NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Naporafenib (LXH254) and spartalizumab (PDR001)

Trial Indication(s)

Advanced solid tumors harboring MAPK pathway alterations

Protocol Number

CLXH254X2101

Protocol Title

A phase I dose finding study of oral LXH254 in adult patients with advanced solid tumors harboring MAPK pathway alterations

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1 (naporafenib) and Phase 3 (spartalizumab)

Study Start/End Dates

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

Reason for Termination

On 04-September-2018, Novartis decided to halt enrollment in all the planned expansion treatment groups of the naporafenib single agent arm. The enrollment halt was not a consequence of any safety concern, and treatment of ongoing patients participating in the study continued according to the protocol.

On 11-August-2020, Novartis decided to halt the enrollment into the study after careful evaluation of the data collected during the naporafenib in combination with spartalizumab expansion study part, and in consideration of the rapidly evolving competitive landscape. The halt was not a consequence of any safety concerns. Ongoing patients at the time of this enrollment halt continued receiving treatment under the CLXH254X2101 trial until permanent discontinuation or were discontinued from CLXH254X2101 trial and rolled over to the CPDRX001X2X01b trial.

The patient enrolment decisions taken on 04-September-2018 and 11-August-2020 resulted in an early study termination. The Sponsor´s decision was not based on any safety/tolerability concerns for naporafenib or any of the naporafenib-based combinations in the explored indications. These decisions were communicated to Investigators and notified to the HAs as applicable. The global LPLV occurred on 19-Feb-2022 and the study early termination was notified to Investigators and HAs as applicable.

Study Design/Methodology

This was a Phase I, open-label, dose finding study with a dose escalation part and a dose expansion part in adult patients with advanced solid tumors harboring documented mitogen-activated protein kinase (MAPK) pathway alterations.

The dose escalation part included two study arms: naporafenib single agent (single agent arm) and naporafenib in combination with spartalizumab (combination arm). The dose escalation for naporafenib single agent and dose level of naporafenib selected for combination treatment with spartalizumab was guided by Bayesian hierarchical logistic regression models (BHLRM). A separate 5-parameter adaptive Bayesian logistic regression model (BLRM), guided by the Escalation with overdose control (EWOC) principle was used to make dose recommendations and estimate the maximum tolerated dose/recommended dose for expansion (MTD/RDE) of naporafenib in combination with spartalizumab.

The dose expansion part was planned to include two study arms, one for naporafenib single agent treatment and another for naporafenib in combination with spartalizumab treatment. According to the decision made on 04-Sep-2018, the dose expansion part for naporafenib single agent was not opened. The dose expansion part for naporafenib in combination with spartalizumab enrolled patients with KRAS-mutated non-small cell lung cancer (NSCLC) and NRAS-mutated melanoma.

Centers

18 centers in 10 countries: Canada(1), United States(3), Netherlands(2), Japan(1), Germany(1), Spain(3), Korea, Republic of(1), Switzerland(1), France(2), Italy(3)

Objectives:

The primary objectives of the trial were:

- To characterize safety and tolerability of naporafenib single agent and identify a recommended dose and regimen for future studies in adult patients with advanced solid tumors harboring MAPK pathway alterations
- To characterize safety and tolerability of naporafenib in combination with spartalizumab and identify a recommended dose and regimen for future studies in adult patients with advanced NSCLC harboring KRAS mutations and NRAS-mutated melanoma

The secondary objectives were:

- To evaluate the preliminary anti-tumor activity of LXH254 single agent and naporafenib in combination with spartalizumab
- To evaluate the pharmacokinetic (PK) profile of naporafenib as single agent or in combination with spartalizumab and spartalizumab in combination with naporafenib
- To assess the pharmacodynamic (PD) effect of naporafenib single agent and naporafenib in combination with spartalizumab

- To assess emergence of anti-spartalizumab antibodies following one or more intravenous (i.v.) infusions of spartalizumab

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

Endpoint	Description
Primary: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) during the on-treatment period	Number of participants with AEs and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs. The on-treatment period is defined as the period from day of first dose of study treatment to 30 days after last dose of any study medication.
Primary: Number of participants with Dose-Limiting Toxicities (DLTs) (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 28 days (first cycle) of treatment with LXH254 single agent or within the first 56 days (first 2 cycles) of treatment with LXH254 in combination with PDR001 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.
Primary: Number of participants with dose reductions and dose interruptions of LXH254	Number of participants with at least one dose reduction of LXH254 and number of participants with at least one dose interruption of LXH254.
Primary: Average number of dose reductions and dose interruptions of LXH254 per participant	Average number of dose reductions of LXH254 per participant and average number of dose interruptions of LXH254 per participant.

Primary: Dose intensity of LXH254	Dose intensity of LXH254 was calculated as actual cumulative dose in milligrams divided by duration of exposure in days.
Primary: Number of participants with dose reductions and dose interruptions of PDR001	Number of participants with at least one dose reduction of PDR001 and number of participants with at least one dose interruption of PDR001. Dose reductions were not permitted for PDR001.
Primary: Average number of dose interruptions of PDR001 per participant	Dose intensity of PDR001 was calculated as actual cumulative dose in milligrams divided by duration of exposure in days.
Primary: Dose intensity of PDR001	Number of participants with at least one dose reduction of PDR001 and number of participants with at least one dose interruption of PDR001. Dose reductions were not permitted for PDR001.
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: Disease Control Rate (DCR) per RECIST v1.1	Tumor response was based on local investigator assessment as per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. DCR per RECIST v1.1 is defined as the percentage of participants with a best overall response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD).

Secondary: Duration of Response (DOR) per RECIST v1.1	DOR only applies to patients for whom best overall response is complete response (CR) or partial response (PR) based on local investigator assessment of overall lesion response according to RECIST v1.1. DOR is defined as the time from the date of first documented response (CR or PR) to the date of first documented disease progression or death due to any cause.
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 or death due to any cause. If a patient had not had an event, PFS was censored at the date of last adequate tumor assessment. PFS was estimated using the Kaplan-Meier Method.
Secondary: Overall Response Rate (ORR) per IrRC (Combination arm only)	Tumor response was based on local investigator assessment as per immune-related Response Criteria (irRC). ORR per irRC is defined as the percentage of participants with a best overall response of immune-related Complete Response (irCR) or immune-related Partial Response (irPR).
Secondary: Disease Control Rate (DCR) per per IrRC (Combination arm only)	Tumor response was based on local investigator assessment as per immune-related Response Criteria (irRC). DCR per IrRC is defined as the percentage of participants with a best overall response of immune-related Complete Response (irCR), immune-related Partial Response (irPR) or immune-related Stable Disease (irSD).

Secondary: Duration of Response (DOR) per IrRC (Combination arm only)	DOR only applies to patients for whom best overall response is immune-related complete response (irCR) or immune-related partial response (irPR) based on local investigator assessment of overall lesion response according to IrRC. DOR is defined as the time from the date of first documented response (irCR or irPR) to the date of first documented disease progression or death due to any cause.
Secondary: Progression-Free Survival (PFS) per IrRC (Combination arm only)	PFS is defined as the time from the date of start of treatment to the date of the first documented and confirmed progression or death due to any cause. If a patient had not had an event, PFS was censored at the date of last adequate tumor assessment. PFS was estimated using the Kaplan-Meier Method.
Secondary: Overall Survival (OS) (Dose expansion only)	OS is defined as the time from date of start of treatment to date of death due to any cause. If a patient was not known to have died, OS time was censored at the date of last contact. OS was estimated using the Kaplan-Meier Method.
Secondary: PK parameters (Cmax, Tmax, AUC0-last) of naporafenib in plasma	PK parameters were calculated based on naporafenib (LXH254) plasma concentrations by using non-compartmental methods. Dosing on Cycle 1 Day 2 was omitted to allow for 48 hours PK sampling. For BID dosing only the morning dose was administered on Cycle 1 Day 1. The duration of each treatment cycle was 28 days.

Secondary: PK parameters (Cmax, Tmax, AUC0-last) of spartalizumab in serum (Dose escalation only)	PK parameters were calculated based on spartalizumab (PDR001) serum concentrations by using non-compartmental methods. The duration of each treatment cycle was 28 days.
Secondary: Percentage change from baseline in relative quantity of DUSP6 in tumor tissue (Single agent arm only)	Tumor specimens were assessed for changes in expression of dual specificity phosphatase 6 (DUSP6) mRNA following treatment.
Secondary: Percentage change from baseline in relative quantity of DUSP6 in blood samples	Blood samples were assessed for changes in expression of dual specificity phosphatase 6 (DUSP6) mRNA following treatment.
Secondary: Number of participants with anti-drug antibodies (ADA) against PDR001	Immunogenicity was evaluated in serum in a validated three-tiered assay approach. Patient ADA status was defined as follows: • ADA-negative at baseline: ADA-negative sample at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline determinant sample, all of which are ADA-negative samples • Treatment-induced ADA-positive = ADA-negative sample at baseline and at least 1 treatment-induced ADA-positive sample • Treatment-boosted ADA-positive = ADA-positive sample at baseline and at least 1 treatment-boosted ADA-positive sample

	• Treatment-unaffected ADA-positive = ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least 1 treatment unaffected ADA-positive sample • Treatment-reduced ADA-positive = ADA-positive sample at baseline and at least 1 post baseline determinant sample, all of which are ADA-negative samples

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

The study treatment was naporafenib (LXH254) administered as a single agent and in combination with spartalizumab (PDR001).

Dose escalation part

In the single agent arm, naporafenib was administered orally on a continuous dosing schedule either once daily (QD) or twice daily (BID). There were six dose levels (100, 200, 300, 400, 800 and 1200 mg) assessed with the QD regimen and four dose levels (200, 400, 600 and 800 mg) assessed with the BID regimen. The duration of a treatment cycle was 28 days.

