3 / 88 (3.41%)
occurrences (all)	2	6	3
Gastroenteritis			
subjects affected / exposed	5 / 89 (5.62%)	3 / 88 (3.41%)	1 / 88 (1.14%)
occurrences (all)	6	4	1
Oral candidiasis			
subjects affected / exposed	2 / 89 (2.25%)	5 / 88 (5.68%)	0 / 88 (0.00%)
occurrences (all)	2	5	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	12 / 89 (13.48%)	12 / 88 (13.64%)	9 / 88 (10.23%)
occurrences (all)	18	16	12
Dyslipidaemia			
subjects affected / exposed	6 / 89 (6.74%)	7 / 88 (7.95%)	6 / 88 (6.82%)
occurrences (all)	6	7	6
Decreased appetite			
subjects affected / exposed	7 / 89 (7.87%)	5 / 88 (5.68%)	2 / 88 (2.27%)
occurrences (all)	7	6	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2012	1. Change in management of elevated blood pressure 2. Estimated glomerular filtration rate (eGFR) thresholds that trigger treatment dose adjustments were revised 3. All renal adverse events will be followed until resolution or stabilization 4. Exclusion criteria revised to ensure adequate washout of previously used investigational products 5. Addition of a maximum permitted duration of acute NSAID use 6. Clarified that the use of lipid-lowering agents and antimalarials are considered part of standard of care therapy 7. Clarified that study subjects will be stratified according to whether their kidney biopsies demonstrate pure Class V or not. 8. Addition of secondary endpoint for presence or absence of active urinary sediment

05 March 2014	1. The name of the Sponsor changed from Vifor International to Aurinia Pharmaceuticals Inc. Responsible personnel contact details were updated accordingly. 2. Inclusion/Exclusion Criteria: - Malignancy exclusion criterion clarified - The requirements for birth control were strengthened 3. Change in electrocardiogram (ECG) assessments 4. MMF dosing description clarified 5. Steroid dosing clarified 6. Addition of window for steroid taper 7. Permissibility of complete steroid withdrawal clarified 8. Voclosporin storage conditions updated 9. Change in size of blister wallet 10. Treatment for overdose clarified 11. Additional PK assessments added for exploratory purposes 12. Samples for biomarker assessment added 13. Addition of change from baseline parameter for QTcF measurement 14. Updated definitions of SAEs 15. Revised pregnancy reporting and management procedures 16. Addition of section regarding discontinuation of study drug due to an AE 17. Additional stratification parameter added 18. Statistical section clarified 19. Assessment of Systemic Lupus Erythematosus Disease Activity Index reduced 20. Addition of Schedule of Assessments 21. Protocol visits and unscheduled visits clarified 22. 24 hr urine collection added to Day 0, Week 24 and Week 48 23. Addition of serum pregnancy test at end of study 24. Urinalysis and blood chemistry clarified 25. Total amount of blood collected clarified 26. Physical examination clarified 27. Withdrawal procedures clarified 28. Screening visits revised 29. Data Safety Monitory Board responsibilities and procedures clarified 30. Informed consent process clarified 31. Blood pressure measurement clarified 32. Editorial Changes made to improve readability and clarity

15 October 2014	1. Inclusion/exclusion criteria - clarified Class III proteinuria to more accurately reflect active Class III lupus nephritis - Clarified kidney biopsy criteria, if a subject has not had a recent kidney biopsy, one may be performed prior to randomization - Severe viral infections was defined - Addition of acceptable contraception methods - Clarified route of cyclophosphamide prohibited - Clarified use of biologic agents - Addition of prohibited medications - Addition of treatment restrictions for P-gp substrates and inhibitors 2. Clarified MMF dosing 3. Clarified Steroid dosing 4. Clarified study assessments after discontinuation due to pregnancies 5. Clarified kidney biopsy SAE reporting 6. Clarified subjects lost to follow-up 7. Clarified primary endpoint to include eGFR ≥60 mL/min/1.73m2 8. Clarified emergency unblinding procedures 9. Clarified process for patients with eGFR decreases >20-30% 10. Clarified total amount of blood collected 11. Clarified required lab test results at time of enrolment 12. Various editorial changes made throughout to improve readability and clarity

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported