

**Sponsor**

Novartis Pharmaceuticals

Generic Drug Name

Naporafenib (LXH254), rineterkib (LTT462), trametinib (TMT212) and ribociclib (LEE011)

Trial Indication(s)

Advanced or metastatic KRAS or BRAF mutant non-small cell lung cancer (NSCLC) or NRAS mutant melanoma

Protocol Number

CLXH254X2102

Protocol Title

A Phase Ib, open-label, multicenter study of oral LXH254-centric combinations in adult patients with advanced or metastatic KRAS or BRAF mutant Non-Small Cell Lung Cancer or NRAS mutant melanoma

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1 (naporafenib, rineterkib) and phase 4 (trametinib, ribociclib)

Study Start/End Dates

Study Start Date: February 24, 2017 (Actual)

Primary Completion Date: April 24, 2024 (Actual)

Study Completion Date: April 24, 2024 (Actual)

Reason for Termination (If applicable)

Novartis made the decision to halt recruitment of new patients to the CLXH254X2102 study for business reasons as of 14-Feb-2022. As a result, no new patients were to be enrolled in the CLXH254X2102 study:

- The arms in BRAF-mutant NSCLC halted recruitment of new patients.
- The naporafenib + ribociclib expansion cohort in NRAS mutant melanoma was not opened for enrollment.
- All planned patients in other study arms had already been enrolled as per protocol.

This decision was not based on any safety/tolerability concerns for any of the naporafenib-based combinations in the explored indications.

Study Design/Methodology

This was a multi-center, open-label, Phase Ib dose escalation study followed by a dose expansion part.

The dose escalation part included three study arms:

- Naporafenib in combination with rineterkib: patients with KRAS/BRAF mutant non-small cell lung carcinoma (NSCLC)
- Naporafenib in combination with trametinib: patients with KRAS/BRAF mutant NSCLC or NRAS mutant melanoma
- Naporafenib in combination with ribociclib: patients with NRAS mutant melanoma

All patients in the dose escalation part of the study, treated with naporafenib in combination with rineterkib, trametinib, or ribociclib, were enrolled based on mutational analysis obtained locally and received oral naporafenib in combination with

oral rineterkib, trametinib, or ribociclib, under fasted condition until the maximum tolerated dose (MTD) was reached or recommended dose (RD) was established.

All patients in the dose expansion part of the study were enrolled based on mutational analysis obtained locally or centrally, and were treated with naporafenib in combination with rineterkib or trametinib at the established RD. Due to the enrollment halt in the study, the naporafenib + ribociclib expansion cohort in NRAS mutant melanoma was not opened for enrollment.

Centers

32 centers in 11 countries: Germany(4), Belgium(1), Australia(2), United States(6), France(3), Italy(5), Spain(6), Poland(1), Korea, Republic of(2), Sweden(1), Israel(1)

Objectives:

The primary objective of the trial was to characterize safety and tolerability of naporafenib in combination with rineterkib or trametinib or ribociclib and identify a recommended dose(s) and regimen(s).

The secondary objectives were:

- To evaluate the preliminary anti-tumor activity of naporafenib in combination with rineterkib or trametinib or ribociclib
- To characterize the pharmacokinetic (PK) profile of naporafenib, rineterkib, trametinib and ribociclib in their respective combinations
- To evaluate the pharmacodynamic effect of naporafenib, rineterkib, trametinib and ribociclib in their respective combinations in tumor

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

The investigational drugs used in this study were naporafenib, rineterkib, trametinib and ribociclib. The study treatment was the combination of naporafenib and rineterkib or the combination of naporafenib and trametinib or the combination of naporafenib and ribociclib.

The study treatment was administered in 28-day dosing cycles in fasted condition.

Naporafenib was administered orally as tablets once daily (QD) at dose levels ranging from 50 to 350 mg, and twice daily (BID) at doses ranging from 200 to 600 mg.

Rineterkib was administered orally as capsules QD at doses ranging from 100 to 300 mg.

Trametinib was administered orally as tablets QD at 0.5 or 1 mg, and at a dose level of 1 mg with a treatment cycle of 2 weeks on and 2 weeks off.

Ribociclib was administered orally as tablets and capsules at 200 or 400 mg with a treatment cycle of 3 weeks on and 1 week off.

The study treatment was continued until the patient 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 to characterize safety and tolerability of naporafenib in combination with rineterkib, or with trametinib or with ribociclib and identify a recommended dose and regimen included: incidence of dose-limiting toxicities (DLT) for dose escalation, incidence and severity of adverse events (AEs), serious adverse events (SAEs) as mentioned in safety assessments, including changes in laboratory values, vital signs and electrocardiograms (ECGs), 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 (MTD/RD) using Dose determining set for the single agent treatment or combination treatment, respectively. Tolerability of study drug treatment was assessed by summarizing dose intensity and dose adjustments for each of the study drugs separately by treatment group. The incidence of treatment-emergent adverse events (new or worsening from baseline) were summarized by system organ class and/or preferred term. Summary tables for AEs included only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. Serious adverse events and non-serious adverse

events during the on-treatment period were tabulated. All deaths (on-treatment and post-treatment) were summarized by treatment group.

The endpoints for the secondary objectives included efficacy endpoints, overall response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS) (for dose expansion part only), PK analyses for naporafenib, rineterkib, trametinib, and ribociclib and changes of pharmacodynamic (PD) marker DUSP6. The assessment of efficacy endpoints was based on RESIST v1.1. No hypothesis testing was performed. For each study treatment, all patients treated at MTD/RD with the same indication and mutation status were pooled into a single treatment group, i.e., KRAS mutant NSCLC patients treated at MTD/RD in one group, BRAF mutant NSCLC patients treated at MTD/RD in one group and NRAS mutant melanoma patients treated at MTD/RD in another group. For efficacy analysis, however, BRAF mutant NSCLC patients were further divided in the subgroup of BRAF mutant V600 and BRAF mutant non-V600, which was applicable to the combination of naporafenib and rineterkib only.

Pharmacokinetic parameters were determined by non-compartmental method(s) using the PK profile of naporafenib, rineterkib, trametinib and ribociclib.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients must have advanced or metastatic NSCLC or cutaneous melanoma
- Presence of KRAS or BRAF mutation (NSCLC) or NRAS mutation (cutaneous melanoma) in tumor tissue
- All patients participating in this clinical trial must have progressed following standard therapy or, in the opinion of the Investigator, no effective standard therapy exists, is tolerated, appropriate or is considered equivalent to study treatment.
- -ECOG (Eastern Cooperative Oncology Group) performance status ≤ 2

Exclusion Criteria:

- Dose expansion – KRAS or NRAS mutant patients groups: Prior treatment with a RAFi (including any BRAFi and pan-RAFi), MEKi and/or ERKi. (Patients with KRAS mutant NSCLC with prior G12C inhibitor treatments are also excluded in the LXH254+trametinib expansion part). BRAF mutant patients group: Prior treatment with any EGFR, ALK, ROS1, KRAS, RAF (both BRAFV600 selective and pan-RAF), MEK1/2 and/or ERK1/2 inhibitors (for patients with BRAF V600 mutant NSCLC, prior treatments with BRAF and MEK1/2 inhibitors are allowed). Patients who have received more than 3 lines of anti-cancer therapy are excluded.
- 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 (PPI) which cannot be discontinued 3 days prior to the start study treatment and for the duration of the study.
- Patients with Gilbert's syndrome or other heritable diseases of bile processing.

Participant Flow Table

Overall Study

Arm/Group Description	LXH5 0mg QD + LTT1 00m g QD	LXH1 00m g QD + LTT1 00m g QD	LXH2 00m g QD + LTT1 00m g QD	LXH2 00m g QD + LTT1 50m g QD	LXH2 00m g QD + LTT3 00m g QD	LXH3 00m g BID + LTT1 00m g QD	LXH3 50m g QD + LTT1 00m g QD	LXH6 00m g BID + LTT1 00m g QD	MTD/ RD LXH4 00m g BID + LTT2 00m g QD	LXH2 00m g BID + TMT 0.5m g QD	LXH4 00m g BID + TMT 1mg QD	LXH4 00m g BID + TMT 1mg QD	MTD/ RD LXH2 00m g BID + TMT 1mg QD	MTD/ RD LXH4 00m g BID + TMT 0.5m g QD	LXH2 00m g BID + LEE4 00m g 3wk on/1 wk off	LXH4 00m g BID + LEE2 00m g 3wk on/1 wk off	LXH4 00m g BID + LEE4 00m g 3wk on/1 wk off	T ot al
	Escal ation part: napor afeni b 50 mg QD + rinete rkib 100 mg QD	Escal ation part: napor afeni b 100 mg QD + rinete rkib 100 mg QD	Escal ation part: napor afeni b 200 mg QD + rinete rkib 100 mg QD	Escal ation part: napor afeni b 200 mg QD + rinete rkib 150 mg QD	Escal ation part: napor afeni b 200 mg QD + rinete rkib 300 mg QD	Escal ation part: napor afeni b 300 mg BID + rinete rkib 100 mg QD	Escal ation part: napor afeni b 350 mg QD + rinete rkib 100 mg QD	Escal ation part: napor afeni b 600 mg BID + rinete rkib 100 mg QD	Escal ation and expa nsion : napor afeni b 400 mg BID + rinete rkib 200 mg QD	Escal ation part: napor afeni b 200 mg BID + trame tinib 0.5 mg QD	Escal ation part: napor afeni b 400 mg BID + trame tinib 1 mg QD	Escal ation part: napor afeni b 400 mg BID + trame tinib 1 mg QD	Escal ation and expa nsion : napor afeni b 200 mg BID + trame tinib 1 mg QD	Escal ation and expa nsion : napor afeni b 400 mg BID + trame tinib 0.5 mg QD	Escal ation part: napor afeni b 200 mg BID + riboci clib 400 mg 3 week s on and 1 week s off	Escal ation part: napor afeni b 400 mg BID + riboci clib 200 mg 3 week s on and 1 week s off	Escal ation part: napor afeni b 400 mg BID + riboci clib 400 mg 3 week s on and 1 week s off	24 1
Started	5	4	6	5	7	5	5	6	58	6	5	6	54	44	6	9	10	0
Comple ted	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Not Completed*	5	4	6	5	7	5	5	6	58	6	5	6	54	44	6	9	10	241
Adverse Event	0	0	0	0	4	0	0	0	2	1	1	0	10	5	0	2	3	28
Death	2	1	0	1	0	0	0	0	6	0	1	1	5	2	0	0	0	19
Physician Decision	0	0	0	0	0	0	1	0	2	0	0	0	1	2	1	0	1	8
Progressive Disease	3	1	4	4	2	5	4	6	39	5	3	5	34	32	5	7	6	165
Subject/Guardian Decision	0	2	2	0	1	0	0	0	9	0	0	0	4	3	0	0	0	21

* Not completed refers to treatment discontinuation. The reasons for discontinuation are listed below.

Baseline Characteristics

LXH5 0mg QD + LTT1 00mg g QD	LXH1 00mg g QD + LTT1 00mg g QD	LXH2 00mg g QD + LTT1 00mg g QD	LXH2 00mg g QD + LTT1 50mg g QD	LXH2 00mg g QD + LTT3 00mg g QD	LXH3 00mg g BID + LTT1 00mg g QD	LXH3 50mg g QD + LTT1 00mg g QD	LXH6 00mg g BID + LTT1 00mg g QD	MTD/ RD LXH4 00mg g BID + LTT2 00mg g QD	LXH2 00mg g BID + TMT 0.5mg g QD	LXH4 00mg g BID + TMT 1mg QD	LXH4 00mg g BID + TMT 1mg 2wk on/2 wk off	MTD/ RD LXH2 00mg g BID + TMT 1mg QD	MTD/ RD LXH4 00mg g BID + TMT 0.5mg g QD	LXH2 00mg g BID + LEE4 00mg g 3wk on/1 wk off	LXH4 00mg g BID + LEE2 00mg g 3wk on/1 wk off	LXH4 00mg g BID + LEE4 00mg g 3wk on/1 wk off	Total
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Arm/ Group Description	Escalation part: naporafenib 50 mg QD + rkinetorib 100 mg QD	Escalation part: naporafenib 100 mg QD + rkinetorib 100 mg QD	Escalation part: naporafenib 200 mg QD + rkinetorib 100 mg QD	Escalation part: naporafenib 200 mg QD + rkinetorib 150 mg QD	Escalation part: naporafenib 200 mg QD + rkinetorib 300 mg QD	Escalation part: naporafenib 300 mg BID + rkinetorib 100 mg QD	Escalation part: naporafenib 350 mg QD + rkinetorib 100 mg QD	Escalation part: naporafenib 600 mg BID + rkinetorib 100 mg QD	Escalation and expansion : naporafenib 400 mg BID + rkinetorib 200 mg QD	Escalation part: naporafenib 200 mg BID + trameetinib 0.5 mg QD	Escalation part: naporafenib 400 mg BID + trameetinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trameetinib 1 mg on and 2 weeks off	Escalation and expansion : naporafenib 200 mg BID + trameetinib 1 mg QD	Escalation and expansion : naporafenib 400 mg BID + trameetinib 0.5 mg QD	Escalation part: naporafenib 200 mg BID + rkinetorib 400 mg 3 weeks on and 1 week off	Escalation part: naporafenib 400 mg BID + rkinetorib 200 mg 3 weeks on and 1 week off	Escalation part: naporafenib 400 mg BID + rkinetorib 400 mg 3 weeks on and 1 week off	
Number of Participants [units : participants]	5	4	6	5	7	5	5	6	58	6	5	6	54	44	6	9	10	241
Baseline Analysis Population Description																		
Age, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)																		
18 - <65 years	3	2	3	3	5	1	4	3	41	2	2	4	26	23	2	5	5	134
65 - <85	2	2	3	2	2	4	1	3	17	4	3	2	28	21	4	4	5	107

years

Age Continuous

(units: years)

Analysis Population Type: Participants

Mean $\pm$ Standard Deviation

	61.4 $\pm$ 14.52	62.0 $\pm$ 11.75	60.2 $\pm$ 10.57	62.4 $\pm$ 7.60	63.9 $\pm$ 7.73	66.2 $\pm$ 9.76	58.0 $\pm$ 13.53	62.0 $\pm$ 11.40	58.3 $\pm$ 10.32	66.3 $\pm$ 6.15	63.6 $\pm$ 5.46	59.2 $\pm$ 10.63	63.3 $\pm$ 12.03	62.5 $\pm$ 9.90	59.0 $\pm$ 16.64	60.6 $\pm$ 10.85	61.2 $\pm$ 11.46	61.4 $\pm$ 10.76
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Sex: Female, Male

(units: participants)

Analysis Population Type: Participants

Count of Participants (Not Applicable)

Female	3	4	2	3	4	2	4	2	23	0	2	5	26	21	3	4	3	111
Male	2	0	4	2	3	3	1	4	35	6	3	1	28	23	3	5	7	130

Race/Ethnicity, Customized

(units: participants)

Analysis Population Type: Participants

Count of Participants (Not Applicable)

White	5	4	5	4	6	4	4	5	39	6	4	6	49	33	4	8	9	195
Asian	0	0	0	0	0	0	0	0	8	0	0	0	0	3	0	0	0	11
Other	0	0	0	1	0	0	1	1	0	0	1	0	1	2	0	0	1	8
Unknown	0	0	0	0	0	0	0	0	11	0	0	0	4	6	2	1	0	24
Missing	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	3

Primary Outcome Result(s)

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

Description	Number of participants with AEs (any AE regardless of seriousness) and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.
Time Frame	From first dose of study treatment to 30 days after last dose, up to approximately 1.3 years (naporafenib + rineterkib), 2.4 years (naporafenib + trametinib) and 3.7 years (naporafenib + ribociclib)
Analysis Population Description	All patients who received at least one dose of study treatment.

