

**Clinical trial results:****A Phase 1/2 Dose-escalation of USL311 as Single Agent and in Combination with Lomustine (CCNU) in Subjects with Advanced Solid Tumors, with Subsequent Single Agent and Combination Phase 2 Cohorts for Subjects with Relapsed/Recurrent Glioblastoma Multiforme (GBM)****Summary**

EudraCT number	2015-004214-14
Trial protocol	ES
Global end of trial date	01 July 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information**Trial identification**

Sponsor protocol code	P311-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02765165
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Proximagen, LLC
Sponsor organisation address	605 Waterford Park Highway 169 North, Suite 240, Plymouth, Minnesota, United States, 55441
Public contact	Chief Medical Officer, Proximagen, LLC, +1 952-658-7440, tcmeng@proximagen.com
Scientific contact	Chief Medical Officer, Proximagen, LLC, +1 952-658-7440, tcmeng@proximagen.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	24 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2020
Global end of trial reached?	Yes
Global end of trial date	01 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1 dose-escalation:

- Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of USL311 as a single agent in subjects with advanced solid tumors for which no standard-of-care (SoC) treatment is recognized or who have failed or are intolerant to the SoC treatment (Part 1).
- Determine the MTD and RP2D of USL311 in combination with lomustine in subjects with advanced solid tumors for which no SoC treatment is recognized or who have failed or are intolerant to the SoC treatment (Part 2).

Phase 2 dose-expansion:

- Determine the percentage PFS-6m of USL311 as a single agent in subjects with relapsed/recurrent GBM who previously received SoC treatment in the first-line setting and who are candidates for re-resection (Part 3).
- Determine the percentage PFS-6m of USL311 in combination with lomustine in subjects with relapsed/recurrent GBM who previously received SOC treatment in the first-line setting and who are candidates for re-resection (Part 4).

Protection of trial subjects:

The study protocol, any protocol amendments, the final approved informed consent form (ICF), relevant supporting information, and all types of subject recruitment information were submitted by the Investigator to an Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB) and approved by the IEC/IRB and regulatory agency (as appropriate) prior to study initiation.

This study was conducted in accordance with International Council for Harmonisation (ICH) of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and United States (US) Code of Federal Regulations (CFR) sections that address clinical research studies, as well as other applicable local ethical and legal requirements.

Written consent was a mandatory condition to participate in the study. It was obtained prior to any study-specific procedures being performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	26
EEA total number of subjects	1

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)	17
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 7 study sites in the following countries: United States (US; 5 sites) and Spain (2 sites).

Pre-assignment

Screening details:

Enrolled subjects participated in only one part (parts 1, 2, 3 or 4) of the study. Due to early termination of the study, no subjects were enrolled in parts 2, 3 or 4.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Part 1a, Cohort 1

Arm description:

USL311, intravenous, once per week, 60 mg/m², in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1a, Cohort 2
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Arm description:

USL311, intravenous, once per week, 120 mg/m², in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1a, Cohort 3
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Arm description:

USL311, intravenous, once per week, 180 mg/m², in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1a, Cohort 4
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Arm description:

USL311, intravenous, once per week, 250 mg/m², in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1b, Cohort 1
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Arm description:

USL311, oral, once per day, 40 mg, in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

USL311 Tablets

Arm title	Part 1b, Cohort 2
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Arm description:

USL311, oral, once per day, 80 mg, in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

USL311 Tablets

Arm title	Part 1b, Cohort 3
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Arm description:

USL311, oral, once per day, 160 mg, in 21-day cycles

Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

USL311 Tablets

Number of subjects in period 1	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3
Started	3	4	3
Completed	0	0	0
Not completed	3	4	3
Study terminated	-	-	-
Physician decision	-	1	-
Adverse Event	-	1	-
Withdrawal by Subject	-	-	-
Progressive disease	3	2	3