In the combination arm of naporafenib and spartalizumab, naporafenib was administered orally on a continuous BID dosing schedule at dose levels of 400 and 600 mg in combination with spartalizumab 400 mg administered on Day 1 of every 28 days via intravenous infusion.

In all arms, dosing of naporafenib on Cycle 1 Day 2 was omitted to allow for 48 hours PK sampling. For BID dosing only the morning dose was administered on Cycle 1 Day 1.

Dose expansion part

Naporafenib 400 mg was administered orally on a continuous BID dosing schedule in combination with spartalizumab 400 mg administered on Day 1 of every 28 days via intravenous infusion.

The study treatment was taken until patients experienced unacceptable toxicity, progressive disease and/or treatment was discontinued at the discretion of the investigator or the patient or due to withdrawal of consent.

Statistical Methods

The endpoints for the primary objective in characterize safety and tolerability of naporafenib single agent and naporafenib in combination with spartalizumab included: incidence of DLT for dose escalation, incidence of AEs, SAEs as mentioned in safety assessments and dose interruptions, reductions, and dose intensity.

Separate adaptive Bayesian models guided by the escalation with overdose control (EWOC) principle were applied for the DLT analyses in each dose escalation part and the estimation of the maximum tolerated dose/recommended dose for expansion (MTD/RDE) using the Dose Determining Set for the single agent treatment or combination treatment, respectively. The Dose Determining Set (DDS) consisted of all patients from the safety set in the dose escalation part of the trial who either met a minimum exposure criterion and had sufficient safety evaluations during the first 28 days of dosing or discontinued earlier due to a DLT during the evaluation period.

Tolerability of study drug treatment was assessed by summarizing the number of dose interruptions and dose reductions per patient. Dose intensity of naporafenib and spartalizumab per patient were also summarized. Adverse events were summarized by treatment groups, for all patients by dose escalation for single agent arm and by dose escalation and dose expansion for combination arm. Tolerability and AE analyses used the Safety Set of each arm. The Safety Set included all patients who received at least one dose (full or partial) of naporafenib or spartalizumab.

The endpoints for the secondary objectives included efficacy endpoints, ORR, DCR, DOR, PFS and OS (for dose expansion part only), PK analyses for naporafenib and spartalizumab, changes of PD marker DUSP6 in tumor and in blood, and assessment of anti-spartalizumab antibodies (ADA). The assessment of efficacy endpoints was based on RECIST v1.1 for each single agent arm and based on RECIST v1.1 and irRC for combination arm by treatment groups. No hypothesis testing was performed. PK parameters were determined by non-compartmental method(s) and summarized by descriptive statistics. Changes in biomarkers in blood and tumor samples were summarized by means of descriptive analysis. ADA incidence in patients were summarized.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- All patients participating in this clinical trial must have progressed following standard therapy, or for whom, in the opinion of the Investigator, no effective standard therapy exists, is tolerated or appropriate.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
- Presence of at least one measurable lesion according to RECIST v1.1.
- Documented MAPK alteration

Additional inclusion criteria for the Dose Expansion part: LXH254 in combination with PDR001:
- Patients with confirmed KRAS-mutated NSCLC
- Patients with confirmed NRAS-mutated melanoma (cutaneous melanoma only)

Exclusion Criteria:
- Prior treatment with a BRAFi, MEKi and/or pan-RAF inihibitors for patients to be enrolled in the dose expansion part. Exceptions may be made after documented agreement between Novartis and Investigator.
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO.
- Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
- Patients receiving proton pump inhibitors which cannot be discontinued 3 days prior to the start study treatment and for the duration of the study.
- Pregnant or nursing (lactating) women

Additional exclusion criteria for LXH254 in combination with PDR001
- History of severe hypersensitivity reactions, which in the opinion of the investigator may cause in increased risk of serious infusion reaction.
- Known human immunodeficiency virus (HIV).

- Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.
- Active, known or suspected autoimmune disease.
- Active infection requiring systemic antibiotic therapy
- Patients requiring systemic steroid therapy or any immunosuppressive therapy (≥10mg/day prednisone or equivalent) which cannot be discontinued at least 7 days prior to first dose of study treatment.
- Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment.

Participant Flow Table

Overall Study

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma	Total
Arm/Group Description	.	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.	
Started	4	4	5	6	12	12	7	12	19	6	6	6	22	21	142
Completed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	4	4	5	6	12	12	7	12	19	6	6	6	22	21	142
Adverse Event	0	0	0	0	0	0	1	0	1	2	0	2	7	1	14
Death	0	0	0	0	2	0	0	0	1	0	1	0	0	1	5
Physician Decision	0	0	0	0	0	0	0	0	0	1	0	0	2	2	5
Progressive Disease	4	3	5	6	10	9	5	11	16	2	5	4	12	16	108

Subject/Guardian Decision	0	1	0	0	0	3	1	1	1	1	0	0	0	1	9
Protocol deviation	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1

Baseline Characteristics

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma	Total
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.	
Number of Participants [units:	4	4	5	6	12	12	7	12	19	6	6	6	22	21	142

participants]															
Age Continuous (units: years) Mean ± Standard Deviation															
	51.0±17.81	47.8±6.24	49.6±12.18	50.2±16.38	59.8±12.33	61.5±17.40	48.7±12.15	58.1±8.80	60.9±12.83	60.2±12.83	66.8±8.18	63.7±6.83	61.5±10.57	63.2±10.29	NA±NA[1]
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)															
Female	2	2	2	2	7	8	4	9	11	3	2	5	12	8	77
Male	2	2	3	4	5	4	3	3	8	3	4	1	10	13	65
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)															
Asian	0	1	1	1	3	3	2	3	3	2	1	2	2	1	25
Black	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Caucasian	4	3	4	5	8	7	4	7	14	4	5	3	20	16	104
Other	0	0	0	0	0	1	1	1	0	0	0	0	0	0	3
Unknown	0	0	0	0	1	1	0	1	1	0	0	1	0	4	9

[1] Not Available

Primary Outcome Result(s)

Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) during the on-treatment period

(Time Frame: From first dose of study medication up to 30 days after last dose, with a maximum duration of 4.6 years for LXH254 single agent and 2.3 years for LXH254+PDR001)

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	12	12	7	12	19	6	6	6	22	21
Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) during the on-treatment period (units: participants) Count of Participants (Not Applicable)														
AEs	4 (100%)	4 (100%)	5 (100%)	6 (100%)	12 (100%)	12 (100%)	7 (100%)	12 (100%)	19 (100%)	6 (100%)	6 (100%)	6 (100%)	21 (95.45%)	21 (100%)
Treatment-related AEs	4 (100%)	4 (100%)	5 (100%)	5 (83.33%)	10 (83.33%)	12 (100%)	7 (100%)	10 (83.33%)	16 (84.21%)	6 (100%)	5 (83.33%)	6 (100%)	20 (90.91%)	19 (90.48%)
SAEs	2 (50%)	1 (25%)	1 (20%)	2 (33.33%)	5 (41.67%)	8 (66.67%)	3 (42.86%)	6 (50%)	13 (68.42%)	6 (100%)	2 (33.33%)	3 (50%)	11 (50%)	8 (38.1%)
Treatment-related SAEs	0 (%)	0 (%)	0 (%)	1 (16.67%)	1 (8.33%)	2 (16.67%)	2 (28.57%)	2 (16.67%)	6 (31.58%)	4 (66.67%)	0 (%)	2 (33.33%)	6 (27.27%)	6 (28.57%)

AEs leading to discontinuation	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (14.29 %)	0 (%)	1 (5.26%)	2 (33.33 %)	0 (%)	2 (33.33%)	7 (31.82%)	2 (9.52%)
Treatment-related AEs leading to discontinuation	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (14.29 %)	0 (%)	1 (5.26%)	1 (16.67 %)	0 (%)	0 (%)	6 (27.27%)	1 (4.76%)
AEs leading to dose adjustment/interruption	2 (50%)	1 (25%)	0 (%)	2 (33.33 %)	4 (33.33 %)	5 (41.67 %)	1 (14.29 %)	2 (16.67 %)	11 (57.89 %)	5 (83.33 %)	4 (66.67%)	5 (83.33%)	13 (59.09%)	10 (47.62%)
AEs requiring additional therapy	4 (100%)	4 (100%)	5 (100%)	6 (100%)	12 (100%)	12 (100%)	7 (100%)	12 (100%)	18 (94.74 %)	6 (100%)	6 (100%)	6 (100%)	20 (90.91%)	18 (85.71%)

Number of participants with Dose-Limiting Toxicities (DLTs) (Dose escalation only)

(Time Frame: 28 days (LXH254 single agent) and 56 days (LXH254 in combination with PDR001))

	LXH254 100 mg QD	**LXH254 200 mg QD**	**LXH254 300 mg QD**	**LXH254 400 mg QD**	**LXH254 800 mg QD**	**LXH254 1200 mg QD**	**LXH254 200 mg BID**	**LXH254 400 mg BID**	**LXH254 600 mg BID**	**LXH254 800 mg BID**	**LXH254 400 mg BID +PDR001**	**LXH254 600 mg BID +PDR001**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days
Number of Participants Analyzed [units: participants]	3	3	5	4	11	9	6	10	14	3	3	2

Number of participants with Dose-Limiting Toxicities (DLTs) (Dose escalation only)
(units: participants)
Count of Participants (Not Applicable)

	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (11.11%)	0 (%)	0 (%)	2 (14.29%)	2 (66.67%)	0 (%)	0 (%)