	LXH5 0mg QD + LTT1 00mg QD	LXH1 00mg QD + LTT1 00mg QD	LXH2 00mg QD + LTT1 00mg QD	LXH2 00mg QD + LTT1 50mg QD	LXH2 00mg QD + LTT3 00mg QD	LXH3 00mg BID + LTT1 00mg QD	LXH3 50mg QD + LTT1 00mg QD	LXH6 00mg BID + LTT1 00mg QD	MTD/ RD LXH4 00mg BID + LTT2 00mg QD	LXH2 00mg BID + TMT0 .5mg QD	LXH4 00mg BID + TMT1 mg QD	LXH4 00mg BID + TMT1 mg QD	LXH4 00mg BID + TMT1 mg 2wk on/2 wk off	MTD/ RD LXH2 00mg BID + TMT1 mg QD	MTD/ RD LXH4 00mg BID + TMT0 .5mg QD	LXH2 00mg BID + LEE4 00mg 3wk on/1 wk off	LXH4 00mg BID + LEE2 00mg 3wk on/1 wk off	LXH4 00mg BID + LEE4 00mg 3wk on/1 wk off
Arm/ Group Description	Escalation part: naporafenib 50 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 100 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 150 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 300 mg QD	Escalation part: naporafenib 300 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 350 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 600 mg QD + rineterkib 100 mg QD	Escalation and expansion: naporafenib 400 mg BID + rineterkib 200 mg QD	Escalation part: naporafenib 200 mg BID + trametinib 0.5 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg QD	Escalation and expansion: naporafenib 200 mg BID + trametinib 1 mg QD	Escalation and expansion: naporafenib 400 mg BID + trametinib 0.5 mg QD	Escalation part: naporafenib 200 mg BID + ribociclib 400 mg 3 weeks on and 1	Escalation part: naporafenib 400 mg BID + ribociclib 200 mg 3 weeks on and 1	Escalation part: naporafenib 400 mg BID + ribociclib 400 mg 3 weeks on and 1

												week s off				week s off	week s off	week s off
Num ber of Partic ipant s Analy zed [units : partic ipant s]	5	4	6	5	7	5	5	6	58	6	5	6	54	44	6	9	10	
Num ber of partic ipant s with Adve rse Event s (AEs) and Serio us Adve rse Event s (SAE s) (units: partici pants)	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	Coun t of Partic ipant s	
	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	(Perc entag e)	
AEs	5 (100%)	4 (100%)	6 (100%)	5 (100%)	7 (100%)	5 (100%)	5 (100%)	6 (100%)	58 (100%)	6 (100%)	5 (100%)	6 (100%)	54 (100%)	44 (100%)	6 (100%)	9 (100%)	10 (100%)	

Treat- ment- related AEs	5 (100%)	4 (100%)	6 (100%)	4 (80%)	7 (100%)	5 (100%)	3 (60%)	5 (83.33%)	56 (96.55%)	6 (100%)	5 (100%)	5 (83.33%)	51 (94.44%)	43 (97.73%)	6 (100%)	9 (100%)	10 (100%)
SAEs	3 (60%)	2 (50%)	4 (66.67%)	5 (100%)	1 (14.29%)	4 (80%)	4 (80%)	2 (33.33%)	38 (65.52%)	4 (66.67%)	3 (60%)	1 (16.67%)	31 (57.41%)	23 (52.27%)	1 (16.67%)	4 (44.44%)	6 (60%)
Treat- ment- related SAEs	1 (20%)	0 (%)	1 (16.67%)	1 (20%)	0 (%)	2 (40%)	1 (20%)	0 (%)	10 (17.24%)	0 (%)	2 (40%)	0 (%)	10 (18.52%)	8 (18.18%)	0 (%)	2 (22.22%)	2 (20%)
Fatal SAEs	0 (%)	1 (25%)	0 (%)	1 (20%)	1 (14.29%)	0 (%)	0 (%)	0 (%)	5 (8.62%)	1 (16.67%)	1 (20%)	0 (%)	5 (9.26%)	3 (6.82%)	0 (%)	0 (%)	0 (%)
Treat- ment- related fatal SAEs	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (1.72%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (2.27%)	0 (%)	0 (%)	0 (%)

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

Description	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 where the relationship to study treatment cannot be ruled out, and is not primarily related to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with naporafenib and rineterkib or trametinib or ribociclib. Other clinically significant toxicities could be considered to be DLTs, even if not CTCAE grade 3 or higher. AEs grade ≥ 3 that were correctable within 7 days and deemed by the Investigator to be not clinically important were not considered DLTs.
Time Frame	28 days (Cycle 1)
Analysis Population Description	All patients who received at least one dose of study treatment during the dose escalation part, and who met the minimum exposure criterion defined in the protocol and had sufficient safety evaluations or had experienced a DLT during Cycle 1.

LXH5 0mg QD +	LXH1 00mg QD +	LXH2 00mg QD +	LXH2 00mg QD +	LXH2 00mg QD +	LXH3 00mg BID +	LXH3 50mg QD +	LXH4 00mg BID +	LXH4 00mg BID +	LXH6 00mg BID +	LXH2 00mg BID +	LXH2 00mg BID +	LXH4 00mg BID +	LXH4 00mg BID +	LXH4 00mg BID +	LXH2 00mg BID +	LXH4 00mg BID +	LXH4 00mg BID +
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	LTT1 00mg QD	LTT1 00mg QD	LTT1 00mg QD	LTT1 50mg QD	LTT3 00mg QD	LTT1 00mg QD	LTT1 00mg QD	LTT2 00mg QD	LTT1 00mg QD	TMT0 .5mg QD	TMT1 mg QD	TMT0 .5mg QD	TMT1 mg QD	TMT1 mg 2wk on/2 wk off	LEE4 00mg 3wk on/1 wk off	LEE2 00mg 3wk on/1 wk off	LEE4 00mg 3wk on/1 wk off
Arm/Group Description	Escalation part: naporafenib 50 mg QD + rinetetrakib 100 mg QD	Escalation part: naporafenib 100 mg QD + rinetetrakib 100 mg QD	Escalation part: naporafenib 200 mg QD + rinetetrakib 100 mg QD	Escalation part: naporafenib 200 mg QD + rinetetrakib 150 mg QD	Escalation part: naporafenib 200 mg QD + rinetetrakib 300 mg QD	Escalation part: naporafenib 300 mg BID + rinetetrakib 100 mg QD	Escalation part: naporafenib 350 mg QD + rinetetrakib 100 mg QD	Escalation part: naporafenib 400 mg BID + rinetetrakib 200 mg QD	Escalation part: naporafenib 600 mg BID + rinetetrakib 100 mg QD	Escalation part: naporafenib 200 mg BID + trametinib 0.5 mg QD	Escalation part: naporafenib 200 mg BID + trametinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 0.5 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg 2 weeks on and 2 weeks off	Escalation part: naporafenib 200 mg BID + ribociclib 400 mg 3 weeks on and 1 week off	Escalation part: naporafenib 400 mg BID + ribociclib 200 mg 3 weeks on and 1 week off	Escalation part: naporafenib 400 mg BID + ribociclib 400 mg 3 weeks on and 1 week off
Number of Participants Analyzed [units: participants]	3	4	4	2	4	4	4	4	5	5	8	8	4	3	6	8	8
Number of participants with Dose-Limiting Toxicities	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)

**(DLTs) –
Dose
escalati
on only**
(units:
participa
nts)

At least one DLT	0 (%)	1 (25%)	0 (%)	0 (%)	1 (25%)	0 (%)	0 (%)	0 (%)	2 (40%)	0 (%)	3 (37.5%)	1 (12.5%)	2 (50%)	0 (%)	0 (%)	0 (%)	2 (25%)
- Amylase increased	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (20%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
- Dermatitis acneiform	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (12.5%)	1 (12.5%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
- Febrile neutropenia	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (12.5%)
- Lipase increased	0 (%)	1 (25%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (12.5%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
- Palmar-plantar erythrodysesthesia syndrome	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (20%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
- Rash	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (20%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (12.5%)

- Rash maculopapular	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (12.5%)	0 (%)	1 (25%)	0 (%)	0 (%)	0 (%)	0 (%)
- Retinal detachment	0 (%)	0 (%)	0 (%)	0 (%)	1 (25%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)
- Stevens-Johnson syndrome	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (25%)	0 (%)	0 (%)	0 (%)	0 (%)

Number of participants with dose reductions and dose interruptions of naporafenib

Description	Number of participants with at least one dose reduction and at least one dose interruption of naporafenib. Dose modification and dose delay were permitted for patients who did not tolerate the protocol-specified dosing schedule. treatment. For the dose escalation part of the study, dose modifications during the DLT evaluation period (first treatment cycle) were only allowed if a DLT was observed and recorded.
Time Frame	From first dose of study treatment to last dose, up to approximately 1.2 years (naporafenib + rineterkib), 2.3 years (naporafenib + trametinib) and 3.6 years (naporafenib + ribociclib)
Analysis Population Description	All patients who received at least one dose of naporafenib

	LXH5 0mg QD + LTT1 00mg QD	LXH1 00mg QD + LTT1 00mg QD	LXH2 00mg QD + LTT1 00mg QD	LXH2 00mg QD + LTT1 50mg QD	LXH2 00mg QD + LTT3 00mg QD	LXH3 00mg QD + LTT1 00mg QD	LXH3 50mg QD + LTT1 00mg QD	LXH6 00mg QD + LTT1 00mg QD	MTD/ RD LXH4 00mg QD + LTT2 00mg QD	LXH2 00mg QD + TMT0 .5mg QD	LXH4 00mg QD + TMT1 mg QD	LXH4 00mg BID + TMT1 mg 2wk on/2 wk off	MTD/ RD LXH2 00mg BID + TMT1 mg QD	MTD/ RD LXH4 00mg BID + TMT0 .5mg QD	LXH2 00mg BID + LEE4 00mg 3wk on/1 wk off	LXH4 00mg BID + LEE2 00mg 3wk on/1 wk off	LXH4 00mg BID + LEE4 00mg 3wk on/1 wk off
Arm/ Group	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation and expan	Escalation part: napor	Escalation part: napor	Escalation part: napor	Escalation and expan	Escalation and expan	Escalation part: napor	Escalation part: napor	Escalation part: napor

Descr iption	afenib 50 mg QD + rinete rkib 100 mg QD	afenib 100 mg QD + rinete rkib 100 mg QD	afenib 200 mg QD + rinete rkib 100 mg QD	afenib 200 mg QD + rinete rkib 150 mg QD	afenib 200 mg QD + rinete rkib 300 mg QD	afenib 300 mg BID + rinete rkib 100 mg QD	afenib 350 mg QD + rinete rkib 100 mg QD	afenib 600 mg BID + rinete rkib 100 mg QD	sion: napor afenib 400 mg BID + rinete rkib 200 mg QD	afenib 200 mg BID + trame tinib 0.5 mg QD	afenib 400 mg BID + trame tinib 1 mg QD	afenib 400 mg BID + trame tinib 1 mg 2 week s on and 2 week s off	sion: napor afenib 200 mg BID + trame tinib 1 mg QD	sion: napor afenib 400 mg BID + trame tinib 0.5 mg QD	afenib 200 mg BID + riboci clib 400 mg 3 week s on and 1 week s off	afenib 400 mg BID + riboci clib 200 mg 3 week s on and 1 week s off	afenib 400 mg BID + riboci clib 400 mg 3 week s on and 1 week s off
Numb er of Partic ipant s Analy zed [units : partic ipant s]	5	4	6	5	7	5	5	6	58	6	5	6	54	44	6	9	10
Numb er of partic ipant s with dose reduc tions and dose interr uption s of napor afeni b	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)	Coun t of Partic ipant s (Perc entag e)

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pants)

At least one dose reduct ion or interru ption	5 (100%)	4 (100%)	6 (100%)	5 (100%)	7 (100%)	5 (100%)	5 (100%)	6 (100%)	58 (100%)	6 (100%)	5 (100%)	6 (100%)	54 (100%)	44 (100%)	6 (100%)	9 (100%)	10 (100%)
At least one dose reduct ion	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	2 (40%)	1 (20%)	3 (50%)	22 (37.93%)	2 (33.33%)	1 (20%)	5 (83.33%)	22 (40.74%)	18 (40.91%)	5 (83.33%)	7 (77.78%)	8 (80%)
At least one dose interru ption	5 (100%)	4 (100%)	6 (100%)	5 (100%)	7 (100%)	5 (100%)	5 (100%)	6 (100%)	58 (100%)	6 (100%)	5 (100%)	6 (100%)	54 (100%)	44 (100%)	6 (100%)	8 (88.89%)	10 (100%)

Number of participants with dose reductions and dose interruptions of rineterkib

Description	Number of participants with at least one dose reduction and at least one dose interruption of rineterkib. Dose modification and dose delay were permitted for patients who did not tolerate the protocol-specified dosing schedule. treatment. For the dose escalation part of the study, dose modifications during the DLT evaluation period (first treatment cycle) were only allowed if a DLT was observed and recorded.
Time Frame	From first dose of study treatment to last dose, up to approximately 1.2 years
Analysis Population Description	All patients who received at least one dose of rineterkib

LXH50mg QD +	LXH100mg QD +	LXH200mg QD +	LXH200mg QD +	LXH200mg QD +	LXH300mg BID +	LXH350mg QD +	LXH600mg BID +	MTD/RD LXH400mg
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	LTT100mg QD	LTT100mg QD	LTT100mg QD	LTT150mg QD	LTT300mg QD	LTT100mg QD	LTT100mg QD	LTT100mg QD	BID + LTT200mg QD
Arm/Group Description	Escalation part: naporafenib 50 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 100 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 150 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 300 mg QD	Escalation part: naporafenib 300 mg BID + rineterkib 100 mg QD	Escalation part: naporafenib 350 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 600 mg BID + rineterkib 100 mg QD	Escalation and expansion: naporafenib 400 mg BID + rineterkib 200 mg QD
Number of Participants Analyzed [units: participants]	5	4	6	5	7	5	5	6	58
Number of participants with dose reductions and dose interruption s of rineterkib (units: participants)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)
At least one dose reduction or interruption	5 (100%)	4 (100%)	6 (100%)	5 (100%)	7 (100%)	5 (100%)	5 (100%)	6 (100%)	55 (94.83%)
At least one dose reduction	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	0 (%)	1 (16.67%)	5 (8.62%)
At least one dose interruption	5 (100%)	4 (100%)	6 (100%)	5 (100%)	7 (100%)	5 (100%)	5 (100%)	6 (100%)	55 (94.83%)

Number of participants with dose reductions and dose interruptions of trametinib

Description	Number of participants with at least one dose reduction and at least one dose interruption of trametinib. Dose modification and dose delay were permitted for patients who did not tolerate the protocol-specified dosing schedule. treatment. For the dose escalation part of the study, dose modifications during the DLT evaluation period (first treatment cycle) were only allowed if a DLT was observed and recorded.
Time Frame	From first dose of study treatment to last dose, up to approximately 2.3 years
Analysis Population Description	All patients who received at least one dose of trametinib

	LXH200mg BID + TMT0.5mg QD	LXH400mg BID + TMT1mg QD	LXH400mg BID + TMT1mg 2wk on/2wk off	MTD/RD LXH200mg BID + TMT1mg QD	MTD/RD LXH400mg BID + TMT0.5mg QD
Arm/Group Description	Escalation part: naporafenib 200 mg BID + trametinib 0.5 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg 2 weeks on and 2 weeks off	Escalation and expansion: naporafenib 200 mg BID + trametinib 1 mg QD	Escalation and expansion: naporafenib 400 mg BID + trametinib 0.5 mg QD
Number of Participants Analyzed [units: participants]	6	5	6	54	44
Number of participants with dose reductions and dose interruptions of trametinib (units: participants)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)
At least one dose reduction or interruption	6 (100%)	5 (100%)	6 (100%)	54 (100%)	44 (100%)
At least one dose reduction	1 (16.67%)	1 (20%)	0 (%)	2 (3.7%)	1 (2.27%)
At least one dose interruption	6 (100%)	5 (100%)	6 (100%)	54 (100%)	44 (100%)

Number of participants with dose reductions and dose interruptions of ribociclib

Description	Number of participants with at least one dose reduction and at least one dose interruption of ribociclib. Dose modification and dose delay were permitted for patients who did not tolerate the protocol-specified dosing schedule. treatment. For the dose escalation part of the study, dose modifications during the DLT evaluation period (first treatment cycle) were only allowed if a DLT was observed and recorded.
Time Frame	From first dose of study treatment to last dose, up to approximately 3.6 years
Analysis Population Description	All patients who received at least one dose of ribociclib

	LXH200mg BID + LEE400mg 3wk on/1wk off	LXH400mg BID + LEE200mg 3wk on/1wk off	LXH400mg BID + LEE400mg 3wk on/1wk off
Arm/Group Description	Escalation part: naporafenib 200 mg BID + ribociclib 400 mg 3 weeks on and 1 weeks off	Escalation part: naporafenib 400 mg BID + ribociclib 200 mg 3 weeks on and 1 weeks off	Escalation part: naporafenib 400 mg BID + ribociclib 400 mg 3 weeks on and 1 weeks off
Number of Participants Analyzed [units: participants]	6	9	10
Number of participants with dose reductions and dose interruptions of ribociclib (units: participants)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)
At least one dose reduction or interruption	6 (100%)	9 (100%)	10 (100%)
At least one dose reduction	0 (%)	0 (%)	0 (%)
At least one dose interruption	6 (100%)	9 (100%)	10 (100%)

Dose intensity of naporafenib

Description	Dose intensity of naporafenib was calculated as cumulative actual dose in milligrams divided by duration of exposure in days.
Time Frame	From first dose of study treatment to last dose, up to approximately 1.2 years (naporafenib + rineterkib), 2.3 years (naporafenib + trametinib) and 3.6 years (naporafenib + ribociclib)

Analysis Population Description
All patients who received at least one dose of naporafenib

Arm/G roup Descri ption	LXH5 0mg QD + LTT1 00mg QD	LXH1 00mg QD + LTT1 00mg QD	LXH2 00mg QD + LTT1 00mg QD	LXH2 00mg QD + LTT1 50mg QD	LXH2 00mg QD + LTT3 00mg QD	LXH3 00mg BID + LTT1 00mg QD	LXH3 50mg QD + LTT1 00mg QD	LXH6 00mg BID + LTT1 00mg QD	MTD/ RD LXH4 00mg BID + LTT2 00mg QD	LXH2 00mg BID + TMT0 .5mg QD	LXH4 00mg BID + TMT1 mg QD	LXH4 00mg BID + TMT1 mg 2wk on/2 wk off	MTD/ RD LXH2 00mg BID + TMT1 mg QD	MTD/ RD LXH4 00mg BID + TMT0 .5mg QD	LXH2 00mg BID + LEE4 00mg 3wk on/1 wk off	LXH4 00mg BID + LEE2 00mg 3wk on/1 wk off	LXH4 00mg BID + LEE4 00mg 3wk on/1 wk off
	Escal ation part: napor afenib 50 mg QD + rinete rkib 100 mg QD	Escal ation part: napor afenib 100 mg QD + rkib 100 mg QD	Escal ation part: napor afenib 200 mg QD + rkib 100 mg QD	Escal ation part: napor afenib 200 mg QD + rkib 150 mg QD	Escal ation part: napor afenib 200 mg QD + rkib 300 mg QD	Escal ation part: napor afenib 300 mg BID + rkib 100 mg QD	Escal ation part: napor afenib 350 mg QD + rkib 100 mg QD	Escal ation part: napor afenib 600 mg BID + rkib 100 mg QD	Escal ation and expan sion: napor afenib 400 mg BID + rinete rkib 200 mg QD	Escal ation part: napor afenib 200 mg BID + trame tinib 0.5 mg QD	Escal ation part: napor afenib 400 mg BID + trame tinib 1 mg QD	Escal ation part: napor afenib 400 mg BID + trame tinib 1 mg 2 week s on and 2 week s off	Escal ation and expan sion: napor afenib 200 mg BID + trame tinib 1 mg QD	Escal ation and expan sion: napor afenib 400 mg BID + trame tinib 0.5 mg QD	Escal ation part: napor afenib 200 mg BID + riboci clib 400 mg 3 week s on and 1 week s off	Escal ation part: napor afenib 400 mg BID + riboci clib 200 mg 3 week s on and 1 week s off	Escal ation part: napor afenib 400 mg BID + riboci clib 400 mg 3 week s on and 1 week s off
Numb er of Partici pants Analy zed [units:	5	4	6	5	7	5	5	6	58	6	5	6	54	44	6	9	10

