NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LXS196 and HDM201 (siremadlin)

Trial Indication(s)

Metastatic uveal melanoma

Protocol Number

CLXS196X2101

Protocol Title

A phase I, multi-center, open-label, study of LXS196, an oral protein kinase C inhibitor, in patients with metastatic uveal melanoma

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: February 2016 (Actual)
Primary Completion Date: January 2022 (Actual)
Study Completion Date: January 2022 (Actual)

Reason for Termination (If applicable)

Novartis communicated the decision to halt further enrollment of subjects in the combination arm to all Investigators on 13-Mar-2019. This decision was based on the minimal clinical activity observed at the doses tested in the combination arm. Therefore, it was decided to not open the combination expansion part of the study. Importantly, the recruitment halt was not a consequence of any safety concern. Following this, the study protocol was amended (amendment 04) and further enrollment in the combination arm (escalation and expansion) was closed.

Study Design/Methodology

This was a phase I, multi-center, open-label, dose escalation and expansion study with two treatment arms (single agent LXS196 and the combination of LXS196 with HDM201) in patients with metastatic uveal melanoma.

In the dose escalation part, the recommended doses of LXS196 as a single agent and in combination with HDM201 were to be determined. Dose escalation was guided by a Bayesian Logistic Regression Model (BLRM). Subjects treated with combination of LXS196 and HDM201, were either treated with an initial 7-day run-in of low dose LXS196 in Cycle 1 or without an LXS196 run-in period.

The dose escalation was to be followed by an expansion part to better characterize the safety and tolerability of the recommended doses of LXS196 as single agent and in combination with HDM201 and make a preliminary assessment of the anti-tumor activity. The expansion part was not opened due to the recruitment halt in the combination arm.

Centers

6 centers in 6 countries: Netherlands(1), Spain(1), France(1), Australia(1), United States(1), Norway(1)

Objectives:

The primary objective of the trial was to characterize the safety and tolerability of LXS196 as a single agent and in combination with HDM201 in adult patients with metastatic uveal melanoma and identify the maximum tolerated dose(s) (MTDs) and/or recommended dose(s) for expansion (RDEs) and regimens of both single agent and combination therapies for future studies.

The secondary objectives were:

- To evaluate the preliminary antitumor activity of LXS196 as a single agent and in combination with HDM201
- To characterize the pharmacokinetic profile of LXS196 when given as a single agent and in combination with HDM201
- To characterize the pharmacokinetic profile of HDM201 when combined with LXS196
- To assess the pharmacodynamic effect of LXS196 as a single agent

Based on the primary and secondary objectives, the following endpoints were assessed:

Endpoint	Description
Primary: Number of participants with Dose-Limiting Toxicities (DLTs) during the first cycle of treatment (Dose escalation only)	A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness or concomitant medications that occurs within the first cycle of treatment with of LXS196 as a single agent and in combination with HDM201 during the dose escalation part of the study. Other clinically significant toxicities may be considered to be DLTs, even if not CTCAE grade 3 or higher. The duration of one treatment cycle was 28 days.
Primary: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)	Number of participants with AEs and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.
Primary: Number of participants with dose reductions and dose interruptions of LXS196	Number of participants with at least one dose reduction of LXS196 and number of participants with at least one dose interruption of LXS196.
Primary: Number of participants with dose reductions and dose interruptions of HDM201	Number of participants with at least one dose reduction of HDM201 and number of participants with at least one dose interruption of HDM201.

Primary: Dose intensity of LXS196	Dose intensity of LXS196 was calculated as actual cumulative dose in milligrams divided by duration of exposure in days.
Primary: Dose intensity of HDM201	Dose intensity of HDM201 was calculated as actual cumulative dose in milligrams divided by duration of exposure in days.
Secondary: Overall Response Rate (ORR) per RECIST v1.1	Tumor response was based on local investigator assessment as per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. ORR per RECIST v1.1 is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR).
Secondary: Progression-Free Survival (PFS) per RECIST v1.1	PFS is defined as the time from the date of start of treatment to the date of the first documented progression per RECIST v1.1 or death due to any cause. Patients who had not progressed or died at the time of the data cut-off were censored at the date of last adequate tumor assessment. PFS was estimated using the Kaplan-Meier Method.
Secondary: PK parameters (Cmax, Tmax, AUC0-t, AUC0-12hr, T1/2, Racc) of LXS196 in plasma	Pharmacokinetic (PK) parameters were calculated based on LXS196 plasma concentrations by using non-compartmental methods. Accumulation ratio (Racc) was calculated as the ratio AUC0-t C1D15/AUC0-t C1D1 for the single agent LXS196 arm and as the ratio AUC0-12hr C1D8/AUC0-12hr C1D1 for the combination arm.
Secondary: PK parameters (Cmax, Tmax, AUC0-24hr, T1/2) of HDM201 in plasma	Pharmacokinetic (PK) parameters were calculated based on HDM201 plasma concentrations by using non-compartmental methods.

	In order to allow the calculation of PK parameters the dosing was modified as follows: No administration of C1D1 evening dose.
Secondary: Fraction of LXS196 not bound to plasma protein (free fraction, fu) (single agent LXS196 arm only)	Plasma protein binding is described as the fraction of LXS196 not bound to plasma protein (free fraction, fu). Plasma protein binding fu(%) were determined with a validated ultrafiltration method.
Secondary: Plasma concentration of AAG protein (single agent LXS196 arm only)	The concentration of alpha 1-acid glycoprotein (AAG) following single agent LXS196 administration was determined in plasma samples.
Secondary: Percent change from baseline in pPKC delta normalized ratio from PBMC samples (single agent LXS196 arm only)	The percent change from baseline in protein kinase C (PKC) delta was performed in pre- and on-treatment peripheral blood mononuclear cells (PBMC) samples from subjects who received LXS196 either on a QD schedule or BID schedule in the single agent arm.

Test Product (s), Dose(s), and Mode(s) of Administration

The study treatment was LXS196 administered as a single agent and in combination with HDM201.

In the single agent arm, LXS196 was administered orally on a continuous dosing schedule either once daily (QD) or twice daily (BID). There were six dose levels (100, 200, 300, 500, 800 and 100 mg) assessed with the QD regimen and three dose levels (200, 300 and 400 mg) assessed with the BID regimen. The duration of a treatment cycle was 28 days.

In the combination LXS196 and HDM201 arm, patients were either treated with an initial 7-day run-in of low dose LXS196 in Cycle 1 or without an LXS196 run-in period. HDM201 was administered orally at a dose of 100 mg on Day 1 and Day 8 of every 28 days across all combination groups.

For subjects treated without a run-in, LXS196 was administered on a continuous BID dosing schedule at the dose levels of 100, 200, 300 or 400 mg.

For subjects treated with a run-in, two schedules were tested as follows:

- run-in 1: 100 mg BID LXS196 for the first 7 days of Cycle 1 followed by LXS196 200 mg BID from Cycle 1 Day 8 onwards.
- run-in 2: 200 mg BID LXS196 for the first 7 days of Cycle 1, followed by the assigned dose of LXS196 BID (300, 400 or 500 mg) from Cycle 1 Day 8 onwards.

In order to allow the calculation of PK parameters the dosing was modified as follows: No administration of Cycle 1 Day 2 (C1D2) dose in the single agent (SA) QD arm, no administration of C1D1 evening dose and both morning and evening doses on C1D2 in the SA BID arm and no administration of C1D1 evening dose in the combination arm.

Patients received study treatment until they experienced unacceptable toxicity that precluded further treatment, progressive disease and/or treatment was discontinued at the discretion of the investigator or the patient. Patients who had localized disease progression but had evidence of clinical benefit may continue treatment.

Statistical Methods

Efficacy

Evaluation of anti-tumor activity was based on Investigator assessment of overall lesion response according to RECIST v1.1. The endpoints used to evaluate anti-tumor activity were best overall response (BOR), ORR, and progression-free survival (PFS) using the Full Analysis Set (FAS).

Pharmacokinetics

All PK analyses were performed based on the PK analysis set unless otherwise specified.

PK parameters for both LXS196 and HDM201 were calculated using non-compartmental methods. The PK parameters included area under the concentration-time curve (AUC), maximum concentration (Cmax), time to reach maximum plasma concentration (Tmax), accumulation ratio (Racc), and terminal elimination half-life (T1/2) after the first dose on Day 1 of Cycle 1 (C1D1), Day 8 of Cycle 1 (C1D8) and Day 15 of Cycle 1 (C1D15). PK parameters were listed, and descriptive statistics of parameters were presented by treatment group.

Pharmacodynamics/Biomarker

The Screening assessment was used as the Baseline value. Any marked changes in the collected proteins (PKC delta) from the PMBC samples were summarized. Baseline and change from Baseline (percent change) were summarized.

Safety

The safety assessment was based on the type and frequency of AEs as well as on the number of laboratory values that fell outside of pre-determined ranges of Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grading limits or normal ranges as appropriate. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and were graded as per the CTCAE version 4.03. Tolerability was assessed using dose interruptions, reductions, and dose intensity. The incidence of Dose limiting toxicities (DLTs) in Cycle 1 was described by treatment group. Identification of the MTD/RDE was based upon the estimation of the probability of DLT in Cycle 1 for subjects in the dose determining set.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Male or female patients ≥18 years of age
- Diagnosis of uveal melanoma with histological or cytological confirmed metastatic disease. Disease must be treatment naive or have progressed (radiologically or clinically) on most recent therapy.
- Willingness to provide newly obtained tumor tissue at baseline and on treatment unless contraindicated by medical risk in the opinion of the treating physician.
- Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm with conventional techniques or as >10 mm with CT scan.
- ECOG performance status ≤ 1

Key Exclusion Criteria:

- Malignant disease other than that being treated in this study.
- Symptomatic or untreated CNS metastases or spinal cord compression. Brain metastasis must be stable with

verification by imaging .
● Impaired cardiac function or clinically significant cardiac diseases
● History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism (applicable to combination part only).
● Patients who are receiving treatment with medications that cannot be discontinued prior to study entry and that are considered to be any of the following:
– known and possible risk for QT prolongation
– known to be strong inducers or inhibitors of CYP3A4/5 (for single agent part); known to be moderate to strong inducers or inhibitors of CYP3A4/5 (for combination part)
– known to be inducers or inhibitors of P-gp
– known to be substrates of CYP3A4/5 and P-gp with a narrow therapeutic index
● Patients with abnormal laboratory values, defined as any of the following:
– AST or ALT > 3 times ULN, AST or ALT > 5 times ULN for patients with liver metastases.
– Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN.
– Absolute neutrophil count (ANC) ≤ 1.5 x109/L.
– Platelets ≤ 100 x 109/L.
– Hemoglobin (Hgb) ≤ 90 g/L (9 g/dL).
– Creatinine > 1.5 x ULN
● Patients receiving live vaccines due to the expected bone marrow toxicity (applicable to combination part only).
● Patients treated with growth factors targeting the myeloid lineage (e.g. G-CSF, GM-CSF and M-CSF) within 2 weeks of starting study treatment. (applicable to combination part only).

Participant Flow Table

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Started	3	4	15	11	1	4	6	18	6
Completed	0	0	0	0	0	0	0	0	0
Not Completed	3	4	15	11	1	4	6	18	6
Death	0	0	0	0	0	0	1	1	0
Progressive Disease	3	4	15	11	1	4	5	17	6
Adverse Event	0	0	0	0	0	0	0	0	0
Physician Decision	0	0	0	0	0	0	0	0	0
Subject/Guardian Decision	0	0	0	0	0	0	0	0	0

Combination arm

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201	Total
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing	LXS196 200 mg administered on a continuous BID dosing	LXS196 300 mg administered on a continuous BID dosing	LXS196 400 mg administered on a continuous BID dosing	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1	

	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	
Started	4	3	5	6	3	6	6	6	107
Completed	0	0	0	0	0	0	0	0	0
Not Completed	4	3	5	6	3	6	6	6	107
Death	0	0	0	0	0	0	0	0	2
Progressive Disease	4	2	4	6	3	6	6	4	101
Adverse Event	0	0	1	0	0	0	0	0	1
Physician Decision	0	1	0	0	0	0	0	0	1
Subject/Guardian Decision	0	0	0	0	0	0	0	2	2

Baseline Characteristics

Single agent arm

	LXS196 100 mg QD	**LXS196 200 mg QD**	**LXS196 300 mg QD**	**LXS196 500 mg QD**	**LXS196 800 mg QD**	**LXS196 1000 mg QD**	**LXS196 200 mg BID**	**LXS196 300 mg BID**	**LXS196 400 mg BID**
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)

Number of Participants [units: participants]	3	4	15	11	1	4	6	18	6
Age Continuous (units: years) Mean ± Standard Deviation									
	53.0±13.86	45.8±4.57	55.9±12.53	54.9±10.44	65.0	58.5±8.19	56.7±13.88	56.7±10.50	57.5±12.90
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)									
Female	2	2	6	5	1	0	0	11	5
Male	1	2	9	6	0	4	6	7	1
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)									
Asian	0	0	0	1	0	0	0	0	0
Caucasian	3	4	13	5	0	4	5	13	4
Unknown	0	0	2	5	1	0	1	5	2

Combination arm

	LXS196 100 mg BID +HDM201	**LXS196 200 mg BID +HDM201**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**	**LXS196 run-in 1 200 mg BID +HDM201**	**LXS196 run-in 2 300 mg BID +HDM201**	**LXS196 run-in 2 400 mg BID +HDM201**	**LXS196 run-in 2 500 mg BID +HDM201**	**Total**
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in	

	100 mg on Day 1 and Day 8 of every 28 days	100 mg on Day 1 and Day 8 of every 28 days	100 mg on Day 1 and Day 8 of every 28 days	100 mg on Day 1 and Day 8 of every 28 days	combination with HDM201 100 mg on Days 1 and 8 of every 28 days	combination with HDM201 100 mg on Days 1 and 8 of every 28 days	combination with HDM201 100 mg on Days 1 and 8 of every 28 days	combination with HDM201 100 mg on Days 1 and 8 of every 28 days	
Number of Participants [units: participants]	4	3	5	6	3	6	6	6	107
Age Continuous (units: years) Mean ± Standard Deviation									
	70.0±3.56	53.3±5.69	53.0±14.61	60.8±8.13	63.3±5.69	44.0±12.76	64.8±6.43	64.5±5.01	56.9±11.29
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)									
Female	3	0	2	4	1	2	1	4	49
Male	1	3	3	2	2	4	5	2	58
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)									
Asian	0	0	0	0	0	0	0	0	1
Caucasian	4	2	3	4	2	6	5	5	82
Unknown	0	1	2	2	1	0	1	1	24

Primary Outcome Result(s)

Number of participants with Dose-Limiting Toxicities (DLTs) during the first cycle of treatment (Dose escalation only)
(Time Frame: 28 days)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	5	6	6
Number of participants with Dose-Limiting Toxicities (DLTs) during the first cycle of treatment (Dose escalation only) (units: participants) Count of Participants (Not Applicable)									
	0 (%)	1 (25%)	0 (%)	3 (27.27%)	1 (100%)	2 (50%)	0 (%)	0 (%)	2 (33.33%)

Combination arm

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6

Number of participants with Dose-Limiting Toxicities (DLTs) during the first cycle of treatment (Dose escalation only) (units: participants) Count of Participants (Not Applicable)								
	0 (%)	0 (%)	0 (%)	2 (33.33%)	0 (%)	0 (%)	1 (16.67%)	2 (33.33%)

Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

(Time Frame: From first dose of study medication up to 30 days after last dose, with a maximum duration of 5 years for LXS196 single agent arm and 1.6 years for the LXS196+HDM201 arm)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6
Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: participants) Count of Participants (Not Applicable)									
AEs	3 (100%)	4 (100%)	14 (93.33%)	10 (90.91%)	1 (100%)	4 (100%)	6 (100%)	18 (100%)	6 (100%)
Treatment-related AEs	2 (66.67%)	4 (100%)	14 (93.33%)	10 (90.91%)	1 (100%)	4 (100%)	5 (83.33%)	17 (94.44%)	6 (100%)
SAEs	0 (%)	1 (25%)	0 (%)	3 (27.27%)	1 (100%)	2 (50%)	1 (16.67%)	5 (27.78%)	1 (16.67%)
Treatment-related SAEs	0 (%)	1 (25%)	0 (%)	3 (27.27%)	1 (100%)	1 (25%)	0 (%)	1 (5.56%)	1 (16.67%)
Fatal SAEs	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (5.56%)	0 (%)

Treatment-related fatal SAEs	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
AEs leading to discontinuation	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (5.56%)	0 (%)
Treatment-related AEs leading to discontinuation	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
AEs leading to dose adjustment/interruption	0 (%)	1 (25%)	3 (20%)	6 (54.55%)	1 (100%)	2 (50%)	1 (16.67%)	5 (27.78%)	4 (66.67%)
AEs requiring additional therapy	3 (100%)	4 (100%)	13 (86.67%)	8 (72.73%)	1 (100%)	3 (75%)	4 (66.67%)	17 (94.44%)	6 (100%)

Combination arm

	LXS196 100 mg BID +HDM201	**LXS196 200 mg BID +HDM201**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**	**LXS196 run-in 1 200 mg BID +HDM201**	**LXS196 run-in 2 300 mg BID +HDM201**	**LXS196 run-in 2 400 mg BID +HDM201**	**LXS196 run-in 2 500 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days

Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6
Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: participants) Count of Participants (Not Applicable)								
AEs	4 (100%)	3 (100%)	5 (100%)	6 (100%)	3 (100%)	6 (100%)	6 (100%)	6 (100%)
Treatment-related AEs	4 (100%)	3 (100%)	5 (100%)	6 (100%)	3 (100%)	6 (100%)	6 (100%)	6 (100%)
SAEs	0 (%)	2 (66.67%)	3 (60%)	3 (50%)	0 (%)	3 (50%)	3 (50%)	1 (16.67%)
Treatment-related SAEs	0 (%)	1 (33.33%)	2 (40%)	3 (50%)	0 (%)	0 (%)	2 (33.33%)	1 (16.67%)
Fatal SAEs	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (16.67%)	0 (%)	0 (%)
Treatment-related fatal SAEs	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
AEs leading to discontinuation	0 (%)	0 (%)	1 (20%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
Treatment-related AEs leading to discontinuation	0 (%)	0 (%)	1 (20%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
AEs leading to dose adjustment/interruption	0 (%)	2 (66.67%)	2 (40%)	6 (100%)	1 (33.33%)	2 (33.33%)	4 (66.67%)	4 (66.67%)
AEs requiring additional therapy	4 (100%)	3 (100%)	5 (100%)	6 (100%)	3 (100%)	6 (100%)	5 (83.33%)	6 (100%)

Number of participants with dose reductions and dose interruptions of LXS196

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 4.9 years for LXS196 single agent arm and 1.5 years for the LXS196+HDM201 arm)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6
Number of participants with dose reductions and dose interruptions of LXS196 (units: participants) Count of Participants (Not Applicable)									
At least 1 dose reduction	0 (%)	1 (25%)	1 (6.67%)	3 (27.27%)	1 (100%)	2 (50%)	0 (%)	0 (%)	2 (33.33%)
At least 1 dose interruption	0 (%)	1 (25%)	3 (20%)	5 (45.45%)	1 (100%)	1 (25%)	1 (16.67%)	3 (16.67%)	2 (33.33%)