Number of participants with dose reductions and dose interruptions of LXH254

(Time Frame: From first dose of study medication up to 30 days after last dose (single agent arm) and up to 150 days after last dose (combination arm), with a maximum duration of 4.6 years for LXH254 single agent and 2.6 years for LXH254+PDR001)

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	12	12	7	12	19	6	6	6	22	21

Number of participants with dose reductions and dose interruptions of LXH254
(units: participants)
Count of Participants (Not Applicable)

At least one dose reduction	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	4 (33.33 %)	8 (42.11 %)	2 (33.33 %)	2 (33.33%)	4 (66.67%)	13 (59.09%)	7 (33.33%)
At least one dose interruption	4 (100%)	4 (100%)	5 (100%)	6 (100%)	12 (100%)	12 (100%)	7 (100%)	12 (100%)	19 (100%)	6 (100%)	6 (100%)	6 (100%)	21 (95.45%)	21 (100%)

Average number of dose reductions and dose interruptions of LXH254 per participant

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 4.5 years for LXH254 single agent and 2.2 years for LXH254+PDR001)

	LXH254 100 mg QD	**LXH254 200 mg QD**	**LXH254 300 mg QD**	**LXH254 400 mg QD**	**LXH254 800 mg QD**	**LXH254 1200 mg QD**	**LXH254 200 mg BID**	**LXH254 400 mg BID**	**LXH254 600 mg BID**	**LXH254 800 mg BID**	**LXH254 400 mg BID +PDR001**	**LXH254 600 mg BID +PDR001**	**LXH254 +PDR001 KRAS NSCLC**	**LXH254 +PDR001 NRAS Melanoma**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	12	12	7	12	19	6	6	6	22	21

Average number of dose reductions and dose interruptions of LXH254 per participant
(units: number of dose reductions/interruptions)
Mean ± Standard Deviation

Dose reductions	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.5 ± 0.80	0.6 ± 0.77	0.8 ± 1.60	1.0 ± 1.67	1.5 ± 1.52	1.7 ± 3.01	0.8 ± 1.37
Dose interruptions	2.8 ± 2.87	1.3 ± 0.50	2.0 ± 1.00	3.3 ± 4.80	1.3 ± 0.49	2.0 ± 1.54	2.0 ± 1.91	1.5 ± 0.67	2.3 ± 1.56	2.2 ± 0.75	3.8 ± 1.94	3.0 ± 1.55	2.5 ± 1.79	2.7 ± 2.00

Dose intensity of LXH254

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 4.5 years for LXH254 single agent and 2.2 years for LXH254+PDR001)

	LXH254 100 mg QD	**LXH254 200 mg QD**	**LXH254 300 mg QD**	**LXH254 400 mg QD**	**LXH254 800 mg QD**	**LXH254 1200 mg QD**	**LXH254 200 mg BID**	**LXH254 400 mg BID**	**LXH254 600 mg BID**	**LXH254 800 mg BID**	**LXH254 400 mg BID +PDR001**	**LXH254 600 mg BID +PDR001**	**LXH254 +PDR001 KRAS NSCLC**	**LXH254 +PDR001 NRAS Melanoma**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units:	4	4	5	6	12	12	7	12	19	6	6	6	22	21

participants]													
Dose intensity of LXH254 (units: mg/day) Mean ± Standard Deviation													
	107.6 ± 38.63	175.6 ± 43.01	383.8 ± 193.57	353.2 ± 54.04	695.9 ± 126.06	945.7 ± 302.75	332.4 ± 111.26	730.1 ± 116.84	890.6 ± 309.77	763.4 ± 389.30	538.6 ± 210.55	641.4 ± 386.63	604.3 ± 186.59	611.8 ± 236.78

Number of participants with dose reductions and dose interruptions of PDR001

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 2.2 years)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	6	6	22	21
Number of participants with dose reductions and dose interruptions of PDR001 (units: participants) Count of Participants (Not Applicable)				
At least one dose reduction	0 (%)	0 (%)	0 (%)	0 (%)
At least one dose interruption	3 (50%)	3 (50%)	5 (22.73%)	4 (19.05%)

Average number of dose interruptions of PDR001 per participant

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 2.2 years)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	6	6	22	21
Average number of dose interruptions of PDR001 per participant (units: number of dose interruptions) Mean ± Standard Deviation				
	0.5 ± 0.55	0.7 ± 0.82	0.3 ± 0.55	0.2 ± 0.54

Dose intensity of PDR001

(Time Frame: From first dose of study medication up to last dose, with a maximum duration of 2.2 years)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma.

	1 of every 28 days	1 of every 28 days	NSCLC. Dose expansion part.	Dose expansion part.
Number of Participants Analyzed [units: participants]	6	6	22	21
Dose intensity of PDR001 (units: mg/day) Mean ± Standard Deviation				
	11.6 ± 2.77	10.6 ± 5.18	12.7 ± 2.85	12.2 ± 2.77

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 4.5 years for LXH254 single agent and 2.2 years for LXH254+PDR001)

	LXH254 100 mg QD	**LXH254 200 mg QD**	**LXH254 300 mg QD**	**LXH254 400 mg QD**	**LXH254 800 mg QD**	**LXH254 1200 mg QD**	**LXH254 200 mg BID**	**LXH254 400 mg BID**	**LXH254 600 mg BID**	**LXH254 800 mg BID**	**LXH254 400 mg BID +PDR001**	**LXH254 600 mg BID +PDR001**	**LXH254 +PDR001 KRAS NSCLC**	**LXH254 +PDR001 NRAS Melanoma**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participant	4	4	5	6	12	12	7	12	19	6	6	6	22	21

s Analyzed [units: participants]														
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 60.2)	20.0 (0.5 to 71.6)	16.7 (0.4 to 64.1)	0 (0.0 to 26.5)	0 (0.0 to 26.5)	0 (0.0 to 41.0)	0 (0.0 to 26.5)	0 (0.0 to 17.6)	0 (0.0 to 45.9)	0 (0.0 to 45.9)	0 (0.0 to 45.9)	13.6 (2.9 to 34.9)	4.8 (0.1 to 23.8)

Disease Control Rate (DCR) per RECIST v1.1

(Time Frame: From start of treatment until end of treatment, assessed up to 4.5 years for LXH254 single agent and 2.2 years for LXH254+PDR001)

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units:	4	4	5	6	12	12	7	12	19	6	6	6	22	21

participants]													
Disease Control Rate (DCR) per RECIST v1.1 (units: percentage of participants) Number (95% Confidence Interval)													
	25.0 (0.6 to 80.6)	25.0 (0.6 to 80.6)	40.0 (5.3 to 85.3)	33.3 (4.3 to 77.7)	33.3 (9.9 to 65.1)	33.3 (9.9 to 65.1)	57.1 (18.4 to 90.1)	50.0 (21.1 to 78.9)	42.1 (20.3 to 66.5)	0 (0.0 to 45.9)	50.0 (11.8 to 88.2)	33.3 (4.3 to 77.7)	45.5 (24.4 to 67.8)	52.4 (29.8 to 74.3)

Duration of Response (DOR) per RECIST v1.1

(Time Frame: From first documented response to first documented disease progression or death due to any cause, assessed up to 4.5 years for LXH254 single agent and 2.2 years for LXH254+PDR001)

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units:	0	0	1	1	0	0	0	0	0	0	0	0	3	1

participants]														
Duration of Response (DOR) per RECIST v1.1 (units: months) Median (95% Confidence Interval)														
		NA (NA to NA)[1]	11.89 (NA to NA)[1]									5.65 (3.75 to NA)[1]	NA (NA to NA)[1]	

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

[

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

(Time Frame: From start of treatment to first documented progression or death due to any cause, assessed up to 4.5 years for LXH254 single agent and 2.2 years for LXH254+PDR001)

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units:	4	4	5	6	12	12	7	12	19	6	6	6	22	21

participants]													
Progression-Free Survival (PFS) per RECIST v1.1 (units: months) Median (95% Confidence Interval)													
	1.87 (1.74 to NA)[1]	1.81 (1.64 to NA)[1]	1.81 (1.48 to NA)[1]	1.58 (0.30 to NA)[1]	1.43 (0.82 to 3.55)	2.83 (1.35 to NA)[1]	2.68 (1.68 to 5.32)	1.91 (1.05 to 2.86)	1.79 (1.68 to NA)[1]	1.77 (0.76 to 3.58)	2.63 (0.72 to NA)[1]	2.89 (0.82 to NA)[1]	3.25 (1.58 to 3.98)	3.68 (1.84 to 5.52)

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

Overall Response Rate (ORR) per IrRC (Combination arm only)

(Time Frame: From start of treatment until end of treatment, assessed up to 2.2 years)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	6	6	22	21
Overall Response Rate (ORR) per IrRC (Combination arm only) (units: percentage of participants) Number (95% Confidence Interval)				
	0 (0.0 to 45.9)	0 (0.0 to 45.9)	13.6 (2.9 to 34.9)	4.8 (0.1 to 23.8)

Disease Control Rate (DCR) per per IrRC (Combination arm only)

(Time Frame: From start of treatment until end of treatment, assessed up to 2.2 years)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	6	6	22	21
Disease Control Rate (DCR) per per IrRC (Combination arm only) (units: percentage of participants) Number (95% Confidence Interval)				
	50.0 (11.8 to 88.2)	33.3 (4.3 to 77.7)	50.0 (28.2 to 71.8)	52.4 (29.8 to 74.3)

Duration of Response (DOR) per IrRC (Combination arm only)

(Time Frame: From first documented response to first documented disease progression or death due to any cause, assessed up to 2.2 years)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated

	400 mg on Day 1 of every 28 days	400 mg on Day 1 of every 28 days	NSCLC. Dose expansion part.	melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	0	0	3	1
Duration of Response (DOR) per IrRC (Combination arm only) (units: months) Median (95% Confidence Interval)				
			5.65 (3.75 to NA)[1]	NA (NA to NA)[1]