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Dose
intens
ity of
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Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)	Medi an (Full Rang e)
47.9 (44 to 49)	84.7 (35 to 98)	192.5 (130 to 198)	179.3 (139 to 198)	179.1 (80 to 200)	496.2 (423 to 579)	343.8 (244 to 344)	716.1 (553 to 1020)	678.1 (215 to 791)	372.7 (226 to 394)	744.4 (691 to 752)	593.7 (363 to 774)	307.3 (109 to 400)	707.2 (180 to 793)	367.6 (262 to 399)	687.2 (472 to 779)	460.3 (204 to 771)

Dose intensity of rineterkib

Description	Dose intensity of rineterkib was calculated as cumulative actual dose in milligrams divided by duration of exposure in days.
Time Frame	From first dose of study treatment to last dose, up to approximately 1.2 years
Analysis Population Description	All patients who received at least one dose of rineterkib

	LXH50mg QD + LTT100mg QD	LXH100mg QD + LTT100mg QD	LXH200mg QD + LTT100mg QD	LXH200mg QD + LTT150mg QD	LXH200mg QD + LTT300mg QD	LXH300mg BID + LTT100mg QD	LXH350mg QD + LTT100mg QD	LXH600mg BID + LTT100mg QD	MTD/RD LXH400mg BID + LTT200mg QD
Arm/Group Description	Escalation part: naporafenib 50 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 100 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 150 mg QD	Escalation part: naporafenib 200 mg QD + rineterkib 300 mg QD	Escalation part: naporafenib 300 mg BID + rineterkib 100 mg QD	Escalation part: naporafenib 350 mg QD + rineterkib 100 mg QD	Escalation part: naporafenib 600 mg BID + rineterkib 100 mg QD	Escalation and expansion: naporafenib 400 mg BID + rineterkib 200 mg QD

Number of Participants Analyzed [units: participants]	5	4	6	5	7	5	5	6	58
Dose intensity of rineterkib (units: mg/day)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)
	95.9 (89 to 98)	84.7 (66 to 98)	96.2 (65 to 99)	134.5 (104 to 149)	268.7 (120 to 300)	91.6 (79 to 100)	98.2 (70 to 100)	88.7 (65 to 123)	177.8 (58 to 200)

Dose intensity of trametinib

Description	Dose intensity of trametinib was calculated as cumulative actual dose in milligrams divided by duration of exposure in days.
Time Frame	From first dose of study treatment to last dose, up to approximately 2.3 years
Analysis Population Description	All patients who received at least one dose of trametinib

	LXH200mg BID + TMT0.5mg QD	LXH400mg BID + TMT1mg QD	LXH400mg BID + TMT1mg 2wk on/2wk off	MTD/RD LXH200mg BID + TMT1mg QD	MTD/RD LXH400mg BID + TMT0.5mg QD
Arm/Group Description	Escalation part: naporafenib 200 mg BID + trametinib 0.5 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg QD	Escalation part: naporafenib 400 mg BID + trametinib 1 mg 2 weeks on and 2 weeks off	Escalation and expansion: naporafenib 200 mg BID + trametinib 1 mg QD	Escalation and expansion: naporafenib 400 mg BID + trametinib 0.5 mg QD
Number of Participants Analyzed [units: participants]	6	5	6	54	44
Dose intensity of trametinib (units: mg/day)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)	Median (Full Range)
	0.5 (0 to 1)	0.9 (0.9 to 1)	0.5 (0 to 1)	0.7 (0 to 1)	0.5 (0 to 1)

Dose intensity of ribociclib

Description	Dose intensity of ribociclib was calculated as cumulative actual dose in milligrams divided by duration of exposure in days.
Time Frame	From first dose of study treatment to last dose, up to approximately 3.6 years
Analysis Population Description	All patients who received at least one dose of ribociclib

	LXH200mg BID + LEE400mg 3wk on/1wk off	LXH400mg BID + LEE200mg 3wk on/1wk off	LXH400mg BID + LEE400mg 3wk on/1wk off
Arm/Group Description	Escalation part: naporafenib 200 mg BID + ribociclib 400 mg 3 weeks on and 1 weeks off	Escalation part: naporafenib 400 mg BID + ribociclib 200 mg 3 weeks on and 1 weeks off	Escalation part: naporafenib 400 mg BID + ribociclib 400 mg 3 weeks on and 1 weeks off
Number of Participants Analyzed [units: participants]	6	9	10
Dose intensity of ribociclib (units: mg/day)	Median (Full Range)	Median (Full Range)	Median (Full Range)
	287.2 (202 to 335)	131.9 (71 to 176)	243.8 (92 to 362)

Secondary Outcome Result(s)

Overall Response Rate (ORR) per RECIST v1.1

Description	ORR is the percentage of patients with a best overall response of complete response (CR) or partial response (PR), based on local investigator assessment per RECIST v1.1. For RECIST v1.1, CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Time Frame	Up to approximately 1.2 years (naporafenib + rineterkib), 2.3 years (naporafenib + trametinib) and 3.6 years (naporafenib + ribociclib)

Arm/Group	Description
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	100 mg QD	100 mg QD	100 mg QD	150 mg QD	300 mg QD	100 mg QD	100 mg QD	100 mg QD	QD in KR AS NS CL C	QD in BR AF V60 0 NS CL C	QD in BR AF non V60 0 NS CL C	0.5 mg QD	1 mg QD	1 mg 2 we eks on and 2 we eks off	QD in NR AS Mel ano ma	QD in KR AS NS CL C	QD in BR AF non V60 0 NS CL C	QD in NR AS Mel ano ma	QD in KR AS NS CL C	QD in BR AF V60 0 NS CL C	400 mg 3 we eks on and 1 we eks off	200 mg 3 we eks on and 1 we eks off	400 mg 3 we eks on and 1 we eks off
Nu mb er of Part icip ant s Ana lyze d [uni ts: part icip ant s]	5	4	6	5	7	5	5	6	30	6	22	6	5	6	16	27	11	17	26	1	6	9	10
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Disease Control Rate (DCR) per RECIST v1.1

Description	DCR is the percentage of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD), based on local investigator assessment per RECIST v1.1. For RECIST v1.1, CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.
Time Frame	Up to approximately 1.2 years (naporafenib + rineterkib), 2.3 years (naporafenib + trametinib) and 3.6 years (naporafenib + ribociclib)
Analysis Population Description	All patients who received at least one dose of study treatment. Patients treated at the recommended dose (RD) were analyzed according to their mutation type.

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Ar m/G rou p Des crip tion	Esc alat ion part : nap oraf eni b 50 mg QD + rine terk ib 100 mg QD	Esc alat ion part : nap oraf eni b 100 mg QD + rine terk ib 100 mg QD	Esc alat ion part : nap oraf eni b 200 mg QD + rine terk ib 100 mg QD	Esc alat ion part : nap oraf eni b 200 mg QD + rine terk ib 150 mg QD	Esc alat ion part : nap oraf eni b 200 mg QD + rine terk ib 300 mg QD	Esc alat ion part : nap oraf eni b 300 mg BID + rine terk ib 100 mg QD	Esc alat ion part : nap oraf eni b 350 mg QD + rine terk ib 100 mg QD	Esc alat ion part : nap oraf eni b 600 mg BID + rine terk ib 100 mg QD	MT D/R D: nap oraf eni b 400 mg BID + rine terk ib 200 mg QD in BR AF V60 0 NS CL C	MT D/R D: nap oraf eni b 400 mg BID + rine terk ib 200 mg QD in BR AF non V60 0 NS CL C	MT D/R D: nap oraf eni b 400 mg BID + tra met inib 0.5 mg QD	Esc alat ion part : nap oraf eni b 200 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	Esc alat ion part : nap oraf eni b 400 mg BID + tra met inib 1 mg QD	Esc alat ion part : nap oraf eni b 400 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	MT D/R D: nap oraf eni b 200 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	MT D/R D: nap oraf eni b 200 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	MT D/R D: nap oraf eni b 400 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	MT D/R D: nap oraf eni b 400 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	MT D/R D: nap oraf eni b 400 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	Esc alat ion part : nap oraf eni b 200 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	Esc alat ion part : nap oraf eni b 400 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C	Esc alat ion part : nap oraf eni b 400 mg BID + tra met inib 1 mg QD in BR AF non V60 0 NS CL C		
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71. 99. 64. 94. 71. 85. 71. 77. 65. 88. 45. 88. 71. 99. 89. 77. 83. 81. 79. 100. 95. 92. 87.
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Duration of Response (DOR) per RECIST v1.1

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| Description | DOR only applied to patients whose best overall response was complete response (CR) or partial response (PR) based on local investigator assessment per RECIST v1.1. DOR is defined as the time between the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed) and the date of first documented progression or death due to underlying cancer. If a patient did not have an event, DOR was censored at the date of last adequate tumor assessment. DOR was analyzed using Kaplan-Meier estimates. |
| Time Frame | Up to approximately 1.2 years (naporafenib + rineterkib), 2.3 years (naporafenib + trametinib) and 3.6 years (naporafenib + ribociclib) |
| Analysis Population Description | All patients who received at least one dose of study treatment and achieved CR or PR. Patients treated at the recommended dose (RD) were analyzed according to their mutation type. |

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| Duration of Response (DO R) per RE CIS T v1.1 (units: months) | Median | Median |
|---|---------------------------|--------|
| | (95% Confidence Interval) | |
| | | | | | | 1.87 (NA to NA) [1] | | 1.84 (NA to NA) [1] | 3.94 (NA to NA) [1] | | 8.00 (7.62 to NA) [1] | | | | 5.59 (3.29 to NA) [1] | 7.16 (NA to NA) [1] | | 16.59 (NA to NA) [1] | 6.44 (NA to NA) [1] | | | | |

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

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

| | |
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| Description | Progression free survival 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. PFS was assessed via local review according to RECIST 1.1. PFS was censored if no PFS event was observed before the analysis cut-off date or the date when a new anti-neoplastic therapy was initiated, whichever occurred first. PFS was analyzed using Kaplan-Meier estimates. |
| Time Frame | Up to approximately 1.2 years (naporafenib + rineterkib), 2.3 years (naporafenib + trametinib) and 3.6 years (naporafenib + ribociclib) |
| Analysis Population Description | All patients who received at least one dose of study treatment. Patients treated at the recommended dose (RD) were analyzed according to their mutation type. |

Page 34

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[1] | 1.8
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NA)
[1] | 2.8
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NA)
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NA)
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[1] Not estimable due to insufficient number of participants with events.

Overall Survival (OS) (expansion only)

| | |
|---------------------------------|---|
| Description | Overall survival is defined as the time from the start of treatment to the date of death due to any cause. OS was analyzed using the Kaplan-Meier method. |
| Time Frame | From first dose of study treatment to the end of the study, up to approximately 7 years |
| Analysis Population Description | All patients who received at least one dose of study treatment during the dose expansion part. Patients were analyzed according to their mutation type. |

| | LXH400mg
BID +
LTT200mg
QD KRAS
NSCLC | LXH400mg
BID +
LTT200mg
QD BRAF
V600 NSCLC | LXH400mg
BID +
LTT200mg
QD BRAF
nonV600
NSCLC | LXH200mg
BID +
TMT1mg QD
NRAS
Melanoma | LXH200mg
BID +
TMT1mg QD
KRAS
NSCLC | LXH200mg
BID +
TMT1mg QD
BRAF
nonV600
NSCLC | LXH400mg
BID +
TMT0.5mg
QD NRAS
Melanoma | LXH400mg
BID +
TMT0.5mg
QD KRAS
NSCLC |
|--------------------------|--|---|---|---|--|---|---|--|
| Arm/Group
Description | MTD/RD
(expansion
only):
naporafenib
400 mg BID +
rineterkib 200
mg QD in
KRAS
NSCLC | MTD/RD
(expansion
only):
naporafenib
400 mg BID +
rineterkib 200
mg QD in
BRAF V600
NSCLC | MTD/RD
(expansion
only):
naporafenib
400 mg BID +
rineterkib 200
mg QD in
BRAF
nonV600
NSCLC | MTD/RD
(expansion
only):
naporafenib
200 mg BID +
trametinib 1
mg QD in
NRAS
Melanoma | MTD/RD
(expansion
only):
naporafenib
200 mg BID +
trametinib 1
mg QD in
KRAS
NSCLC | MTD/RD
(expansion
only):
naporafenib
200 mg BID +
trametinib 1
mg QD in
BRAF
nonV600
NSCLC | MTD/RD
(expansion
only):
naporafenib
400 mg BID +
trametinib 0.5
mg QD in
NRAS
Melanoma | MTD/RD
(expansion
only):
naporafenib
400 mg BID +
trametinib 0.5
mg QD in
KRAS
NSCLC |

| Number of
Participants Analyzed
[units: participants] | 25 | 6 | 21 | 15 | 20 | 9 | 15 | 20 |
|--|---|---|---|---|---|---|---|---|
| Overall Survival (OS)
(expansion only)
(units: months) | Median
(95%
Confidence
Interval) | Median
(95%
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Interval) | Median
(95%
Confidence
Interval) | Median
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Confidence
Interval) | Median
(95%
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Interval) | Median
(95%
Confidence
Interval) | Median
(95%
Confidence
Interval) | Median
(95%
Confidence
Interval) |
| | 8.94
(7.20 to
21.59) | 4.90
(1.97 to NA) ^[1] | 8.84
(3.58 to
18.60) | 9.91
(6.21 to NA) ^[1] | 13.04
(4.60 to NA) ^[1] | 8.94
(0.49 to NA) ^[1] | 6.24
(2.27 to
18.99) | 14.09
(5.65 to
19.42) |

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

Maximum observed plasma concentration (C_{max}) of naporafenib

| | |
|---------------------------------------|---|
| Description | Pharmacokinetic (PK) parameters were calculated based on naporafenib plasma concentrations by using non-compartmental methods. C _{max} is defined as the maximum (peak) observed concentration following a dose. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis
Population
Description | Patients in the pharmacokinetic analysis set (PAS) who received naporafenib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH5
0mg
QD +
LTT1
00mg
QD | LXH1
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
50mg
QD | LXH2
00mg
QD +
LTT3
00mg
QD | LXH3
00mg
QD +
LTT1
00mg
QD | LXH3
50mg
QD +
LTT1
00mg
QD | LXH6
00mg
QD +
LTT1
00mg
QD | MTD/
RD
LXH4
00mg
QD +
LTT2
00mg
QD | LXH2
00mg
QD +
TMT0
.5mg
QD | LXH4
00mg
QD +
TMT1
mg
QD | LXH4
00mg
BID +
TMT1
mg
2wk
on/2
wk
off | MTD/
RD
LXH2
00mg
BID +
TMT1
mg
QD | MTD/
RD
LXH4
00mg
BID +
TMT0
.5mg
QD | LXH2
00mg
BID +
LEE4
00mg
3wk
on/1
wk
off | LXH4
00mg
BID +
LEE2
00mg
3wk
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off | LXH4
00mg
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QD +
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QD | 400
mg
BID +
trame
tinib 1
mg 2
week
s on
and 2
week
s off | napor
afenib
200
mg
BID +
trame
tinib 1
mg
QD | napor
afenib
400
mg
BID +
trame
tinib
0.5
mg
QD | 200
mg
BID +
riboci
clib
400
mg 3
week
s on
and 1
week
s off | 400
mg
BID +
riboci
clib
200
mg 3
week
s on
and 1
week
s off | 400
mg
BID +
riboci
clib
400
mg 3
week
s on
and 1
week
s off |
| Numbe
r of
Partici
pants
Analyz
ed
[units:
partici
pants] | 5
(C1D
1), 3
(C1D
15) | 4
(C1D
1), 3
(C1D
15) | 5
(C1D
1), 5
(C1D
15) | 5
(C1D
1), 4
(C1D
15) | 5
(C1D
1), 1
(C1D
15) | 5
(C1D
1), 4
(C1D
15) | 5
(C1D
1), 5
(C1D
15) | 6
(C1D
1), 4
(C1D
15) | 52
(C1D
1), 36
(C1D
15) | 6
(C1D
1), 6
(C1D
15) | 5
(C1D
1), 4
(C1D
15) | 6
(C1D
1), 1
(C1D
15) | 53
(C1D
1), 43
(C1D
15) | 44
(C1D
1), 35
(C1D
15) | 6
(C1D
1), 6
(C1D
15) | 9
(C1D
1), 5
(C1D
15) | 0
(C1D
1), 0
(C1D
15) |
| Maxim
um
observ
ed
plasma
conce
ntratio
n
(Cmax)
of
napora
fenib
(units:
ng/mL) | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion | Mean
±
Stan
dard
Devia
tion |
| Cycle 1
Day 1 | 228 ±
133 | 356 ±
158 | 1590
± 760 | 848 ±
349 | 766 ±
386 | 1360
± 621 | 1710
± 927 | 2390
±
1380 | 1550
± 772 | 1300
± 803 | 1800
± 727 | 1810
± 766 | 985 ±
655 | 1650
± 952 | 1130
± 383 | 1970
±
1340 | |

| | | | | | | | | | | | | | | | | |
|---------|-------|-------|-------|--------|------|--------|--------|--------|--------|--------|-------|------|-------|--------|-------|--------|
| Cycle 1 | 292 ± | 554 ± | 1760 | 1560 | | 4310 | 3090 | 3430 | 3490 | 3780 | 3740 | 5390 | 2500 | 4370 | 2150 | 4180 |
| Day 15 | 258 | 328 | ± 259 | ± 1470 | 1040 | ± 2000 | ± 1080 | ± 2690 | ± 1410 | ± 2410 | ± 711 | | ± 992 | ± 3210 | ± 915 | ± 2380 |