Combination arm

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards

	100 mg on Day 1 and Day 8 of every 28 days	100 mg on Day 1 and Day 8 of every 28 days	100 mg on Day 1 and Day 8 of every 28 days	100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6
Number of participants with dose reductions and dose interruptions of LXS196 (units: participants) Count of Participants (Not Applicable)								
At least 1 dose reduction	0 (%)	0 (%)	1 (20%)	3 (50%)	0 (%)	1 (16.67%)	2 (33.33%)	4 (66.67%)
At least 1 dose interruption	0 (%)	2 (66.67%)	2 (40%)	4 (66.67%)	1 (33.33%)	2 (33.33%)	4 (66.67%)	5 (83.33%)

Number of participants with dose reductions and dose interruptions of HDM201

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 1.5 years)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days

Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6
Number of participants with dose reductions and dose interruptions of HDM201 (units: participants) Count of Participants (Not Applicable)								
At least 1 dose reduction	0 (%)	0 (%)	0 (%)	0 (%)	1 (33.33%)	0 (%)	1 (16.67%)	0 (%)
At least 1 dose interruption	0 (%)	0 (%)	0 (%)	1 (16.67%)	1 (33.33%)	1 (16.67%)	3 (50%)	1 (16.67%)

Dose intensity of LXS196

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 4.9 years for LXS196 single agent arm and 1.5 years for the LXS196+HDM201 arm)

Single agent arm

	LXS196 100 mg QD	**LXS196 200 mg QD**	**LXS196 300 mg QD**	**LXS196 500 mg QD**	**LXS196 800 mg QD**	**LXS196 1000 mg QD**	**LXS196 200 mg BID**	**LXS196 300 mg BID**	**LXS196 400 mg BID**
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6
Dose intensity of LXS196 (units: mg/day) Median (Full Range)									
	100.0 (100.0 to 100.0)	197.9 (113.2 to 369.1)	297.3 (125.5 to 333.6)	485.2 (191.6 to 495.2)	475.9 (475.9 to 475.9)	745.3 (330.3 to 994.0)	392.6 (328.6 to 536.8)	591.9 (488.1 to 599.0)	690.8 (286.2 to 797.3)

Combination arm

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6
Dose intensity of LXS196 (units: mg/day) Median (Full Range)								
	198.8 (196.4 to 256.3)	357.1 (345.8 to 398.8)	594.6 (393.2 to 597.4)	671.1 (543.5 to 798.6)	388.1 (344.5 to 391.1)	579.3 (303.7 to 585.7)	726.3 (494.4 to 789.5)	783.8 (539.3 to 922.8)

Dose intensity of HDM201

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 1.5 years)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID	LXS196 200 mg administered on a continuous BID	LXS196 300 mg administered on a continuous BID	LXS196 400 mg administered on a continuous BID	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then

	dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6
Dose intensity of HDM201 (units: mg/day) Median (Full Range)								
	10.1 (7.4 to 25.0)	8.0 (8.0 to 11.1)	11.1 (8.5 to 18.2)	8.2 (7.4 to 25.0)	7.1 (5.0 to 8.0)	8.3 (7.8 to 8.7)	8.2 (6.8 to 8.8)	8.2 (7.4 to 11.1)

Secondary Outcome Result(s)

Overall Response Rate (ORR) per RECIST v1.1

(Time Frame: From start of treatment until end of treatment, assessed up to 4.9 years for LXS196 single agent arm and 1.5 years for the LXS196+HDM201 arm)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6

Overall Response Rate (ORR) per RECIST v1.1 (units: percentage of participants) Number (95% Confidence Interval)									
	0 (0.0 to 70.8)	0 (0.0 to 60.2)	6.7 (0.2 to 31.9)	9.1 (0.2 to 41.3)	0 (0.0 to 97.5)	0 (0.0 to 60.2)	16.7 (0.4 to 64.1)	11.1 (1.4 to 34.7)	16.7 (0.4 to 64.1)

Combination arm

	LXS196 100 mg BID +HDM201	**LXS196 200 mg BID +HDM201**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**	**LXS196 run-in 1 200 mg BID +HDM201**	**LXS196 run-in 2 300 mg BID +HDM201**	**LXS196 run-in 2 400 mg BID +HDM201**	**LXS196 run-in 2 500 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6	3	6	6	6
Overall Response Rate (ORR) per RECIST v1.1 (units: percentage of participants) Number (95% Confidence Interval)								
	0 (0.0 to 60.2)	0 (0.0 to 70.8)	0 (0.0 to 52.2)	0 (0.0 to 45.9)	0 (0.0 to 70.8)	0 (0.0 to 45.9)	0 (0.0 to 45.9)	0 (0.0 to 45.9)

Progression-Free Survival (PFS) per RECIST v1.1

(Time Frame: From start of treatment until end of treatment, assessed up to 4.9 years for LXS196 single agent arm and 1.5 years for the LXS196+HDM201 arm)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6
Progression-Free Survival (PFS) per RECIST v1.1 (units: months) Median (95% Confidence Interval)									
	3.5 (1 to NA)[1]	7.2 (1 to NA)[1]	3.6 (1 to 7)	3.5 (1 to 3.5)	3.5 (NA to NA)[1]	5.4 (3 to NA)[1]	2.7 (0 to NA)[1]	3.7 (2 to 5)	7.3 (1 to NA)[1]

[1] Not estimable due to insufficient number of participants with events.

Combination arm

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201	LXS196 run-in 1 200 mg BID +HDM201	LXS196 run-in 2 300 mg BID +HDM201	LXS196 run-in 2 400 mg BID +HDM201	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed	4	3	5	6	3	6	6	6

[units: participants]								
Progression-Free Survival (PFS) per RECIST v1.1 (units: months) Median (95% Confidence Interval)								
	2.6 (1 to NA)[1]	3.7 (1 to NA)[1]	1.7 (1 to NA)[1]	5.4 (1 to NA)[1]	4.2 (3 to NA)[1]	3.5 (1 to NA)[1]	4.7 (3 to NA)[1]	3.7 (1 to NA)[1]

[1] Not estimable due to insufficient number of participants with events.

Maximum observed plasma concentration (Cmax) of LXS196 on Cycle 1 Day 1 (C1D1)

(Time Frame: SA arm: pre-dose, 0.5, 1, 2, 4, 6, 12 (BID dosing only), 24 and 48 hours post dose on C1D1. Combo arm: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

Single agent arm

	LXS196 100 mg QD	**LXS196 200 mg QD**	**LXS196 300 mg QD**	**LXS196 500 mg QD**	**LXS196 800 mg QD**	**LXS196 1000 mg QD**	**LXS196 200 mg BID**	**LXS196 300 mg BID**	**LXS196 400 mg BID**
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	3	15	10	1	4	6	17	5
Maximum observed plasma concentration (Cmax) of LXS196 on Cycle 1 Day 1 (C1D1) (units: ng/mL) Mean ± Standard Deviation									
	776 ± 69.8	3540 ± 1250	5580 ± 3220	4970 ± 1800	6080	5410 ± 2160	4070 ± 3390	4100 ± 1610	4350 ± 1610

Statistical Analysis

Groups	LXS196 100 mg QD, LXS196 200 mg QD, LXS196 300 mg QD, LXS196 500 mg QD, LXS196 800 mg QD,

	LXS196 1000 mg QD, LXS196 200 mg BID, LXS196 300 mg BID, LXS196 400 mg BID	
Method	Other Power model	Cmax values were log-transformed and analyzed using a power model: ln(Cmax)=alpha+beta*ln(dose)+error.
Slope	0.59	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified range (0.90, 1.10)
90 % Confidence Interval 2-Sided	0.36 to 0.81	

Combination arm

	LXS196 100 mg BID +HDM201 (C1D1)	**LXS196 200 mg BID +HDM201 (C1D1)**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	7	19	5	6
Maximum observed plasma concentration (Cmax) of LXS196 on Cycle 1 Day 1 (C1D1) (units: ng/mL) Mean ± Standard Deviation				
	2020 ± 828	3920 ± 1940	5510 ± 2280	5930 ± 2250

Statistical Analysis

Groups	LXS196 100 mg BID +HDM201 (C1D1), LXS196 200 mg BID +HDM201 (C1D1), LXS196 300 mg BID +HDM201, LXS196 400 mg BID +HDM201	
Method	Other Power model	Cmax values were log-transformed and analyzed using a power model: ln(Cmax)=alpha+beta*ln(dose)+error.
Slope	0.80	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.84, 1.16).
90 % Confidence Interval 2-Sided	0.50 to 1.10	

Maximum observed plasma concentration (Cmax) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 6 and 12 hours (BID dosing only) and 24 hours (QD dosing only) post dose on C1D15. The duration of one cycle was 28 days.)

