Clinical trial results:
A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis

Summary

EudraCT number	2016-004045-81
Trial protocol	BG ES NL PL HR
Global end of trial date	10 October 2019

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-2016-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03021499
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aurinia Pharmaceuticals Inc.
Sponsor organisation address	1203-4464 Markham St, Victoria, Canada,
Public contact	Clinical Trials Information, Aurinia Pharmaceuticals Inc., 1 (250) 744-2487, clinicaltrials@auriniapharma.com
Scientific contact	Clinical Trials Information, Aurinia Pharmaceuticals Inc., 1 (250) 744-2487, 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	10 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2019
Global end of trial reached?	Yes
Global end of trial date	10 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Orelvo (voclosporin) compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active lupus nephritis (LN)

Protection of trial subjects:

A Data and Safety Monitoring Board (DSMB) was constituted to monitor the safety of study participants and to evaluate the safety and efficacy of voclosporin in the treatment of active LN.
The DSMB comprised three members, including a nephrologist and a rheumatologist, who were independent of Aurinia and recognized for their clinical expertise in LN.
Safety criteria included AEs, serious adverse events (SAEs) and abnormal clinical laboratory tests. Efficacy was evaluated using the primary endpoint of renal response and other relevant markers of disease activity as recommended by the committee. Blinded and partially unblinded (where appropriate) individual subject data were reviewed on an ongoing basis for safety and efficacy, and final results were reviewed for safety and efficacy findings. The DSMB also evaluated protocol adherence and subject withdrawal. Based on the observed benefits or adverse effects, the DSMB made recommendations to Aurinia concerning continuation, termination, or modifications of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2017
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	Japan: 13
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Malaysia: 12
Country: Number of subjects enrolled	Philippines: 23
Country: Number of subjects enrolled	Thailand: 22
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Vietnam: 15
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Belarus: 14
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 37

Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Colombia: 21
Country: Number of subjects enrolled	Dominican Republic: 13
Country: Number of subjects enrolled	Guatemala: 13
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Peru: 19
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	357
EEA total number of subjects	12

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)	355
From 65 to 84 years	2
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

Arm description:

Voclosporin 23.7 mg BID

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 was orally administered at a dose of 23.7 mg BID given as three 7.9 mg softgel capsules per dose for 52 weeks

Arm title	Placebo

Arm description:

Matching placebo softgel 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 softgel capsules were orally administered at a dose of 3 capsules BID for 52 weeks

Number of subjects in period 1	Voclosporin	Placebo
Started	179	178
Completed	163	147
Not completed	16	31
Adverse event, serious fatal	1	5
Physician decision	2	3
Lack of Efficacy	-	1
Prohibited medication required	1	-
Protocol Non-compliance	1	1
Consent withdrawn by subject	7	14
Adverse event, non-fatal	1	-
Subject withdrew prior to first dose	1	-
Lost to follow-up	1	3
Unblinding of Study Treatment	-	1
Pregnancy	1	-
Subject Decided to Stop Medication	-	2
Subject Moved to a new Country	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Voclosporin
Reporting group description: Voclosporin 23.7 mg BID	
Reporting group title	Placebo
Reporting group description: Matching placebo softgel capsules	

Reporting group values	Voclosporin	Placebo	Total
Number of subjects	179	178	357
Age categorical Units: Subjects			
Adults (18-64 years)	179	176	355
From 65-84 years	0	2	2
Age continuous Units: years			
arithmetic mean	32.8	33.6	
standard deviation	± 10.93	± 11.00	-
Gender categorical Units: Subjects			
Female	161	152	313
Male	18	26	44
Race Units: Subjects			
White	68	61	129
Black or African American	21	13	34
American Indian or Alaska Native	0	4	4
Asian	53	56	109
Multiple Race	0	1	1
Other	37	43	80
Ethnicity Units: Subjects			
Hispanic or Latino	57	59	116
Not Hispanic or Latino	122	118	240
Unknown	0	1	1
Years since diagnosis of systemic lupus erythematosus			
Number of years since diagnosis of systemic lupus erythematosus			
Units: years			
arithmetic mean	6.6	6.9	
standard deviation	± 6.41	± 6.07	-
Years since diagnosis of lupus nephritis			
Number of years since diagnosis of lupus nephritis			
Units: years			
arithmetic mean	4.6	4.7	
standard deviation	± 5.07	± 4.89	-
Years since first significant proteinuria			

Number of years since first significant proteinuria			
Units: years			
arithmetic mean	4.8	4.6	
standard deviation	± 5.2	± 4.51	-
Baseline Urine Protein Creatinine Ratio			
Baseline Urine Protein Creatinine Ratio (Average of pre-randomization values)			
Units: mg/mg			
arithmetic mean	4.14	3.87	
standard deviation	± 2.711	± 2.363	-
Baseline estimated glomerular filtration rate			
Baseline estimated glomerular filtration rate CKD Epi formula (lowest pre-randomization value)			
Units: mL/min/1.73m2			
arithmetic mean	92.1	90.4	
standard deviation	± 30.60	± 28.97	-

End points

End points reporting groups

Reporting group title	Voclosporin
Reporting group description: Voclosporin 23.7 mg BID	
Reporting group title	Placebo
Reporting group description: Matching placebo softgel capsules	

Primary: Number of Participants with Adjudicated Renal Response at Week 52

End point title	Number of Participants with Adjudicated Renal Response at Week 52

End point description:

The primary efficacy endpoint was the number of subjects showing renal response at Week 52. Renal response was adjudicated based on blinded data by an independent Clinical Endpoints Committee based on meeting the following criteria:
- UPCR of ≤0.5 mg/mg, and
- eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and
- Received no rescue medication for LN and
- Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, prior to assessment

Note: To be disqualified from renal response, the subject had to fail both eGFR measures (i.e., confirmed eGFR <60 mL/min/1.73 m2 AND confirmed >20% drop from BL) and have an associated treatment-related or disease-related AE that impacted eGFR Withdrawals prior to Week 52 with insufficient Week 52 data to determine response were defined non responders. Subjects who discontinued study drug but continued to attend study visits had their data assessed for respon

End point type	Primary
End point timeframe: 52 Weeks	

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Participants	73	40		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The primary endpoint was the proportion of subjects showing renal response at Week 52 as adjudicated by the Clinical Endpoints Committee.

Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.64
upper limit	4.27

Secondary: Number of Participants with Reduction in Urine Protein Creatinine Ratio to 0.5 mg/mg or less

End point title	Number of Participants with Reduction in Urine Protein Creatinine Ratio to 0.5 mg/mg or less

End point description:

End point type	Secondary

End point timeframe:

52 Weeks

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: participants	116	78		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Renal Response at Week 24

End point title	Number of Participants with Renal Response at Week 24

End point description:

Number of subjects showing renal response at Week 24. Renal response was adjudicated based on blinded data by an Independent Clinical Endpoints Committee based on:
- UPCR of ≤0.5 mg/mg, and
- eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and
- Received no rescue medication for LN, and did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 16 through 24, just prior to the renal response assessment.
Note: To be disqualified from renal response, the subject had to fail both eGFR measures (i.e., confirmed eGFR <60 mL/min/1.73 m2 AND confirmed >20% drop from BL) & have an associated treatment-related or disease-related AE that impacted eGFR. Subjects who withdrew prior to the Week 24 assessment and provided insufficient Week 24 data to
determine response were defined as non-responders. Subjects who discontinued study drug but

continued to attend study visits had their data assessed for response.