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

| | |
|---------------------|--|
| Description | PK parameters were calculated based on naporafenib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC calculation. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis Population | Patients in the pharmacokinetic analysis set (PAS) who received naporafenib and had an available value for the outcome measure at the corresponding timepoint. |
| Description | |

| | LXH5
0mg
QD +
LTT1
00mg
QD | LXH1
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
50mg
QD | LXH2
00mg
QD +
LTT3
00mg
QD | LXH3
00mg
BID +
LTT1
00mg
QD | LXH3
50mg
QD +
LTT1
00mg
QD | LXH6
00mg
BID +
LTT1
00mg
QD | MTD/
RD
LXH4
00mg
BID +
LTT2
00mg
QD | LXH2
00mg
BID +
TMT0
.5mg
QD | LXH4
00mg
BID +
TMT1
mg
QD | LXH4
00mg
BID +
TMT1
mg
2wk
on/2
wk
off | MTD/
RD
LXH2
00mg
BID +
TMT1
mg
QD | MTD/
RD
LXH4
00mg
BID +
TMT0
.5mg
QD | LXH2
00mg
BID +
LEE4
00mg
3wk
on/1
wk
off | LXH4
00mg
BID +
LEE2
00mg
3wk
on/1
wk
off | LXH4
00mg
BID +
LEE4
00mg
3wk
on/1
wk
off |
|-----------------------|---|--|--|--|--|---|--|---|--|---|---|---|--|--|---|---|---|
| Arm/Group Description | Escalation part: naporafenib 50 mg QD + rinete rkib 100 | Escalation part: naporafenib 100 mg QD + rinete rkib 100 | Escalation part: naporafenib 200 mg QD + rinete rkib 100 | Escalation part: naporafenib 200 mg QD + rinete rkib 150 | Escalation part: naporafenib 200 mg QD + rinete rkib 300 | Escalation part: naporafenib 300 mg BID + rinete rkib 100 | Escalation part: naporafenib 350 mg QD + rinete rkib 100 | Escalation part: naporafenib 600 mg BID + rinete rkib 100 | Escalation and expansion: naporafenib 400 mg BID + rinete rkib | Escalation part: naporafenib 200 mg BID + trame tinib 0.5 | Escalation part: naporafenib 400 mg BID + trame tinib 1 mg QD | Escalation part: naporafenib 400 mg BID + trame tinib 1 mg 2 week | Escalation and expansion: naporafenib 200 mg BID + trame tinib 1 | Escalation and expansion: naporafenib 400 mg BID + trame tinib | Escalation part: naporafenib 200 mg BID + riboci clib 400 mg 3 | Escalation part: naporafenib 400 mg BID + riboci clib 200 mg 3 | Escalation part: naporafenib 400 mg BID + riboci clib 400 mg 3 |

| | mg
QD | mg
QD | mg
QD | mg
QD | mg
QD | mg
QD | mg
QD | mg
QD | 200
mg
QD | mg
QD | | s on
and 2
week
s off | mg
QD | 0.5
mg
QD | week
s on
and 1
week
s off | week
s on
and 1
week
s off | week
s on
and 1
week
s off |
|---|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|-------------------------------------|------------------------------------|------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--|--|--|
| Number of
Participants
Analyzed
[units:
participants] | 5
(C1D
1), 3
(C1D
15) | 4
(C1D
1), 3
(C1D
15) | 5
(C1D
1), 5
(C1D
15) | 5
(C1D
1), 3
(C1D
15) | 5
(C1D
1), 1
(C1D
15) | 5
(C1D
1), 3
(C1D
15) | 5
(C1D
1), 5
(C1D
15) | 6
(C1D
1), 3
(C1D
15) | 51
(C1D
1), 35
(C1D
15) | 6
(C1D
1), 6
(C1D
15) | 5
(C1D
1), 4
(C1D
15) | 6
(C1D
1), 1
(C1D
15) | 52
(C1D
1), 42
(C1D
15) | 44
(C1D
1), 35
(C1D
15) | 6
(C1D
1), 6
(C1D
15) | 8
(C1D
1), 5
(C1D
15) | 0
(C1D
1), 0
(C1D
15) |
| Area
under
the
plasma
concentration-
time
curve
from
time
zero to
the
time of
the last
quantifiable
concentration
(AUClast)
of
naprofenib
(units:
h*ng/mL) | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation | Mean
±
Standard
Deviation |

| | | | | | | | | | | | | | | | | |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Cycle 1 | 3830 | 7330 | 2030 | 1460 | 1520 | 2850 | 3030 | 4760 | 3110 | 2560 | 3690 | 3130 | 1720 | 2800 | 1070 | 3610 |
| Day 1 | ± | ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± |
| | 2770 | 2980 | 9700 | 7260 | 4530 | 1570 | 9230 | 3240 | 1870 | 2390 | 1560 | 1750 | 1500 | 2160 | 4840 | 3340 |
| | | | | | | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cycle 1 | 4080 | 6290 | 2340 | 2350 | | 4790 | 4240 | 6970 | 4490 | 7180 | 8040 | | 3650 | 6870 | 2420 | 5590 |
| Day 15 | ± | ± | 0 ± | 0 ± | 1110 | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 0 ± | 3720 | 0 ± | 0 ± | 0 ± | 0 ± |
| | 2990 | 4240 | 6350 | 1210 | 0 | 1180 | 1910 | 4910 | 2920 | 5720 | 3270 | 0 | 2310 | 7050 | 1450 | 4050 |
| | | | | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |

Maximum observed plasma concentration (Cmax) of rineterkib

| | |
|---------------------------------|--|
| Description | PK parameters were calculated based on rineterkib plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis Population Description | Patients in the pharmacokinetic analysis set (PAS) who received rineterkib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH50mg
QD +
LTT100mg
QD | LXH100mg
QD +
LTT100mg
QD | LXH200mg
QD +
LTT100mg
QD | LXH200mg
QD +
LTT150mg
QD | LXH200mg
QD +
LTT300mg
QD | LXH300mg
BID +
LTT100mg
QD | LXH350mg
QD +
LTT100mg
QD | LXH600mg
BID +
LTT100mg
QD | MTD/RD
LXH400mg
BID +
LTT200mg
QD |
|--|--|---|---|---|---|--|---|--|---|
| Arm/Group Description | Escalation part:
naporafenib
50 mg QD +
rineterkib
100 mg QD | Escalation part:
naporafenib
100 mg QD
+ rineterkib
100 mg QD | Escalation part:
naporafenib
200 mg QD
+ rineterkib
100 mg QD | Escalation part:
naporafenib
200 mg QD
+ rineterkib
150 mg QD | Escalation part:
naporafenib
200 mg QD
+ rineterkib
300 mg QD | Escalation part:
naporafenib
300 mg BID
+ rineterkib
100 mg QD | Escalation part:
naporafenib
350 mg QD
+ rineterkib
100 mg QD | Escalation part:
naporafenib
600 mg BID
+ rineterkib
100 mg QD | Escalation and expansion:
naporafenib
400 mg BID
+ rineterkib
200 mg QD |
| Number of Participants Analyzed [units: participants] | 5 (C1D1), 3 (C1D15) | 4 (C1D1), 3 (C1D15) | 5 (C1D1), 5 (C1D15) | 5 (C1D1), 4 (C1D15) | 6 (C1D1), 1 (C1D15) | 5 (C1D1), 5 (C1D15) | 5 (C1D1), 4 (C1D15) | 6 (C1D1), 4 (C1D15) | 51 (C1D1), 33 (C1D15) |

| Maximum observed plasma concentration (C _{max}) of rineterkib (units: ng/mL) | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation | Mean ± Standard Deviation |
|--|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Cycle 1 Day 1 | 373 ± 108 | 208 ± 58.7 | 565 ± 404 | 366 ± 108 | 1220 ± 684 | 335 ± 206 | 447 ± 142 | 272 ± 147 | 751 ± 514 |
| Cycle 1 Day 15 | 1090 ± 733 | 638 ± 204 | 988 ± 271 | 1040 ± 270 | 3070 | 756 ± 283 | 940 ± 414 | 324 ± 209 | 1550 ± 550 |

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}) of rineterkib

| | |
|---------------------------------|--|
| Description | PK parameters were calculated based on rineterkib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC calculation. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis Population Description | Patients in the pharmacokinetic analysis set (PAS) who received rineterkib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH50mg QD + LTT100mg QD | LXH100mg QD + LTT100mg QD | LXH200mg QD + LTT100mg QD | LXH200mg QD + LTT150mg QD | LXH200mg QD + LTT300mg QD | LXH300mg BID + LTT100mg QD | LXH350mg QD + LTT100mg QD | LXH600mg BID + LTT100mg QD | MTD/RD LXH400mg BID + LTT200mg QD |
|-------------------------------|--|---|---|---|---|--|---|--|---|
| Arm/Group Description | Escalation part: naporafenib 50 mg QD + rineterkib 100 mg QD | Escalation part: naporafenib 100 mg QD + rineterkib 100 mg QD | Escalation part: naporafenib 200 mg QD + rineterkib 100 mg QD | Escalation part: naporafenib 200 mg QD + rineterkib 150 mg QD | Escalation part: naporafenib 200 mg QD + rineterkib 300 mg QD | Escalation part: naporafenib 300 mg BID + rineterkib 100 mg QD | Escalation part: naporafenib 350 mg QD + rineterkib 100 mg QD | Escalation part: naporafenib 600 mg BID + rineterkib 100 mg QD | Escalation and expansion: naporafenib 400 mg BID + rineterkib 200 mg QD |
| Number of Participants | 5 (C1D1), 3 (C1D15) | 4 (C1D1), 3 (C1D15) | 5 (C1D1), 5 (C1D15) | 5 (C1D1), 4 (C1D15) | 6 (C1D1), 1 (C1D15) | 5 (C1D1), 4 (C1D15) | 5 (C1D1), 4 (C1D15) | 6 (C1D1), 3 (C1D15) | 51 (C1D1), 32 (C1D15) |

Analyzed [units:
participants]

Area under the
plasma
concentration-
time curve from
time zero to the
time of the last
quantifiable
concentration
(AUClast) of
rineterkib
(units: h*ng/mL)

| | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation |
|----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Cycle 1 Day 1 | 5350 ± 2090 | 4020 ± 1000 | 7800 ± 5830 | 6970 ± 2000 | 18900 ± 9090 | 5770 ± 3650 | 7190 ± 3200 | 5230 ± 3390 | 13100 ± 7810 |
| Cycle 1 Day 15 | 14600 ± 5890 | 9120 ± 3980 | 13600 ± 3900 | 14800 ± 3780 | 47900 | 9800 ± 4220 | 9980 ± 2430 | 8010 ± 4480 | 20800 ± 11300 |

Maximum observed plasma concentration (Cmax) of trametinib

| | |
|---------------------------------|--|
| Description | PK parameters were calculated based on trametinib plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis Population Description | Patients in the pharmacokinetic analysis set (PAS) who received trametinib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH200mg BID +
TMT0.5mg QD | LXH400mg BID +
TMT1mg QD | LXH400mg BID +
TMT1mg 2wk
on/2wk off | MTD/RD LXH200mg
BID + TMT1mg QD | MTD/RD LXH400mg
BID + TMT0.5mg
QD |
|-----------------------|---|---|--|--|--|
| Arm/Group Description | Escalation part:
naporafenib 200 mg
BID + trametinib 0.5
mg QD | Escalation part:
naporafenib 400 mg
BID + trametinib 1
mg QD | Escalation part:
naporafenib 400 mg
BID + trametinib 1 | Escalation and
expansion:
naporafenib 200 mg | Escalation and
expansion:
naporafenib 400 mg |

| | | | mg 2 weeks on and
2 weeks off | BID + trametinib 1
mg QD | BID + trametinib 0.5
mg QD |
|---|--|--|--|--|--|
| Number of Participants Analyzed
[units: participants] | 6 (C1D1), 6 (C1D15) | 5 (C1D1), 3 (C1D15) | 0 (C1D1), 0 (C1D15) | 52 (C1D1), 41
(C1D15) | 42 (C1D1), 34
(C1D15) |
| Maximum observed plasma
concentration (C_{max}) of trametinib
(units: ng/mL) | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation | Mean
± Standard
Deviation |
| Cycle 1 Day 1 | 1.45 ± 0.927 | 2.19 ± 0.536 | | 3.77 ± 2.84 | 1.5 ± 1.08 |
| Cycle 1 Day 15 | 7.88 ± 3.3 | 10.8 ± 4.66 | | 17.9 ± 6.45 | 7.06 ± 3.21 |

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}) of trametinib

| | |
|---------------------------------------|--|
| Description | PK parameters were calculated based on trametinib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC calculation. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis
Population
Description | Patients in the pharmacokinetic analysis set (PAS) who received trametinib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH200mg BID +
TMT0.5mg QD | LXH400mg BID +
TMT1mg QD | LXH400mg BID +
TMT1mg 2wk
on/2wk off | MTD/RD LXH200mg
BID + TMT1mg QD | MTD/RD LXH400mg
BID + TMT0.5mg
QD |
|--|---|---|--|---|---|
| Arm/Group Description | Escalation part:
naporafenib 200 mg
BID + trametinib 0.5
mg QD | Escalation part:
naporafenib 400 mg
BID + trametinib 1
mg QD | Escalation part:
naporafenib 400 mg
BID + trametinib 1
mg 2 weeks on and
2 weeks off | Escalation and
expansion:
naporafenib 200 mg
BID + trametinib 1
mg QD | Escalation and
expansion:
naporafenib 400 mg
BID + trametinib 0.5
mg QD |
| Number of Participants Analyzed
[units: participants] | 6 (C1D1), 6 (C1D15) | 5 (C1D1), 3 (C1D15) | 0 (C1D1), 0 (C1D15) | 51 (C1D1), 39
(C1D15) | 42 (C1D1), 34
(C1D15) |

| Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of trametinib (units: h*ng/mL) | Mean
± Standard Deviation | Mean
± Standard Deviation | Mean
± Standard Deviation | Mean
± Standard Deviation | Mean
± Standard Deviation |
|---|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| Cycle 1 Day 1 | 18.7 ± 5.7 | 36.1 ± 15 | | 46.2 ± 25.1 | 17.2 ± 13.7 |
| Cycle 1 Day 15 | 126 ± 36.5 | 203 ± 72.4 | | 304 ± 125 | 128 ± 58.1 |

Maximum observed plasma concentration (Cmax) of ribociclib

| | |
|---------------------------------|--|
| Description | PK parameters were calculated based on ribociclib plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis Population Description | Patients in the pharmacokinetic analysis set (PAS) who received ribociclib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH200mg BID + LEE400mg
3wk on/1wk off | LXH400mg BID + LEE200mg
3wk on/1wk off | LXH400mg BID + LEE400mg
3wk on/1wk off |
|--|--|--|--|
| Arm/Group Description | Escalation part: naporafenib
200 mg BID + ribociclib 400 mg
3 weeks on and 1 weeks off | Escalation part: naporafenib
400 mg BID + ribociclib 200 mg
3 weeks on and 1 weeks off | Escalation part: naporafenib
400 mg BID + ribociclib 400 mg
3 weeks on and 1 weeks off |
| Number of Participants Analyzed [units: participants] | 0 (C1D1), 0 (C1D15) | 8 (C1D1), 4 (C1D15) | 9 (C1D1), 6 (C1D15) |
| Maximum observed plasma concentration (Cmax) of ribociclib (units: ng/mL) | Mean
± Standard Deviation | Mean
± Standard Deviation | Mean
± Standard Deviation |
| Cycle 1 Day 1 | | 219 ± 176 | 546 ± 301 |
| Cycle 1 Day 15 | | 374 ± 213 | 1300 ± 841 |

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

| | |
|---------------------------------|--|
| Description | PK parameters were calculated based on ribociclib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC calculation. |
| Time Frame | pre-dose, 0.5, 1, 2, 3, 4, 8 and 24 hours after administration on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and 48 hours after administration on C1D1. The duration of one cycle was 28 days. |
| Analysis Population Description | Patients in the pharmacokinetic analysis set (PAS) who received ribociclib and had an available value for the outcome measure at the corresponding timepoint. |

| | LXH200mg BID + LEE400mg
3wk on/1wk off | LXH400mg BID + LEE200mg
3wk on/1wk off | LXH400mg BID + LEE400mg
3wk on/1wk off |
|--|--|--|--|
| Arm/Group Description | Escalation part: naporafenib
200 mg BID + ribociclib 400 mg
3 weeks on and 1 weeks off | Escalation part: naporafenib
400 mg BID + ribociclib 200 mg
3 weeks on and 1 weeks off | Escalation part: naporafenib
400 mg BID + ribociclib 400 mg
3 weeks on and 1 weeks off |
| Number of Participants Analyzed [units: participants] | 0 (C1D1), 0 (C1D15) | 7 (C1D1), 4 (C1D15) | 9 (C1D1), 6 (C1D15) |
| Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of ribociclib (units: h*ng/mL) | Mean
± Standard Deviation | Mean
± Standard Deviation | Mean
± Standard Deviation |
| Cycle 1 Day 1 | | 2860 ± 2350 | 5300 ± 3800 |
| Cycle 1 Day 15 | | 4320 ± 3680 | 17500 ± 11100 |

Percentage change from baseline in relative quantity of DUSP6 expression

| | |
|-------------|---|
| Description | DUSP6 mRNA levels were assessed in paired tumor biopsy samples to evaluate the expression of DUSP6. |
| Time Frame | Baseline (pre-dose) and Cycle 1 Day 15. The duration of one cycle was 28 days. |

Analysis Population Description
 Patients who received at least one dose of study treatment and had paired tumor biopsy samples.