Number of subjects in period 1	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2
Started	3	6	3
Completed	0	0	0
Not completed	3	6	3
Study terminated	-	-	1
Physician decision	-	-	-
Adverse Event	-	-	-
Withdrawal by Subject	-	2	-
Progressive disease	3	4	2

Number of subjects in period 1	Part 1b, Cohort 3
Started	4
Completed	0
Not completed	4
Study terminated	2
Physician decision	-
Adverse Event	-
Withdrawal by Subject	-
Progressive disease	2

Period 2

Period 2 title	Post-treatment Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Part 1a, Cohort 1
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Arm description:

USL311, intravenous, once per week, 60 mg/m², in 21-day cycles

Arm type	Experimental
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Investigational medicinal product name	USL311
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Injection
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Routes of administration	Intravenous use
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Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1a, Cohort 2
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Arm description:

USL311, intravenous, once per week, 120 mg/m², in 21-day cycles

Arm type	Experimental
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Investigational medicinal product name	USL311
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Injection
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Routes of administration	Intravenous use
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Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1a, Cohort 3
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Arm description:

USL311, intravenous, once per week, 180 mg/m², in 21-day cycles

Arm type	Experimental
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Investigational medicinal product name	USL311
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Injection
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Routes of administration	Intravenous use
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Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1a, Cohort 4
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Arm description:

USL311, intravenous, once per week, 250 mg/m², in 21-day cycles

Arm type	Experimental
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Investigational medicinal product name	USL311
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Injection
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Routes of administration	Intravenous use
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Dosage and administration details:

USL311 Injection Solution

Arm title	Part 1b, Cohort 1
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Arm description:

USL311, oral, once per day, 40 mg, in 21-day cycles

Arm type	Experimental
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Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
USL311 Tablets	
Arm title	Part 1b, Cohort 2
Arm description:	
USL311, oral, once per day, 80 mg, in 21-day cycles	
Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
USL311 Tablets	
Arm title	Part 1b, Cohort 3
Arm description:	
USL311, oral, once per day, 160 mg, in 21-day cycles	
Arm type	Experimental
Investigational medicinal product name	USL311
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
USL311 Tablets	

Number of subjects in period 2	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3
Started	1	3	3
Completed	0	0	0
Not completed	1	3	3
Initiation of subsequent treatment	-	-	1
Death	1	2	1
Withdrawal by Subject	-	1	-
Lost to follow-up	-	-	-
Site terminated by Sponsor	-	-	1
Study terminated by the Sponsor	-	-	-

Number of subjects in period 2	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2
Started	3	3	3
Completed	0	0	0
Not completed	3	3	3

Initiation of subsequent treatment	1	-	-
Death	1	1	1
Withdrawal by Subject	-	-	-
Lost to follow-up	1	-	-
Site terminated by Sponsor	-	-	-
Study terminated by the Sponsor	-	2	2

Number of subjects in period 2	Part 1b, Cohort 3
Started	1
Completed	0
Not completed	1
Initiation of subsequent treatment	-
Death	-
Withdrawal by Subject	-
Lost to follow-up	-
Site terminated by Sponsor	-
Study terminated by the Sponsor	1

Baseline characteristics

Reporting groups

Reporting group title	Part 1a, Cohort 1
Reporting group description:	
USL311, intravenous, once per week, 60 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 2
Reporting group description:	
USL311, intravenous, once per week, 120 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 3
Reporting group description:	
USL311, intravenous, once per week, 180 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 4
Reporting group description:	
USL311, intravenous, once per week, 250 mg/m ² , in 21-day cycles	
Reporting group title	Part 1b, Cohort 1
Reporting group description:	
USL311, oral, once per day, 40 mg, in 21-day cycles	
Reporting group title	Part 1b, Cohort 2
Reporting group description:	
USL311, oral, once per day, 80 mg, in 21-day cycles	
Reporting group title	Part 1b, Cohort 3
Reporting group description:	
USL311, oral, once per day, 160 mg, in 21-day cycles	