	LXS196 100 mg QD	**LXS196 200 mg QD**	**LXS196 300 mg QD**	**LXS196 500 mg QD**	**LXS196 800 mg QD**	**LXS196 1000 mg QD**	**LXS196 200 mg BID**	**LXS196 300 mg BID**	**LXS196 400 mg BID**
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	3	14	9	0	2	5	17	4
Maximum observed plasma									

concentration (Cmax) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm (units: ng/mL) Mean ± Standard Deviation	1190 ± 217	2500 ± 252	3860 ± 2220	4170 ± 1930	5110 ± 2180	2910 ± 1990	2860 ± 569	2100 ± 462

Statistical Analysis

Groups	LXS196 100 mg QD, LXS196 200 mg QD, LXS196 300 mg QD, LXS196 500 mg QD, LXS196 800 mg QD, LXS196 1000 mg QD	
Method	Other Power model	Cmax values were log-transformed and analyzed using a power model: ln(Cmax)=alpha+beta*ln(dose)+error.
Slope	0.60	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.90, 1.10).
90 % Confidence Interval 2-Sided	0.38 to 0.82	

Statistical Analysis

Groups	LXS196 200 mg BID, LXS196 300 mg BID, LXS196 400 mg BID

Method	Other Power model	Cmax values were log-transformed and analyzed using a power model: ln(Cmax)=alpha+beta*ln(dose)+error.
Slope	-0.14	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.68, 1.32).
90 % Confidence Interval 2-Sided	-0.68 to 0.40	

Maximum observed plasma concentration (Cmax) of LXS196 on Cycle 1 Day 8 (C1D8) - Combination of LXS196 and HDM201 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6
Maximum observed plasma concentration (Cmax) of LXS196 on Cycle 1 Day 8 (C1D8) - Combination of LXS196 and HDM201 arm (units: ng/mL) Mean ± Standard Deviation				
	2000 ± 860	3800 ± 1220	3310 ± 987	3290 ± 1220

Statistical Analysis

Groups	LXS196 100 mg BID +HDM201, LXS196 200 mg BID +HDM201, LXS196 300 mg BID

	+HDM201, LXS196 400 mg BID +HDM201	
Method	Other Power model	Cmax values were log-transformed and analyzed using a power model: ln(Cmax)=alpha+beta*ln(dose)+error.
Slope	0.35	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.84, 1.14).
90 % Confidence Interval 2-Sided	0.03 to 0.66	

Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 1 (C1D1)

(Time Frame: SA arm: pre-dose, 0.5, 1, 2, 4, 6, 12 (BID dosing only), 24 and 48 hours post dose on C1D1. Combo arm: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	3	15	10	1	4	6	17	5
Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 1 (C1D1) (units: hours) Median (Full Range)									
	1.00 (0.500 to 6.00)	1.00 (0.500 to 2.00)	1.00 (0.483 to 3.97)	1.03 (0.500 to 2.00)	0.483 (0.483 to 0.483)	2.00 (1.00 to 6.05)	0.525 (0.483 to 2.00)	1.00 (0.333 to 4.00)	1.03 (0.467 to 1.03)

Combination arm

	LXS196 100 mg BID +HDM201 (C1D1)	LXS196 200 mg BID +HDM201 (C1D1)	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	7	19	5	6
Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 1 (C1D1) (units: hours) Median (Full Range)				
	1.08 (0.500 to 4.03)	1.00 (0.483 to 4.00)	1.00 (0.500 to 3.92)	1.00 (0.500 to 4.00)

Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 6 and 12 hours (BID dosing only) and 24 hours (QD dosing only) post dose on C1D15. The duration of one cycle was 28 days.)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	3	14	9	0	2	5	17	4
Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm (units: hours) Median (Full Range)									

1.00 (1.00 to 4.00)	1.00 (0.500 to 1.00)	1.00 (0.483 to 2.05)	1.07 (0.467 to 2.00)		0.792 (0.583 to 1.00)	1.00 (0.500 to 4.00)	0.567 (0.467 to 4.00)	0.842 (0.500 to 1.95)

Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 8 (C1D8) - Combination of LXS196 and HDM201 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	3	5	6
Time to reach maximum plasma concentration (Tmax) of LXS196 on Cycle 1 Day 8 (C1D8) - Combination of LXS196 and HDM201 arm (units: hours) Median (Full Range)				
	2.03 (0.483 to 2.08)	1.07 (1.00 to 2.00)	1.02 (0.500 to 2.07)	2.00 (0.400 to 4.00)

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-t) of LXS196 on Cycle 1 Day 1 (C1D1) – Single agent LXS196 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 6 and 12 hours (BID dosing only) and 24 hours (QD dosing only) post dose on C1D15. The duration of one cycle was 28 days.)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)

Number of Participants Analyzed [units: participants]	3	3	15	10	1	4	6	17	5
Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-t) of LXS196 on Cycle 1 Day 1 (C1D1) – Single agent LXS196 arm (units: hr*ng/mL) Mean ± Standard Deviation									
	8670 ± 2490	19100 ± 4270	40200 ± 26300	50700 ± 17000	54300	74300 ± 30100	18600 ± 14500	20500 ± 10200	18100 ± 7690

Statistical Analysis

Groups	LXS196 100 mg QD, LXS196 200 mg QD, LXS196 300 mg QD, LXS196 500 mg QD, LXS196 800 mg QD, LXS196 1000 mg QD, LXS196 200 mg BID, LXS196 300 mg BID, LXS196 400 mg BID	
Method	Other Power model	AUCt values were log-transformed and analyzed using a power model: ln(AUCt)=alpha+beta*ln(dose)+error.
Slope	0.93	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.90, 1.10).
90 % Confidence Interval 2-Sided	0.69 to 1.17	

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-t) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 6 and 12 hours (BID dosing only) and 24 hours (QD dosing only) post dose on C1D15. The duration of one cycle was 28 days.)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	2	3	13	9	0	2	5	12	4
Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-t) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm (units: hr*ng/mL) Mean ± Standard Deviation									
	10400 ± 776	13200 ± 3260	30500 ± 18700	45700 ± 16700		48300 ± 7600	16900 ± 7530	19100 ± 5540	15900 ± 2810

Statistical Analysis

Groups	LXS196 100 mg QD, LXS196 200 mg QD, LXS196 300 mg QD, LXS196 500 mg QD, LXS196 800 mg QD, LXS196 1000 mg QD	
Method	Other Power model	AUCt values were log-transformed and analyzed using a power model: ln(AUCt)=alpha+beta*ln(dose)+error.
Slope	0.83	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.90, 1.10).

90 % Confidence Interval 2-Sided	0.56 to 1.11	

Statistical Analysis

Groups	LXS196 200 mg BID, LXS196 300 mg BID, LXS196 400 mg BID	
Method	Other Power model	AUCt values were log-transformed and analyzed using a power model: ln(AUCt)=alpha+beta*ln(dose)+error.
Slope	0.09	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.68, 1.32).
90 % Confidence Interval 2-Sided	-0.45 to 0.64	

Area under the plasma concentration-time curve from time zero to 12 hours (AUC0-12hr) of LXS196 on Cycle 1 Day 1 (C1D1) – Combination of LXS196 and HDM201 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201 (C1D1)	LXS196 200 mg BID +HDM201 (C1D1)	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	7	19	5	6

Area under the plasma concentration-time curve from time zero to 12 hours (AUC0-12hr) of LXS196 on Cycle 1 Day 1 (C1D1) – Combination of LXS196 and HDM201 arm

(units: hr*ng/mL) Mean ± Standard Deviation				
	9910 ± 3170	19500 ± 10800	28100 ± 16400	35300 ± 12100

Statistical Analysis

Groups	LXS196 100 mg BID +HDM201 (C1D1), LXS196 200 mg BID +HDM201 (C1D1), LXS196 300 mg BID +HDM201, LXS196 400 mg BID +HDM201	
Method	Other Power model	AUC0-12hr values were log-transformed and analyzed using a power model: ln(AUC0-12hr)= alpha+beta*ln(dose)+error.
Slope	0.90	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.84, 1.16).
90 % Confidence Interval 2-Sided	0.59 to 1.21	

Area under the plasma concentration-time curve from time zero to 12 hours (AUC0-12hr) of LXS196 on Cycle 1 Day 8 (C1D8) – Combination of LXS196 and HDM201 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing	LXS196 200 mg administered on a continuous BID dosing	LXS196 300 mg administered on a continuous BID dosing	LXS196 400 mg administered on a continuous BID dosing

	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	1	2	2	2
Area under the plasma concentration-time curve from time zero to 12 hours (AUC0-12hr) of LXS196 on Cycle 1 Day 8 (C1D8) – Combination of LXS196 and HDM201 arm (units: hr*ng/mL) Mean ± Standard Deviation				
	11700	17900 ± 5210	23400 ± 6950	23100 ± 4620

Statistical Analysis

Groups	LXS196 100 mg BID +HDM201, LXS196 200 mg BID +HDM201, LXS196 300 mg BID +HDM201, LXS196 400 mg BID +HDM201	
Method	Other Power model	AUC0-12hr values were log-transformed and analyzed using a power model: ln(AUC0-12hr)= alpha+beta*ln(dose)+error.
Slope	0.50	Dose proportionality was concluded across the whole dose range if the 90% CI for the slope (beta) was completely contained within a pre-specified critical range (0.84, 1.14).
90 % Confidence Interval 2-Sided	0.13 to 0.87	

Terminal elimination half-life (T1/2) of LXS196 on Cycle 1 Day 1 (C1D1)

(Time Frame: SA arm: pre-dose, 0.5, 1, 2, 4, 6, 12 (BID dosing only), 24 and 48 hours post dose on C1D1. Combo arm: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

Single agent arm

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	2	3	15	10	1	4	6	16	5
Terminal elimination half-life (T1/2) of LXS196 on Cycle 1 Day 1 (C1D1) (units: hours) Mean ± Standard Deviation									
	8.49 ± 1.41	8.52 ± 2.01	10.8 ± 1.65	10.2 ± 1.27	8.85	10.0 ± 1.42	13.1 ± 1.76	12.1 ± 2.29	13.8 ± 2.94

Combination arm

	LXS196 100 mg BID +HDM201 (C1D1)	LXS196 200 mg BID +HDM201 (C1D1)	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	15	4	5
Terminal elimination half-life (T1/2) of LXS196 on Cycle 1 Day 1 (C1D1) (units: hours) Mean ± Standard Deviation				

	6.69 ± 0.356	7.64 ± 2.00	8.96 ± 0.852	10.3 ± 1.75

Terminal elimination half-life (T1/2) of LXS196 on Cycle 1 Day 8 (C1D1) - Combination of LXS196 and HDM201 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	1	2	2	2
Terminal elimination half-life (T1/2) of LXS196 on Cycle 1 Day 8 (C1D1) - Combination of LXS196 and HDM201 arm (units: hours) Mean ± Standard Deviation				
	4.86	8.13 ± 1.86	6.97 ± 2.69	7.08 ± 1.63