| | LXH5
0mg
QD +
LTT1
00mg
QD | LXH1
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
50mg
QD | LXH2
00mg
QD +
LTT3
00mg
QD | LXH3
00mg
BID +
LTT1
00mg
QD | LXH3
50mg
QD +
LTT1
00mg
QD | LXH6
00mg
BID +
LTT1
00mg
QD | MTD/
RD
LXH4
00mg
BID +
LTT2
00mg
QD | LXH2
00mg
BID +
TMT0
.5mg
QD | LXH4
00mg
BID +
TMT1
mg
QD | LXH4
00mg
BID +
TMT1
mg
2wk
on/2
wk
off | MTD/
RD
LXH2
00mg
BID +
TMT1
mg
QD | MTD/
RD
LXH4
00mg
BID +
TMT0
.5mg
QD | LXH2
00mg
BID +
LEE4
00mg
3wk
on/1
wk
off | LXH4
00mg
BID +
LEE2
00mg
3wk
on/1
wk
off | LXH4
00mg
BID +
LEE4
00mg
3wk
on/1
wk
off |
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QD | Escal
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QD +
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part:
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rinete
rkib
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QD | Escal
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part:
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QD | Escal
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part:
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afenib
400
mg
BID +
trame
tinib
1 mg
QD | Escal
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part:
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400
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BID +
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1 mg
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partici
pants]

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relativ
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DUSP
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(units:
%
chang
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baseli
ne)

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Rang
e) | Medi
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| -5.8 | -56.2 | | | -1.9 | -20.2 | | | -51.2 | | -61.8 | -73.0 | -81.7 | -64.4 | | -39.7 | -3.5 |
| (-18.5 | (-56.2 | | | (-1.9 | (-56.9 | | | (-88.3 | | (-87.4 | (-77.4 | (-94.8 | (-79.4 | | (-58.9 | (-3.5 |
| to - | to - | | | to - | to - | | | to - | | to - | to - | to - | to - | | to - | to - |
| 6.9) | 56.2) | | | 1.9) | 16.4) | | | 19.0) | | 36.3) | 68.6) | 57.7) | 60.3) | | 35.7) | 3.5) |

Post-Hoc Outcome Result(s)

All-Collected Deaths

| | |
|-------------|--|
| Description | On-treatment deaths were collected from first dose of study treatment to 30 days after last dose. Survival follow-up (FU) deaths were collected from 31 days after last dose until end of study. All deaths refer to the sum of on-treatment and survival FU deaths. |
| Time Frame | On-treatment deaths: up to approximately 1.3 years (naporafenib + rineterkib), 2.4 years (naporafenib + trametinib) and 3.7 years (naporafenib + ribociclib). Survival FU deaths: up to approximately 7 years |

Analysis Population Description
All patients who received at least one dose of study treatment.

| | LXH5
0mg
QD +
LTT1
00mg
QD | LXH1
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
00mg
QD | LXH2
00mg
QD +
LTT1
50mg
QD | LXH2
00mg
QD +
LTT3
00mg
QD | LXH3
00mg
QD +
LTT1
00mg
QD | LXH3
50mg
QD +
LTT1
00mg
QD | LXH6
00mg
QD +
LTT1
00mg
QD | MTD/
RD
LXH4
00mg
QD +
LTT2
00mg
QD | LXH2
00mg
QD +
TMT0
.5mg
QD | LXH4
00mg
QD +
TMT1
mg
QD | LXH4
00mg
QD +
TMT1
mg
2wk
on/2
wk
off | MTD/
RD
LXH2
00mg
QD +
TMT1
mg
QD | MTD/
RD
LXH4
00mg
QD +
TMT0
.5mg
QD | LXH2
00mg
QD +
LEE4
00mg
3wk
on/1
wk
off | LXH4
00mg
QD +
LEE2
00mg
3wk
on/1
wk
off | LXH4
00mg
QD +
LEE4
00mg
3wk
on/1
wk
off |
|--|--|--|--|--|--|--|--|--|--|--|--|---|--|--|--|--|--|
| Arm/G
roup
Descri
ption | Escal
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napor
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50 mg
QD +
rinete
rkib
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mg
QD | Escal
ation
part:
napor
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mg
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rinete
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mg
QD | Escal
ation
part:
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afenib
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val), | 6 (on-
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val), |

| participants] | | | | | | | | | 58
(all) | | | | 54
(all) | | 44
(all) | | 10
(all) | |
|---|---|---|---|---|---|---|---|---|-------------|---|---|---|-------------|----|-------------|---|-------------|--|
| All-Collected Deaths
(units: participants) | | | | | | | | | | | | | | | | | | |
| On-treatment deaths | 4 | 1 | 2 | 1 | 1 | 2 | 0 | 2 | 7 | 1 | 1 | 3 | 15 | 9 | 0 | 0 | 2 | |
| Survival follow-up deaths | 0 | 0 | 1 | 3 | 1 | 2 | 3 | 1 | 30 | 4 | 2 | 2 | 22 | 18 | 2 | 4 | 3 | |
| All deaths | 4 | 1 | 3 | 4 | 2 | 4 | 3 | 3 | 37 | 5 | 3 | 5 | 37 | 27 | 2 | 4 | 5 | |

Safety Results

| | |
|--|---|
| Time Frame | On-treatment: From first dose of study treatment to 30 days after last dose, up to approximately 1.3 years (naporafenib + rineterkib), 2.4 years (naporafenib + trametinib) and 3.7 years (naporafenib + ribociclib).
Deaths in survival period: from 31 days after last dose until end of study, up to approximately 7 years. |
| Source Vocabulary for Table Default | MedDRA (27.0) |
| Collection Approach for Table Default | Systematic Assessment |

On-treatment period

Page 51

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|----|----|---|----|---|---|---|----|----|-----------|-----------|-----------|
| | | | | | | | | | | | | | | | | | | | ks
off | ks
off | ks
off |
| Total
Number
Affected | 4 | 1 | 2 | 1 | 1 | 2 | 0 | 2 | 2 | 5 | 7 | 1 | 4 | 2 | 1 | 3 | 15 | 9 | 0 | 0 | 2 |
| Total
Number
At
Risk | 5 | 4 | 6 | 5 | 7 | 5 | 5 | 6 | 6 | 52 | 58 | 6 | 10 | 9 | 5 | 6 | 54 | 44 | 6 | 9 | 10 |

Survival period

| | | | | | | | | | | MT
D/R
D | MT
D/R
D | | | | | | LXH
400
mg
D | MT
D/R
D | MT
D/R
D | LXH
200
mg
D | LXH
400
mg
D | LXH
400
mg
D | | | | | | | | |
|----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------|------------------------------------|-------------------------------|---|-------------------------------|-------------------------------------|--|--|---|
| | | | | | | | | | | LXH
400
mg
D | LXH
400
mg
D | LXH
200
mg
D | LXH
200
mg
D | LXH
400
mg
D | LXH
400
mg
D | LXH
400
mg
D | LXH
400
mg
D | LXH
400
mg
D | LXH
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D | LXH
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mg
D | LXH
400
mg
D | | | | | | | | |
| | | | | | | | | | | LXH
50
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+ | LXH
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QD
+ | LXH
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4 | LTT
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N =
6 | LTT
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N =
5 | LTT
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7 | LTT
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N =
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N =
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mg
QD
N =
9 | TMT
1mg
QD
N =
5 | TMT
2wk
on/2
wk
off
N =
6 | TMT
1mg
QD
N =
54 | TMT
0.5
mg
QD
N =
44 | LEE
400
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3wk
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wk
off
N =
6 | LEE
200
mg
3wk
on/1
wk
off
N =
9 | LEE
400
mg
3wk
on/1
wk
off
N =
10 |
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No
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od. | surv
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No
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No
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od. | surv
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No
AEs
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No
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ng
this
peri
od. | surv
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No
AEs
wer
e
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od. | surv
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No
AEs
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ival
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No
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e
colle
cted
duri
ng
this
peri
od. | surv
ival
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duri
ng
this
peri
od. | surv
ival
peri
od.
No
AEs
wer
e
colle
cted
duri
ng
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peri
od. |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| Total
Nu
mbe
r
Affe
cted | 0 | 0 | 1 | 3 | 1 | 2 | 3 | 1 | 1 | 29 | 30 | 4 | 3 | 1 | 2 | 2 | 22 | 18 | 2 | 4 | 3 |
| Total
Nu
mbe
r At
Risk | 1 | 3 | 4 | 4 | 6 | 3 | 5 | 4 | 4 | 47 | 51 | 5 | 6 | 7 | 4 | 3 | 39 | 35 | 6 | 9 | 8 |

Serious Adverse Events

Time Frame

From first dose of study treatment to 30 days after last dose, up to approximately 1.3 years (naporafenib + rineterkib), 2.4 years (naporafenib + trametinib) and 3.7 years (naporafenib + ribociclib).

**Source Vocabulary
for Table Default** MedDRA (27.0)

**Collection
Approach for Table
Default** Systematic Assessment

| | | | | | | | | | | MT
D/R
D | MT
D/R
D | | | | | LX
H40
0m | MT
D/R
D | MT
D/R
D | LX
H20
0m | LX
H40
0m | LX
H40
0m |
|--------------------------|--|---|---|---|---|--|---|--|--|---|--|--|--|--|--|--|--|--|--|--|--|
| | | | | | | | | | | LX
H40
0m | LX
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0m | LX
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| | | | | | | | | | | TM | TM | TM | TM | TM | TM | TM | TM | TM | TM | TM | TM |
| | | | | | | | | | | 5m | 5m | 5m | 5m | 5m | 5m | 5m | 5m | 5m | 5m | 5m | 5m |
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| | | | | | | | | | | QD | QD | QD | QD | QD | QD | QD | QD | QD | QD | QD | QD |
| | | | | | | | | | | N = | N = | N = | N = | N = | N = | N = | N = | N = | N = | N = | N = |
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| Total #
Affected by
any
Serious
Adverse
Event | 3 | 2 | 4 | 5 | 1 | 4 | 4 | 5 | 2 | 33 | 38 | 4 | 7 | 4 | 3 | 1 | 31 | 23 | 1 | 4 | 6 |
| Total #
at Risk
by any
Serious
Adverse
Event | 5 | 4 | 6 | 5 | 7 | 5 | 5 | 6 | 6 | 52 | 58 | 6 | 10 | 9 | 5 | 6 | 54 | 44 | 6 | 9 | 10 |
| Blood
and
lymphatic
system
disorders | | | | | | | | | | | | | | | | | | | | | |
| Anaemia | 1 (2
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| Febrile
neutropenia | 0 (0
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| Cardiac disorders | | | | | | | | | | | | | | | | | | | | | |
| Acute coronary syndrome | 0 (0
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| Dysphagia | 0 (0
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| Gastric ulcer | 0 (0
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| Intestinal obstruction | 0 (0
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%) | 0 (0
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%) |
| Obstructive pancreatitis | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) |

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|---|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|--------------------|-------------------|
| Pancr
eatitis | 0 (0
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| Small
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nal
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orrhage | 0 (0
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| Upper
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tinal
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orrhage | 0 (0
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| Volvu
lus of
small
bowel | 0 (0
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| Vomit
ing | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
.92
%) | 1 (1
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (2
.27
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) |
| General
disorders and
administration
site
conditions | | | | | | | | | | | | | | | | | | | | | |
| Asthe
nia | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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1.11
%) | 0 (0
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%) |

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|---------------------------------------|--------------|--------------|--------------|-------------|-------------|--------------|-------------|-------------|--------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|
| Catheter site discharge | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 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 .85 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Gait disturbance | 0 (0 .00 %) | 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 .92 %) | 1 (1 .72 %) | 0 (0 .00 %) | 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 0.00 %) |
| General physical health deterioration | 1 (2 0.00 %) | 0 (0 .00 %) | 1 (1 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 6.67 %) | 2 (3 .85 %) | 2 (3 .45 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 3 (5 .56 %) | 1 (2 .27 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 0.00 %) |
| Influenza like illnesses | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 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 .85 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Non-cardiac chest pain | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 .85 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Oedema peripheral | 0 (0 .00 %) | 1 (2 5.00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Pain | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (2 0.00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 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 (2 .27 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |

| | | | | | | | | | | | | | | | | | | | | | |
|-----------------------------|-------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|
| Pyrexia | 0 (0
.00
%) | 1 (2
5.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5
.77
%) | 3 (5
.17
%) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
.70
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Sudden death | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hepatobiliary disorders | | | | | | | | | | | | | | | | | | | | | |
| Autoimmune hepatitis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Infections and infestations | | | | | | | | | | | | | | | | | | | | | |
| Abdominal sepsis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
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.85
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) |
| Bacteraemia | 0 (0
.00
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
.70
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Bronchitis | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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0.00
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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| Cellulitis | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 2 (3
.70
%) | 0 (0
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%) | 0 (0
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%) |
| COVID-19 | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) | 1 (1
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%) | 2 (3
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|--|-------------------|-------------------|-------------------|--------------------|-------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| Device
related
infection | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
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%) | 0 (0
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%) | 2 (3
.70
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
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| Endocarditis | 0 (0
.00
%) | 0 (0
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.00
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| Erysipelas | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
0.00
%) |
| Gastroenteritis | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) |
| Infection | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (2
0.00
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%) | 0 (0
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| Influenza | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.92
%) | 1 (1
.72
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Lower
respiratory
tract
infection | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Pneumocystis
jirovecii
pneumonia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.92
%) | 1 (1
.72
%) | 0 (0
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|-------------------------------|-------------------|-------------------|--------------------|--------------------|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| Pneumonia | 1 (2
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (2
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1
.92
%) | 1 (1
.72
%) | 0 (0
.00
%) | 2 (2
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
.70
%) | 2 (4
.55
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Postoperative wound infection | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Pustule | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Respiratory tract infection | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.85
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Sepsis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 1 (1
.85
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Septic shock | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.92
%) | 1 (1
.72
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Skin infection | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.85
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Urinary tract infection | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 1 (2
0.00
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%) | 1 (1
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%) | 0 (0
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%) |

**Injury,
poisoning and
procedural**

**compl
ications**

| | | | | | | | | | | | | | | | | | | | | | | |
|------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Femur fracture | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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.00
%) | 1 (1
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%) | 1 (1
.72
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) |
| Post procedural complication | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Spinal fracture | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Toxicity to various agents | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
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%) | 0 (0
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%) |

**Investi
gations**

| | |
|------------------------------------|--------------------|
| Alanine aminotransferase increased | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Aspartate aminotransferase | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |

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|-------------------------------------|------------|-----------|-----------|-----------|-----------|------------|-----------|-----------|-----------|------------|------------|-----------|------------|-----------|-----------|-----------|------------|-----------|-----------|------------|-----------|
| increased | | | | | | | | | | | | | | | | | | | | | |
| Blood creatinine increased | 1 (20.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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 (10.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (18.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Blood pressure decreased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (19.20%) | 1 (17.20%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Electrocardiogram QT prolonged | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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 (11.10%) | 0 (0.00%) |
| Gamma-glutamyltransferase increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (19.20%) | 1 (17.20%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Lipase increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (10.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (18.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Oxygen saturation decreased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |

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|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Weight decreased | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.72
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Metabolism and nutrition disorders | | | | | | | | | | | | | | | | | | | | | |
| Decreased appetite | 0 (0
.00
%) | 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 (3
.85
%) | 2 (3
.45
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Dehydration | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.72
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hyperkalemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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6.67
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Hypонатremia | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | | | | | | | | | | | | |
| Arthralgia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.92
%) | 1 (1
.72
%) | 0 (0
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|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| Back pain | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) | 1 (1
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) |
| Bone pain | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
1.11
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Pain in extremity | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | | | | | | | | | | | | | | | | | |
| Acute myeloid leukemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Basal cell carcinoma | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
.85
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Malignant neoplasm progression | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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|---|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Meta
stase
s to
adren
als | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 1 (2
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%) | 0 (0
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%) |
| Meta
stase
s to
centr
al
nervo
us
syste
m | 0 (0
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| Oncol
ogic
compl
icatio
n | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Tumo
ur
pain | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
6.67
%) | 0 (0
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%) | 0 (0
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%) | 1 (1
.72
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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.00
%) | 1 (1
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%) | 1 (2
.27
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) |
| Nervou
s
system
disorde
rs | | | | | | | | | | | | | | | | | | | | | |
| Acute
polyn
europ
athy | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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| Ataxi
a | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) | 1 (1
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) |
| Brain
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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 (2
.27
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Peripheral ischaemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
.72
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

Other (Not Including Serious) Adverse Events

Time Frame From first dose of study treatment to 30 days after last dose, up to approximately 1.3 years (naporafenib + rineterkib), 2.4 years (naporafenib + trametinib) and 3.7 years (naporafenib + ribociclib).