Reporting group values	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3
Number of subjects	3	4	3
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	46.7	53.5	57.7
standard deviation	± 24.83	± 16.20	± 17.79
Gender categorical			
Units: Subjects			
Female	1	2	0
Male	2	2	3

Reporting group values	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2
Number of subjects	3	6	3
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean standard deviation	60.3 ± 10.97	62.5 ± 14.60	72.0 ± 9.17
Gender categorical Units: Subjects			
Female	3	3	2
Male	0	3	1

Reporting group values	Part 1b, Cohort 3	Total	
Number of subjects	4	26	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean standard deviation	57.3 ± 6.95	-	
Gender categorical Units: Subjects			
Female	1	12	
Male	3	14	

End points

End points reporting groups

Reporting group title	Part 1a, Cohort 1
Reporting group description:	
USL311, intravenous, once per week, 60 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 2
Reporting group description:	
USL311, intravenous, once per week, 120 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 3
Reporting group description:	
USL311, intravenous, once per week, 180 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 4
Reporting group description:	
USL311, intravenous, once per week, 250 mg/m ² , in 21-day cycles	
Reporting group title	Part 1b, Cohort 1
Reporting group description:	
USL311, oral, once per day, 40 mg, in 21-day cycles	
Reporting group title	Part 1b, Cohort 2
Reporting group description:	
USL311, oral, once per day, 80 mg, in 21-day cycles	
Reporting group title	Part 1b, Cohort 3
Reporting group description:	
USL311, oral, once per day, 160 mg, in 21-day cycles	
Reporting group title	Part 1a, Cohort 1
Reporting group description:	
USL311, intravenous, once per week, 60 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 2
Reporting group description:	
USL311, intravenous, once per week, 120 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 3
Reporting group description:	
USL311, intravenous, once per week, 180 mg/m ² , in 21-day cycles	
Reporting group title	Part 1a, Cohort 4
Reporting group description:	
USL311, intravenous, once per week, 250 mg/m ² , in 21-day cycles	
Reporting group title	Part 1b, Cohort 1
Reporting group description:	
USL311, oral, once per day, 40 mg, in 21-day cycles	
Reporting group title	Part 1b, Cohort 2
Reporting group description:	
USL311, oral, once per day, 80 mg, in 21-day cycles	
Reporting group title	Part 1b, Cohort 3
Reporting group description:	
USL311, oral, once per day, 160 mg, in 21-day cycles	
Subject analysis set title	Part 1a, Dose-escalation, All Intravenous Cohorts
Subject analysis set type	Full analysis
Subject analysis set description:	
USL311, intravenous, once per week, starting at 60 mg/m ² , in 21-day cycles	
Subject analysis set title	Part 1b, Dose-escalation, All Oral Cohorts

Subject analysis set type	Full analysis
Subject analysis set description: USL311, oral, once per day, starting at 40 mg, in 21 day cycles	
Subject analysis set title	Part 1, Dose-escalation, All Cohorts
Subject analysis set type	Full analysis
Subject analysis set description: USL311, intravenous once per week, starting at 60 mg/m ² , or oral once per day, starting at 40 mg, in 21-day cycles	
Subject analysis set title	Part 1a, Cohort 1
Subject analysis set type	Full analysis
Subject analysis set description: USL311, intravenous, once per week over 2 hours, 60 mg/m ² , in 21-day cycles. Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1a, Cohort 2
Subject analysis set type	Full analysis
Subject analysis set description: USL311, intravenous, once per week over 2 hours, 120 mg/m ² , in 21-day cycles. Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1a, Cohort 3a
Subject analysis set type	Full analysis
Subject analysis set description: USL311, intravenous, once per week over 2 hours, 180 mg/m ² , in 21-day cycles. Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1a, Cohort 3b
Subject analysis set type	Full analysis
Subject analysis set description: USL311, intravenous, once per week over 4 hours, 180 mg/m ² , in 21-day cycles. Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1a, Cohort 4
Subject analysis set type	Full analysis
Subject analysis set description: USL311, intravenous, once per week over 4 hours, 250 mg/m ² , in 21-day cycles. Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1b, Cohort 1
Subject analysis set type	Full analysis
Subject analysis set description: USL311, oral, once per day, 40 mg, in 21-day cycles Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1b, Cohort 2
Subject analysis set type	Full analysis
Subject analysis set description: USL311, oral, once per day, 80 mg, in 21-day cycles Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	
Subject analysis set title	Part 1b, Cohort 3
Subject analysis set type	Full analysis
Subject analysis set description: USL311, oral, once per day, 160 mg, in 21-day cycles Subjects who received scheduled dose and had sufficient PK samples for determination of parameters	