Accumulation ratio (Racc) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 6, 12 (BID dosing only), 24 and 48 hours post dose on C1D1 and pre-dose, 0.5, 1, 2, 4, 6 and 12 hours (BID dosing only) and 24 hours (QD dosing only) post dose on C1D15.)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	2	2	13	8	0	2	5	12	3

Accumulation ratio (Racc) of LXS196 on Cycle 1 Day 15 (C1D15) – Single agent LXS196 arm (units: ratio) Mean ± Standard Deviation								
	1.27 ± 0.570	0.750 ± 0.145	0.934 ± 0.307	0.793 ± 0.214	0.718 ± 0.161	1.11 ± 0.611	1.15 ± 0.403	0.738 ± 0.204

Accumulation ratio (Racc) of LXS196 on Cycle 1 Day 8 (C1D8) - Combination of LXS196 and HDM201 arm

(Time Frame: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1 and pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	**LXS196 200 mg BID +HDM201**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	1	2	2	2
Accumulation ratio (Racc) of LXS196 on Cycle 1 Day 8 (C1D8) - Combination of LXS196 and HDM201 arm (units: ratio) Mean ± Standard Deviation				
	0.987	1.49 ± 0.140	0.543 ± 0.0222	0.801 ± 0.234

Maximum observed plasma concentration (Cmax) of HDM201 on Cycle 1 Day 1 (C1D1)

(Time Frame: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201 (C1D1)	**LXS196 200 mg BID +HDM201 (C1D1)**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days

Number of Participants Analyzed [units: participants]	7	19	5	6
Maximum observed plasma concentration (Cmax) of HDM201 on Cycle 1 Day 1 (C1D1) (units: ng/mL) Mean ± Standard Deviation				
	804 ± 304	919 ± 322	705 ± 232	581 ± 110

Maximum observed plasma concentration (Cmax) of HDM201 on Cycle 1 Day 8 (C1D8)

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201 (C1D8)	LXS196 300 mg BID +HDM201 (C1D8)	LXS196 400 mg BID +HDM201 (C1D8)	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 300 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 400 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	6	10	11	6
Maximum observed plasma concentration (Cmax) of HDM201 on Cycle 1 Day 8 (C1D8) (units: ng/mL) Mean ± Standard Deviation					
	831 ± 440	777 ± 349	631 ± 219	513 ± 177	502 ± 395

Time to reach maximum plasma concentration (Tmax) of HDM201 on Cycle 1 Day 1 (C1D1)

(Time Frame: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201 (C1D1)	LXS196 200 mg BID +HDM201 (C1D1)	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on	LXS196 200 mg BID in combination with HDM201 on	LXS196 300 mg administered on a continuous BID dosing	LXS196 400 mg administered on a continuous BID dosing

	C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	7	19	5	6
Time to reach maximum plasma concentration (Tmax) of HDM201 on Cycle 1 Day 1 (C1D1) (units: hours) Median (Full Range)				
	4.00 (1.97 to 4.08)	2.02 (0.933 to 7.87)	4.00 (1.00 to 19.3)	4.09 (3.93 to 8.00)

Time to reach maximum plasma concentration (Tmax) of HDM201 on Cycle 1 Day 8 (C1D8)

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201 (C1D8)	LXS196 300 mg BID +HDM201 (C1D8)	LXS196 400 mg BID +HDM201 (C1D8)	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 300 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 400 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	4	6	10	11	6
Time to reach maximum plasma concentration (Tmax) of HDM201 on Cycle 1 Day 8 (C1D8) (units: hours) Median (Full Range)					
	3.02 (2.00 to 4.08)	4.00 (2.07 to 4.00)	3.98 (1.00 to 7.75)	4.00 (1.02 to 8.00)	0.950 (0 to 7.87)

Area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24hr) of HDM201 on Cycle 1 Day 1 (C1D1)

(Time Frame: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201 (C1D1)	LXS196 200 mg BID +HDM201 (C1D1)	LXS196 300 mg BID +HDM201	LXS196 400 mg BID +HDM201
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	7	19	5	6
Area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24hr) of HDM201 on Cycle 1 Day 1 (C1D1) (units: hr*ng/mL) Mean ± Standard Deviation				
	10000 ± 2870	11100 ± 3790	9220 ± 2210	8870 ± 2260

Area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24hr) of HDM201 on Cycle 1 Day 8 (C1D8)

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	LXS196 200 mg BID +HDM201 (C1D8)	LXS196 300 mg BID +HDM201 (C1D8)	LXS196 400 mg BID +HDM201 (C1D8)	LXS196 run-in 2 500 mg BID +HDM201
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 300 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 400 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days
Number of Participants Analyzed [units: participants]	3	6	9	10	6

Area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24hr) of HDM201 on Cycle 1 Day 8 (C1D8) (units: hr*ng/mL) Mean ± Standard Deviation					
	12400 ± 1340	10200 ± 2520	9560 ± 3270	8460 ± 3410	7160 ± 4360

Terminal elimination half-life (T1/2) of HDM201 on Cycle 1 Day 1 (C1D1)

(Time Frame: pre-dose, 0.5, 1, 2, 4, 8 and 24 hours post dose on C1D1. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201 (C1D1)	**LXS196 200 mg BID +HDM201 (C1D1)**	**LXS196 300 mg BID +HDM201**	**LXS196 400 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 1 who received LXS196 100 mg during the first 7 days of Cycle 1	LXS196 200 mg BID in combination with HDM201 on C1D1, including the patients in the run-in 2 who received LXS196 200 mg during the first 7 days of Cycle 1	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days
Number of Participants Analyzed [units: participants]	7	18	3	4
Terminal elimination half-life (T1/2) of HDM201 on Cycle 1 Day 1 (C1D1) (units: hours) Mean ± Standard Deviation				
	11.8 ± 3.61	10.9 ± 3.47	7.79 ± 1.61	15.0 ± 9.32

Terminal elimination half-life (T1/2) of HDM201 on Cycle 1 Day 8 (C1D8)

(Time Frame: pre-dose, 0.5, 1, 2, 4 and 8 hours post dose on C1D8. The duration of one cycle was 28 days.)

	LXS196 100 mg BID +HDM201	**LXS196 200 mg BID +HDM201 (C1D8)**	**LXS196 300 mg BID +HDM201 (C1D8)**	**LXS196 400 mg BID +HDM201 (C1D8)**	**LXS196 run-in 2 500 mg BID +HDM201**
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 300 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 400 mg BID in combination with HDM201 on C1D8, either treated with an initial 7-day run-in or without	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days

Number of Participants Analyzed [units: participants]	0	0	0	1	3
Terminal elimination half-life (T1/2) of HDM201 on Cycle 1 Day 8 (C1D1) (units: hours) Mean ± Standard Deviation					
				7.37	11.2 ± 3.15

Fraction of LXS196 not bound to plasma protein (free fraction, fu) - Single agent LXS196 arm

(Time Frame: Pre-dose, 6 and 24 hours post-dose on Cycle 1 Day 1 and Day 15. The duration of one cycle was 28 days.)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6
Fraction of LXS196 not bound to plasma protein (free fraction, fu) - Single agent LXS196 arm (units: percentage) Mean ± Standard Deviation									
C1D1, Pre-dose (n=0,0,0,0,0,0,0,0,0)									
C1D1, 6 hours (n=2,4,11,10,1,4,5,18,6)	0.0 ± 0.01	0.0 ± 0.02	0.0 ± 0.02	0.1 ± 0.02	0.1	0.1 ± 0.03	0.0 ± 0.00	0.0 ± 0.01	0.0 ± 0.01
C1D1, 24 hours (n=2,3,15,11,1,4,3,17,5)	0.0 ± 0.01	0.0 ± 0.01	0.0 ± 0.01	0.0 ± 0.02	0.0	0.1 ± 0.02	0.0 ± 0.02	0.0 ± 0.01	0.0 ± 0.01
C1D15, Pre-dose (n=0,0,0,0,0,0,0,0,0)									
C1D15, 6 hours (n=3,3,14,10,1,2,5,16,6)	0.0 ± 0.01	0.0 ± 0.02	0.1 ± 0.02	0.1 ± 0.01	0.1	0.1 ± 0.02	0.0 ± 0.00	0.1 ± 0.02	0.1 ± 0.01

C1D15, 24 hours (n=3,3,13,9,1,4,0,0,0)	0.0 ± 0.00	0.0 ± 0.01	0.0 ± 0.01	0.0 ± 0.01	0.1	0.0 ± 0.00

Plasma concentration of AAG protein - Single agent LXS196 arm

(Time Frame: Pre-dose on Cycle 1, Cycle 2, Cycle 3, and Cycle 4. The duration of one cycle was 28 days.)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	4	15	11	1	4	6	18	6
Plasma concentration of AAG protein - Single agent LXS196 arm (units: µg/mL) Mean ± Standard Deviation									
Cycle 1 Pre-dose (n=3,4,15,11,1,4,6,18,6)	1076.7 ± 61.10	1019.0 ± 398.70	1096.4 ± 561.70	1021.6 ± 437.50	1000.0	887.0 ± 287.50	986.5 ± 491.80	954.5 ± 396.80	852.7 ± 214.70
Cycle 2 Pre-dose (n=3,1,15,11,1,4,5,17,6)	961.0 ± 260.90	540.0	961.6 ± 406.60	899.9 ± 399.80	558.0	707.8 ± 118.20	851.6 ± 159.50	777.6 ± 201.90	718.2 ± 290.10
Cycle 3 Pre-dose (n=1,2,12,7,1,4,3,14,5)	1090.0	1254.5 ± 912.90	1044.8 ± 562.20	750.9 ± 289.20	661.0	910.0 ± 244.60	799.0 ± 52.70	789.6 ± 235.00	636.6 ± 86.10
Cycle 4 Pre-dose (n=0,3,15,11,1,4,6,18,6)		1431.7 ± 1131.70	1132.7 ± 578.70	784.4 ± 335.10	534.0	808.0 ± 148.70	937.3 ± 246.10	783.4 ± 205.10	652.2 ± 241.80