Source Vocabulary for Table Default MedDRA (27.0)

Collection Approach for Table Default Systematic Assessment

Frequent Event Reporting Threshold 5%

| | | | | | | | | | | | | | | | | | | | | |
|-----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------------------------|---------------------------------|----------------------------------|----------------------------------|------------------------------------|------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------------|------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| LX
H50
mg
QD
+
LTT | LX
H10
0m
g
QD
+ | LX
H20
0m
g
QD
+ | LX
H20
0m
g
QD
+ | LX
H20
0m
g
QD
+ | LXH
300
mg
BID
+
LTT | LX
H35
0m
g
QD
+ | LX
H40
0m
g
BID
+ | LX
H60
0m
g
BID
+ | MT
D/R
D
LXH
400
mg | MT
D/R
D
LXH
400
mg | LX
H20
0m
g
BID
+ | LX
H20
0m
g
BID
+ | LX
H40
0m
g
BID
+ | LX
H40
0m
g
BID
+ | LX
H40
0m
g
BID
+ | MT
D/R
D
LXH
200
mg | MT
D/R
D
LXH
400
mg | LX
H20
0m
g
BID
+ | LX
H40
0m
g
BID
+ | LX
H40
0m
g
BID
+ |
|-----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------------------------|---------------------------------|----------------------------------|----------------------------------|------------------------------------|------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------------|------------------------------------|----------------------------------|----------------------------------|----------------------------------|

| | 100
mg
QD
N =
5 | LTT
100
mg
QD
N =
4 | LTT
100
mg
QD
N =
6 | LTT
150
mg
QD
N =
5 | LTT
300
mg
QD
N =
7 | 100
mg
QD
N =
5 | LTT
100
mg
QD
N =
5 | LTT
200
mg
QD
N =
6 | LTT
100
mg
QD
N =
6 | BID
+
LTT
200
mg
QD
N =
52 | BID
+
LTT
200
mg
QD
N =
58 | TM
T0.
5m
g
QD
N =
6 | TM
T1
mg
QD
N =
10 | TM
T0.
5m
g
QD
N =
9 | TM
T1
mg
QD
N =
5 | TM
T1
mg
2wk
on/
2wk
off
N =
6 | BID
+
TM
T1
mg
QD
N =
54 | BID
+
TM
T0.5
mg
QD
N =
44 | LEE
400
mg
3wk
on/
1wk
off
N =
6 | LEE
200
mg
3wk
on/
1wk
off
N =
9 | LEE
400
mg
3wk
on/
1wk
off
N =
10 |
|--|--|---|---|---|---|--|--|--|--|---|--|--|--|--|--|--|--|--|--|--|--|
| Arm/Gro
up
Descript
ion | Esc
alati
on
part
:
nap
oraf
enib
50
mg
QD
+
rinet
erki
b
100
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
100
mg
QD
+
rinet
erki
b
100
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
200
mg
QD
+
rinet
erki
b
100
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
200
mg
QD
+
rinet
erki
b
150
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
200
mg
QD
+
rinet
erki
b
300
mg
QD | Esc
alati
on
part:
nap
oraf
enib
300
mg
BID
+
rinet
erki
b
100
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
350
mg
BID
+
rinet
erki
b
100
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
400
mg
BID
+
rinet
erki
b
200
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
600
mg
BID
+
rinet
erki
b
100
mg
QD | Exp
ansi
on
part:
nap
oraf
enib
400
mg
BID
+
rinet
erki
b
200
mg
QD | Esc
alati
on
and
exp
ansi
on:
nap
oraf
enib
400
mg
BID
+
rinet
erki
b
200
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
200
mg
BID
+
tra
meti
nib
0.5
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
200
mg
BID
+
tra
meti
nib
1
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
400
mg
BID
+
tra
meti
nib
0.5
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
400
mg
BID
+
tra
meti
nib
1
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
400
mg
BID
+
tra
meti
nib
1
mg
2
wee
ks
on
and
2
wee
ks
off | Esc
alati
on
and
exp
ansi
on:
nap
oraf
enib
200
mg
BID
+
tra
meti
nib
1
mg
QD | Esc
alati
on
and
exp
ansi
on:
nap
oraf
enib
400
mg
BID
+
tra
meti
nib
0.5
mg
QD | Esc
alati
on
part
:
nap
oraf
enib
200
mg
BID
+
ribo
cicli
b
400
mg
3
wee
ks
on
and
1
wee
ks
off | Esc
alati
on
part
:
nap
oraf
enib
400
mg
BID
+
ribo
cicli
b
200
mg
3
wee
ks
on
and
1
wee
ks
off | Esc
alati
on
part
:
nap
oraf
enib
400
mg
BID
+
ribo
cicli
b
400
mg
3
wee
ks
on
and
1
wee
ks
off |
| Total #
Affected
by any
Other
Adverse
Event | 5 | 4 | 6 | 5 | 7 | 5 | 5 | 6 | 6 | 52 | 58 | 6 | 10 | 9 | 5 | 6 | 53 | 44 | 6 | 9 | 10 |

| Total #
at Risk
by any
Other
Adverse
Event | 5 | 4 | 6 | 5 | 7 | 5 | 5 | 6 | 6 | 52 | 58 | 6 | 10 | 9 | 5 | 6 | 54 | 44 | 6 | 9 | 10 |
|---|--------------------|--------------------|--------------------|--------------------|-------------------|---------------------|-------------------|--------------------|--------------------|-----------------|-----------------|--------------------|--------------------|--------------------|-------------------|--------------------|-----------------|-----------------|--------------------|--------------------|--------------------|
| Blood and lymphatic system disorders | | | | | | | | | | | | | | | | | | | | | |
| Anaemia | 2 (4
0.00
%) | 1 (2
5.00
%) | 1 (1
6.67
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 5 (1
00.0
0%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 21 (40.3
8%) | 22 (37.9
3%) | 4 (6
6.67
%) | 1 (1
0.00
%) | 2 (2
2.22
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 18 (33.3
3%) | 13 (29.5
5%) | 1 (1
6.67
%) | 3 (3
3.33
%) | 3 (3
0.00
%) |
| Eosinophilia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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 (1.85
%) | 1 (2.27
%) | 0 (0
.00
%) | 1 (1.11
%) | 0 (0
.00
%) |
| Hyperleukocytosis | 0 (0
.00
%) | 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 (1.92
%) | 1 (1.72
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 2 (4.55
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Iron deficiency anaemia | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Leukocytosis | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5.56
%) | 2 (4.55
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Leukopenia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0.00
%) | 1 (1.72
%) | 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 (2.22
%) | 0 (0
.00
%) |
| Lymphadenopathy | 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
6.67
%) | 4 (7.69
%) | 4 (6.90
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 3 (5
77%
) | 4 (6
90%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
70%
) | 2 (4
55%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 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
%) | 0 (0
.00
%) | 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 (2
27%
) | 0 (0
.00
%) | 2 (2
2.22
%) | 2 (2
0.00
%) |
| Neutrophilia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
92%
) | 1 (1
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Thrombocytopenia | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 2 (3
85%
) | 2 (3
45%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 4 (7
41%
) | 3 (6
82%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Cardiac disorders | | | | | | | | | | | | | | | | | | | | | |
| Atrial fibrillation | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 1 (1
4.29
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
85%
) | 2 (3
45%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
85%
) | 0 (0
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Bradycardia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Cardiac disorder | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Heart valve incompetence | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Mitral valve incompetence | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
85%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|---|------------------|-------------------|------------------|-------------------|-------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|------------------|-------------------|-------------------|
| Nodal rhythm | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
.00
) | 0 (0
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) | 0 (0
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) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Palpitations | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
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
) | 0 (0
.00
) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
.00
) | 1 (1
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 3 (5
56%
) | 1 (2
27%
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Sinus tachycardia | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Tachycardia | 0 (0
.00
) | 1 (2
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) | 1 (1
6.67
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) | 2 (3
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) | 3 (5
17%
) | 0 (0
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) | 1 (1
1.11
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| Ventricular extrasystoles | 0 (0
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) | 1 (1
4.29
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| Congenital, familial and genetic disorders | | | | | | | | | | | | | | | | | | | | | |
| Hydrocele | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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| Ear and labyrinth disorders | | | | | | | | | | | | | | | | | | | | | |

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|--|--------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|--------------------|--------------------|
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cusis | 0 (0
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| Tinnitu
s | 0 (0
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| Vertig
o | 0 (0
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92%
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72%
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| Endocri
ne
disorder
s | | | | | | | | | | | | | | | | | | | | | |
| Glucoc
orticoi
d
deficie
ncy | 0 (0
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| Hypert
hyroidi
sm | 0 (0
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| Hypot
hyroidi
sm | 1 (2
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%) | 0 (0
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%) | 1 (1
0.00
%) |
| Eye
disorder
s | | | | | | | | | | | | | | | | | | | | | |
| Anisoc
oria | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
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| Blepha
ritis | 0 (0
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%) | 0 (0
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%) | 1 (1
6.67
%) | 2 (3.
70%
) | 1 (2.
27%
) | 0 (0
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%) | 0 (0
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|--|-------------------|-------------------|-------------------|-------------------|--------------------|------------------|-------------------|--------------------|-------------------|------------------|------------------|--------------------|-------------------|-------------------|-------------------|--------------------|------------------|------------------|--------------------|-------------------|--------------------|
| Blindness | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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%) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
92%
) | 2 (3
45%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Cataract | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 2 (2
0.00
%) |
| Cystoid macular oedema | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
4.29
%) | 0 (0
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| Detachment of macular retinal pigment epithelium | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
4.29
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Dry eye | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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%) | 1 (1
6.67
%) | 0 (0
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%) | 2 (3
85%
) | 3 (5
17%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 2 (3
3.33
%) | 0 (0
00%
) | 2 (4
55%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Eyelid rash | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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| Lacrimation increased | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Macular detachment | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
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|---------------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|-------------------|--------------------|-------------------|--------------------|--------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| Macular oedema | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 3 (5.
77%
) | 3 (5.
17%
) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Macular thickening | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
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%) | 1 (1
6.67
%) | 0 (0
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%) | 0 (0
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) | 1 (1.
72%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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| Miosis | 0 (0
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%) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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| Optic disc haemorrhage | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1.
85%
) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Pseudophakia | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 1 (1
0.00
%) |
| Retinal detachment | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (2
8.57
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
85%
) | 2 (3.
45%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 2 (3.
70%
) | 1 (2.
27%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Retinal oedema | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) | 1 (1.
85%
) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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| Retinal thickening | 0 (0
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%) | 1 (1
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%) | 0 (0
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72%
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Retinopathy | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 7 (1
3.46
%) | 7 (1
2.07
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
70%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Serous retinal detachment | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 1 (2
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%) | 0 (0
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|-----------------------------------|-------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|
| Subretinal fluid | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 4 (7.
69%
) | 4 (6.
90%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) |
| Vision blurred | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 4 (7.
69%
) | 4 (6.
90%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Visual acuity reduced | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
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) | 0 (0.
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%) | 0 (0
.00
%) |
| Visual impairment | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 2 (4
0.00
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 0 (0
.00
%) | 5 (9.
62%
) | 7 (1
2.07
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) |
| Gastrointestinal disorders | | | | | | | | | | | | | | | | | | | | | |
| Abdominal discomfort | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
00%
) | 2 (4.
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) |
| Abdominal pain | 0 (0
.00
%) | 2 (5
0.00
%) | 3 (5
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
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%) | 1 (1
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%) | 1 (1
6.67
%) | 6 (1
1.11
%) | 2 (4.
55%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 3 (3
0.00
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| Abdominal pain upper | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 2 (3.
85%
) | 2 (3.
45%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 6 (1
1.11
%) | 5 (1
1.36
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Anal fissure | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
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) | 0 (0
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%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Anal incontinence | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 1 (1
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%) | 0 (0.
00%
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%) | 0 (0
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%) | 0 (0.
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%) |

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|----------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------------|-------------|-----------|-----------|-----------|-----------|-----------|-------------|-------------|-----------|-----------|-----------|
| Anorectal discomfort | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (4.29%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Aphthous ulcer | 0 (0.00%) | 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 (92%) | 1 (72%) | 1 (6.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (85%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Breath odour | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (4.29%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.11%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (4.55%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Constipation | 1 (2.00%) | 0 (0.00%) | 1 (6.67%) | 1 (2.00%) | 0 (0.00%) | 3 (6.00%) | 1 (2.00%) | 1 (1.67%) | 1 (1.67%) | 11 (21.15%) | 12 (20.69%) | 1 (1.67%) | 0 (0.00%) | 2 (2.22%) | 0 (0.00%) | 0 (0.00%) | 11 (20.37%) | 13 (29.55%) | 1 (6.67%) | 2 (2.22%) | 5 (5.00%) |
| Diarrhoea | 0 (0.00%) | 2 (5.00%) | 3 (5.00%) | 2 (4.00%) | 3 (4.29%) | 3 (6.00%) | 2 (4.00%) | 3 (5.00%) | 3 (5.00%) | 19 (36.54%) | 22 (37.93%) | 0 (0.00%) | 4 (4.00%) | 3 (3.33%) | 3 (6.00%) | 4 (6.67%) | 24 (44.44%) | 14 (31.82%) | 1 (6.67%) | 2 (2.22%) | 2 (2.00%) |
| Dry mouth | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (4.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.67%) | 0 (0.00%) | 3 (5.77%) | 4 (6.90%) | 0 (0.00%) | 1 (1.00%) | 1 (1.11%) | 2 (4.00%) | 1 (1.67%) | 4 (7.41%) | 2 (4.55%) | 0 (0.00%) | 1 (1.11%) | 0 (0.00%) |
| Dyspepsia | 0 (0.00%) | 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 (3.85%) | 2 (3.45%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.85%) | 4 (9.09%) | 0 (0.00%) | 0 (0.00%) | 1 (1.00%) |
| Dysphagia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (4.29%) | 1 (2.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (9.2%) | 1 (7.2%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.00%) | 0 (0.00%) | 1 (1.85%) | 1 (2.27%) | 0 (0.00%) | 0 (0.00%) | 1 (1.00%) |
| Flatulence | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) | 0 (0.00%) | 0 (0.00%) | 1 (7.2%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Gastrointestinal | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.00%) | 0 (0.00%) | 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 (6.67%) | 0 (0.00%) | 2 (4.55%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------|-----------------|------------------|-------------------|-------------------|-------------------|-------------------|-----------------|-----------------|-------------------|-------------------|-------------------|
| haemo
rrhage | | | | | | | | | | | | | | | | | | | | | |
| Gastro
intesti
nal
pain | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
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.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Gastro
oesop
hageal
reflux
diseas
e | 0 (0
.00
) | 1 (2
5.00
) | 0 (0
.00
) | 0 (0
.00
) | 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
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 4 (7.
41%) | 1 (2.
27%) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Gingiv
al
bleedi
ng | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 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
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1.
85%) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Haem
atoche
zia | 0 (0
.00
) | 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.
92%) | 1 (1.
72%) | 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
1.11
) | 0 (0
.00
) |
| Haem
orrhoid
s | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 2 (3.
85%) | 3 (5.
17%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 1 (2.
27%) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
0.00
) |
| Hyper
aesthe
sia
teeth | 0 (0
.00
) | 1 (2
5.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
4.29
) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Lip dry | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
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) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Nause
a | 2 (4
0.00
) | 2 (5
0.00
) | 4 (6
6.67
) | 3 (6
0.00
) | 2 (2
8.57
) | 1 (2
0.00
) | 0 (0
.00
) | 3 (5
0.00
) | 1 (1
6.67
) | 18 (34.6
2%) | 21 (36.2
1%) | 0 (0
.00
) | 1 (1
0.00
) | 3 (3
3.33
) | 1 (2
0.00
) | 1 (1
6.67
) | 13 (24.0
7%) | 18 (40.9
1%) | 2 (3
3.33
) | 3 (3
3.33
) | 4 (4
0.00
) |
| Oral
disord
er | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 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
6.67
) | 1 (1.
85%) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |

| | | | | | | | | | | | | | | | | | | | | | |
|-----------------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|---------------------|--------------------|--------------------|--------------------|--------------------|
| Oral
mucosal
eruption | 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
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
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) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Pancr
eatitis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
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) | 0 (0.
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Proctal
gia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) |
| Rectal
haemo
rrhage | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
85%
) | 2 (3.
45%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Stoma
titis | 0 (0
.00
%) | 1 (2
5.00
%) | 2 (3
3.33
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2
0.00
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 8 (1
5.38
%) | 8 (1
3.79
%) | 0 (0
.00
%) | 1 (1
0.00
%) | 2 (2
2.22
%) | 2 (4
0.00
%) | 2 (3
3.33
%) | 11 (7
20.3
%) | 8 (1
8.18
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 1 (1
0.00
%) |
| Tongu
e dry | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Tootha
che | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Vomiti
ng | 0 (0
.00
%) | 1 (2
5.00
%) | 2 (3
3.33
%) | 1 (2
0.00
%) | 2 (2
8.57
%) | 2 (4
0.00
%) | 1 (2
0.00
%) | 2 (3
3.33
%) | 2 (3
3.33
%) | 18 (34.6
2%) | 20 (34.4
8%) | 0 (0
.00
%) | 0 (0
.00
%) | 4 (4
4.44
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 10 (18.5
2%) | 12 (27.2
7%) | 2 (3
3.33
%) | 2 (2
2.22
%) | 3 (3
0.00
%) |