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

Progression-Free Survival (PFS) per IrRC (Combination arm only)

(Time Frame: From start of treatment to first documented and confirmed progression or death due to any cause, assessed up to 2.2 years)

	LXH254 400 mg BID +PDR001	**LXH254 600 mg BID +PDR001**	**LXH254 +PDR001 KRAS NSCLC**	**LXH254 +PDR001 NRAS Melanoma**
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	6	6	22	21
Progression-Free Survival (PFS) per IrRC (Combination arm only) (units: months) Median (95% Confidence Interval)				
	2.63 (0.72 to NA)[1]	3.48 (0.82 to NA)[1]	3.48 (1.58 to 4.50)	3.71 (1.87 to 5.91)

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

Overall Survival (OS) (Dose expansion only)

(Time Frame: From start of treatment to death due to any cause, assessed up to 2.2 years)

	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	22	21
Overall Survival (OS) (Dose expansion only) (units: months) Median (95% Confidence Interval)		
	12.88 (6.08 to 20.63)	9.40 (6.08 to NA)[1]

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

Maximum observed plasma concentration (Cmax) of LXH254

(Time Frame: pre-dose, 0.5, 1, 2, 3, 4, 8, 24 and 48 hours post-dose on Cycle 1 Day 1 (C1D1) and pre-dose, 0.5, 1, 2, 3, 4, 12 (BID dosing only) and 24 hours (QD dosing only) post-dose on Cycle 1 Day 15 (C1D15))

LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 +PDR001 KRAS	LXH254 +PDR001 NRAS

											+PDR001	**+PDR001**	**NSCLC**	**Melanoma**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	9	12	7	12	19	5	5	5	22	20
Maximum observed plasma concentration (Cmax) of LXH254 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)														
C1D1 (n=3,1,4,4,8,7,3,10,11,4,5,1,12,13)	413 (28.4%)	470	1150 (10.5%)	1660 (37.4%)	3200 (36.0%)	4370 (22.7%)	772 (63.5%)	1460 (71.1%)	2140 (38.9%)	3100 (28.6%)	2430 (35.0%)	1880	2000 (46.9%)	1250 (62.2%)
C1D15 (n=2,2,3,4,7,5,4,1,6,1,1,1,6,3)	579 (30.8%)	1330 (22.5%)	1340 (26.1%)	2080 (48.8%)	4650 (25.9%)	6600 (58.9%)	913 (66.4%)	5350	5470 (30.4%)	2850	3130	3520	4320 (31.6%)	4110 (43.6%)

Statistical Analysis

Groups	LXH254 100 mg QD, LXH254 200 mg QD, LXH254 300 mg QD, LXH254 400 mg QD, LXH254 800 mg QD, LXH254 1200 mg QD, LXH254 200 mg BID, LXH254 400 mg BID, LXH254 600 mg BID	
Method	Other Power model	Cmax was log-transformed and analyzed using a power model: log(Cmax)=alpha+beta*log(dose)+ε. BID doses 200-600mg were converted to mg/day for analysis
Slope	1.00	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 (0.91, 1.09).
90 % Confidence Interval 2-Sided	0.82 to 1.18	

Time to reach maximum plasma concentration (Tmax) of LXH254

(Time Frame: pre-dose, 0.5, 1, 2, 3, 4, 8, 24 and 48 hours post-dose on Cycle 1 Day 1 (C1D1) and pre-dose, 0.5, 1, 2, 3, 4, 12 (BID dosing only) and 24 hours (QD dosing only) post-dose on Cycle 1 Day 15 (C1D15))

	LXH254 100 mg QD	**LXH254 200 mg QD**	**LXH254 300 mg QD**	**LXH254 400 mg QD**	**LXH254 800 mg QD**	**LXH254 1200 mg QD**	**LXH254 200 mg BID**	**LXH254 400 mg BID**	**LXH254 600 mg BID**	**LXH254 800 mg BID**	**LXH254 400 mg BID +PDR001**	**LXH254 600 mg BID +PDR001**	**LXH254 +PDR001 KRAS NSCLC**	**LXH254 +PDR001 NRAS Melanoma**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with	LXH254 600 mg administered on a continuous BID dosing schedule in combination with	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-

											PDR001 400 mg on Day 1 of every 28 days	PDR001 400 mg on Day 1 of every 28 days	mutated NSCLC. Dose expansion part.	mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	9	12	7	12	19	5	5	5	22	20
Time to reach maximum plasma concentration (Tmax) of LXH254 (units: hours) Median (Full Range)														
C1D1 (n=3,1,4,4,8,7,3,10,11,4,5,1,12,13)	2.98 (2.97 to 7.62)	2.92 (2.92 to 2.92)	4.07 (3.00 to 4.33)	5.32 (2.83 to 7.83)	4.03 (2.87 to 4.30)	3.97 (2.95 to 7.67)	3.20 (3.00 to 7.63)	3.54 (2.92 to 7.62)	4.02 (3.02 to 7.93)	3.61 (2.98 to 7.55)	4.00 (2.00 to 8.05)	2.15 (2.15 to 2.15)	3.09 (2.07 to 4.02)	3.08 (1.25 to 7.50)
C1D15 (n=2,2,3,4,7,5,4,1,6,1,1,1,6,3)	5.95 (4.00 to 7.90)	3.52 (2.98 to 4.05)	3.00 (2.83 to 3.05)	3.68 (2.95 to 7.58)	3.00 (2.30 to 8.00)	2.92 (2.77 to 11.2)	0 (0 to 0.250)	4.08 (4.08 to 4.08)	4.08 (2.23 to 7.95)	0 (0 to 0)	4.00 (4.00 to 4.00)	0 (0 to 0)	4.00 (3.00 to 7.50)	4.00 (3.97 to 4.00)

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-last) of LXH254

(Time Frame: pre-dose, 0.5, 1, 2, 3, 4, 8, 24 and 48 hours post-dose on Cycle 1 Day 1 (C1D1) and pre-dose, 0.5, 1, 2, 3, 4, 12 (BID dosing only) and 24 hours (QD dosing only) post-dose on Cycle 1 Day 15 (C1D15))

	LXH254 100 mg QD	**LXH254 200 mg QD**	**LXH254 300 mg QD**	**LXH254 400 mg QD**	**LXH254 800 mg QD**	**LXH254 1200 mg QD**	**LXH254 200 mg BID**	**LXH254 400 mg BID**	**LXH254 600 mg BID**	**LXH254 800 mg BID**	**LXH254 400 mg BID +PDR001**	**LXH254 600 mg BID +PDR001**	**LXH254 +PDR001 KRAS NSCLC**	**LXH254 +PDR001 NRAS Melanoma**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID	LXH254 600 mg administered on a contin	LXH254 400 mg BID in combination with PDR001 400 mg	LXH254 400 mg BID in combination with PDR001 400 mg

										dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	uous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	in patients with KRAS-mutated NSCLC. Dose expansion part.	in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	9	12	7	12	19	5	5	5	22	20
Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-last) of LXH254 (units: h*ng/mL) Geometric Mean (Geometric Coefficient of Variation)														
C1D1 (n=3,1,4,4,8,7,3,10,11,4,5,1,12,13)	2040 (25.9%)	2460	5540 (18.1%)	8400 (4 8.0%)	16100 (44.6%)	21200 (23.3%)	3750 (46.5%)	7260 (61.0%)	10500 (41.1%)	16800 (27.1%)	11100 (41.2%)	1040 0	7340 (6 4.9%)	5450 (6 5.4%)
C1D15 (n=2,2,3,4,7,5,1,1,6,0,1,0,6,3)	4880 (9.1%)	9010 (6.0%)	7620 (36.9%)	11800 (52.3%)	23900 (48.1%)	48400 (69.5%)	139	43600	43600 (17.2%)		26100		33900 (38.0%)	37500 (39.3%)

Statistical Analysis

Groups	LXH254 100 mg QD, LXH254 200 mg QD, LXH254 300 mg QD, LXH254 400 mg QD, LXH254 800 mg QD, LXH254 1200 mg QD, LXH254 200 mg BID,

	LXH254 400 mg BID, LXH254 600 mg BID	
Method	Other Power model	AUC was log-transformed and analyzed using a power model: log(AUC)=alpha+beta*log(dose)+ε. BID doses 200-600mg were converted to mg/day for analysis
Slope	1.06	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 (0.91, 1.09).
90 % Confidence Interval 2-Sided	0.91 to 1.21	

Maximum observed serum concentration (Cmax) of PDR001 (Dose escalation only)

(Time Frame: Dosing on Cycle 1: pre-dose, 1 hour (C1D1), 24 hours (C1D2), 168 hours (C1D8), 336 hours (C1D15) and 672 hours (pre-C2D1 dose). Dosing on Cycle 3: pre-dose, 1 hour (C3D1), 24 hours (C3D2), 168 hours (C3D8), 336 hours (C3D15) and 672 hours (pre-C4D1 dose).)

	LXH254 400 mg BID +PDR001	**LXH254 600 mg BID +PDR001**
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days
Number of Participants Analyzed [units: participants]	5	5
Maximum observed serum concentration (Cmax) of PDR001 (Dose escalation only) (units: µg/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n=3,4)	102 (22.3%)	104 (9.9%)

C1D15 (n=3,5)	12.8 (508.8%)	36.8 (13.8%)
C2D1 (n=2,1)	38.1 (NA%)[1]	37.6
C3D1 (n=3,1)	96.2 (45.9%)	120
C3D15 (n=3,1)	21.8 (1272.7%)	71.4
C4D1 (n=3,1)	56.4 (44.2%)	60.3

[1] Not available

Time to reach maximum serum concentration (Tmax) of PDR001 (Dose escalation only)

(Time Frame: Dosing on Cycle 1: pre-dose, 1 hour (C1D1), 24 hours (C1D2), 168 hours (C1D8), 336 hours (C1D15) and 672 hours (pre-C2D1 dose). Dosing on Cycle 3: pre-dose, 1 hour (C3D1), 24 hours (C3D2), 168 hours (C3D8), 336 hours (C3D15) and 672 hours (pre-C4D1 dose).)