Percent change from baseline in pPKC delta normalized ratio from PBMC samples - Single agent LXS196 arm

(Time Frame: Pre-dose on Cycle 1 Day 1 (baseline) and 6 hours post-dose on Cycle 1 Day 1)

	LXS196 100 mg QD	LXS196 200 mg QD	LXS196 300 mg QD	LXS196 500 mg QD	LXS196 800 mg QD	LXS196 1000 mg QD	LXS196 200 mg BID	LXS196 300 mg BID	LXS196 400 mg BID

Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	1	3	13	8	1	3	4	12	6
Percent change from baseline in pPKC delta normalized ratio from PBMC samples - Single agent LXS196 arm (units: percentage change) Mean ± Standard Deviation									
	-50.0	-46.6 ± 18.71	-25.4 ± 92.97	-64.3 ± 16.87	-68.9	-12.6 ± 39.96	-9.2 ± 35.53	-35.3 ± 51.21	-20.3 ± 51.71

Safety Results

All-Cause Mortality

Single agent arm

	LXS196 100 mg QD N = 3	LXS196 200 mg QD N = 4	LXS196 300 mg QD N = 15	LXS196 500 mg QD N = 11	LXS196 800 mg QD N = 1	LXS196 1000 mg QD N = 4	All LXS196 QD Patients N = 38	LXS196 200 mg BID N = 6	LXS196 300 mg BID N = 18	LXS196 400 mg BID N = 6	All LXS196 BID Patients N = 30	All LXS196 SA Patients N = 68
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	All LXS196 once daily (QD) patients	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)	All LXS196 twice daily (BID) patients	All LXS196 single agent (SA) patients
Total participants affected	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	3 (16.67%)	0 (0.00%)	4 (13.33%)	5 (7.35%)

Combination arm

	LXS196 100 mg BID +HDM201 N = 4	LXS196 200 mg BID +HDM201 N = 3	LXS196 30 0mg BID +HDM201 N = 5	LXS196 400 mg BID +HDM201 N = 6	All patients without run-in N = 18	LXS196 run-in 1 200 mg BID +HDM201 N = 3	LXS196 run-in 2 300 mg BID +HDM201 N = 6	LXS196 run-in 2 400 mg BID +HDM201 N = 6	LXS196 run-in 2 500 mg BID +HDM201 N = 6	All patients with run-in N = 21	All combo patients N = 39
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	All LXS196+HDM201 patients without run-in	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	All LXS196+HDM201 patients with run-in	All LXS196+HDM201 patients
Total participants affected	1 (25.00 %)	1 (33.33 %)	1 (20.00 %)	1 (16.67 %)	4 (22.22%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	1 (4.76%)	5 (12.82%)

Serious Adverse Events by System Organ Class

Time Frame	From first dose of study medication up to 30 days after last dose, with a maximum duration of 5 years for LXS196 single agent arm and 1.6 years for the LXS196+HDM201 arm
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days after last dose.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment

Single agent arm

	LXS196 100 mg QD N = 3	LXS196 200 mg QD N = 4	LXS196 300 mg QD N = 15	LXS196 500 mg QD N = 11	LXS196 800 mg QD N = 1	LXS196 1000 mg QD N = 4	All LXS196 QD Patients N = 38	LXS196 200 mg BID N = 6	LXS196 300 mg BID N = 18	LXS196 400 mg BID N = 6	All LXS196 BID Patients N = 30	All LXS196 SA Patients N = 68
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	All LXS196 once daily (QD) patients	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)	All LXS196 twice daily (BID) patients	All LXS196 single agent (SA) patients
Total participants affected	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	3 (27.27 %)	1 (100.00 %)	2 (50.00 %)	7 (18.42 %)	1 (16.67 %)	5 (27.78 %)	1 (16.67 %)	7 (23.33 %)	14 (20.59 %)
Blood and lymphatic system disorders												
Pancytopenia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thrombocytopenia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)

Eye disorders												
Eyelid bleeding	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Gastrointestinal disorders												
Abdominal pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Constipation	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Diarrhoea	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Nausea	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Vomiting	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
General disorders and administration site conditions												
Fatigue	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General physical health deterioration	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Malaise	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema peripheral	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Pyrexia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Hepatobiliary disorders												
Hepatic cytolysis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Hepatic failure	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Infections and infestations												
Cellulitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Gastrointestinal infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes simplex	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (25.00 %)	2 (5.26%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	3 (4.41%)
Sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications												
Overdose	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations												
Neutrophil count decreased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Platelet count decreased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign,												

malignant and unspecified (incl cysts and polyps)												
Malignant neoplasm progression	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tumour pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders												
Acute kidney injury	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Respiratory, thoracic and mediastinal disorders												
Haemoptysis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders												
Rash pruritic	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Vascular disorders												
Hypotension	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	3 (27.27 %)	1 (100.00 %)	1 (25.00 %)	5 (13.16 %)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	1 (3.33%)	6 (8.82%)

Combination arm

	LXS196 100 mg BID +HDM201 N = 4	LXS196 200 mg BID +HDM201 N = 3	LXS196 30 0mg BID +HDM201 N = 5	LXS196 400 mg BID +HDM201 N = 6	All patients without run-in N = 18	LXS196 run-in 1 200 mg BID +HDM201 N = 3	LXS196 run-in 2 300 mg BID +HDM201 N = 6	LXS196 run-in 2 400 mg BID +HDM201 N = 6	LXS196 run-in 2 500 mg BID +HDM201 N = 6	All patients with run-in N = 21	All combo patients N = 39
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	All LXS196+HDM201 patients without run-in	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	All LXS196+HDM201 patients with run-in	All LXS196+HDM201 patients
Total participants affected	0 (0.00%)	2 (66.67%)	3 (60.00%)	3 (50.00%)	8 (44.44%)	0 (0.00%)	3 (50.00%)	3 (50.00%)	1 (16.67%)	7 (33.33%)	15 (38.46%)
Blood and lymphatic system disorders											
Pancytopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Thrombocytopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	2 (9.52%)	2 (5.13%)

Eye disorders											
Eyelid bleeding	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders											
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	2 (5.13%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Vomiting	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	3 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7.69%)
General disorders and administration site conditions											
Fatigue	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (9.52%)	2 (5.13%)
Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Pyrexia	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Hepatobiliary disorders											
Hepatic cytolysis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Hepatic failure	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Infections and infestations											
Cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Herpes simplex	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Injury, poisoning and procedural complications											
Overdose	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Investigations											
Neutrophil count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Platelet count decreased	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)											
Malignant neoplasm progression	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Tumour pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Renal and urinary disorders											
Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders											
Haemoptysis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Skin and subcutaneous tissue disorders											
Rash pruritic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders											
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (9.52%)	4 (10.26%)

Other Adverse Events by System Organ Class

Time Frame	From first dose of study medication up to 30 days after last dose, with a maximum duration of 5 years for LXS196 single agent arm and 1.6 years for the LXS196+HDM201 arm
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days after last dose.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

Single agent arm

	LXS196 100 mg QD N = 3	**LXS196 200 mg QD N = 4**	**LXS196 300 mg QD N = 15**	**LXS196 500 mg QD N = 11**	**LXS196 800 mg QD N = 1**	**LXS196 1000 mg QD N = 4**	**All LXS196 QD Patients N = 38**	**LXS196 200 mg BID N = 6**	**LXS196 300 mg BID N = 18**	**LXS196 400 mg BID N = 6**	**All LXS196 BID Patients N = 30**	**All LXS196 SA Patients N = 68**
Arm/Group Description	LXS196 100 mg once daily (QD)	LXS196 200 mg once daily (QD)	LXS196 300 mg once daily (QD)	LXS196 500 mg once daily (QD)	LXS196 800 mg once daily (QD)	LXS196 1000 mg once daily (QD)	All LXS196 once daily (QD) patients	LXS196 200 mg twice daily (BID)	LXS196 300 mg twice daily (BID)	LXS196 400 mg twice daily (BID)	All LXS196 twice daily (BID) patients	All LXS196 single agent (SA) patients
Total participants affected	3 (100.0 0%)	4 (100.0 0%)	14 (93.3 3%)	10 (90.9 1%)	1 (100.0 0%)	4 (100.0 0%)	36 (94.7 4%)	6 (100.0 0%)	18 (100.0 0%)	6 (100.0 0%)	30 (100.0 0%)	66 (97.0 6%)
Blood and lymphatic system disorders												
Anaemia	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	2 (11.11 %)	0 (0.00%)	2 (6.67%)	4 (5.88%)
Leukopenia	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)

Neutropenia	0 (0.00%)	0 (0.00%)	3 (20.00%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	5 (13.16%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (6.67%)	7 (10.29%)
Thrombocytopenia	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Cardiac disorders												
Sinus bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Ear and labyrinth disorders												
Deafness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Middle ear inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Endocrine disorders												
Hypothyroidism	1 (33.33%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)
Eye disorders												
Blepharitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Cataract	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Conjunctivitis allergic	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Dry eye	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)

Eczema eyelids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Eye inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Eye irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Keratitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Ocular hyperaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Ocular hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Periorbital oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Retinal detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Visual acuity reduced	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitreous detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders												
Abdominal distension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Abdominal pain	1 (33.33%)	1 (25.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	3 (10.00%)	6 (8.82%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	2 (13.33%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	4 (10.53%)	0 (0.00%)	3 (16.67%)	0 (0.00%)	3 (10.00%)	7 (10.29%)
Anal fissure	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)