Primary: Phase 1: Maximum Tolerated Dose (MTD)

End point title	Phase 1: Maximum Tolerated Dose (MTD) ^[1]
End point description: The MTD was defined as the highest safe dose (mg/m ²) administered where safe is defined by having at least a 50% probability that the dose limiting toxicity (DLT) rate is less than 33%, as determined by a modified continuous reassessment model.	

999 = An MTD was not determined for Part 1a due to early termination of intravenous dosing and change to oral dosing

End point type	Primary
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End point timeframe:

Assessed weekly during treatment period. Median duration of exposure was 5.14 (range 2.1-17.3) weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for this endpoint

End point values	Part 1a, Dose-escalation, All Intravenous Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mg/m ²				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Maximum Tolerated Dose (MTD)

End point title	Phase 1: Maximum Tolerated Dose (MTD) ^[2]
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End point description:

The MTD was defined as the highest safe dose (mg) administered where safe is defined by having at least a 50% probability that the dose limiting toxicity (DLT) rate is less than 33%, as determined by a modified continuous reassessment model.

999 = An MTD was not determined in Part 1b due to study termination

End point type	Primary
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End point timeframe:

Assessed weekly during treatment period. Median duration of exposure was 6.00 (range 0.3-30.0) weeks.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for this endpoint

End point values	Part 1b, Dose-escalation, All Oral Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mg				
number (not applicable)	999			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Progression Free Survival (PFS) at 6 Months (PFS-6m)

End point title	Percentage Progression Free Survival (PFS) at 6 Months (PFS-6m)
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End point description:

Percentage of subjects who were without progression at 6 months as assessed radiographically with response to treatment determined by Response Evaluation Criteria in Solid Tumors (RECIST) or Response Assessment in Neuro-Oncology (RANO) criteria. Due to early termination of study in Phase 1, efficacy outcomes, including PFS-6m, were not analyzed for subjects in Part 1a or Part 1b. Therefore no subjects were included in this analysis population.

End point type	Secondary
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End point timeframe:

Once every 6 weeks during treatment

End point values	Part 1, Dose-escalation, All Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[3]			
Units: Subjects				
number (not applicable)				

Notes:

[3] - Due to early termination of study in Phase 1, efficacy outcomes, including PFS-6m, were not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Percentage of subjects alive five years after start of treatment. Due to early termination of study in Phase 1, efficacy outcomes, including OS, were not analyzed for subjects in Part 1a or Part 1b. Therefore no subjects were included in this analysis population.

End point type	Secondary
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End point timeframe:

Weekly during treatment or every 12 weeks during follow-up

End point values	Part 1, Dose-escalation, All Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[4]			
Units: Subjects				
number (not applicable)				

Notes:

[4] - Due to early termination of study in Phase 1, efficacy outcomes, including OS, were not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression Free Survival (PFS)

End point title	Median Progression Free Survival (PFS)
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End point description:

Time after initiation of treatment before disease progression. Due to early termination of study in Phase 1, efficacy outcomes, including median PFS, were not analyzed for subjects in Part 1a or Part 1b. Therefore no subjects were included in this analysis population.