End point type	Secondary

End point timeframe:

Week 24

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Participants	58	35		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Voclosporin
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Odds ratio (OR)
Point estimate	2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	3.72

Secondary: Number of Participants with Partial Renal Response at Weeks 24 & 52

End point title	Number of Participants with Partial Renal Response at Weeks 24 & 52

End point description:

Number of subjects with partial Renal Response (defined as a 50% reduction in UPCR from baseline) at week 24 and at week 52. Baseline UPCR is the average of 2 pre-randomisation values.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Participants				
Partial Response at Week 24	126	89		
Partial Response at Week 52	125	92		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	3.79

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	3.51

Secondary: Number of Participants achieving, and remaining in, renal response

(Urine Protein Creatinine ratio ≤0.5 mg/mg)	
End point title	Number of Participants achieving, and remaining in, renal response (Urine Protein Creatinine ratio ≤0.5 mg/mg)
End point description:	
Duration in days until second occurrence of UPCR >0.5 mg/mg in subjects who achieve a reduction in UPCR to below 0.5 mg/mg	
End point type	Secondary
End point timeframe:	
Week 52	

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Participants				
Subjects Achieving UPCR ≤0.5 mg/mg	116	78		
Subjects with Second Occurrence of UPCR >0.5 mg/mg	53	37		
Subjects without Second Occurrence UPCR >0.5 mg/mg	63	41		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.646
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.25

Secondary: Number of Participants achieving 50% reduction in Urine Protein Creatinine Ratio	
End point title	Number of Participants achieving 50% reduction in Urine Protein Creatinine Ratio
End point description:	
End point type	Secondary

End point timeframe:

Week 52

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Participants				
Participants with 50% UPCR Reduction	173	135		
Participants without 50% UPCR Reduction	6	43		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 50% Reduction in Urine Protein Creatinine Ratio (Number of Days)

End point title	Time to 50% Reduction in Urine Protein Creatinine Ratio (Number of Days)

End point description:

Time in days to reduction in Urine Protein Creatinine ratio to decrease by 50% compared to baseline. Baseline is the average of two pre-randomisation values.

End point type	Secondary

End point timeframe:

Week 52

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: days				
median (confidence interval 95%)	29 (29 to 32)	63 (57 to 87)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Time taken to reach 50% reduction in urine protein creatinine ratio

Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Hazard ratio (HR)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.62
upper limit	2.6

Secondary: Change From Baseline in estimated Glomerular Filtration Rate

End point title	Change From Baseline in estimated Glomerular Filtration Rate
End point description:	
Change from baseline by visit in estimated Glomerular Filtration rate (eGFR). eGFR is corrected to a maximum value of 90 ml/min/1.73 m2	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52	

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)				
Baseline	78.3 (± 15.83)	77.4 (± 16.98)		
Week 2 Change from Baseline	-1.5 (± 9.44)	3.3 (± 10.12)		
Week 4 Change from Baseline	-0.4 (± 10.39)	3.2 (± 9.86)		
Week 8 Change from Baseline	-0.9 (± 13.1)	3.8 (± 11.27)		
Week 12 Change from Baseline	-0.3 (± 11.74)	3.3 (± 12.85)		
Week 16 Change from Baseline	-0.1 (± 12.27)	2.8 (± 13.25)		
Week 20 Change from Baseline	-0.7 (± 12.09)	3.2 (± 13.04)		
Week 24 Change from Baseline	-0.3 (± 13.8)	2.8 (± 13.84)		
Week 30 Change from Baseline	-0.8 (± 14.2)	1.8 (± 14.4)		
Week 36 Change from Baseline	-1.9 (± 14.89)	1.5 (± 14.84)		
Week 42 Change from Baseline	-2.8 (± 16.7)	1.5 (± 15.53)		
Week 48 Change from Baseline	-3.6 (± 17.2)	1.1 (± 15.71)		
Week 52 Change from Baseline	-1.5 (± 16.16)	1.5 (± 15)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 2	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	-1.9
Variability estimate	Standard error of the mean
Dispersion value	1.39

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 4	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	1.39

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 8	
Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	-1.9
Variability estimate	Standard error of the mean
Dispersion value	1.39

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 12	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	1.39

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 16	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	1.4

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 20	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	1.4

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	1.41

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 30	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	1.42

Statistical analysis title	Statistical Analysis 9
Statistical analysis description: Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 36	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	1.43

Statistical analysis title	Statistical Analysis 10
Statistical analysis description: Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 42	
Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	1.44