Ascites	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	2 (6.67%)	2 (2.94%)
Constipation	1 (33.33%)	2 (50.00%)	4 (26.67%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	9 (23.68%)	1 (16.67%)	4 (22.22%)	2 (33.33%)	7 (23.33%)	16 (23.53%)
Diarrhoea	2 (66.67%)	2 (50.00%)	6 (40.00%)	4 (36.36%)	1 (100.00%)	4 (100.00%)	19 (50.00%)	3 (50.00%)	11 (61.11%)	3 (50.00%)	17 (56.67%)	36 (52.94%)
Dry mouth	0 (0.00%)	1 (25.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.41%)
Dyspepsia	0 (0.00%)	1 (25.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	1 (5.56%)	2 (33.33%)	4 (13.33%)	6 (8.82%)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Gastritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)
Gingival pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Lip dry	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Mouth ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	2 (66.67%)	2 (50.00%)	10 (66.67%)	8 (72.73%)	1 (100.00%)	4 (100.00%)	27 (71.05%)	3 (50.00%)	15 (83.33%)	3 (50.00%)	21 (70.00%)	48 (70.59%)
Odynophagia	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Stomatitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)

Vomiting	2 (66.67 %)	2 (50.00 %)	6 (40.00 %)	5 (45.45 %)	0 (0.00%)	0 (0.00%)	15 (39.47%)	0 (0.00%)	8 (44.44 %)	3 (50.00 %)	11 (36.67 %)	26 (38.24%)
General disorders and administration site conditions												
Asthenia	0 (0.00%)	1 (25.00 %)	3 (20.00 %)	4 (36.36 %)	0 (0.00%)	0 (0.00%)	8 (21.05 %)	1 (16.67 %)	4 (22.22 %)	2 (33.33 %)	7 (23.33 %)	15 (22.06%)
Face oedema	1 (33.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Fatigue	0 (0.00%)	0 (0.00%)	8 (53.33 %)	1 (9.09%)	0 (0.00%)	3 (75.00 %)	12 (31.58%)	0 (0.00%)	6 (33.33 %)	1 (16.67 %)	7 (23.33 %)	19 (27.94%)
Feeling cold	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Generalised oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	1 (3.33%)	1 (1.47%)
Hyperplasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00 %)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Influenza like illness	2 (66.67 %)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	2 (50.00 %)	5 (13.16 %)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	1 (3.33%)	6 (8.82%)
Malaise	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Oedema peripheral	1 (33.33 %)	1 (25.00 %)	2 (13.33 %)	1 (9.09%)	0 (0.00%)	0 (0.00%)	5 (13.16 %)	2 (33.33 %)	4 (22.22 %)	1 (16.67 %)	7 (23.33 %)	12 (17.65%)
Pyrexia	0 (0.00%)	0 (0.00%)	2 (13.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	3 (4.41%)
Terminal agitation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Xerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)

Hepatobiliary disorders												
Biliary tract disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Cholestasis	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Hepatic cytolysis	0 (0.00%)	0 (0.00%)	1 (6.67%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	4 (5.88%)
Hepatic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders												
Hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Seasonal allergy	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Infections and infestations												
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	2 (6.67%)	3 (4.41%)
Cystitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Eye infection	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Folliculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Gastroenteritis viral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)

Herpes zoster	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Klebsiella bacteraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	3 (20.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	4 (10.53%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	3 (10.00%)	7 (10.29%)
Onychomycosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral herpes	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Oral infection	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Periodontitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Peritonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash pustular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Rhinitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (6.67%)	2 (2.94%)

Urinary tract infection	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Vulvovaginal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Vulvovaginal mycotic infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Injury, poisoning and procedural complications												
Foot fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Joint injury	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Ligament sprain	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Investigations												
Alanine aminotransferase increased	0 (0.00%)	1 (25.00%)	4 (26.67%)	3 (27.27%)	0 (0.00%)	1 (25.00%)	9 (23.68%)	1 (16.67%)	5 (27.78%)	3 (50.00%)	9 (30.00%)	18 (26.47%)
Amylase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	2 (2.94%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	1 (6.67%)	4 (36.36%)	0 (0.00%)	0 (0.00%)	5 (13.16%)	1 (16.67%)	4 (22.22%)	3 (50.00%)	8 (26.67%)	13 (19.12%)
Bilirubin conjugated increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)

Blood alkaline phosphatase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (6.67%)	5 (7.35%)
Blood bilirubin increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	1 (5.56%)	1 (16.67%)	3 (10.00%)	5 (7.35%)
Blood creatinine increased	0 (0.00%)	1 (25.00%)	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	3 (50.00%)	2 (11.11%)	0 (0.00%)	5 (16.67%)	8 (11.76%)
Blood lactate dehydrogenase increased	0 (0.00%)	0 (0.00%)	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)
Blood prolactin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Blood thyroid stimulating hormone increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Electrocardiogram QT prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eosinophil count increased	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Gamma-glutamyltransferase increased	0 (0.00%)	1 (25.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	2 (6.67%)	4 (5.88%)
Lipase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	2 (2.94%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Neutrophil count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	2 (6.67%)	3 (4.41%)
Nitrite urine	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Platelet count decreased	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Protein total abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Transaminases increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight decreased	0 (0.00%)	0 (0.00%)	2 (13.33%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	4 (5.88%)
Weight increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	2 (33.33%)	3 (10.00%)	4 (5.88%)
White blood cell count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders												
Decreased appetite	0 (0.00%)	1 (25.00%)	0 (0.00%)	4 (36.36%)	0 (0.00%)	0 (0.00%)	5 (13.16%)	1 (16.67%)	2 (11.11%)	2 (33.33%)	5 (16.67%)	10 (14.71%)
Hypercalcaemia	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (6.67%)	4 (5.88%)
Hypercreatininaemia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)
Hyperlipasaemia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Hypocalcaemia	0 (0.00%)	1 (25.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	4 (5.88%)

Hypophosphataemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders												
Arthralgia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	2 (11.11%)	1 (16.67%)	4 (13.33%)	6 (8.82%)
Back pain	0 (0.00%)	0 (0.00%)	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	1 (5.56%)	1 (16.67%)	2 (6.67%)	4 (5.88%)
Bone pain	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Flank pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Groin pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscular weakness	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myalgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	2 (6.67%)	2 (2.94%)
Pain in extremity	0 (0.00%)	2 (50.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	4 (5.88%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)												

Bowen's disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Cancer pain	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Parathyroid tumour benign	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Tumour pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Nervous system disorders												
Dizziness	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	1 (25.00%)	3 (7.89%)	1 (16.67%)	1 (5.56%)	1 (16.67%)	3 (10.00%)	6 (8.82%)
Dizziness postural	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Dysaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Dysgeusia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	1 (5.56%)	1 (16.67%)	3 (10.00%)	4 (5.88%)
Hypergeusia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Nervous system disorder	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Neuralgia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Post herpetic neuralgia	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Presyncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	3 (4.41%)

Sciatica	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Psychiatric disorders												
Anxiety	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (6.67%)	3 (4.41%)
Claustrophobia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	2 (2.94%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (6.67%)	3 (4.41%)
Panic attack	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Renal and urinary disorders												
Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Chromaturia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Chronic kidney disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Pollakiuria	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)

Proteinuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Renal vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders												
Amenorrhoea	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Scrotal oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Respiratory, thoracic and mediastinal disorders												
Cough	0 (0.00%)	0 (0.00%)	2 (13.33%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	3 (7.89%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	3 (10.00%)	6 (8.82%)
Dysphonia	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (25.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Hypoxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Oropharyngeal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleural effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleuritic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rhinitis allergic	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Rhinorrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Skin and subcutaneous tissue disorders												
Acne	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (5.26%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (6.67%)	4 (5.88%)
Alopecia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (6.67%)	2 (2.94%)
Butterfly rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Dermatitis acneiform	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	3 (16.67%)	1 (16.67%)	5 (16.67%)	7 (10.29%)
Dermatitis exfoliative generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Dry skin	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (9.09%)	0 (0.00%)	1 (25.00%)	3 (7.89%)	1 (16.67%)	4 (22.22%)	1 (16.67%)	6 (20.00%)	9 (13.24%)
Ecchymosis	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)

Eczema	0 (0.00%)	0 (0.00%)	2 (13.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.94%)
Eosinophilic cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	2 (2.94%)
Hair colour changes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ingrowing nail	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Lichenoid keratosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail ridging	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Night sweats	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Onycholysis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Petechiae	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Photosensitivity reaction	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Prurigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (18.18%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	3 (16.67%)	1 (16.67%)	4 (13.33%)	6 (8.82%)
Rash	0 (0.00%)	0 (0.00%)	4 (26.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (10.53%)	0 (0.00%)	5 (27.78%)	1 (16.67%)	6 (20.00%)	10 (14.71%)

Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Rash papular	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Rash vesicular	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Rosacea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Skin depigmentation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Skin lesion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (3.33%)	1 (1.47%)
Transient acantholytic dermatosis	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)
Vitiligo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (3.33%)	1 (1.47%)
Vascular disorders												
Aortic aneurysm	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hot flush	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (6.67%)	4 (5.88%)
Hypertension	0 (0.00%)	1 (25.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	2 (6.67%)	4 (5.88%)
Hypotension	0 (0.00%)	0 (0.00%)	1 (6.67%)	2 (18.18%)	1 (100.00%)	1 (25.00%)	5 (13.16%)	0 (0.00%)	3 (16.67%)	3 (50.00%)	6 (20.00%)	11 (16.18%)
Phlebitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.47%)

Superficial vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Combination arm