**General
disorder
s and
administ
ration
site
conditio
ns**

| | | | | | | | | | | | | | | | | | | | | | |
|---------------------------------------|------------------|-------------------|-------------------|------------------|-------------------|-------------------|------------------|-------------------|-------------------|-----------------|-----------------|-------------------|-------------------|-------------------|------------------|-------------------|-----------------|-----------------|-------------------|-------------------|-------------------|
| Asthenia | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 2 (2
8.57
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
6.67
) | 2 (3
3.33
) | 13 (25.0
0%) | 14 (24.1
4%) | 1 (1
6.67
) | 0 (0
.00
) | 3 (3
3.33
) | 0 (0
.00
) | 0 (0
.00
) | 12 (22.2
2%) | 12 (27.2
7%) | 2 (3
3.33
) | 1 (1
1.11
) | 1 (1
0.00
) |
| Axillary pain | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1.92%
) | 1 (1.72%
) | 0 (0
.00
) | 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
0.00
) |
| Chest 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
) | 0 (0.00%
) | 0 (0.00%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1.11%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.00%
) | 1 (2.27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Chills | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 2 (3.85%
) | 3 (5.17%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2.00%
) | 0 (0
.00
) | 2 (3.70%
) | 2 (4.55%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
0.00
) |
| Fatigue | 0 (0
.00
) | 1 (2
5.00
) | 2 (3
3.33
) | 0 (0
.00
) | 2 (2
8.57
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 12 (23.0
8%) | 12 (20.6
9%) | 2 (3
3.33
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 2 (3
3.33
) | 7 (12.96%
) | 3 (6.82%
) | 2 (3
3.33
) | 3 (3
3.33
) | 2 (2
0.00
) |
| General physical health deterioration | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 2 (3
3.33
) | 1 (1
6.67
) | 2 (3.85%
) | 4 (6.90%
) | 0 (0
.00
) | 1 (1
0.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 4 (7.41%
) | 1 (2.27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Generalised oedema | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 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 (1.85%
) | 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
) | 0 (0
.00
) | 1 (1.92%
) | 1 (1.72%
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0.00%
) | 1 (2.27%
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) |
| Localised oedema | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.00%
) | 0 (0.00%
) | 0 (0
.00
) | 1 (1
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1.85%
) | 0 (0.00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Mucosal | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 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
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.00%
) | 1 (2.27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |

| | | | | | | | | | | | | | | | | | | | | | |
|-------------------------|-------------------|-------------------|-------------------|-------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------|-------------------|-------------------|-------------------|-------------------|
| inflammation | | | | | | | | | | | | | | | | | | | | | |
| Non-cardiac chest pain | 1 (2
0.00
) | 0 (0
.00
) | 2 (3
3.33
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 1 (2
0.00
) | 1 (1
6.67
) | 1 (1
6.67
) | 2 (3.
85%) | 3 (5.
17%) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 1 (2
0.00
) | 0 (0
.00
) | 2 (3.
70%) | 3 (6.
82%) | 1 (1
6.67
) | 1 (1
1.11
) | 1 (1
0.00
) |
| Oedema peripheral | 1 (2
0.00
) | 1 (2
5.00
) | 1 (1
6.67
) | 1 (2
0.00
) | 0 (0
.00
) | 2 (4
0.00
) | 0 (0
.00
) | 2 (3
3.33
) | 1 (1
6.67
) | 7 (1
3.46
) | 9 (1
5.52
) | 1 (1
6.67
) | 2 (2
0.00
) | 1 (1
1.11
) | 2 (4
0.00
) | 2 (3
3.33
) | 15 (27.7
8%) | 6 (1
3.64
) | 0 (0
.00
) | 0 (0
.00
) | 3 (3
0.00
) |
| Pain | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 1 (1
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1.
85%) | 2 (4.
55%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Peripheral swelling | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 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
1.11
) | 1 (1
0.00
) |
| Pyrexia | 0 (0
.00
) | 0 (0
.00
) | 2 (3
3.33
) | 1 (2
0.00
) | 0 (0
.00
) | 3 (6
0.00
) | 1 (2
0.00
) | 0 (0
.00
) | 1 (1
6.67
) | 12 (23.0
8%) | 12 (20.6
9%) | 1 (1
6.67
) | 2 (2
0.00
) | 3 (3
3.33
) | 1 (2
0.00
) | 1 (1
6.67
) | 14 (25.9
3%) | 10 (22.7
3%) | 2 (3
3.33
) | 2 (2
2.22
) | 3 (3
0.00
) |
| Xerosis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
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
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1.
85%) | 2 (4.
55%) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
0.00
) |
| Hepatobiliary disorders | | | | | | | | | | | | | | | | | | | | | |
| Autoimmune hepatitis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 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
1.11
) | 0 (0
.00
) |
| Cholecystitis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0.
00%) | 0 (0.
00%) | 0 (0
.00
) | 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
0.00
) |

| | | | | | | | | | | | | | | | | | | | | | |
|-----------------------------|-----------|-----------|------------|-----------|------------|-----------|-----------|-----------|-----------|-----------|-----------|------------|-----------|-----------|-----------|------------|-----------|-----------|------------|-----------|-----------|
| Cholelithiasis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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 (1.00%) |
| Cholestasis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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 (1.11%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 3 (6.82%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Hepatic pain | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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 (1.00%) |
| Hyperbilirubinemia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 4 (7.69%) | 4 (6.90%) | 1 (1.667%) | 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 (1.00%) |
| Infections and infestations | | | | | | | | | | | | | | | | | | | | | |
| Abscesses | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Bacteriuria | 0 (0.00%) | 1 (2.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Bronchitis | 1 (2.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.429%) | 1 (2.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (3.85%) | 2 (3.45%) | 1 (1.667%) | 0 (0.00%) | 0 (0.00%) | 1 (2.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Cellulitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.00%) | 0 (0.00%) | 0 (0.00%) | 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 (5.56%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.00%) |
| Conjunctivitis | 0 (0.00%) | 0 (0.00%) | 1 (1.667%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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 (1.667%) | 0 (0.00%) | 2 (4.55%) | 0 (0.00%) | 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 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 3 (5.56%) | 1 (2.27%) | 1 (1.667%) | 0 (0.00%) | 0 (0.00%) |

| | | | | | | | | | | | | | | | | | | | | | |
|----------------------------|------------------|------------------|-------------------|-------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|-------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|-------------------|------------------|
| Cystitis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 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 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Erysipelas | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 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
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 2 (4
55%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Folliculitis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 3 (6
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Fungal infection | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Gastrointestinal infection | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
92%
) | 1 (1
72%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Genital infection fungal | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 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 (2
0.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Gingival abscess | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Gingivitis | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Herpes virus infection | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 2 (4
55%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hordeolum | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |

| | | | | | | | | | | | | | | | | | | | | | |
|---|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Infecte
d cyst | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
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| Soft tissue infection | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 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 (1.00 %) |
| Suspected 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 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (16.67 %) | 1 (1.85 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.00 %) |
| Tooth abscess | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 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 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.27 %) | 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 (0.00 %) | 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 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.85 %) | 1 (2.27 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Urinary tract infection | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (16.67 %) | 1 (16.67 %) | 3 (5.77 %) | 4 (6.90 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.11 %) | 0 (0.00 %) | 1 (16.67 %) | 3 (5.56 %) | 1 (2.27 %) | 1 (16.67 %) | 1 (1.11 %) | 0 (0.00 %) |
| Injury, poisoning and procedural complications | | | | | | | | | | | | | | | | | | | | | |
| Fall | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 2 (3.33 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (3.45 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.27 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Head injury | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (16.67 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.72 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |

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| Procedural pain | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.85 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Scratch | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (16.67 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (17.72 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Sunburn | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 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 %) | 0 (0.00 %) |
| Tooth fracture | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Traumatic haematoma | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Investigations | | | | | | | | | | | | | | | | | | | | | |
| Alanine aminotransferase increased | 0 (0.00 %) | 1 (25.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 5 (9.62 %) | 5 (8.62 %) | 0 (0.00 %) | 1 (1.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 11 (20.37 %) | 7 (15.91 %) | 4 (6.67 %) | 3 (3.33 %) | 5 (5.00 %) |
| Amylase increased | 0 (0.00 %) | 1 (25.00 %) | 1 (16.67 %) | 0 (0.00 %) | 1 (14.29 %) | 2 (4.00 %) | 0 (0.00 %) | 1 (16.67 %) | 1 (16.67 %) | 10 (19.23 %) | 11 (18.97 %) | 0 (0.00 %) | 3 (3.00 %) | 1 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 11 (20.37 %) | 5 (11.36 %) | 2 (3.33 %) | 1 (1.11 %) | 1 (1.00 %) |
| Aspartate aminotransferase increased | 0 (0.00 %) | 1 (25.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 3 (5.77 %) | 3 (5.17 %) | 1 (1.67 %) | 2 (2.00 %) | 1 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 15 (27.78 %) | 8 (18.18 %) | 4 (6.67 %) | 3 (3.33 %) | 5 (5.00 %) |

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| Bilirubin conjugated increased | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.27 %) | 0 (0.00 %) | 1 (1.11 %) | 0 (0.00 %) |
| Blood albumin decreased | 2 (4.00 %) | 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 (1.92 %) | 1 (1.72 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.11 %) | 1 (2.00 %) | 0 (0.00 %) | 2 (3.70 %) | 1 (2.27 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Blood albumin increased | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Blood alkaline phosphatase increased | 0 (0.00 %) | 1 (2.50 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 3 (5.77 %) | 3 (5.17 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (2.22 %) | 0 (0.00 %) | 1 (1.67 %) | 7 (1.29 %) | 7 (1.59 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Blood bilirubin increased | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 4 (7.69 %) | 4 (6.90 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.85 %) | 1 (2.27 %) | 0 (0.00 %) | 3 (3.33 %) | 1 (1.00 %) |
| Blood cholesterol 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 %) | 1 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.85 %) | 1 (2.27 %) | 1 (1.67 %) | 0 (0.00 %) | 1 (1.00 %) |
| Blood creatinine phosphokinase | 0 (0.00 %) | 1 (2.50 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.67 %) | 0 (0.00 %) | 9 (17.31 %) | 10 (17.24 %) | 4 (6.67 %) | 3 (3.00 %) | 2 (2.22 %) | 1 (2.00 %) | 1 (1.67 %) | 20 (37.04 %) | 11 (25.00 %) | 2 (3.33 %) | 1 (1.11 %) | 1 (1.00 %) |

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| C-reactive protein increased | 2 (4
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%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Ejection fraction decreased | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Electrocardiogram QT prolonged | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (3
3.33
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1.
85%
) | 3 (6.
82%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 1 (1
0.00
%) |
| Electrocardiogram T wave abnormal | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Gamma-glutamyltransferase increased | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 3 (5.
77%
) | 4 (6.
90%
) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (2
2.22
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 5 (9.
26%
) | 6 (1
3.64
%) | 1 (1
6.67
%) | 1 (1
1.11
%) | 2 (2
0.00
%) |
| Haemoglobin | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
70%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|----------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|--------------|------------|------------|------------|------------|------------|--------------|------------|------------|------------|------------|
| decreased | | | | | | | | | | | | | | | | | | | | | |
| Lipase increased | 0 (0.00 %) | 1 (2.50 %) | 1 (1.67 %) | 0 (0.00 %) | 2 (2.86 %) | 1 (2.00 %) | 0 (0.00 %) | 2 (3.33 %) | 2 (3.33 %) | 8 (15.38 %) | 10 (17.24 %) | 1 (1.67 %) | 3 (3.00 %) | 3 (3.33 %) | 0 (0.00 %) | 1 (1.67 %) | 14 (25.93 %) | 8 (8.18 %) | 2 (3.33 %) | 1 (1.11 %) | 1 (1.00 %) |
| Lymphocyte count decreased | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.67 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.72 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (3.70 %) | 0 (0.00 %) | 1 (1.67 %) | 0 (0.00 %) | 1 (1.00 %) |
| Myoglobin blood 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 %) | 1 (1.11 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.85 %) | 1 (2.27 %) | 1 (1.67 %) | 0 (0.00 %) | 0 (0.00 %) |
| Neutrophil count decreased | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.67 %) | 0 (0.00 %) | 1 (1.00 %) |
| Neutrophil count increased | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.67 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Platelet count decreased | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (3.85 %) | 2 (3.45 %) | 1 (1.67 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (3.70 %) | 2 (4.55 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (2.00 %) |
| Protein total decreased | 1 (2.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.00 %) | 0 (0.00 %) | 1 (1.67 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.72 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (2.27 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| SARS-CoV-2 test | 0 (0.00 %) | 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 (5.77 %) | 3 (5.17 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (1.67 %) | 1 (1.85 %) | 3 (6.82 %) | 0 (0.00 %) | 1 (1.11 %) | 1 (1.00 %) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|-------------------|-------------------|--------------------|-------------------|--------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|--------------------|--------------------|
| negati
ve | | | | | | | | | | | | | | | | | | | | | |
| SARS-
CoV-2
test
positiv
e | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 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 (3.
70%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Transa
minas
es
increa
sed | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Tropo
nin T
increa
sed | 0 (0
.00
%) | 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.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 2 (4.
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Weight
decrea
sed | 1 (2
0.00
%) | 1 (2
5.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 2 (4
0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 5 (9.
62%
) | 6 (1
0.34
%) | 0 (0
.00
%) | 1 (1
0.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5.
56%
) | 2 (4.
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Weight
increa
sed | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| White
blood
cell
count
decrea
sed | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 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
6.67
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 3 (3
0.00
%) |
| White
blood
cell
count
increa
sed | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Metaboli
sm and
nutrition | | | | | | | | | | | | | | | | | | | | | |

**disorder
s**

| | | | | | | | | | | | | | | | | | | | | | |
|-----------------------------------|-------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|---------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|------------------|-------------------|-------------------|
| Cache
xia | 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
6.67
) | 1 (1
92%
) | 1 (1
72%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Cell
death | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 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
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Decre
ased
appetit
e | 1 (2
0.00
) | 0 (0
.00
) | 1 (1
6.67
) | 2 (4
0.00
) | 1 (1
4.29
) | 1 (2
0.00
) | 0 (0
.00
) | 2 (3
3.33
) | 1 (1
6.67
) | 18 (34.6
2%
) | 20 (34.4
8%
) | 1 (1
6.67
) | 2 (2
0.00
) | 1 (1
1.11
) | 2 (4
0.00
) | 1 (1
6.67
) | 7 (1
2.96
) | 10 (22.7
3%
) | 0 (0
.00
) | 1 (1
1.11
) | 1 (1
0.00
) |
| Dehyd
ration | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 1 (2
0.00
) | 0 (0
.00
) | 2 (3
3.33
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hyper
amyla
saemi
a | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
4.29
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 1 (1
92%
) | 2 (3
45%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
00%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hyper
calcae
mia | 1 (2
0.00
) | 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
92%
) | 1 (1
72%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hyper
choles
terolae
mia | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 1 (1
92%
) | 2 (3
45%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hyper
creatin
inaemi
a | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
4.29
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hyper
glycae
mia | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 3 (5
77%
) | 4 (6
90%
) | 1 (1
6.67
) | 1 (1
0.00
) | 2 (2
2.22
) | 1 (2
0.00
) | 1 (1
6.67
) | 2 (3
70%
) | 3 (6
82%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Hyper
kalae
mia | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 1 (1
4.29
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 1 (1
92%
) | 2 (3
45%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
00%
) | 2 (4
55%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |

| | | | | | | | | | | | | | | | | | | | | | |
|-------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Hyperlipasemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
0.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 1 (1
85%
) | 1 (2
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hyperphosphatemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
00%
) | 1 (1
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hyperuricemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 4 (7
69%
) | 5 (8
62%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 1 (2
27%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hypoalbuminemia | 0 (0
.00
%) | 1 (2
5.00
%) | 1 (1
6.67
%) | 1 (2
0.00
%) | 2 (2
8.57
%) | 0 (0
00%
) | 1 (2
0.00
%) | 1 (1
6.67
%) | 1 (1
6.67
%) | 11 (21.1
5%
) | 12 (20.6
9%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 3 (3
3.33
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 7 (1
2.96
%) | 7 (1
5.91
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hypocalcemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (4
0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1
6.67
%) | 2 (3
85%
) | 3 (5
17%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 2 (2
2.22
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 2 (3
70%
) | 2 (4
55%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Hypokalaemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
92%
) | 2 (3
45%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5
56%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Hypomagnesaemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 1 (1
4.29
%) | 2 (4
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
85%
) | 2 (3
45%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 1 (2
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hyponatraemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 2 (3
3.33
%) | 1 (1
6.67
%) | 7 (1
3.46
%) | 9 (1
5.52
%) | 2 (3
3.33
%) | 1 (1
0.00
%) | 2 (2
2.22
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 3 (5
56%
) | 5 (1
1.36
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hypophosphataemia | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 3 (4
2.86
%) | 1 (2
0.00
%) | 1 (2
0.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 3 (5
77%
) | 4 (6
90%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5
56%
) | 0 (0
00%
) | 1 (1
6.67
%) | 2 (2
2.22
%) | 1 (1
0.00
%) |
| Hypoproteinaemia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
92%
) | 1 (1
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 2 (3
70%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|-------------------|--------------------|-------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|
| Iron deficiency | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Magnesium deficiency | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | | | | | | | | | | | | |
| Arthralgia | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 0 (0
.00
%) | 2 (2
8.57
%) | 0 (0.
00%
) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 4 (7.
69%
) | 4 (6.
90%
) | 0 (0
.00
%) | 2 (2
0.00
%) | 2 (2
2.22
%) | 2 (4
0.00
%) | 1 (1
6.67
%) | 5 (9.
26%
) | 6 (1
3.64
%) | 3 (5
0.00
%) | 0 (0
.00
%) | 2 (2
0.00
%) |
| Back pain | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 5 (9.
62%
) | 5 (8.
62%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 3 (3
3.33
%) | 0 (0
.00
%) | 0 (0
.00
%) | 5 (9.
26%
) | 4 (9.
09%
) | 1 (1
6.67
%) | 1 (1
1.11
%) | 1 (1
0.00
%) |
| Bone pain | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
85%
) | 2 (3.
45%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 2 (4.
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Dactylitis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Groin pain | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 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
1.11
%) | 0 (0
.00
%) |
| Joint swelling | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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 (6.
82%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Muscle | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 2 (4
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 2 (4.
55%
) | 1 (1
6.67
%) | 1 (1
1.11
%) | 1 (1
0.00
%) |