	LXH254 400 mg BID +PDR001	**LXH254 600 mg BID +PDR001**
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days
Number of Participants Analyzed [units: participants]	5	5
Time to reach maximum serum concentration (Tmax) of PDR001 (Dose escalation only) (units: hours) Median (Full Range)		
C1D1 (n=3,4)	0.950 (0 to 1.00)	1.03 (0 to 1.08)
C1D15 (n=3,5)	329 (328 to 333)	335 (330 to 338)

C2D1 (n=2,1)	670 (668 to 671)	670 (670 to 670)
C3D1 (n=3,1)	0.933 (0 to 0.983)	24.3 (24.3 to 24.3)
C3D15 (n=3,1)	332 (331 to 333)	333 (333 to 333)
C4D1 (n=3,1)	672 (667 to 672)	670 (670 to 670)

Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-last) of PDR001 (Dose escalation only)

(Time Frame: Dosing on Cycle 1: pre-dose, 1 hour (C1D1), 24 hours (C1D2), 168 hours (C1D8), 336 hours (C1D15) and 672 hours (pre-C2D1 dose). Dosing on Cycle 3: pre-dose, 1 hour (C3D1), 24 hours (C3D2), 168 hours (C3D8), 336 hours (C3D15) and 672 hours (pre-C4D1 dose).)

	LXH254 400 mg BID +PDR001	**LXH254 600 mg BID +PDR001**
Arm/Group Description	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days
Number of Participants Analyzed [units: participants]	5	5
Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-last) of PDR001 (Dose escalation only) (units: h*µg/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n=2,3)	49.6 (26.0%)	54.3 (9.1%)

C1D15 (n=3,5)	4220 (501.3%)	12300 (13.5%)
C2D1 (n=1,1)	25500	25200
C3D1 (n=2,1)	740 (9819.6%)	17300
C3D15 (n=3,1)	7250 (1273.8%)	23700
C4D1 (n=2,1)	37700 (44.7%)	40400

Percentage change from baseline in relative quantity of DUSP6 in tumor tissue (Single agent arm only)

(Time Frame: Baseline (screening) and post-baseline (Cycle 1 Day 15). The duration of each cycle was 28 days.)

	LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)
Number of Participants Analyzed [units: participants]	3	1	2	4	3	6	1	5	3	0
Percentage change from baseline in relative quantity of DUSP6 in tumor tissue (Single agent arm only) (units: percentage change) Median (Full Range)	15.1 (-19.2 to 37.6)	-41.8 (-41.8 to -41.8)	-29.8 (-36.4 to -23.2)	-9.4 (-91.9 to 27.0)	-32.6 (-54.9 to 24.0)	-36.9 (-74.3 to 52.6)	-42.6 (-42.6 to -42.6)	-15.9 (-66.9 to 22.3)	4.6 (-20.0 to 29.5)	

Percentage change from baseline in relative quantity of DUSP6 in blood samples

(Time Frame: Baseline (before treatment period) and post-baseline (assessed throughout the treatment up to maximum one day after last dose))

LXH254 100 mg QD	LXH254 200 mg QD	LXH254 300 mg QD	LXH254 400 mg QD	LXH254 800 mg QD	LXH254 1200 mg QD	LXH254 200 mg BID	LXH254 400 mg BID	LXH254 600 mg BID	LXH254 800 mg BID	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma

Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	4	4	5	6	12	12	7	12	19	6	6	6	21	20
Percentage change from baseline in relative quantity of DUSP6 in blood samples (units: percentage change) Median (Full Range)	87.3 (58.6 to 128.2)	209.3 (161.2 to 251.9)	175.1 (79.6 to 204.2)	143.9 (106.3 to 656.8)	188.8 (73.5 to 596.4)	114.4 (57.5 to 319.9)	265.5 (122.7 to 404.6)	225.5 (32.4 to 601.3)	132.1 (66.4 to 401.1)	189.8 (50.5 to 572.7)	158.9 (88.6 to 487.7)	128.6 (83.4 to 202.1)	128.9 (-15.0 to 413.4)	117.5 (3.9 to 351.6)

Number of participants with anti-drug antibodies (ADA) against PDR001

(Time Frame: Baseline (before first dose) and post-baseline (assessed throughout the treatment up to Cycle 6). The duration of each treatment cycle was 28 days.)

	LXH254 400 mg BID +PDR001	LXH254 600 mg BID +PDR001	LXH254 +PDR001 KRAS NSCLC	LXH254 +PDR001 NRAS Melanoma
Arm/Group Description	LXH254 400 mg administered on	LXH254 600 mg administered on	LXH254 400 mg BID in	LXH254 400 mg BID in

	a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	combination with PDR001 400 mg in patients with KRAS-mutated NSCLC. Dose expansion part.	combination with PDR001 400 mg in patients with NRAS-mutated melanoma. Dose expansion part.
Number of Participants Analyzed [units: participants]	3	5	19	19
Number of participants with anti-drug antibodies (ADA) against PDR001 (units: participants) Count of Participants (Not Applicable)				
ADA-negative at baseline	3 (100%)	5 (100%)	16 (84.21%)	14 (73.68%)
ADA-positive at baseline	0 (%)	0 (%)	3 (15.79%)	2 (10.53%)
ADA-negative post-baseline	2 (66.67%)	4 (80%)	11 (57.89%)	12 (63.16%)
Treatment-induced ADA-positive	1 (33.33%)	1 (20%)	6 (31.58%)	2 (10.53%)
Treatment-boosted ADA-positive	0 (%)	0 (%)	1 (5.26%)	0 (%)
Treatment-unaffected ADA-positive	0 (%)	0 (%)	1 (5.26%)	2 (10.53%)
Treatment-reduced ADA-positive	0 (%)	0 (%)	1 (5.26%)	0 (%)

Safety Results

All-Cause Mortality

	LXH 254 100 mg QD N = 4	LXH 254 200 mg QD N = 4	LXH 254 300 mg QD N = 5	LXH 254 400 mg QD N = 6	LXH254 800 mg QD N = 12	LXH254 1200 mg QD N = 12	LXH 254 200 mg BID N = 7	LXH254 400 mg BID N = 12	LXH 254 600 mg BID N = 19	LXH254 800 mg BID N = 6	All single agent N = 87	LXH254 400 mg BID +PDR001 N = 6	LXH254 600 mg BID +PDR001 N = 6	All combination in dose escalation N = 12	LXH254 +PDR001 KRAS NSCLC N = 22	LXH254 +PDR001 NRAS Melanoma N = 21	All dose expansion N = 43
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	All patients treated with LXH254 single agent in the dose escalation part	LXH254 400 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	LXH254 600 mg administered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	All patients treated with the combination LXH254+PDR001 in the dose escalation part	LXH254 400 mg BID in combination with PDR001 400 mg in patients with KRAS-mutated NSCLC	LXH254 400 mg BID in combination with PDR001 400 mg in patients with NRAS-mutated melanoma	All patients treated with the combination LXH254+PDR001 in the dose expansion part
Total partici	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (25.00%)	2 (16.67%)	0 (0.00%)	3 (25.00%)	1 (5.26%)	2 (33.33%)	11 (12.64%)	4 (66.67%)	1 (16.67%)	5 (41.67%)	5 (22.73%)	6 (28.57%)	11 (25.58%)

pants affected

Serious Adverse Events by System Organ Class

Time Frame	From first dose of study medication up to 30 days after last dose (single agent arm) and up to 150 days after last dose (combination arm), with a maximum duration of 4.6 years for LXH254 single agent and 2.6 years for LXH254+PDR001
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days after last dose (single agent arm) and plus 150 days after last dose (combination arm)
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment

	LXH254 100 mg QD N = 4	**LXH254 200 mg QD N = 4**	**LXH254 300 mg QD N = 5**	**LXH254 400 mg QD N = 6**	**LXH254 800 mg QD N = 12**	**LXH254 1200 mg QD N = 12**	**LXH254 200 mg BID N = 7**	**LXH254 400 mg BID N = 12**	**LXH254 600 mg BID N = 19**	**LXH254 800 mg BID N = 6**	**All single agent N = 87**	**LXH254 400 mg BID +PDR001 N = 6**	**LXH254 600 mg BID +PDR001 N = 6**	**All combination in dose escalation N = 12**	**LXH254 +PDR001 KRAS NSCLC N = 22**	**LXH254 +PDR001 NRAS Melanoma N = 21**	**All dose expansion N = 43**
Arm/Group Description	LXH254 100 mg once daily (QD)	LXH254 200 mg once daily (QD)	LXH254 300 mg once daily (QD)	LXH254 400 mg once daily (QD)	LXH254 800 mg once daily (QD)	LXH254 1200 mg once daily (QD)	LXH254 200 mg twice daily (BID)	LXH254 400 mg twice daily (BID)	LXH254 600 mg twice daily (BID)	LXH254 800 mg twice daily (BID)	All patients treated with LXH254 single agent in the dose	LXH254 400 mg administered on a continuous BID dosin	LXH254 600 mg administered on a continuous BID dosin	All patients treated with the combination LXH254 +PDR001 in the dose	LXH254 400 mg BID in combination with PDR001 400 mg in patient	LXH254 400 mg BID in combination with PDR001 400	All patients treated with the combination LXH254 +PDR001 in the dose