	LXS196 100 mg BID +HDM201 N = 4	**LXS196 200 mg BID +HDM201 N = 3**	**LXS196 30 0mg BID +HDM201 N = 5**	**LXS196 400 mg BID +HDM201 N = 6**	**All patients without run-in N = 18**	**LXS196 run-in 1 200 mg BID +HDM201 N = 3**	**LXS196 run-in 2 300 mg BID +HDM201 N = 6**	**LXS196 run-in 2 400 mg BID +HDM201 N = 6**	**LXS196 run-in 2 500 mg BID +HDM201 N = 6**	**All patients with run-in N = 21**	**All combo patients N = 39**
Arm/Group Description	LXS196 100 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 200 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 300 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	LXS196 400 mg administered on a continuous BID dosing schedule in combination with HDM201 100 mg on Day 1 and Day 8 of every 28 days	All LXS196+HDM201 patients without run-in	LXS196 100 mg BID for the first 7 days of Cycle 1 (run-in 1) and then from Cycle 1 Day 8 onwards LXS196 200 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 300 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 400 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	LXS196 200 mg BID for the first 7 days of Cycle 1 (run-in 2) and then from Cycle 1 Day 8 onwards LXS196 500 mg BID in combination with HDM201 100 mg on Days 1 and 8 of every 28 days	All LXS196+HDM201 patients with run-in	All LXS196+HDM201 patients
Total participants affected	4 (100.00%)	3 (100.00%)	5 (100.00%)	6 (100.00%)	18 (100.00%)	3 (100.00%)	6 (100.00%)	6 (100.00%)	6 (100.00%)	21 (100.00%)	39 (100.00%)
Blood and lymphatic											

system disorders											
Anaemia	0 (0.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	4 (22.22%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	3 (14.29%)	7 (17.95%)
Leukopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (9.52%)	4 (10.26%)
Thrombocytopenia	0 (0.00%)	1 (33.33%)	1 (20.00%)	1 (16.67%)	3 (16.67%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	2 (9.52%)	5 (12.82%)
Cardiac disorders											
Sinus bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders											
Deafness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Middle ear inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endocrine disorders											
Hypothyroidism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders											
Blepharitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Cataract	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Conjunctivitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry eye	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eczema eyelids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Keratitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ocular hyperaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ocular hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Periorbital oedema	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	2 (5.13%)
Retinal detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Visual acuity reduced	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Vitreous detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Gastrointestinal disorders											
Abdominal distension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	1 (2.56%)

Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (9.52%)	2 (5.13%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	2 (9.52%)	2 (5.13%)
Anal fissure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ascites	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Constipation	0 (0.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	3 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7.69%)
Diarrhoea	0 (0.00%)	0 (0.00%)	2 (40.00%)	4 (66.67%)	6 (33.33%)	2 (66.67%)	2 (33.33%)	4 (66.67%)	5 (83.33%)	13 (61.90%)	19 (48.72%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	1 (2.56%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	2 (5.13%)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gingival pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lip dry	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth ulceration	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)

Nausea	4 (100.0 0%)	2 (66.67 %)	5 (100.0 0%)	6 (100.0 0%)	17 (94.44%)	2 (66.67 %)	6 (100.0 0%)	4 (66.67 %)	6 (100.0 0%)	18 (85.71%)	35 (89.74%)
Odynophagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Stomatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vomiting	4 (100.0 0%)	0 (0.00%)	3 (60.00 %)	5 (83.33 %)	12 (66.67%)	0 (0.00%)	5 (83.33 %)	4 (66.67 %)	3 (50.00 %)	12 (57.14%)	24 (61.54%)
General disorders and administration site conditions											
Asthenia	1 (25.00 %)	1 (33.33 %)	2 (40.00 %)	1 (16.67 %)	5 (27.78%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	0 (0.00%)	1 (4.76%)	6 (15.38%)
Face oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	1 (25.00 %)	3 (100.0 0%)	2 (40.00 %)	2 (33.33 %)	8 (44.44%)	2 (66.67 %)	2 (33.33 %)	0 (0.00%)	0 (0.00%)	4 (19.05%)	12 (30.77%)
Feeling cold	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Generalised oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperplasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza like illness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67 %)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Malaise	1 (25.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (33.33 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Non-cardiac chest pain	0 (0.00%)	1 (33.33 %)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33 %)	2 (11.11%)	1 (33.33 %)	1 (16.67 %)	0 (0.00%)	2 (33.33 %)	4 (19.05%)	6 (15.38%)

Pyrexia	0 (0.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	4 (22.22%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	5 (12.82%)
Terminal agitation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Xerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders											
Biliary tract disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholestasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Hepatic cytolysis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	1 (2.56%)
Immune system disorders											
Hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Seasonal allergy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations											
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Folliculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroenteritis viral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	3 (7.69%)
Klebsiella bacteraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Onychomycosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Oral candidiasis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Oral herpes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Periodontitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peritonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Rash pustular	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Rhinitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Upper respiratory tract infection	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.13%)
Vulvovaginal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vulvovaginal mycotic infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications											
Foot fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Joint injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ligament sprain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations											
Alanine aminotransferase increased	1 (25.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	5 (27.78%)	1 (33.33%)	2 (33.33%)	0 (0.00%)	2 (33.33%)	5 (23.81%)	10 (25.64%)
Amylase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aspartate aminotransferase increased	1 (25.00%)	1 (33.33%)	1 (20.00%)	2 (33.33%)	5 (27.78%)	1 (33.33%)	3 (50.00%)	0 (0.00%)	2 (33.33%)	6 (28.57%)	11 (28.21%)

Bilirubin conjugated increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Blood bilirubin increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (9.52%)	3 (7.69%)
Blood lactate dehydrogenase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood prolactin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood thyroid stimulating hormone increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Electrocardiogram QT prolonged	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Eosinophil count increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	1 (2.56%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Lipase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Neutrophil count decreased	1 (25.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	4 (22.22%)	1 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (9.52%)	6 (15.38%)
Nitrite urine	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Platelet count decreased	2 (50.00%)	1 (33.33%)	0 (0.00%)	1 (16.67%)	4 (22.22%)	2 (66.67%)	2 (33.33%)	1 (16.67%)	0 (0.00%)	5 (23.81%)	9 (23.08%)
Protein total abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transaminases increased	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Weight decreased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	3 (14.29%)	4 (10.26%)
Weight increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
White blood cell count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Metabolism and nutrition disorders											
Decreased appetite	0 (0.00%)	1 (33.33%)	1 (20.00%)	3 (50.00%)	5 (27.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (50.00%)	3 (14.29%)	8 (20.51%)
Hypercalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Hypercreatinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperlipasaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Hypocalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Hypophosphataemia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Musculoskeletal and connective tissue disorders											
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	2 (5.13%)
Back pain	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (9.52%)	3 (7.69%)
Bone pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Flank pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Groin pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Myalgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in extremity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)											

Bowen's disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cancer pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Parathyroid tumour benign	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tumour pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders											
Dizziness	0 (0.00%)	0 (0.00%)	2 (40.00%)	1 (16.67%)	3 (16.67%)	2 (66.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	3 (14.29%)	6 (15.38%)
Dizziness postural	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysgeusia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.13%)
Headache	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	3 (7.69%)
Hypergeusia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neuralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post herpetic neuralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Presyncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	1 (2.56%)

Sciatica	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders											
Anxiety	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Claustrophobia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Depression	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Panic attack	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders											
Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Chromaturia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic kidney disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)

Proteinuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal failure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Reproductive system and breast disorders											
Amenorrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Scrotal oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders											
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (11.11%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (9.52%)	4 (10.26%)
Dysphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	2 (9.52%)	2 (5.13%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Hypoxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Nasal congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.13%)

Oropharyngeal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Pleural effusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Pleuritic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Rhinitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rhinorrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders											
Acne	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alopecia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Butterfly rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dermatitis acneiform	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	0 (0.00%)	3 (50.00%)	1 (16.67%)	4 (19.05%)	6 (15.38%)
Dermatitis exfoliative generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry skin	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (5.13%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)

Eosinophilic cellulitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hair colour changes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Hyperhidrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	2 (5.13%)
Ingrowing nail	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lichenoid keratosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Nail discolouration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Nail ridging	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Night sweats	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Onycholysis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Petechiae	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Photosensitivity reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Prurigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus	0 (0.00%)	0 (0.00%)	2 (40.00%)	3 (50.00%)	5 (27.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	6 (15.38%)
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (5.56%)	1 (33.33%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (9.52%)	3 (7.69%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Rash papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash vesicular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rosacea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin depigmentation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin lesion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transient acantholytic dermatosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitiligo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders											
Aortic aneurysm	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.56%)
Hot flush	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	2 (11.11%)	0 (0.00%)	2 (33.33%)	1 (16.67%)	3 (50.00%)	6 (28.57%)	8 (20.51%)
Phlebitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Superficial vein thrombosis	0 (0.00%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)

Conclusion:

LXS196 has a tendency to have higher exposure when given in combination with HDM201 when compared to single-agent LXS196, but no conclusion of drug-drug interaction (DDI) could be drawn. The combination of LXS196 and HDM201 was found to be safe and AEs manageable with some events requiring drug interruption or dose reduction.

The MTDs were declared as follows:

- without run-in: LXS196 300 mg BID + HDM201 100 mg (Day 1 and Day 8 of every 28 days).
- with run-in: LXS196 400 mg BID + HDM201 100 mg (Day 1 and Day 8 of every 28 days) where run-in dose was 200 mg BID LXS196 given for the first 7 days of cycle 1.

Based on the objective response (CR + PR), LXS196 in combination with HDM201 showed limited anti-tumor activity relative to LXS196 as a single agent in subjects with metastatic uveal melanoma. The enrollment in the combination arm was halted and the dose expansion part was not opened based on the limited clinical activity observed in the preliminary data collected during the dose escalation part of the study.

Date of Clinical Trial Report

27-Jul-2022