End point type	Secondary
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End point timeframe:

Every 6 weeks during treatment

End point values	Part 1, Dose-escalation, All Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[5]			
Units: Months				
number (not applicable)				

Notes:

[5] - Due to early termination of study in Phase 1 median PFS was not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR%)

End point title	Objective Response Rate (ORR%)
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End point description:

Percentage of patients whose disease decreased (Partial response) and/or disappears (Complete response) after initiation of treatment. Due to early termination of study in Phase 1, efficacy outcomes, including ORR% were not analyzed for subjects in Part 1a or Part 1b. Therefore no subjects were included in this analysis population.

End point type	Secondary
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End point timeframe:

Every 6 weeks

End point values	Part 1, Dose-escalation, All Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[6]			
Units: Subjects				
number (not applicable)				

Notes:

[6] - Due to early termination of study in Phase 1, efficacy outcomes, including ORR% were not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Concentration (Cmax)

End point title	Peak Concentration (Cmax)
End point description:	Peak USL311 concentration (Cmax) in plasma. 999 = CV% not calculable as 1 subject
End point type	Secondary
End point timeframe:	Day 1

End point values	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3a	Part 1a, Cohort 3b
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	4	1	2
Units: ng/mL				
geometric mean (geometric coefficient of variation)	48.2 (± 41.1)	69.1 (± 66.9)	200 (± 999)	168 (± 94)

End point values	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2	Part 1b, Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	5	3	4
Units: ng/mL				
geometric mean (geometric coefficient of variation)	107 (± 37.2)	2.06 (± 84.6)	4.74 (± 32.4)	6.68 (± 58.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Concentration (Tmax)

End point title	Time to Peak Concentration (Tmax)
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End point description:

Time to peak concentration of USL311 in plasma

End point type Secondary

End point timeframe:

Day 1

End point values	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3a	Part 1a, Cohort 3b
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	4	1	2
Units: Hours				
median (full range (min-max))	1.05 (1.02 to 2.03)	1.04 (1.02 to 2.03)	0.53 (0.53 to 0.53)	2.28 (0.5 to 4.05)

End point values	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2	Part 1b, Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	5	3	4
Units: Hours				
median (full range (min-max))	2.55 (2.05 to 3.05)	0.63 (0.48 to 2)	0.67 (0.53 to 1)	0.565 (0.52 to 0.98)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve (AUC)

End point title Area Under the Concentration Versus Time Curve (AUC)

End point description:

Area under the curve versus time from time 0 to infinity for USL311 concentration in plasma

999 = CV% not calculable as 1 subject

End point type Secondary

End point timeframe:

Day 1

End point values	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3a	Part 1a, Cohort 3b
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	4	1	2
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	181 (\pm 101)	437 (\pm 16.7)	711 (\pm 999)	1193 (\pm 48.3)

End point values	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2	Part 1b, Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	5	3	4
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1059 (\pm 15.3)	5.95 (\pm 54.1)	16.4 (\pm 51)	30.4 (\pm 56.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events collected from informed consent to last visit during treatment period (post treatment follow-up visit or end of treatment visit, whichever was last).

Adverse event reporting additional description:

Survival information only was collected quarterly during long term follow-up. Deaths during follow-up phase were not captured as serious adverse events unless considered related.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Part 1a, Cohort 1
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Reporting group description:

USL311, intravenous, once per week, 60 mg/m², in 21-day cycles

Reporting group title	Part 1a, Cohort 2
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Reporting group description:

USL311, intravenous, once per week, 120 mg/m², in 21-day cycles

Reporting group title	Part 1a, Cohort 3
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Reporting group description:

USL311, intravenous, once per week, 180 mg/m², in 21-day cycles

Reporting group title	Part 1a, Cohort 4
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Reporting group description:

USL311, intravenous, once per week, 250 mg/m², in 21-day cycles

Reporting group title	Part 1b, Cohort 1
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Reporting group description:

USL311, oral, once per day, 40 mg, in 21-day cycles

Reporting group title	Part 1b, Cohort 2
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Reporting group description:

USL311, oral, once per day, 80 mg, in 21-day cycles

Reporting group title	Part 1b, Cohort 3
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Reporting group description:

USL311, oral, once per day, 160 mg, in 21-day cycles

Serious adverse events	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (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			
Haemorrhage intracranial			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (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
Encephalopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (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
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (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
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	3 / 6 (50.00%)	1 / 3 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Encephalopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Seizure			

subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (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

Serious adverse events	Part 1b, Cohort 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Haemorrhage intracranial subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders Pneumonia aspiration subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders Mental status changes subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders Acute kidney injury subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders Hypercalcaemia			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Part 1a, Cohort 1	Part 1a, Cohort 2	Part 1a, Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 4 (75.00%)	1 / 3 (33.33%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Mucosal inflammation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Cervical cyst			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Menopausal symptoms subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Ovarian cyst subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Investigations Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 3	1 / 3 (33.33%) 3
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1
Blood urea increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Seizure subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Amnesia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Aphasia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Brain oedema subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Facial paralysis			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Hemiparesis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Hypersomnia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Memory impairment subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Eye disorders Diplopia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 2	0 / 3 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1
Erythema subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Arthritis			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Cystitis			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 3	0 / 3 (0.00%) 0
Decreased appetite			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Hyperglycaemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0
Hypokalaemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 3 (33.33%) 2
Hypomagnesaemia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 3 (33.33%) 2
Hyponatraemia			
subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0

Non-serious adverse events	Part 1a, Cohort 4	Part 1b, Cohort 1	Part 1b, Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	6 / 6 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Flushing			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Cervical cyst			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Menopausal symptoms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ovarian cyst			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Sleep disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 3 (66.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Amnesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Aphasia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Brain oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Facial paralysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hemiparesis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypersomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Eye disorders			
Diplopia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1

Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 1b, Cohort 3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gait disturbance			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Reproductive system and breast disorders Cervical cyst subjects affected / exposed occurrences (all) Menopausal symptoms subjects affected / exposed occurrences (all) Ovarian cyst subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Investigations Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		

Blood urea increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Seizure subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Amnesia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2		
Aphasia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Brain oedema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Cognitive disorder			

<p>subjects affected / exposed occurrences (all)</p> <p>Facial paralysis subjects affected / exposed occurrences (all)</p> <p>Hemiparesis subjects affected / exposed occurrences (all)</p> <p>Hypersomnia subjects affected / exposed occurrences (all)</p> <p>Memory impairment subjects affected / exposed occurrences (all)</p>	<p>0 / 4 (0.00%) 0</p> <p>1 / 4 (25.00%) 2</p> <p>1 / 4 (25.00%) 1</p> <p>0 / 4 (0.00%) 0</p> <p>0 / 4 (0.00%) 0</p>		
<p>Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)</p>	<p>0 / 4 (0.00%) 0</p>		
<p>Eye disorders Diplopia subjects affected / exposed occurrences (all)</p> <p>Vision blurred subjects affected / exposed occurrences (all)</p>	<p>1 / 4 (25.00%) 3</p> <p>0 / 4 (0.00%) 0</p>		
<p>Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)</p> <p>Vomiting subjects affected / exposed occurrences (all)</p> <p>Abdominal distension subjects affected / exposed occurrences (all)</p> <p>Constipation</p>	<p>0 / 4 (0.00%) 0</p> <p>0 / 4 (0.00%) 0</p> <p>0 / 4 (0.00%) 0</p>		