											escalation part	g schedule in combination with PDR001 400 mg on Day 1 of every 28 days	g schedule in combination with PDR001 400 mg on Day 1 of every 28 days	escalation part	s with KRAS-mutated NSCLC	mg in patients with NRAS-mutated melanoma	expansion part
Total participants affected	2 (50.00%)	1 (25.00%)	1 (20.00%)	2 (33.33%)	5 (41.67%)	8 (66.67%)	3 (42.86%)	6 (50.00%)	13 (68.42%)	6 (100.00%)	47 (54.02%)	2 (33.33%)	3 (50.00%)	5 (41.67%)	11 (50.00%)	8 (38.10%)	19 (44.19%)
Blood and lymphatic system disorders																	
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (16.67%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders																	
Acute coronary syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (4.76%)	1 (2.33%)
Atrial fibrillation	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Supraventricular tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Endocrine disorders																	
Hypophysitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (4.76%)	1 (2.33 %)
Eye disorders																	
Eye 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 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (4.5 5%)	0 (0.00%)	1 (2.33 %)
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%)	1 (8.33%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.2 6%)	0 (0.0 0%)	3 (3.4 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	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 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (4.5 5%)	0 (0.00%)	1 (2.33 %)
Intestinal	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 (5.2 6%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)

obstruction																
Mechanical ileus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (16.67%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14 .29%)	0 (0.00%)	1 (5.2 6%)	0 (0.0 0%)	2 (2.3 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Rectal haemorrhage	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 (5.2 6%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Subileus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (16.67%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Vomiting	1 (25 .00%)	0 (0.00%)	0 (0.00%)	1 (16 .67%)	0 (0.00%)	0 (0.00%)	1 (14 .29%)	0 (0.00%)	2 (10. 53%)	0 (0.0 0%)	5 (5.7 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (4. 76%)	1 (2.33 %)
General disorders and administration site conditions																	
Asthenia	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 (5.2 6%)	1 (16.67%)	2 (2.3 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	2 (9.0 9%)	0 (0.00%)	2 (4.65 %)
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%)	1 (5.2 6%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
General physical health	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	3 (25 .00%)	0 (0.00%)	1 (8.33%)	1 (5.2 6%)	0 (0.0 0%)	6 (6.9 0%)	1 (16.67%)	0 (0.0 0%)	1 (8.33 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)

deterioration																
Inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	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 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (4.5 5%)	0 (0.00%)	1 (2.33 %)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	2 (2.3 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	2 (9.52%)	2 (4.65 %)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	1 (16.67%)	1 (8.33 %)	0 (0.0 0%)	1 (4.76%)	1 (2.33 %)
Hepatobiliary disorders																	
Cholangitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Infections and infestations																	
Bacteraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
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%)	1 (5.2 6%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
COVID-19	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (4.76%)	1 (2.33 %)
Enterocolitis infectious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	1 (8.33 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)

Mucosal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
Spontaneous bacterial peritonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	1 (25.00%)	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%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications																	
Fall	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations																	
Alanine aminotransferase 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%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Aspartate	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (4.55%)	0 (0.00%)	1 (2.33%)

aminotransferase increased																
Blood creatinine 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 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67%)	0 (0.0 0%)	1 (8.33 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Metabolism and nutrition disorders																
Decreased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	1 (4.55%)	0 (0.00%)	1 (2.33 %)
Dehydration	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.0 0%)	3 (3.45%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	1 (4.76%)	1 (2.33 %)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (16.67%)	1 (1.15%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Hyponatraemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	4 (66.67%)	4 (4.60%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Musculoskeletal and connective tissue																

disorders																
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	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 (8.33%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Pain in extremity	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	2 (9.52%)	2 (4.65%)
Polyarthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (4.55%)	0 (0.00%)	1 (2.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)																
Cancer pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders																
Cerebrovascular accident	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (9.09%)	0 (0.00%)	2 (4.65%)

Demyelinating polyneuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.0 0%)	2 (2.30%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)
Dysarthria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Guillain-Barre syndrome	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 (5.26%)	0 (0.0 0%)	1 (1.15%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)
Headache	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.15%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)
Idiopathic intracranial hypertension	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.15%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)
Lethargy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.0 0%)	1 (16.67%)	1 (8.33%)	0 (0.0 0%)	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%)	1 (8.33%)	1 (5.26%)	0 (0.0 0%)	2 (2.30%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Neuropathy peripheral	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (16.67%)	3 (3.45%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)
Paraneoplastic neurological syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.0 0%)	0 (0.0 0%)	1 (1.15%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)

Peripheral sensory neuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seizure	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders																
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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mental status 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%)	1 (16.67%)	1 (1.15%)	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%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders																

Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (9.09%)	0 (0.00%)	2 (4.65%)
Immune-mediated lung 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 (5.26%)	0 (0.00%)	1 (1.15%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Pneumonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (4.76%)	1 (2.33%)
Pneumothorax	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (8.33%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Skin and subcutaneous tissue disorders																	
Pruritus	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	2 (33.33%)	2 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Vascular disorders																	

Deep 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 (0.0 0%)	1 (16.67%)	1 (1.1 5%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)
Hypotension	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 (5.2 6%)	0 (0.0 0%)	1 (1.1 5%)	0 (0.0 0%)	1 (16.67%)	1 (8.33 %)	0 (0.0 0%)	0 (0.00%)	0 (0.00 %)

Other Adverse Events by System Organ Class

Time Frame	From first dose of study medication up to 30 days after last dose (single agent arm) and up to 150 days after last dose (combination arm), with a maximum duration of 4.6 years for LXH254 single agent and 2.6 years for LXH254+PDR001
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days after last dose (single agent arm) and plus 150 days after last dose (combination arm)
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LXH 254 100 mg QD N = 4	**LXH 254 200 mg QD N = 4**	**LXH 254 300 mg QD N = 5**	**LXH 254 400 mg QD N = 6**	**LXH254 800 mg QD N = 12**	**LXH254 1200 mg QD N = 12**	**LXH 254 200 mg BID N = 7**	**LXH 254 400 mg BID N = 12**	**LXH254 600 mg BID N = 19**	**LXH 254 800 mg BID N = 6**	**All single agent N = 87**	**LXH 254 400 mg BID +PDR001 N = 6**	**LXH 254 600 mg BID +PDR001 N = 6**	**All combination dose escalation N = 12**	**LXH 254 +PDR001 KRAS NSCLC N = 22**	**LXH254 +PDR001 NRAS Melanoma N = 21**	**All dose expansion N = 43**
Arm/Group Description	LXH254 100 mg once	LXH254 200 mg once	LXH254 300 mg once	LXH254 400 mg once	LXH254 800 mg once	LXH254 1200 mg once	LXH254 200 mg twice	LXH254 400 mg twice	LXH254 600 mg twice	LXH254 800 mg twice	All patients treated with	LXH254 400 mg admin	LXH254 600 mg admin	All patients treated with the combin	LXH254 400 mg BID in	LXH254 400 mg BID in combi	All patients treated with the combin

	daily (QD)	daily (QD)	daily (QD)	daily (QD)	daily (QD)	daily (QD)	daily (BID)	daily (BID)	daily (BID)	daily (BID)	LXH254 single agent in the dose escalation part	istered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	istered on a continuous BID dosing schedule in combination with PDR001 400 mg on Day 1 of every 28 days	ation LXH254 +PDR001 in the dose escalation part	combination with PDR001 400 mg in patients with KRAS-mutated NSCLC	nation with PDR001 400 mg in patients with NRAS-mutated melanoma	ation LXH254 +PDR001 in the dose expansion part
Total participants affected	4 (100.00%)	4 (100.00%)	5 (100.00%)	6 (100.00%)	12 (100.00%)	12 (100.00%)	6 (85.71%)	11 (91.67%)	19 (100.00%)	6 (100.00%)	85 (97.70%)	6 (100.00%)	6 (100.00%)	12 (100.00%)	21 (95.45%)	21 (100.00%)	42 (97.67%)
Blood and lymphatic system disorders																	
Anaemia	1 (25.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	3 (25.00%)	2 (16.67%)	1 (14.29%)	2 (16.67%)	4 (21.05%)	1 (16.67%)	16 (18.39%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	2 (9.09%)	6 (28.57%)	8 (18.60%)
Eosinophilia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (14.29%)	3 (6.98%)
Leukocytosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (5.26%)	1 (16.67%)	4 (4.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	2 (4.65%)

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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (14.29%)	3 (6.98%)
Monoclonal B-cell lymphocytosis	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders																	
Arrhythmia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrial fibrillation	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrial flutter	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (8.33%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Bundle branch block right	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pericardial 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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Sinus arrhythmia	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Sinus bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Supraventricular extrasystoles	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	2 (9.09%)	0 (0.0 0%)	2 (4.65 %)
Congenital, familial and genetic disorders																	
Left ventricle outflow tract obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Ear and labyrinth disorders																	
Sudden hearing loss	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (4.55%)	0 (0.0 0%)	1 (2.33 %)
Endocrine disorders																	

Adrenal insufficiency	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
Inappropriate antidiuretic hormone secretion	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders																	
Amaurosis fugax	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blindness transient	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 (5.26%)	0 (0.00%)	1 (1.15%)	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%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry eye	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Glaucoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Keratitis	0 (0.00%)	1 (25.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Lacrimation 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%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Punctate keratitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retinopathy	0 (0.00%)	1 (25.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Scleral thinning	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Subretinal fluid	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Vision blurred	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders																	
Abdominal discomfort	0 (0.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal distension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (13.64%)	0 (0.00%)	3 (6.98%)