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 48	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	1.45

Statistical analysis title	Statistical Analysis 12
Statistical analysis description:	
Change from Baseline in Corrected eGFR (mL/min/1.73m2) at Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	1.46

Secondary: Change in Baseline in Urinary Protein Creatinine Ratio

End point title	Change in Baseline in Urinary Protein Creatinine Ratio

End point description:

Change from baseline by visit in Urine Protein Creatinine ratio. Baseline is the average of two pre-randomisation values.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 and 52

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: mg/mg				
arithmetic mean (standard deviation)				
Baseline	4.14 (± 2.711)	3.87 (± 2.363)		
Week 2 Change from Baseline	-1.46 (± 1.991)	-0.7 (± 2.312)		
Week 4 Change from Baseline	-1.98 (± 2.29)	-1.07 (± 2.155)		
Week 8 Change from Baseline	-2.23 (± 2.213)	-1.43 (± 2.448)		
Week 12 Change from Baseline	-2.56 (± 2.293)	-1.48 (± 2.688)		
Week 16 Change from Baseline	-2.75 (± 2.462)	-1.58 (± 2.81)		
Week 20 Change from Baseline	-2.74 (± 2.968)	-1.54 (± 2.82)		
Week 24 Change from Baseline	-2.74 (± 2.567)	-1.59 (± 2.899)		
Week 30 Change from Baseline	-2.66 (± 3.336)	-1.7 (± 3.112)		
Week 36 Change from Baseline	-2.74 (± 2.871)	-1.63 (± 3.188)		
Week 42 Change from Baseline	-2.91 (± 2.522)	-1.78 (± 3.39)		
Week 48 Change from Baseline	-2.71 (± 2.807)	-1.8 (± 3.004)		
Week 52 Change from Baseline	-2.65 (± 2.872)	-1.88 (± 3.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change from Baseline in UPCR (mg/mg) at Week 2	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.22

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change from Baseline in UPCR (mg/mg) at Week 4	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.187

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change from Baseline in UPCR (mg/mg) at Week 8	
Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.181

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Change from Baseline in UPCR (mg/mg) at Week 12	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.55
Variability estimate	Standard error of the mean
Dispersion value	0.196

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Change from Baseline in UPCR (mg/mg) at Week 16	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.76
Variability estimate	Standard error of the mean
Dispersion value	0.214

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Change from Baseline in UPCR (mg/mg) at Week 20	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.63
upper limit	-0.68
Variability estimate	Standard error of the mean
Dispersion value	0.241

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Change from Baseline in UPCR (mg/mg) at Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	-0.72
Variability estimate	Standard error of the mean
Dispersion value	0.222

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Change from Baseline in UPCR (mg/mg) at Week 30	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.284

Statistical analysis title	Statistical Analysis 9
Statistical analysis description: Change from Baseline in UPCR (mg/mg) at Week 36	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	-0.69
Variability estimate	Standard error of the mean
Dispersion value	0.264

Statistical analysis title	Statistical Analysis 10
Statistical analysis description: Change from Baseline in UPCR (mg/mg) at Week 42	
Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	-0.86
Variability estimate	Standard error of the mean
Dispersion value	0.256

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
Change from Baseline in UPCR (mg/mg) at Week 48	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	-0.55
Variability estimate	Standard error of the mean
Dispersion value	0.256

Statistical analysis title	Statistical Analysis 12
Statistical analysis description:	
Change from Baseline in UPCR (mg/mg) at Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.52
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.27

Secondary: Number of Participants with Renal Response with Low Dose Steroids

End point title	Number of Participants with Renal Response with Low Dose Steroids
End point description:	
Programmed Renal Response while on low dose steroids (<2.5 mg/day) for the preceding 8 weeks at weeks 24 and 52	
End point type	Secondary
End point timeframe:	
Week 24 and Week 52	

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Participants				
Renal Response at Week 24	32	16		
Renal Response at Week 52	64	36		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Renal Response at Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	4.71

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Renal Response at Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	4

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

End point title	Change from Baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA - SLEDAI)