<p>subjects affected / exposed occurrences (all)</p> <p>Diarrhoea subjects affected / exposed occurrences (all)</p> <p>Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)</p>	<p>0 / 4 (0.00%) 0</p> <p>1 / 4 (25.00%) 1</p> <p>0 / 4 (0.00%) 0</p>		
<p>Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)</p>	<p>0 / 4 (0.00%) 0</p>		
<p>Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)</p> <p>Erythema subjects affected / exposed occurrences (all)</p> <p>Pruritus subjects affected / exposed occurrences (all)</p> <p>Dermatitis contact subjects affected / exposed occurrences (all)</p> <p>Rash maculo-papular subjects affected / exposed occurrences (all)</p>	<p>0 / 4 (0.00%) 0</p>		
<p>Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)</p> <p>Musculoskeletal chest pain subjects affected / exposed occurrences (all)</p> <p>Myalgia</p>	<p>0 / 4 (0.00%) 0</p> <p>0 / 4 (0.00%) 0</p>		

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Arthritis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Infections and infestations Bacteraemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Cystitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Decreased appetite subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	Amendment 1: • For Part 1 and Part 2, added neurological examinations and for Part 3 and Part 4 added additional neurological examinations to safely assess possible neurological effects of USL311; • For Part 3 and Part 4, added statement about the maximum number of pre-surgical doses allowed; • For Part 3 and Part 4, clarified subjects must have fully recovered from surgery; • For all study parts, clarified subjects were monitored closely for at least 7 hours after the start of the infusion for their first dose of USL311; • For all study parts, clarified how electrocardiograms (ECGs) were collected and how continuous telemetry monitoring was performed; • For Part 1 and Part 2, clarified RANO criteria used for response assessment for all primary brain tumors; • Added exclusion criterion of subjects with lymphoma as primary cancer; • For all study parts, clarified the use of information obtained through standard-of-care procedures; • Reduced the volume of cerebrospinal fluid (CSF) collected during sample collection for all study parts due to additional information gained from analytical method development.
01 June 2016	Amendment 2: • In Part 1, clarified weight was collected at Screening instead of the Baseline Visit (Day -1); • Changed the neurological examination at clinic discharge, for the first dosing day of USL311 for each study part, to between the 5-hour nominal time point up to clinic discharge; • Added windows for the time-matched ECG collection and safety ECG collection to allow for some flexibility in the collection at the clinical sites; • Updated Inclusion Criterion to allow for 24-hour urine collection to determine the creatinine clearance corrected for body surface area (BSA), per Investigator discretion; • Updated Inclusion Criterion to also include electrolyte values above the upper limit of normal (ULN) if considered not clinically significant per the Investigator; • Removed the Inclusion Criterion to have the surgical sterilization procedure occur 6 months prior to receiving study drug(s); • In Part 1, clarified the Baseline Visit was part of the Screening Phase because the day of dosing was the beginning of the Treatment Phase.
22 December 2016	Amendment 3: • A study update noting observations of a potential USL311 dose-related increase in QT interval with a time-dependent profile correlating with plasma/blood USL311 concentrations was added; • An increase in infusion time was added based on the observation of prolongation of QT interval; • Clarification that bone marrow and renal/hepatic function parameters must meet entry criteria thresholds at Screening and Baseline Visits for subjects to be eligible for study treatment; • Clarification that QT changes were followed using the Fridericia correction; • Clarification that the pre-surgical dose of USL311 administered in Part 3 and Part 4 were at the defined recommended phase 2 dose (RP2D); • Added cautionary guidance on subjects avoiding unprotected sun exposure due to the unknown phototoxicity potential of USL311; • Clarification on Safety ECG thresholds for USL311 dose modification decision making.
02 August 2018	Amendment 4: • Update clinical study findings; • Added Part 1a (oral) cohort; • Increase number of subjects; • Addition of exclusion criteria for allergy/hypersensitivity to components of USL311 and conditions that may affect USL311 absorption; • Addition of concomitant medication and dietary restrictions; • Added oral dose and dosing information; • Removed stromal cell-derived factor 1 (SDF-1) from Part 1b and beyond; • Changes to assessments throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 June 2020	The decision to terminate the study was based on PK modeling after the 160 mg oral dose and on likely achievable exposures. It was not based on any observed safety signal.	-

Notes:

Limitations and caveats

None reported