Abdominal pain	0 (0.00%)	2 (50.00%)	0 (0.00%)	1 (16.67%)	2 (16.67%)	0 (0.0 0%)	2 (28.57%)	1 (8.33%)	6 (31.58%)	0 (0.00%)	14 (16.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	3 (14.29%)	4 (9.30%)
Abdominal pain upper	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.0 0%)	1 (2.33%)
Anal erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Aphthous ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Ascites	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	1 (8.33%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Constipation	2 (50.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	3 (25.00%)	1 (8.33%)	1 (14.29%)	4 (33.33%)	9 (47.37%)	1 (16.67%)	24 (27.59%)	1 (16.67%)	2 (33.33%)	3 (25.00%)	7 (31.82%)	5 (23.81%)	12 (27.91%)
Diarrhoea	2 (50.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	1 (8.33%)	1 (14.29%)	2 (16.67%)	2 (10.53%)	0 (0.00%)	11 (12.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (18.18%)	1 (4.76%)	5 (11.63%)
Dry mouth	1 (25.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	1 (8.33%)	1 (5.26%)	0 (0.00%)	7 (8.05%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	3 (14.29%)	3 (6.98%)
Duodenal stenosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	1 (14.29%)	1 (8.33%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.0 0%)	2 (4.65%)
Dysphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)

Faecaloma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ileus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	2 (50.00%)	1 (25.00%)	2 (40.00%)	1 (16.67%)	2 (16.67%)	5 (41.67%)	0 (0.00%)	4 (33.33%)	5 (26.32%)	1 (16.67%)	23 (26.44%)	2 (33.33%)	3 (50.00%)	5 (41.67%)	6 (27.27%)	5 (23.81%)	11 (25.58%)
Oesophageal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral dysaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (10.53%)	0 (0.00%)	3 (3.45%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Pancreatitis	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Rectal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Small intestinal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Stomatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	1 (16.67%)	5 (5.75%)	2 (33.33%)	3 (50.00%)	5 (41.67%)	0 (0.00%)	2 (9.52%)	2 (4.65%)
Subileus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (16.67%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Vomiting	1 (25.00%)	2 (50.00%)	1 (20.00%)	2 (33.33%)	5 (41.67%)	2 (16.67%)	0 (0.00%)	2 (16.67%)	1 (5.26%)	1 (16.67%)	17 (19.54%)	1 (16.67%)	3 (50.00%)	4 (33.33%)	1 (4.55%)	0 (0.0 0%)	1 (2.33%)
General disorders and administration site conditions																	
Asthenia	0 (0.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	2 (28.57%)	0 (0.00%)	1 (5.26%)	1 (16.67%)	6 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (27.27%)	3 (14.29%)	9 (20.93%)
Chills	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (8.33%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Drug withdrawal syndrome	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)

Facial pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	3 (75.00%)	2 (50.00%)	1 (20.00%)	0 (0.00%)	3 (25.00%)	7 (58.33%)	1 (14.29%)	3 (25.00%)	7 (36.84%)	1 (16.67%)	28 (32.18%)	1 (16.67%)	3 (50.00%)	4 (33.33%)	7 (31.82%)	3 (14.29%)	10 (23.26%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Impaired healing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.30%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Malaise	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (25.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	6 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (14.29%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
Oedema peripheral	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (8.33%)	3 (15.79%)	2 (33.33%)	9 (10.34%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (22.73%)	0 (0.00%)	5 (11.63%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	3 (3.45%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	3 (13.64%)	1 (4.76%)	4 (9.30%)
Pyrexia	1 (25.00%)	0 (0.00%)	1 (20.00%)	2 (33.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	6 (6.90%)	1 (16.67%)	4 (66.67%)	5 (41.67%)	8 (36.36%)	3 (14.29%)	11 (25.58%)

Hepatobiliary disorders																
Hepatic haemorrhage	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Hyperbilirubinaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Immune system disorders																
Contrast media reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Infections and infestations																
Abdominal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Candida infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Clostridium difficile infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)

Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (4.55%)	0 (0.0 0%)	1 (2.33 %)
Encephalitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (16.67%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Enterocolitis infectious	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Erysipelas	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (4.55%)	1 (4.76%)	2 (4.65 %)
Folliculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	1 (4.76%)	1 (2.33 %)
Gastroenteritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Genital infection fungal	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Localised infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	3 (3.45%)	1 (16.67%)	1 (16.67%)	2 (16.67%)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Oral herpes	1 (25.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	1 (4.76%)	1 (2.33 %)

Paronychia	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	1 (4.76%)	1 (2.33 %)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	1 (16.67%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Postoperative wound infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Pustule	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	1 (4.55%)	0 (0.0 0%)	1 (2.33 %)
Rash pustular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	1 (4.55%)	2 (9.52%)	3 (6.98 %)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Scrotal abscess	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	2 (16.67%)	0 (0.0 0%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	1 (4.76%)	1 (2.33 %)
Soft tissue infection	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)

Spontaneous bacterial peritonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.0%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Systemic infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.0%)	1 (14.29%)	0 (0.00%)	0 (0.0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	1 (4.55%)	0 (0.0%)	1 (2.33%)
Urinary tract infection	2 (50.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	1 (16.67%)	5 (5.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Varicella zoster virus infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)
Injury, poisoning and procedural complications																	
Contusion	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.00%)
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	1 (16.67%)	1 (16.67%)	2 (16.67%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Femur fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0%)	0 (0.0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)

Head injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hip fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle strain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post-traumatic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Radiation oesophagitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper limb 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%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations																	
Activated partial thromboplastin time 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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alanine aminotransferase	0 (0.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	4 (19.05%)	5 (11.63%)

increased																
Amylase increased	0 (0.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	2 (16.67%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	3 (15.79%)	0 (0.00%)	7 (8.05%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (4.55%)	1 (4.76%)	2 (4.65%)
Aspartate aminotransferase increased	0 (0.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	1 (14.29%)	1 (8.33%)	1 (5.26%)	0 (0.00%)	6 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	3 (14.29%)	4 (9.30%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Blood bilirubin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	4 (21.05%)	1 (16.67%)	5 (5.75%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (4.55%)	4 (19.05%)	5 (11.63%)
Blood cholesterol increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (8.33%)	2 (10.53%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	1 (4.55%)	2 (9.52%)	3 (6.98%)
Blood creatinine	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.0 0%)	1 (14.29%)	1 (8.33%)	2 (10.53%)	1 (16.67%)	7 (8.05%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	3 (14.29%)	5 (11.63%)

increased																
Blood uric acid increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Brain natriuretic peptide 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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
C-reactive protein 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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	2 (4.65%)
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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Electrocardiogram T wave inversion	0 (0.00%)	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 (1.15%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gamma-glutamyltransferase	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (14.29%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	5 (5.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	2 (4.65%)

increased																
Hepatic enzyme 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%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inflammatory marker increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
International normalised ratio increased	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lipase increased	1 (25.00%)	1 (25.00%)	2 (40.00%)	1 (16.67%)	3 (25.00%)	0 (0.00%)	1 (14.29%)	1 (8.33%)	3 (15.79%)	0 (0.00%)	13 (14.94%)	1 (16.67%)	1 (16.67%)	2 (16.67%)	2 (9.09%)	2 (9.52%)	4 (9.30%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Platelet count decreased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
SARS-CoV-2 test positive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Transaminases increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urine output decreased	1 (25.00%)	0 (0.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (2.33%)
Weight decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	1 (8.33%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	1 (4.55%)	1 (2.33%)
White blood cell count increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	2 (40.00%)	2 (33.33%)	2 (16.67%)	5 (41.67%)	0 (0.00%)	3 (25.00%)	4 (21.05%)	0 (0.00%)	19 (21.84%)	1 (16.67%)	2 (33.33%)	3 (25.00%)	6 (27.27%)	2 (9.52%)	8 (18.60%)
Dehydration	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Electrolyte imbalance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypercalcaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Hypergl ycaemia	1 (25 .00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	1 (8.3 3%)	0 (0. 00%)	0 (0. 00%)	3 (15. 79%)	1 (16 .67%)	6 (6. 90%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	2 (9. 09%)	0 (0.0 0%)	2 (4.65 %)
Hyperka laemia	1 (25 .00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14 .29%)	0 (0. 00%)	0 (0.0 0%)	1 (16 .67%)	3 (3. 45%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	1 (4. 55%)	2 (9.5 2%)	3 (6.98 %)
Hypern atraemi a	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0. 00%)	1 (8. 33%)	0 (0.0 0%)	0 (0. 00%)	1 (1. 15%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hyperur icaemia	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14 .29%)	0 (0. 00%)	0 (0.0 0%)	0 (0. 00%)	1 (1. 15%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hypoalb uminae mia	1 (25 .00%)	0 (0. 00%)	0 (0. 00%)	2 (33 .33%)	1 (8.3 3%)	2 (16. 67%)	1 (14 .29%)	1 (8. 33%)	1 (5.2 6%)	1 (16 .67%)	10 (1 1.49 %)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hypocal caemia	1 (25 .00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0. 00%)	0 (0. 00%)	1 (5.2 6%)	1 (16 .67%)	3 (3. 45%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hypogly caemia	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14 .29%)	0 (0. 00%)	0 (0.0 0%)	0 (0. 00%)	1 (1. 15%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hypokal aemia	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14 .29%)	2 (16 .67%)	0 (0.0 0%)	0 (0. 00%)	3 (3. 45%)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hypoma gnesae mia	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0. 00%)	1 (8. 33%)	1 (5.2 6%)	0 (0. 00%)	2 (2. 30%)	0 (0. 00%)	1 (16 .67%)	1 (8.33 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)
Hyponat raemia	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	1 (16 .67%)	2 (16. 67%)	0 (0.0 0%)	0 (0. 00%)	2 (16 .67%)	4 (21. 05%)	1 (16 .67%)	10 (1 1.49 %)	0 (0. 00%)	0 (0. 00%)	0 (0.00 %)	1 (4. 55%)	3 (14. 29%)	4 (9.30 %)
Hypoph osphata emia	0 (0. 00%)	0 (0. 00%)	0 (0. 00%)	2 (33 .33%)	0 (0.0 0%)	1 (8.3 3%)	0 (0. 00%)	0 (0. 00%)	1 (5.2 6%)	1 (16 .67%)	5 (5. 75%)	0 (0. 00%)	1 (16 .67%)	1 (8.33 %)	0 (0. 00%)	0 (0.0 0%)	0 (0.00 %)

Malnutrition	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitamin D deficiency	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders																
Arthralgia	1 (25.00%)	1 (25.00%)	1 (20.00%)	0 (0.00%)	1 (8.33%)	2 (16.67%)	1 (14.29%)	2 (16.67%)	2 (10.53%)	0 (0.00%)	11 (12.64%)	2 (33.33%)	1 (16.67%)	3 (25.00%)	1 (4.55%)	3 (14.29%)	4 (9.30%)
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (8.33%)	2 (10.53%)	0 (0.00%)	5 (5.75%)	2 (33.33%)	1 (16.67%)	3 (25.00%)	3 (13.64%)	1 (4.76%)	4 (9.30%)
Flank 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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Groin pain	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle spasms	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	4 (19.05%)	6 (13.95%)
Muscular weakness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (4.76%)	2 (4.65%)
Musculoskeletal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	1 (4.55%)	0 (0.00%)	1 (2.33%)

chest pain																
Musculoskeletal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Myalgia	0 (0.00%)	1 (25.00%)	2 (40.00%)	0 (0.00%)	2 (16.67%)	3 (25.00%)	1 (14.29%)	4 (33.33%)	4 (21.05%)	1 (16.67%)	18 (20.69%)	0 (0.00%)	2 (33.33%)	2 (16.67%)	6 (27.27%)	0 (0.00%)	6 (13.95%)
Neck pain	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
Pain in extremity	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (10.53%)	0 (0.00%)	4 (4.60%)	2 (33.33%)	1 (16.67%)	3 (25.00%)	2 (9.09%)	3 (14.29%)	5 (11.63%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)																	
Melanocytic naevus	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seborrhoeic 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%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Tumour haemorrhage	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Tumour pain	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	1 (16.67%)	4 (4.60%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Nervous system disorders																	
Cubital tunnel syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Demyelinating polyneuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Dizziness	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	2 (16.67%)	0 (0.00%)	1 (8.33%)	3 (15.79%)	0 (0.00%)	9 (10.34%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	1 (4.55%)	3 (14.29%)	4 (9.30 %)
Dysaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Dysgeusia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Epilepsy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Formication	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Headache	1 (25.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	3 (25.00%)	1 (8.33%)	0 (0.00%)	4 (33.33%)	5 (26.32%)	0 (0.00%)	16 (18.39%)	1 (16.67%)	1 (16.67%)	2 (16.67%)	2 (9.09%)	2 (9.52%)	4 (9.30 %)

Hypoaesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune-mediated neuropathy	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Migraine	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	1 (16.67%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neuropathy peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	2 (9.52%)	3 (6.98%)
Paraesthesia	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (4.76%)	2 (4.65%)
Peripheral motor neuropathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral sensory neuropathy	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (16.67%)	4 (4.60%)	2 (33.33%)	1 (16.67%)	3 (25.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Restless legs syndrome	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Sciatica	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Somnolence	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tremor	1 (25.00%)	0 (0.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Product issues																	
Device occlusion	1 (25.00%)	0 (0.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders																	
Agitation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anxiety	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	1 (8.33%)	1 (5.26%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
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%)	1 (16.67%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Delirium	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	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%)	0 (0.00%)	1 (8.33%)	1 (8.33%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hallucination	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Insomnia	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (8.33%)	2 (10.53%)	0 (0.00%)	6 (6.90%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
Mood altered	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bladder spasm	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cystitis haemorrhagic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Micturition urgency	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oliguria	0 (0.00%)	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 (1.15%)	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%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary retention	0 (0.00%)	1 (25.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract obstruction	0 (0.00%)	1 (25.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders																	
Erectile dysfunction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Genital 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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pelvic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaginal mucosal blistering	0 (0.00%)	1 (25.00%)	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 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders																	

Aspiration	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (33.33%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	5 (5.75%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	6 (27.27%)	1 (4.76%)	7 (16.28%)
Dysphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (4.55%)	0 (0.0 0%)	1 (2.33 %)
Dyspnoea	1 (25.00%)	1 (25.00%)	1 (20.00%)	1 (16.67%)	4 (33.33%)	2 (16.67%)	1 (14.29%)	1 (8.33%)	3 (15.79%)	1 (16.67%)	16 (18.39 %)	1 (16.67%)	2 (33.33%)	3 (25.0 0%)	6 (27.27%)	1 (4.76%)	7 (16.28%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	1 (14.29%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	1 (16.67%)	0 (0.00%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Hiccups	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Hypoxia	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	1 (8.33%)	0 (0.0 0%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	1 (16.67%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Immune-mediated lung disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Lung disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)
Lung infiltration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.0 0%)	0 (0.0 0%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	1 (16.67%)	1 (8.33 %)	0 (0.00%)	0 (0.0 0%)	0 (0.00 %)

Nasal congestion	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	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%)	1 (8.33%)	2 (10.53%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.09%)	1 (4.76%)	3 (6.98%)
Pleural effusion	1 (25.00%)	0 (0.00%)	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 (1.15%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	3 (13.64%)	1 (4.76%)	4 (9.30%)
Pneumothorax	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Productive cough	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	4 (4.60%)	0 (0.00%)	1 (16.67%)	1 (8.33%)	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%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alopecia	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	2 (16.67%)	1 (5.26%)	0 (0.00%)	6 (6.90%)	1 (16.67%)	0 (0.00%)	1 (8.33%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
Dermatitis acneiform	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	2 (16.67%)	4 (33.33%)	3 (42.86%)	5 (41.67%)	6 (31.58%)	0 (0.00%)	22 (25.29%)	1 (16.67%)	2 (33.33%)	3 (25.00%)	2 (9.09%)	5 (23.81%)	7 (16.28%)
Dry skin	1 (25.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	2 (10.53%)	0 (0.00%)	6 (6.90%)	0 (0.00%)	2 (33.33%)	2 (16.67%)	2 (9.09%)	0 (0.00%)	2 (4.65%)

Eczema asteatotic	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 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nail discolouration	1 (25.00%)	0 (0.00%)	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 (1.15%)	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%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Onycho clasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain of skin	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Palmar-plantar erythrodysaesthesia syndrome	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	3 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.33%)
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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Pruritus	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	1 (8.33%)	5 (41.67%)	0 (0.00%)	3 (25.00%)	6 (31.58%)	0 (0.00%)	17 (19.54%)	1 (16.67%)	2 (33.33%)	3 (25.00%)	3 (13.64%)	6 (28.57%)	9 (20.93%)
Rash	0 (0.00%)	3 (75.00%)	0 (0.00%)	1 (16.67%)	2 (16.67%)	3 (25.00%)	1 (14.29%)	3 (25.00%)	7 (36.84%)	2 (33.33%)	22 (25.29%)	2 (33.33%)	1 (16.67%)	3 (25.00%)	8 (36.36%)	9 (42.86%)	17 (39.53%)

Rash macular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	2 (16.67%)	3 (25.00%)	1 (14.29%)	1 (8.33%)	2 (10.53%)	2 (33.33%)	12 (13.79%)	1 (16.67%)	2 (33.33%)	3 (25.00%)	2 (9.09%)	0 (0.00%)	2 (4.65%)
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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (13.64%)	0 (0.00%)	3 (6.98%)
Skin 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%)	1 (5.26%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin hyperpigmentation	0 (0.00%)	1 (25.00%)	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 (1.15%)	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%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.26%)	0 (0.00%)	2 (2.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (2.33%)
Vascular disorders																	
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%)	1 (16.67%)	1 (1.15%)	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%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	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 (9.09%)	0 (0.00%)	2 (4.65%)
Thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Conclusion:

- MTD/RDE at 600 mg BID was identified for the naporafenib single agent treatment
- No MTD was formally identified for naporafenib single agent QD (the highest dose tested and tolerated was 1200 mg QD). MTD was not reached for the combination treatment; RDE was declared at naporafenib 400 mg BID in combination with spartalizumab 400 mg Q4W
- The overall safety profile of naporafenib is acceptable. The most common toxicities were gastrointestinal disorders (nausea and vomiting) and skin disorders (dermatitis, rash and pruritus)
- Plasma peak drug concentration (Cmax) and drug exposure (AUC0-t) after oral doses of naporafenib as single agent increased in an approximate dose-proportional manner across the dose range tested between 100 mg and 1200 mg QD after single dose at C1D1 and after multiple doses at C1D15. The PK profiles of naporafenib and spartalizumab, when given in combination, were generally consistent with PK profiles of individual drugs. No drug-drug interactions are expected between naporafenib and spartalizumab
- Reduction of DUSP6 mRNA levels in paired tumor samples was observed after single agent treatment indicating pharmacodynamic activity of naporafenib at the doses tested
- The naporafenib single agent treatment showed limited anti-tumor activity in this heavily pre-treated and heterogeneous patient population treated with different doses of naporafenib
- The combination treatment of naporafenib plus spartalizumab showed limited anti-tumor activity in this heavily pre-treated and heterogenous patient population

Date of Clinical Trial Report

28-Oct-2022