End point description:

SELENA-SLEDAI were analyzed using a mixed effect model repeated measures (MMRM) analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model. Results are expressed as differences between treatment arms along with the associated 95% CI. The least squares means (LS means) and their corresponding 95% confidence intervals of the change from baseline values are also presented for each visit and for the overall change.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)				
Week 24 Change from Baseline	-4.5 (-5.4 to -3.7)	-4.1 (-5.0 to -3.2)		
Week 52 Change from Baseline	-6 (-6.7 to -5.2)	-5.5 (-6.3 to -4.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change from Baseline at Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.373
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.6

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change from Baseline at Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.277
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.4

Secondary: Change from Baseline in Patient Report Outcomes

End point title	Change from Baseline in Patient Report Outcomes

End point description:

Health-related quality of life (HRQoL) information was collected using the Short Form Health Survey (SF-

36) HRQoL assessment and the LupusPRO (v1.7) assessment.
- SF-36 is a 36-item patient-reported questionnaire of patient health
- LupusPro assessment is a patient-reported questionnaire regarding the effect of lupus or its treatment on the patient's health, quality of life, and the medical care received related to lupus.

End point type	Secondary
End point timeframe:	
Week 24 and Week 52	

End point values	Voclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
SF-36 Change from Baseline at Week 24	6.64 (4.34 to 8.93)	7.11 (4.80 to 9.42)		
SF-36 Change from Baseline at Week 52	10.44 (8.04 to 12.83)	10.81 (8.37 to 13.25)		
LupusPRO HRQOL Change from Baseline at Week 24	7.76 (5.40 to 10.13)	6.06 (3.68 to 8.45)		
LupusPRO HRQOL Change from Baseline at Week 52	9.24 (6.78 to 11.70)	9.84 (7.33 to 12.35)		
LupusPRO non-HRQOL Change from Baseline at Week 24	1.06 (-1.32 to 3.44)	2.94 (0.54 to 5.35)		
LupusPRO non-HRQOL Change from Baseline at Week 52	4.08 (1.60 to 6.56)	3.74 (1.22 to 6.26)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
SF-36 Change from Baseline Week 24	
Comparison groups	Placebo v Voclosporin
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.733
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.21
upper limit	2.26
Variability estimate	Standard error of the mean
Dispersion value	1.389

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: SF-36 Change from Baseline at Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.801
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.29
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	1.481

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: LupusPRO HRQOL Change from Baseline at Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	4.54
Variability estimate	Standard error of the mean
Dispersion value	1.442

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: LupusPRO HRQOL Change from Baseline at Week 52	
Comparison groups	Voclosporin v Placebo

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.695
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.62
upper limit	2.42
Variability estimate	Standard error of the mean
Dispersion value	1.535

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
LupusPRO non-HRQOL Change from Baseline at Week 24	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.72
upper limit	0.94
Variability estimate	Standard error of the mean
Dispersion value	1.439

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
LupusPRO non-HRQOL Change from Baseline at Week 52	
Comparison groups	Voclosporin v Placebo
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.826
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.826

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.67
upper limit	3.35
Variability estimate	Standard error of the mean
Dispersion value	1.531

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs occurring after first dose and up to 30 days post-last dose of voclosporin/placebo	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Voclosporin
Reporting group description: Voclosporin 23.7 mg BID	
Reporting group title	Placebo Oral Capsule
Reporting group description: Matching placebo	

Serious adverse events	Voclosporin	Placebo Oral Capsule	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 178 (20.79%)	38 / 178 (21.35%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 178 (1.69%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 178 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	1 / 178 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (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			
Pleural effusion			
subjects affected / exposed	1 / 178 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus pleurisy			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 178 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Developmental hip dysplasia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (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 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (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			
Cerebral infarction			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus encephalitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropsychiatric lupus			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 178 (1.69%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (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			
Acute kidney injury			
subjects affected / exposed	4 / 178 (2.25%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 178 (1.12%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	1 / 178 (0.56%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure			
subjects affected / exposed	1 / 178 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	3 / 178 (1.69%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (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	7 / 178 (3.93%)	8 / 178 (4.49%)	
occurrences causally related to treatment / all	1 / 8	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastroenteritis			