| | | | | | | | | | | | | | | | | | | | | |
|----------------------------|-----------|------------|------------|------------|------------|------------|-----------|-----------|-----------|-----------|-----------|------------|------------|------------|-----------|------------|-----------|-----------|------------|------------|
| spasms | | | | | | | | | | | | | | | | | | | | |
| Muscular weakness | 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%) | 3 (5.77%) | 3 (5.17%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Musculoskeletal chest pain | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 3 (5.77%) | 3 (5.17%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 3 (6.82%) | 0 (0.00%) | 0 (0.00%) |
| Musculoskeletal 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%) | 0 (0.00%) | 0 (0.00%) | 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 (10.00%) |
| Musculoskeletal pain | 0 (0.00%) | 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 (19.2%) | 1 (17.2%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (37.0%) | 1 (22.7%) | 0 (0.00%) | 0 (0.00%) |
| Myalgia | 0 (0.00%) | 0 (0.00%) | 1 (16.67%) | 0 (0.00%) | 2 (28.57%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 5 (9.62%) | 5 (8.62%) | 1 (16.67%) | 0 (0.00%) | 1 (11.11%) | 0 (0.00%) | 0 (0.00%) | 2 (37.0%) | 3 (68.2%) | 3 (50.00%) | 1 (11.11%) |
| Neck pain | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (16.67%) | 2 (37.0%) | 1 (22.7%) | 0 (0.00%) | 0 (0.00%) |
| Osteoarthritis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Osteoporosis | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Pain in extremity | 0 (0.00%) | 0 (0.00%) | 1 (16.67%) | 0 (0.00%) | 1 (14.29%) | 2 (40.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 4 (7.69%) | 4 (6.90%) | 1 (16.67%) | 2 (20.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 3 (55.6%) | 1 (22.7%) | 1 (16.67%) | 2 (22.22%) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|------------------|------------------|------------------|------------------|------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|-------------------|
| Pain in jaw | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Spinal pain | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Temporomandibular joint 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 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Trismus | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
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) | 0 (0
00%
) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
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) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
0.00
) |
| Neoplasms
benign, malignant and unspecified (incl cysts and polyps) | | | | | | | | | | | | | | | | | | | | | |
| Tumour haemorrhage | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
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) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Tumour pain | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 2 (4
55%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Nervous system disorders | | | | | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | | | |
|--------------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|
| Akathisia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Balance disorder | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Brain oedema | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1
6.67
%) | 0 (0.
00%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Burning sensation | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 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 (2.
27%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Cognitive disorder | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1
6.67
%) | 0 (0.
00%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Disturbance in attention | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Dizziness | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 3 (5.
77%
) | 3 (5.
17%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 2 (4.
55%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 3 (3
0.00
%) |
| Dysaesthesia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 2 (3.
70%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Dysgeusia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 4 (9.
09%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Headache | 0 (0
.00
%) | 1 (2
5.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 2 (3
3.33
%) | 8 (1
5.38
%) | 9 (1
5.52
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 4 (7.
41%
) | 7 (1
5.91
%) | 1 (1
6.67
%) | 2 (2
2.22
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|-------------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|------------------|--------------------|-------------------|-------------------|--------------------|--------------------|--------------------|------------------|------------------|--------------------|--------------------|--------------------|
| Hemiparesis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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 (4
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hypoesthesia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
00%
) | 1 (1
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 2 (4
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Intercostal neuralgia | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Myoclonus | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Nervous system disorder | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Neuralgia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3
3.33
%) | 3 (5
56%
) | 1 (2
27%
) | 2 (3
3.33
%) | 2 (2
2.22
%) | 0 (0
.00
%) |
| Neuropathy peripheral | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5
77%
) | 3 (5
17%
) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (2
2.22
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 4 (7
41%
) | 3 (6
82%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Parasthesia | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 1 (2
0.00
%) | 2 (3
3.33
%) | 0 (0
.00
%) | 4 (7
69%
) | 6 (1
0.34
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
85%
) | 2 (4
55%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Parosmia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
00%
) | 0 (0
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) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Peripheral sensory | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 4 (7
69%
) | 4 (6
90%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
85%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| neuropathy | | | | | | | | | | | | | | | | | | | | | |
|------------------------|-----------|------------|-----------|-----------|-----------|------------|------------|------------|-----------|------------|------------|------------|-----------|------------|------------|------------|------------|------------|------------|-----------|------------|
| Presyncope | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (16.67%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Restless legs syndrome | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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%) | 0 (0.00%) | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (38.50%) | 2 (34.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) | 1 (12.50%) | 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%) | 0 (0.00%) | 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 (12.50%) | 0 (0.00%) | 1 (16.67%) | 0 (0.00%) | 1 (10.00%) |
| Somnolence | 0 (0.00%) | 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 (19.20%) | 1 (17.20%) | 1 (16.70%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (45.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Speech disorder | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 1 (17.20%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Syncope | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (33.33%) | 0 (0.00%) | 1 (19.20%) | 3 (51.70%) | 0 (0.00%) | 0 (0.00%) | 1 (11.10%) | 1 (20.00%) | 0 (0.00%) | 1 (12.50%) | 1 (22.70%) | 0 (0.00%) | 0 (0.00%) | 1 (10.00%) |
| Taste disorder | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 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%) | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Tremor | 0 (0.00%) | 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 (19.20%) | 1 (17.20%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (45.50%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Vlith nerve palsies | 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%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |

Psychiatric disorders

| | | | | | | | | | | | | | | | | | | | | | |
|------------------|------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|-------------------|------------------|-------------------|
| Anxiety | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
00%
) | 1 (1
72%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Depression | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
4.29
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
92%
) | 1 (1
72%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
1.11
) | 1 (2
0.00
) | 1 (1
6.67
) | 0 (0
00%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Insomnia | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 1 (2
0.00
) | 1 (1
6.67
) | 1 (1
6.67
) | 2 (3
85%
) | 3 (5
17%
) | 0 (0
.00
) | 1 (1
0.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 7 (1
2.96
) | 2 (4
55%
) | 1 (1
6.67
) | 0 (0
.00
) | 1 (1
0.00
) |
| Irritability | 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
6.67
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Reading disorder | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
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) | 0 (0
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) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |

Renal and urinary disorders

| | | | | | | | | | | | | | | | | | | | | | |
|---------------------|------------------|------------------|------------------|------------------|------------------|-------------------|------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|-------------------|------------------|
| Acute kidney injury | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 1 (1
92%
) | 2 (3
45%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Bilirubinuria | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 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
1.11
) | 0 (0
.00
) |
| Dysuria | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
00%
) | 1 (1
72%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 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
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Micturition urgency | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Nocturia | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Pollakiuria | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 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
1.11
%) | 0 (0
.00
%) |
| Renal failure | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 2 (4.
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Renal pain | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
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%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 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
0.00
%) |
| Urinary tract discomfort | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Reproductive system and breast disorders | | | | | | | | | | | | | | | | | | | | | |
| Breast 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
%) | 0 (0.
00%
) | 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
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Breast inflammation | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|-------------------|--------------------|-------------------|-------------------|-------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Pelvic pain | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Vagina
l
haemo
rrhage | 0 (0
.00
%) | 1 (2
5.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 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
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Vulvov
aginal
drynes
s | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Vulvov
aginal
inflam
mation | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Respiratory,
thoracic
and
mediastinal
disorders | | | | | | | | | | | | | | | | | | | | | |
| Acute
pulmo
nary
oedema | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Acute
respira
tory
failure | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Bronc
hitis
chronic | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|---------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|--------------------|--------------------|--------------------|
| Cough | 1 (2
0.00
%) | 1 (2
5.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (4
0.00
%) | 1 (2
0.00
%) | 3 (5
0.00
%) | 2 (3
3.33
%) | 5 (9.
62%
) | 8 (1
3.79
%) | 0 (0
.00
%) | 2 (2
0.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 6 (1
1.11
%) | 8 (1
8.18
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Dry
throat | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Dysph
onia | 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
6.67
%) | 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 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Dyspn
oea | 2 (4
0.00
%) | 2 (5
0.00
%) | 1 (1
6.67
%) | 2 (4
0.00
%) | 1 (1
4.29
%) | 2 (4
0.00
%) | 2 (4
0.00
%) | 4 (6
6.67
%) | 1 (1
6.67
%) | 12 (23.0
8%
) | 16 (27.5
9%
) | 1 (1
6.67
%) | 2 (2
0.00
%) | 1 (1
1.11
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 11 (20.3
7%
) | 11 (25.0
0%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
0.00
%) |
| Epista
xis | 0 (0
.00
%) | 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.
92%
) | 1 (1.
72%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 3 (5.
56%
) | 2 (4.
55%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Haem
optysis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
85%
) | 2 (3.
45%
) | 2 (3
3.33
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
70%
) | 2 (4.
55%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Hypoxi
a | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2
0.00
%) | 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
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Lung
disord
er | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Nasal
crustin
g | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
1.11
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1.
85%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Nasal
inflam
mation | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 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
6.67
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Nasal
polyps | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|-------------|-------------|-------------|-------------|------------|------------|------------|-------------|------------|-------------|--------------|------------|-------------|-------------|-------------|------------|-------------|--------------|-------------|-------------|-------------|
| Oropharyngeal pain | 0 (0.00 %) | 0 (0.00 %) | 1 (16.67 %) | 0 (0.00 %) | 0 (0.00 %) | 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 (11.11 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (45.56 %) | 1 (16.67 %) | 0 (0.00 %) | 1 (10.00 %) |
| Pleural effusion | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (33.33 %) | 0 (0.00 %) | 4 (76.92 %) | 6 (100.00 %) | 0 (0.00 %) | 1 (10.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (18.75 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | |
| Pleuritic pain | 0 (0.00 %) | 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 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (18.75 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | |
| 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 %) | 1 (10.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (37.50 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | |
| 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 %) | 0 (0.00 %) | 1 (11.11 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (22.73 %) | 0 (0.00 %) | 0 (0.00 %) | |
| Productive cough | 0 (0.00 %) | 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 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (37.50 %) | 5 (113.64 %) | 0 (0.00 %) | 0 (0.00 %) | |
| Pulmonary embolism | 1 (20.00 %) | 1 (25.00 %) | 1 (16.67 %) | 1 (20.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (38.46 %) | 2 (38.46 %) | 0 (0.00 %) | 1 (10.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (37.50 %) | 1 (22.73 %) | 1 (16.67 %) | 1 (10.00 %) | |
| Pulmonary 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 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 1 (20.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | |
| Skin and subcutaneous tissue disorders | | | | | | | | | | | | | | | | | | | | | |
| Acne | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) | 2 (37.50 %) | 1 (22.73 %) | 1 (16.67 %) | 0 (0.00 %) | |

| | | | | | | | | | | | | | | | | | | | | | |
|----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|---------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|---------------------|-------------------|-------------------|-------------------|
| Alopecia | 0 (0
.00
) | 1 (2
5.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 1 (1
92%
) | 1 (1
72%
) | 0 (0
.00
) | 1 (1
0.00
) | 1 (1
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 4 (7
41%
) | 5 (1
1.36
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Angioedema | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 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
1.11
) | 0 (0
.00
) |
| Dermatitis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 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
6.67
) | 0 (0
.00
) | 0 (0
.00
) |
| Dermatitis acneiform | 1 (2
0.00
) | 3 (7
5.00
) | 3 (5
0.00
) | 1 (2
0.00
) | 3 (4
2.86
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 2 (3
3.33
) | 16 (30.7
7%
) | 16 (27.5
9%
) | 3 (5
0.00
) | 5 (5
0.00
) | 4 (4
4.44
) | 1 (2
0.00
) | 1 (1
6.67
) | 17 (31.4
8%
) | 10 (22.7
3%
) | 2 (3
3.33
) | 0 (0
.00
) | 2 (2
0.00
) |
| Dermatosis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 2 (4
55%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Dry skin | 0 (0
.00
) | 1 (2
5.00
) | 2 (3
3.33
) | 1 (2
0.00
) | 0 (0
.00
) | 1 (2
0.00
) | 1 (2
0.00
) | 1 (1
6.67
) | 0 (0
.00
) | 5 (9
62%
) | 6 (1
0.34
) | 0 (0
.00
) | 2 (2
0.00
) | 3 (3
3.33
) | 1 (2
0.00
) | 1 (1
6.67
) | 11 (20.3
7%
) | 9 (2
0.45
) | 1 (1
6.67
) | 0 (0
.00
) | 0 (0
.00
) |
| Eczema | 0 (0
.00
) | 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 (3
85%
) | 2 (3
45%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
85%
) | 1 (2
27%
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Erythema | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (2
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 1 (1
6.67
) | 2 (3
85%
) | 2 (3
45%
) | 0 (0
.00
) | 1 (1
0.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 3 (5
56%
) | 1 (2
27%
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Hyperhidrosis | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
00%
) | 0 (0
.00
) | 1 (1
1.11
) | 0 (0
.00
) |
| Hypertrophic scars | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 0 (0
.00
) | 0 (0
.00
) | 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
85%
) | 2 (4
55%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |
| Macule | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) | 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
1.11
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
00%
) | 1 (2
27%
) | 0 (0
.00
) | 0 (0
.00
) | 0 (0
.00
) |

| | | | | | | | | | | | | | | | | | | | | | |
|--|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|--------------------|--------------------|--------------------|
| Night sweats | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Pain of skin | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 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
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Palmar-plantar erythrodysesthesia syndrome | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 1 (1
6.67
%) | 2 (3.
85%
) | 3 (5.
17%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 2 (2
2.22
%) | 2 (4
0.00
%) | 1 (1
6.67
%) | 6 (1
1.11
%) | 3 (6.
82%
) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (2
0.00
%) |
| Pruritus | 1 (2
0.00
%) | 2 (5
0.00
%) | 4 (6
6.67
%) | 2 (4
0.00
%) | 1 (1
4.29
%) | 2 (4
0.00
%) | 2 (4
0.00
%) | 2 (3
3.33
%) | 3 (5
0.00
%) | 14 (26.9
2%
) | 16 (27.5
9%
) | 1 (1
6.67
%) | 2 (2
0.00
%) | 2 (2
2.22
%) | 2 (4
0.00
%) | 1 (1
6.67
%) | 8 (1
4.81
%) | 12 (27.2
7%
) | 3 (5
0.00
%) | 2 (2
2.22
%) | 2 (2
0.00
%) |
| Pruritus allergic | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 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
0.00
%) |
| Purpura | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Rash | 0 (0
.00
%) | 1 (2
5.00
%) | 2 (3
3.33
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (6
0.00
%) | 1 (2
0.00
%) | 2 (3
3.33
%) | 3 (5
0.00
%) | 18 (34.6
2%
) | 20 (34.4
8%
) | 3 (5
0.00
%) | 2 (2
0.00
%) | 4 (4
4.44
%) | 3 (6
0.00
%) | 5 (8
3.33
%) | 24 (44.4
4%
) | 25 (56.8
2%
) | 1 (1
6.67
%) | 6 (6
6.67
%) | 6 (6
0.00
%) |
| Rash erythematous | 0 (0
.00
%) | 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.
92%
) | 1 (1.
72%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Rash macular | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 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
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|----------------------------------|-------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|-------------------|--------------------|--------------------|--------------------|-------------------|---------------------|--------------------|-------------------|--------------------|--------------------|
| Rash macul
o-
papula
r | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 1 (2
0.00
%) | 1 (2
0.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 9 (1
7.31
%) | 10 (4
17.2
%) | 0 (0
.00
%) | 4 (4
0.00
%) | 1 (1
1.11
%) | 2 (4
0.00
%) | 0 (0
.00
%) | 12 (2
22.2
%) | 3 (6.
82%
) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (2
0.00
%) |
| Rash papula
r | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
4.29
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5.
56%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Rash pruritic | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 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
0.00
%) |
| Rash vesicul
ar | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Seborr
hoec
dermat
itis | 0 (0
.00
%) | 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.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 2 (3.
70%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Skin exfolia
tion | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
92%
) | 1 (1.
72%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 1 (2.
27%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
| Skin fissure
s | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 2 (4
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 3 (5.
77%
) | 3 (5.
17%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 2 (2
2.22
%) | 0 (0
.00
%) | 0 (0
.00
%) | 7 (1
2.96
%) | 9 (2
0.45
%) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Skin irritatio
n | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 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
0.00
%) |
| Skin lesion | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 1 (1
0.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 1 (2.
27%
) | 0 (0
.00
%) | 1 (1
1.11
%) | 0 (0
.00
%) |
| Skin ulcer | 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
6.67
%) | 0 (0.
00%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (1.
85%
) | 0 (0.
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |

| | | | | | | | | | | | | | | | | | | | | | |
|---------------------------|--------------|--------------|-------------|--------------|-------------|--------------|--------------|--------------|--------------|-------------|-------------|--------------|--------------|--------------|--------------|-------------|-------------|-------------|--------------|--------------|--------------|
| Solar urticaria | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 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 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Vitiligo | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (2 27 %) | 0 (0 .00 %) | 1 (1 1.11 %) | 0 (0 .00 %) |
| Xeroderma | 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 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 85 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Vascular disorders | | | | | | | | | | | | | | | | | | | | | |
| Deep vein thrombosis | 1 (2 0.00 %) | 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 92 %) | 1 (1 72 %) | 0 (0 .00 %) | 1 (1 0.00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 2 (3 70 %) | 0 (0 .00 %) | 1 (1 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Hypertension | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (2 0.00 %) | 0 (0 .00 %) | 3 (5 56 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Hypotension | 0 (0 .00 %) | 1 (2 5.00 %) | 0 (0 .00 %) | 1 (2 0.00 %) | 0 (0 .00 %) | 1 (2 0.00 %) | 1 (2 0.00 %) | 1 (1 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 72 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 1.11 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 85 %) | 1 (2 27 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Lymphoedema | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 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 0.00 %) |
| Peripheral ischaemia | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 6.67 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 72 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |
| Peripheral venous disease | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 0.00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 1 (1 85 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) | 0 (0 .00 %) |

| | | | | | | | | | | | | | | | | | | | | | |
|------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|------------------|-------------------|-------------------|-------------------|
| Thrombosis | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 1 (2
0.00
%) | 0 (0
.00
%) | 0 (0
.00
%) | 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
85%
) | 0 (0
00%
) | 0 (0
.00
%) | 0 (0
.00
%) | 0 (0
.00
%) |
|------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|------------------|-------------------|-------------------|-------------------|

Conclusion:

- Naporafenib 400 mg BID + rineterkib 200 mg QD was proposed as RD for the naporafenib and rineterkib combination.
- Naporafenib 200 mg BID + trametinib 1 mg QD and naporafenib 400 mg BID + trametinib 0.5 mg QD were proposed as RDs for the naporafenib and trametinib combination.
- The RD for the combination of naporafenib and ribociclib was not determined.
- The overall safety profile of naporafenib in combination with rineterkib, trametinib, or ribociclib was acceptable.
- Plasma peak drug concentration (C_{max}) and drug exposure (AUC) after oral doses of naporafenib in combination with rineterkib, trametinib, or ribociclib increased in an approximate dose-proportional manner across the dose range tested at Cycle 1 Day 1 and Day 15. No pharmacokinetic drug-drug interactions were evident between naporafenib and rineterkib, trametinib, or ribociclib.
- Reduction of DUSP6 mRNA levels in paired tumor samples was observed after study treatment administration, indicating pharmacodynamic activity of naporafenib in combination with rineterkib or trametinib or ribociclib at the doses tested.
- The combination treatment of naporafenib plus trametinib showed encouraging anti-tumor activity in adult patients with advanced or metastatic NRAS mutant melanoma and limited anti-tumor activity in adult patients with advanced or metastatic KRAS mutant NSCLC.
- The combination treatment of naporafenib plus rineterkib showed limited anti-tumor activity in adult patients with advanced or metastatic KRAS mutant NSCLC.



- The combination treatment of naporafenib plus rineterkib or trametinib was tested in limited number of patients with V600 or non V600 BRAF mutant NSCLC, and the antitumor activity remains to be further evaluated.

Date of Clinical Trial Report

30-Jan-2025