subjects affected / exposed	3 / 178 (1.69%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 178 (1.12%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 178 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 178 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			

subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 178 (0.00%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess			

subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 178 (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	Voclosporin	Placebo Oral Capsule	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	161 / 178 (90.45%)	156 / 178 (87.64%)	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	43 / 178 (24.16%)	15 / 178 (8.43%)	
occurrences (all)	61	19	
Vascular disorders			
Hypertension			
subjects affected / exposed	35 / 178 (19.66%)	14 / 178 (7.87%)	
occurrences (all)	38	15	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 178 (16.29%)	11 / 178 (6.18%)	
occurrences (all)	34	16	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	11 / 178 (6.18%)	11 / 178 (6.18%)	
occurrences (all)	11	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 178 (10.11%)	10 / 178 (5.62%)	
occurrences (all)	19	11	
Leukopenia			
subjects affected / exposed	7 / 178 (3.93%)	10 / 178 (5.62%)	
occurrences (all)	8	12	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	34 / 178 (19.10%)	21 / 178 (11.80%)	
occurrences (all)	43	23	
Abdominal pain upper			
subjects affected / exposed	13 / 178 (7.30%)	1 / 178 (0.56%)	
occurrences (all)	13	2	
Abdominal pain			

subjects affected / exposed	10 / 178 (5.62%)	2 / 178 (1.12%)	
occurrences (all)	11	3	
Nausea			
subjects affected / exposed	10 / 178 (5.62%)	17 / 178 (9.55%)	
occurrences (all)	10	18	
Dyspepsia			
subjects affected / exposed	10 / 178 (5.62%)	3 / 178 (1.69%)	
occurrences (all)	10	3	
Vomiting			
subjects affected / exposed	5 / 178 (2.81%)	12 / 178 (6.74%)	
occurrences (all)	6	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 178 (7.30%)	3 / 178 (1.69%)	
occurrences (all)	13	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 178 (5.62%)	5 / 178 (2.81%)	
occurrences (all)	10	5	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	11 / 178 (6.18%)	5 / 178 (2.81%)	
occurrences (all)	14	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 178 (4.49%)	17 / 178 (9.55%)	
occurrences (all)	9	20	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	31 / 178 (17.42%)	26 / 178 (14.61%)	
occurrences (all)	44	33	
Viral upper respiratory tract infection			
subjects affected / exposed	20 / 178 (11.24%)	18 / 178 (10.11%)	
occurrences (all)	24	20	
Urinary tract infection			

subjects affected / exposed	17 / 178 (9.55%)	13 / 178 (7.30%)	
occurrences (all)	25	14	
Herpes zoster			
subjects affected / exposed	13 / 178 (7.30%)	9 / 178 (5.06%)	
occurrences (all)	13	9	
Influenza			
subjects affected / exposed	12 / 178 (6.74%)	10 / 178 (5.62%)	
occurrences (all)	15	12	
Gastroenteritis			
subjects affected / exposed	7 / 178 (3.93%)	10 / 178 (5.62%)	
occurrences (all)	8	10	
Pharyngitis			
subjects affected / exposed	3 / 178 (1.69%)	9 / 178 (5.06%)	
occurrences (all)	3	11	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	3 / 178 (1.69%)	9 / 178 (5.06%)	
occurrences (all)	3	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2017	1. Time point for primary efficacy endpoint changed from Week 24 to Week 52 2. Change in the primary and secondary efficacy endpoints for renal response 3. Addition of secondary efficacy endpoint for decrease in eGFR 4. Change in the time window of the biopsy used for screening and to include Class V lupus nephritis 5. Change in handling increases in blood pressure or hypertension and pulse 6. Change in stratification of randomization 7. Addition of the evaluation of biomarkers 8. Clarification of regarding definition of treatment emergent adverse events 9. Editorial changes for clarification made throughout

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported