Clinical trial results:
A Phase Ib/II, Multicenter, Open-label, Dose Escalation Study of LGX818 in Combination with MEK162 in Adult Subjects with BRAF V600 - Dependent Advanced Solid Tumors.

Summary

EudraCT number	2011-005875-17
Trial protocol	ES IT BE FR
Global end of trial date	09 March 2023

Results information

Result version number	v1 (current)
This version publication date	19 March 2024
First version publication date	19 March 2024

Trial information

Trial identification

Sponsor protocol code	C4221005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01543698
WHO universal trial number (UTN)	-
Other trial identifiers	CMEK162X2110: Study id

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1b: To estimate the MTD(s) and/or RP2D(s) of oral LGX818 in combination with oral MEK162 and of oral LGX818 combination with oral MEK162 and oral LEE011 in patients with BRAF V600-dependent advanced solid tumors.

Phase 2: To assess clinical efficacy of the LGX818 and MEK162 dual combination and LGX818 and MEK162 and LEE011 triple combination in the respective Phase 2 populations.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	189
EEA total number of subjects	84

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	149
From 65 to 84 years	37
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Phase1b:subjects with V-raf murine sarcoma viral oncogene homolog B1(BRAF)V600-dependent advanced solid tumors.Phase2:BRAF V600 mutant metastatic colorectal cancer(mCRC)[Arm1,dual];BRAF V600 mutant melanoma:progressed after prior selective BRAF inhibitor [Arm 2,dual];metastatic BRAF mutant melanoma:naïve to BRAF inhibitor [Arm3,dual]/[ArmA,triple].

Pre-assignment

Screening details:

189 subjects were enrolled. Phase1b:47 subjects for dual and 21 for triple combo. Phase2: a) Dual combo- Arm1(mCRC)=11; Arm2 (prior BRAFi melanoma) =26; Arm3 (BRAFi-naïve melanoma)=42 subjects b) Triple combo-ArmA (BRAFi-naïve melanoma) =42 subjects. Dual combo of LGX818 (enco) and MEK162 (bini) and triple combo of LGX818, MEK162 and LEE011 (ribo).

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg

Arm description:

Subjects received Encorafenib 50 milligram (mg) once daily (QD) and Binimetinib 45 mg twice a daily (BID) orally 4 weeks till sponsor/investigator determined the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 50 mg was administered orally.

Arm title	Phase 1b: Enco 100 mg+ Bini 45 mg

Arm description:

Subjects received Encorafenib 100 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 100 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Arm title	Phase 1b: Enco 400 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 400 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 400 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b: Enco 450 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450 mg was administered orally

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b: Enco 600 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 600 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 600 mg was administered orally.

Arm title	Phase 1b: Enco 800 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 800 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 800 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 100 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 100 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 200 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 200 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 400 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 400 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of

4 weeks, and Ribociclib 600 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 600 mg was administered orally.

Arm title	Phase 2: Arm1(mCRC):Enco+Bini

Arm description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450,600 mg was administered orally.

Arm title	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini

Arm description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450,600 mg was administered orally.

Arm title	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini

Arm description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Capsule, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450,600 mg was administered orally.

Arm title	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo

Arm description:

Subjects received Encorafenib 200 mg QD (MTD), Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: Ribociclib 600 mg was administered orally.	
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Number of subjects in period 1	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg
Started	6	5	4
Completed	6	5	4

Number of subjects in period 1	Phase 1b: Enco 400 mg+Bini 45 mg	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg
Started	5	13	8
Completed	5	13	8

Number of subjects in period 1	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg
Started	6	4	5
Completed	6	4	5

Number of subjects in period 1	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	Phase 2: Arm1(mCRC):Enco+
Started	6	6	11
Completed	6	6	11

Number of subjects in period 1	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Started	26	42	42
Completed	26	42	42

Period 2

Period 2 title	Phase 1b
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg

Arm description:

Participants received Encorafenib 50 milligram (mg) once daily (QD) and Binimetinib 45 mg twice a daily (BID) orally 4 weeks till sponsor/investigator determined the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 50 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b: Enco 100 mg+ Bini 45 mg

Arm description:

Subjects received Encorafenib 100 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 100 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or

withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Arm title	Phase 1b: Enco 400 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 400 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 400 mg was administered orally.

Arm title	Phase 1b: Enco 450 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450 mg was administered orally

Arm title	Phase 1b: Enco 600 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 600 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 600 mg was administered orally.

Arm title	Phase 1b: Enco 800 mg+Bini 45 mg

Arm description:

Subjects received Encorafenib 800 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 800 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 100 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 100 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 200 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 200 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of

4 weeks, and Ribociclib 400 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 400 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Arm title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg

Arm description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib 600 mg was administered orally.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Number of subjects in period 2[1]	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg
Started	6	5	4
Completed	0	0	0
Not completed	6	5	4
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	-	1	-
Disease progression	2	4	3
Adverse event, non-fatal	1	-	-
Administrative problems	1	-	-
Protocol deviation	2	-	-

Number of subjects in period 2[1]	Phase 1b: Enco 400 mg+Bini 45 mg	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg
Started	5	13	8
Completed	0	0	0
Not completed	5	13	8
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	-	-
Disease progression	2	10	6
Adverse event, non-fatal	1	2	2
Administrative problems	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 2[1]	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg
Started	6	4	5
Completed	0	0	0
Not completed	6	4	5
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	1	-	-
Disease progression	5	3	4
Adverse event, non-fatal	-	-	1
Administrative problems	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 2[1]	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg
Started	6	6

Completed	0	0
Not completed	6	6
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	-
Disease progression	5	1
Adverse event, non-fatal	1	2
Administrative problems	-	2
Protocol deviation	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants enrolled in Phase 1b was included in this period.

Period 3

Period 3 title	Phase 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Phase 2: Arm1 (mCRC):Enco+Bini

Arm description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450,600 mg was administered orally.

Arm title	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini

Arm description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450,600 mg was administered orally.

Arm title	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini

Arm description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 450,600 mg was administered orally.

Arm title	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo

Arm description:

Subjects received Encorafenib 200 mg QD (MTD), Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 200 mg was administered orally.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: Ribociclib 600 mg was administered orally.	
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib 45 mg was administered orally.

Number of subjects in period 3	Phase 2: Arm1 (mCRC):Enco+Bini	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini
Started	11	26	42
Completed	0	0	0
Not completed	11	26	42
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	-	-	3
Disease progression	10	21	30
Adverse event, non-fatal	1	3	5
Administrative problems	-	-	3
Protocol deviation	-	1	-

Number of subjects in period 3	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Started	42
Completed	0
Not completed	42
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Disease progression	25
Adverse event, non-fatal	14
Administrative problems	1
Protocol deviation	-

Reporting groups

Reporting group title	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg

Reporting group description:

Subjects received Encorafenib 50 milligram (mg) once daily (QD) and Binimetinib 45 mg twice a daily (BID) orally 4 weeks till sponsor/investigator determined the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 100 mg+ Bini 45 mg

Reporting group description:

Subjects received Encorafenib 100 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 400 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 400 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 450 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 600 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 600 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 800 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 800 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 100 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 200 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 400 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm1(mCRC):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo

Reporting group description:

Subjects received Encorafenib 200 mg QD (MTD), Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg
Number of subjects	6	5	4
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	3	4	4
>=65 years	3	1	0
Age continuous Units: years			
arithmetic mean	55.5	55.2	44.0
standard deviation	± 18.17	± 6.91	± 14.05
Sex: Female, Male Units: Subjects			
Female	2	3	4
Male	4	2	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	4	5	2
Asian	2	0	2
Other- Race	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	0	0	0
Chinese	2	0	2
Other- Ethnicity	4	5	2

Reporting group values	Phase 1b: Enco 400 mg+Bini 45 mg	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg
Number of subjects	5	13	8
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	4	10	6
>=65 years	1	3	2
Age continuous Units: years			
arithmetic mean	49.0	52.2	52.0
standard deviation	± 16.39	± 17.69	± 16.90
Sex: Female, Male Units: Subjects			
Female	1	5	3
Male	4	8	5
Race/Ethnicity, Customized Units: Subjects			
Caucasian	5	12	8
Asian	0	1	0
Other- Race	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	0	0	0
Chinese	0	1	0
Other- Ethnicity	5	12	8

Reporting group values	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg
Number of subjects	6	4	5
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	5	4	4
>=65 years	1	0	1
Age continuous Units: years			
arithmetic mean	55.5	48.5	51.4
standard deviation	± 14.71	± 6.76	± 19.24
Sex: Female, Male Units: Subjects			
Female	4	1	4
Male	2	3	1
Race/Ethnicity, Customized Units: Subjects			
Caucasian	6	4	5
Asian	0	0	0
Other- Race	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	0	0	0

Chinese	0	0	0
Other- Ethnicity	6	4	5

Reporting group values	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	Phase 2: Arm1(mCRC):Enco+Bini
Number of subjects	6	6	11
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	3	6	9
>=65 years	3	0	2
Age continuous Units: years			
arithmetic mean	58.0	42.3	55.3
standard deviation	± 13.45	± 9.58	± 9.18
Sex: Female, Male Units: Subjects			
Female	1	4	3
Male	5	2	8
Race/Ethnicity, Customized Units: Subjects			
Caucasian	6	6	11
Asian	0	0	0
Other- Race	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	0	0	0
Chinese	0	0	0
Other- Ethnicity	6	6	11

Reporting group values	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Number of subjects	26	42	42
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	22	33	32
>=65 years	4	9	10
Age continuous Units: years			
arithmetic mean	52.0	54.7	52.0
standard deviation	± 14.23	± 13.96	± 15.70
Sex: Female, Male Units: Subjects			
Female	11	12	19
Male	15	30	23
Race/Ethnicity, Customized Units: Subjects			
Caucasian	24	37	42

Asian	1	0	0
Other- Race	1	5	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	2	1	1
Chinese	0	0	0
Other- Ethnicity	24	41	41

Reporting group values	Total		
Number of subjects	189		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	149		
>=65 years	40		
Age continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	77		
Male	112		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	177		
Asian	6		
Other- Race	6		
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	4		
Chinese	5		
Other- Ethnicity	180		

End points reporting groups

Reporting group title	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg

Reporting group description:

Subjects received Encorafenib 50 milligram (mg) once daily (QD) and Binimetinib 45 mg twice a daily (BID) orally 4 weeks till sponsor/investigator determined the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 100 mg+ Bini 45 mg

Reporting group description:

Subjects received Encorafenib 100 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 400 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 400 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 450 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 600 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 600 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 800 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 800 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 100 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 200 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 400 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm1(mCRC):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo

Reporting group description:

Subjects received Encorafenib 200 mg QD (MTD), Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg

Reporting group description:

Participants received Encorafenib 50 milligram (mg) once daily (QD) and Binimetinib 45 mg twice a daily (BID) orally 4 weeks till sponsor/investigator determined the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 100 mg+ Bini 45 mg

Reporting group description:

Subjects received Encorafenib 100 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 400 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 400 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 450 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 600 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 600 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 800 mg+Bini 45 mg

Reporting group description:

Subjects received Encorafenib 800 mg QD and Binimetinib 45 mg BID orally for 4 weeks till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 100 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 200 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 400 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg BID orally for 3 weeks on, 1 week off schedule, till sponsor/investigator determined MTD and/or RP2D, until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm1 (mCRC):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Reporting group title	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo

Reporting group description:

Subjects received Encorafenib 200 mg QD (MTD), Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule until disease progression, unacceptable toxicity or withdrawal of informed consent, whichever occurred first.

Primary: Number of Subjects With Dose Limiting Toxicities (DLTs): Phase 1b

End point title	Number of Subjects With Dose Limiting Toxicities (DLTs): Phase 1b[1]

End point description:

DLT was defined as an adverse event or abnormal laboratory value assessed as at least possibly related to the study medication, as clinically relevant, as unrelated to disease, disease progression, inter-current illness, or concomitant medications, which occurred (less than equal to) <=28 days following the first dose of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 (cycle 1) and met the defined

criteria for the study. Dose Determining Set (DDS) included all Phase 1b subjects from the safety set who either completed a minimum exposure requirement and had sufficient safety evaluations or discontinued prematurely due to a DLT. All subjects reported under "Number of Subjects Analyzed" contributed data to this endpoint measure.

End point type	Primary

End point timeframe:

Phase 1b: Cycle 1 (28 days following the first dose of LGX818 and MEK162 or LGX818 and MEK162 and LEE011)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	2	4
Units: Subjects	0	0	0	0

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Subjects	0	0	1	0

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Disease Control Rate (DCR) at Week 16: Phase 2, Arm 1 (mCRC Subjects)

End point title	Disease Control Rate (DCR) at Week 16: Phase 2, Arm 1 (mCRC Subjects)[2]

End point description:

DCR was defined as percentage of subjects with a best overall response of complete response (CR), partial response (PR) or stable disease (SD). As per Response Evaluation Criteria in Solid tumors Response Evaluation Criteria in Solid Tumors (RECIST) v1.1: CR was defined as complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must have a

reduction in short axis less than (<)10 millimeter [mm]). PR was defined as more than equal to (>=) 30 percent (%) decrease under baseline of sum of diameters of all target lesions taking as reference the baseline sum of diameters. SD was defined as neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease (PD). Full Analysis Set (FAS) included all subjects who received at least one dose of LGX818 or MEK162 or LEE011.

End point type	Primary

End point timeframe:

Phase 2: Week 16

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Phase 2: Arm1 (mCRC):Enco+ Bini			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage of subjects				
number (confidence interval 95%)	63.6 (30.8 to 89.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR): Phase 2, Arms 2, 3 and A

End point title	Objective Response Rate (ORR): Phase 2, Arms 2, 3 and A[3]

End point description:

ORR was defined as the percentage of subjects with a best overall response of CR or PR. As per RECIST v1.1, CR was defined as complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must have a reduction in short axis <10 mm. PR was defined as >= 30% decrease under baseline of sum of diameters of all target lesions taking as reference the baseline sum of diameters. FAS included all subjects who received at least one dose of LGX818 or MEK162 or LEE011.

End point type	Primary

End point timeframe:

Phase 2: From Day 1 of dosing till complete response or partial response achieved (maximum exposure of treatment for Phase 2 was 111.5 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Phase 2: Arm 2 (prior BRAFi melanoma):En co+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):En co+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):En co+Bini+Ribo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	42	42	
Units: Percentage of subjects				
number (confidence interval 95%)	42.3 (23.4 to 63.1)	66.7 (50.5 to 80.4)	59.5 (43.3 to 74.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs): Overall Grades and AEs of Grade 3/4: Phase 1b

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs): Overall Grades and AEs of Grade 3/4: Phase 1b

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. TEAEs were those events with onset dates occurring during the on-treatment period (the time from the Day 1 up to 30 days after last dose). AEs were graded according to CTCAE version 4.03 as Grade 1 indicates Mild AE, Grade 2 indicates Moderate AE, Grade 3 indicates severe AE, and grade 4 indicates life-threatening consequences; urgent intervention indicated. Grade 5 indicates death related to AE. Safety set included all subjects who received at least one dose of LGX818 or MEK162 or LEE011 and had at least one valid post-baseline safety assessment.

End point type	Secondary

End point timeframe:

Phase 1b: Day 1 up to 30 days after last dose (maximum treatment exposure for Phase 1b was 118.3 months)

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: Subjects				
Overall Grades	6	5	4	5
Grade 3/4	5	2	2	4

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Subjects				
Overall Grades	13	8	6	4
Grade 3/4	8	6	6	4

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Subjects				
Overall Grades	5	6	6	
Grade 3/4	4	6	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity With Extrapolation of the Terminal Phase (AUCinf) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity With Extrapolation of the Terminal Phase (AUCinf) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

AUCinf was reported in unit of measure as hour*nanogram per millilitre (h*ng/mL). FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, "Number Analyzed" signifies number of subjects evaluable for specified categories.99999 signifies data could not be calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose, 0.5,1.5,2.5,4,6,8 and 24 hours (hr) post dose on Day 1 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib; n=6,5,4,4,13,7,5,4,4,3,5	3740 (± 2350)	11700 (± 6200)	22000 (± 9790)	42000 (± 23600)
Binimetinib; n=5,4,3,3,11,7,4,4,4,3,4	2190 (± 1350)	1930 (± 529)	3730 (± 2250)	1960 (± 1140)
Ribociclib;n=0,0,0,0,0,0,0,4,5,4,4	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	321 (± 225)	271 (± 28.9)	631 (± 296)	275 (± 121)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,1,3,1,0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco	Phase 1b: Enco	Phase 1b: Enco	Phase 1b: Enco

	450 mg+Bini 45 mg	600 mg+Bini 45 mg	800 mg+Bini 45 mg	200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib; n=6,5,4,4,13,7,5,4,4,3,5	36700 (± 19400)	57400 (± 27100)	40200 (± 12100)	15000 (± 7360)
Binimetinib; n=5,4,3,3,11,7,4,4,4,3,4	2750 (± 1490)	3090 (± 1600)	2340 (± 462)	2160 (± 1580)
Ribociclib;n=0,0,0,0,0,0,0,4,5,4,4	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	1040 (± 665)
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	361 (± 184)	449 (± 302)	361 (± 78.1)	173 (± 55.6)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,1,3,1,0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	194 (± 99999)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib; n=6,5,4,4,13,7,5,4,4,3,5	9960 (± 5940)	18900 (± 9900)	17400 (± 9480)	
Binimetinib; n=5,4,3,3,11,7,4,4,4,3,4	3000 (± 932)	3110 (± 1450)	2970 (± 458)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,4,4	3030 (± 1600)	7930 (± 5180)	18200 (± 10400)	
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	337 (± 29.2)	99999 (± 99999)	239 (± 79.1)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,1,3,1,0	601 (± 225)	1340 (± 99999)	2160 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With TEAEs: Overall Grades and AEs of Grade 3/4: Phase 2

End point title	Number of Subjects With TEAEs: Overall Grades and AEs of Grade 3/4: Phase 2

End point description:

An AE was any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. TEAEs were those events with onset dates occurring during the on-treatment period (the time from the Day 1 up to 30 days after last dose). AEs were graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 as Grade 1 indicates Mild AE, Grade 2 indicates Moderate AE, Grade 3 indicates severe AE, and grade 4 indicates life-threatening consequences; urgent intervention indicated. Grade 5 indicates death related to AE. Safety set included all subjects who received at least one dose of LGX818 or MEK162 or LEE011 and had at least one valid post-baseline safety assessment.

End point type	Secondary

End point timeframe:

Phase 2: Day 1 up to 30 days after last dose (maximum treatment exposure for Phase 2 was 111.5 months)

End point values	Phase 2: Arm1 (mCRC):Enco+ Bini	Phase 2: Arm 2 (prior BRAFi melanoma):En co+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):En co+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):En co+Bini+Ribo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	26	42	42
Units: Subjects				
Overall Grades	11	26	42	42
Grade 3/4	5	15	27	34

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Area Under the Concentration-Time Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, “Number Analyzed” signifies number of subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose, 0.5,1.5,2.5,4,6,8 and 24 hr post dose on Day 1 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetini b 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib; n=6,5,4,4,13,7,6,4,5,6,6	3690 (± 2340)	11500 (± 6070)	22000 (± 9750)	40200 (± 21700)
Binimetinib; n=6,5,3,4,13,7,4,4,5,6,6	1990 (± 1130)	1990 (± 715)	3300 (± 1990)	1870 (± 867)
Ribociclib; n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Metabolite of Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	276 (± 184)	280 (± 50.5)	372 (± 320)	241 (± 82.5)
Metabolite of Ribociclib; n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib; n=6,5,4,4,13,7,6,4,5,6,6	36100 (± 19300)	57000 (± 26800)	38100 (± 11800)	11400 (± 4530)
Binimetinib; n=6,5,3,4,13,7,4,4,5,6,6	2330 (± 1220)	2790 (± 1480)	2120 (± 478)	1520 (± 663)
Ribociclib; n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	806 (± 549)
Metabolite of Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	287 (± 122)	340 (± 244)	307 (± 78.4)	156 (± 53.8)
Metabolite of Ribociclib; n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	81.4 (± 41.0)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib; n=6,5,4,4,13,7,6,4,5,6,6	9280 (± 4190)	12700 (± 5020)	15800 (± 7160)	
Binimetinib; n=6,5,3,4,13,7,4,4,5,6,6	2470 (± 878)	2020 (± 843)	2320 (± 635)	
Ribociclib; n=0,0,0,0,0,0,0,4,5,6,6	2550 (± 1280)	6700 (± 3720)	14500 (± 7490)	
Metabolite of Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	259 (± 54.3)	168 (± 109)	161 (± 81.9)	
Metabolite of Ribociclib; n=0,0,0,0,0,0,0,4,5,6,6	397 (± 145)	758 (± 231)	1200 (± 320)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast at Steady State (AUClast,ss) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	AUClast at Steady State (AUClast,ss) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose,0.5,1.5, 2.5, 4, 6, 8 and 24 hr post dose on Day 15 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	2620 (± 1260)	5510 (± 1280)	4620 (± 1640)	10200 (± 2280)
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	2950 (± 1380)	2610 (± 873)	2660 (± 1900)	2110 (± 1220)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	147 (± 152)	173 (± 125)	118 (± 70.7)	119 (± 96.5)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	15900 (± 8730)	27300 (± 17900)	25300 (± 7240)	6310 (± 2340)
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	2550 (± 901)	2590 (± 1640)	2540 (± 529)	2180 (± 1180)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	462 (± 129)
Metabolite of Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	157 (± 104)	132 (± 142)	190 (± 79.8)	149 (± 136)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	255 (± 131)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	

Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	8210 (± 2550)	11800 (± 7000)	15700 (± 6060)	
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	2820 (± 954)	2740 (± 1230)	2970 (± 1180)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	1520 (± 979)	5620 (± 3730)	10100 (± 2970)	
Metabolite of Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	210 (± 68.4)	176 (± 92.5)	169 (± 48.5)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	729 (± 267)	2150 (± 399)	3260 (± 891)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to Tau After First Dose (AUCtau) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Area Under the Concentration-Time Curve From Time Zero to Tau After First Dose (AUCtau) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose, 0.5,1.5,2.5,4,6,8 and 24 hr post dose on Day 1 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,5,4,4,3,5	3700 (± 2320)	11500 (± 6070)	22000 (± 9750)	40200 (± 21700)
Binimetinib;n=5,4,3,3,11,7,4,4,4,3,4	2130 (± 1330)	1860 (± 532)	3600 (± 2160)	1890 (± 1110)
Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	307 (± 222)	265 (± 27.9)	585 (± 304)	257 (± 109)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,3,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini	Phase 1b: Enco 600 mg+Bini	Phase 1b: Enco 800 mg+Bini	Phase 1b: Enco 200 mg+Bini

	45 mg	45 mg	45 mg	45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,5,4,4,3,5	36300 (± 19000)	57000 (± 26800)	40000 (± 12100)	14800 (± 7140)
Binimetinib;n=5,4,3,3,11,7,4,4,4,3,4	2650 (± 1410)	3010 (± 1560)	2280 (± 477)	1790 (± 979)
Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	845 (± 504)
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	338 (± 162)	430 (± 291)	344 (± 82.0)	152 (± 32.3)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,3,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	98.9 (± 25.9)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,5,4,4,3,5	9940 (± 5900)	18700 (± 9730)	17300 (± 9300)	
Binimetinib;n=5,4,3,3,11,7,4,4,4,3,4	2900 (± 939)	2860 (± 1320)	2900 (± 453)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	2550 (± 1280)	6700 (± 3720)	14500 (± 7490)	
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	322 (± 23.5)	99999 (± 99999)	230 (± 79.1)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,3,5,6,6	397 (± 145)	758 (± 231)	1200 (± 320)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau at Steady State (AUCtau,ss) of Encorafenib, Binimetinib and Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	AUCtau at Steady State (AUCtau,ss) of Encorafenib, Binimetinib and Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, “Number Analyzed” signifies number of subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose,0.5,1.5, 2.5, 4, 6, 8 and 24 hr post dose on Day 15 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	2620 (± 1260)	5510 (± 1280)	4620 (± 1640)	10200 (± 2280)
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	2950 (± 1380)	2610 (± 873)	2660 (± 1900)	2110 (± 1220)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=3,3,2,2,7,2,4,2,4,4,5	261 (± 136)	237 (± 107)	126 (± 59.5)	194 (± 75.8)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	15900 (± 8730)	27300 (± 17900)	25300 (± 7240)	6310 (± 2340)
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	2550 (± 901)	2590 (± 1640)	2540 (± 529)	2180 (± 1180)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	462 (± 129)
Metabolite of Binimetinib;n=3,3,2,2,7,2,4,2,4,4,5	221 (± 83.5)	304 (± 77.7)	225 (± 25.1)	265 (± 33.4)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	255 (± 131)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	8210 (± 2550)	11800 (± 7000)	15700 (± 6060)	
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	2820 (± 954)	2740 (± 1230)	2970 (± 1180)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	1520 (± 979)	5620 (± 3730)	10100 (± 2970)	

Metabolite of Binimetinib;n=3,3,2,2,7,2,4,2,4,4,5	219 (± 71.5)	207 (± 69.7)	175 (± 52.8)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	729 (± 267)	2150 (± 399)	3260 (± 891)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Encorafenib, Binimetinib, Ribociclib Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Maximum Observed Plasma Concentration (Cmax) of Encorafenib, Binimetinib, Ribociclib Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, “Number Analyzed” signifies number of subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose, 0.5,1.5,2.5,4,6,8 and 24 hr post dose on Day 1 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,6,4,5,6,6	855 (± 480)	1930 (± 652)	3820 (± 1550)	6930 (± 1950)
Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	635 (± 402)	587 (± 147)	986 (± 771)	532 (± 227)
Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	79.3 (± 55.3)	75.3 (± 10.7)	90.8 (± 88.0)	67.9 (± 32.0)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,6,4,5,6,6	7620 (± 3350)	10300 (± 3170)	7880 (± 2910)	2920 (± 499)

Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	807 (± 398)	901 (± 480)	621 (± 160)	462 (± 85.6)
Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	74.2 (± 37.5)
Metabolite of Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	85.1 (± 34.9)	93.5 (± 67.0)	81.1 (± 32.4)	41.8 (± 13.2)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	5.90 (± 1.73)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,6,4,5,6,6	3190 (± 1010)	3450 (± 1140)	4200 (± 1020)	
Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	867 (± 232)	560 (± 213)	703 (± 222)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	219 (± 95.2)	554 (± 251)	1220 (± 701)	
Metabolite of Binimetinib;n=6,5,3,4,13,7,4,4,5,6,6	83.2 (± 28.2)	40.2 (± 22.3)	45.0 (± 25.4)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,6,6	28.7 (± 7.82)	58.0 (± 39.6)	73.8 (± 24.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax at Steady State (Cmax,ss) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Cmax at Steady State (Cmax,ss) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, “Number Analyzed” signifies number of subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose,0.5,1.5, 2.5,4, 6,8 and 24 hr post dose on Day 15 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: ng/mL				
arithmetic mean (standard deviation)				

Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	587 (± 321)	1190 (± 409)	1060 (± 194)	3760 (± 1380)
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	693 (± 283)	568 (± 233)	616 (± 438)	553 (± 336)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	39.7 (± 43.7)	36.0 (± 25.9)	27.3 (± 12.6)	31.7 (± 25.9)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	4320 (± 2260)	11100 (± 14100)	7320 (± 2700)	1670 (± 453)
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	638 (± 283)	716 (± 321)	726 (± 206)	584 (± 181)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	43.7 (± 16.1)
Metabolite of Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	38.8 (± 21.8)	35.0 (± 25.3)	47.3 (± 19.5)	38.3 (± 25.4)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	16.8 (± 9.77)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: ng/mL				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,6,4,5,5,5	2320 (± 779)	2480 (± 1090)	2590 (± 929)	
Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	778 (± 160)	563 (± 262)	609 (± 261)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	146 (± 111)	493 (± 258)	752 (± 304)	
Metabolite of Binimetinib;n=6,5,2,4,11,6,5,4,4,5,5	55.1 (± 26.5)	33.2 (± 16.7)	33.7 (± 12.8)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	49.7 (± 19.5)	155 (± 30.5)	195 (± 56.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life (t1/2) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Elimination Half-life (t1/2) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, "Number Analyzed" signifies number of subjects evaluable for specified categories. 99999 signifies data could not be calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose, 0.5,1.5,2.5,4,6,8 and 24 hr post dose on Day 1 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,5,4,4,3,5	3.68 (± 0.605)	3.65 (± 0.351)	2.88 (± 0.121)	4.19 (± 2.13)
Binimetinib;n=5,4,3,3,11,7,4,4,4,3,4	2.36 (± 0.427)	2.37 (± 0.704)	2.10 (± 0.522)	2.51 (± 0.472)
Ribociclib;n=0,0,0,0,0,0,0,4,5,4,4	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	2.82 (± 0.757)	2.00 (± 0.0542)	2.95 (± 0.739)	2.58 (± 0.737)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,1,3,1,1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,5,4,4,3,5	3.47 (± 0.402)	3.21 (± 0.550)	3.04 (± 0.0935)	3.25 (± 0.375)
Binimetinib;n=5,4,3,3,11,7,4,4,4,3,4	2.22 (± 0.439)	2.12 (± 0.314)	1.99 (± 0.601)	3.73 (± 1.78)
Ribociclib;n=0,0,0,0,0,0,0,4,5,4,4	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	8.71 (± 2.32)
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	2.64 (± 0.604)	2.28 (± 0.546)	2.37 (± 0.517)	3.39 (± 1.57)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,1,3,1,1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	23.2 (± 99999)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,4,4,13,7,5,4,4,3,5	2.10 (± 0.451)	2.95 (± 1.13)	2.59 (± 0.567)	
Binimetinib;n=5,4,3,3,11,7,4,4,4,3,4	2.45 (± 1.19)	3.11 (± 1.01)	1.98 (± 0.523)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,4,4	7.97 (± 1.24)	10.3 (± 3.94)	7.71 (± 0.408)	
Metabolite of Binimetinib;n=5,3,2,3,9,5,4,3,4,0,4	2.49 (± 0.528)	99999 (± 99999)	2.32 (± 0.455)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,1,3,1,1	15.4 (± 6.92)	7.99 (± 99999)	15.9 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2 at Steady State (t1/2,ss) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	t1/2 at Steady State (t1/2,ss) of Encorafenib, Binimetinib, Ribociclib, Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, “Number Analyzed” signifies number of subjects evaluable for specified categories. 99999 signifies data could not be calculated due to insufficient number of subjects.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose,0.5,1.5, 2.5,4,6,8 and 24 hr post dose on Day 15 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib;n=5,4,2,3,11,6,6,4,5,5,4	4.74 (± 1.18)	4.47 (± 0.380)	4.32 (± 1.25)	4.21 (± 0.724)
Binimetinib;n=2,4,1,4,9,0,3,3,3,4,4	4.74 (± 1.43)	4.80 (± 1.40)	3.28 (± 99999)	4.20 (± 1.36)
Ribociclib;n=0,0,0,0,0,0,0,4,4,4,3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=2,2,1,1,5,2,3,1,3,2,2	4.51 (± 1.23)	7.23 (± 5.44)	2.07 (± 99999)	4.61 (± 99999)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,4,2,2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini	Phase 1b: Enco 600 mg+Bini	Phase 1b: Enco 800 mg+Bini	Phase 1b: Enco 200 mg+Bini

	45 mg	45 mg	45 mg	45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib;n=5,4,2,3,11,6,6,4,5,5,4	3.57 (± 0.688)	3.40 (± 0.223)	3.37 (± 0.511)	3.98 (± 0.331)
Binimetinib;n=2,4,1,4,9,0,3,3,3,4,4	3.61 (± 1.14)	99999 (± 99999)	2.91 (± 0.157)	4.04 (± 2.03)
Ribociclib;n=0,0,0,0,0,0,0,4,4,4,3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	13.2 (± 2.26)
Metabolite of Binimetinib;n=2,2,1,1,5,2,3,1,3,2,2	2.79 (± 1.23)	4.06 (± 0.195)	3.33 (± 0.524)	5.12 (± 99999)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,4,2,2	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	18.3 (± 3.23)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib;n=5,4,2,3,11,6,6,4,5,5,4	3.24 (± 0.776)	4.00 (± 0.922)	3.52 (± 0.237)	
Binimetinib;n=2,4,1,4,9,0,3,3,3,4,4	2.67 (± 1.40)	3.69 (± 1.16)	5.21 (± 1.75)	
Ribociclib;n=0,0,0,0,0,0,0,4,4,4,3	11.4 (± 6.07)	8.49 (± 2.80)	10.3 (± 5.32)	
Metabolite of Binimetinib;n=2,2,1,1,5,2,3,1,3,2,2	2.58 (± 0.626)	3.44 (± 0.115)	4.38 (± 2.14)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,4,4,2,2	15.7 (± 6.62)	15.0 (± 6.27)	18.6 (± 2.76)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS): Phase 2

End point title	Progression Free Survival (PFS): Phase 2

End point description:

PFS was defined as the time from the start of study treatment to the date of the event defined as the first documented progression or death due to any cause. If a subject did not have an event, PFS was censored at the date of last adequate tumor assessment. Per RECIST 1.1, PD= At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2. Unequivocal progression of existing non-target lesions. Kaplan-Meier method was used for analysis. FAS included all subjects who received at least one dose of LGX818 or MEK162 or LEE011.

End point type	Secondary

End point timeframe:

Phase 2: From start of study drug until documented PD or death due to any cause or censoring date (maximum exposure of treatment in Phase 2 was 111.5 months)

End point values	Phase 2: Arm1 (mCRC):Enco+ Bini	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	26	42	42
Units: Months				
median (confidence interval 95%)	5.4 (2.1 to 9.0)	3.8 (3.4 to 9.3)	7.5 (5.7 to 12.2)	9.0 (5.6 to 11.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio (RA) of Encorafenib, Binimetinib, Ribociclib Metabolite of Binimetinib and Ribociclib: Phase 1b

End point title	Accumulation Ratio (RA) of Encorafenib, Binimetinib, Ribociclib Metabolite of Binimetinib and Ribociclib: Phase 1b

End point description:

Accumulation ratio was calculated as AUCtau,ss/AUCtau. FAS evaluated. All subjects reported under "Number of Subjects Analyzed" contributed data to the table; however, may not have evaluable data for every category. Here, "Number Analyzed" signifies number of subjects evaluable for specified categories. 99999 signifies data could not be calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Phase 1b: Pre dose, 0.5,1.5,2.5,4,6,8 and 24 hr post dose on Day 1 and 15 of Cycle 1

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: Ratio				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,5,4,4,3,4	0.857 (± 0.351)	0.601 (± 0.322)	0.298 (± 0.0682)	0.348 (± 0.125)
Binimetinib;n=5,4,2,4,9,6,4,4,3,2,4	1.51 (± 0.248)	1.26 (± 0.152)	1.07 (± 0.142)	0.989 (± 0.353)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Metabolite of Binimetinib;n=3,1,1,2,4,1,3,1,3,0,4	0.899 (± 0.542)	0.588 (± 99999)	0.285 (± 99999)	0.954 (± 0.0302)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,3,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Ratio				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,5,4,4,3,4	0.458 (± 0.188)	0.473 (± 0.215)	0.690 (± 0.291)	0.460 (± 0.134)
Binimetinib;n=5,4,2,4,9,6,4,4,3,2,4	1.03 (± 0.339)	0.969 (± 0.297)	1.19 (± 0.472)	1.29 (± 0.572)
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	0.640 (± 0.282)
Metabolite of Binimetinib;n=3,1,1,2,4,1,3,1,3,0,4	0.546 (± 0.300)	0.499 (± 99999)	0.569 (± 0.0381)	1.56 (± 99999)
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,3,5,5,5	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	2.81 (± 0.619)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Ratio				
arithmetic mean (standard deviation)				
Encorafenib;n=6,5,2,3,11,6,5,4,4,3,4	0.841 (± 0.178)	0.833 (± 0.463)	0.806 (± 0.393)	
Binimetinib;n=5,4,2,4,9,6,4,4,3,2,4	0.778 (± 0.102)	1.19 (± 0.324)	1.08 (± 0.316)	
Ribociclib;n=0,0,0,0,0,0,0,4,5,5,5	0.734 (± 0.404)	1.11 (± 0.753)	0.712 (± 0.168)	
Metabolite of Binimetinib;n=3,1,1,2,4,1,3,1,3,0,4	0.726 (± 0.194)	99999 (± 99999)	0.910 (± 0.195)	
Metabolite of Ribociclib;n=0,0,0,0,0,0,0,3,5,5,5	1.93 (± 0.684)	2.73 (± 0.517)	2.97 (± 0.548)	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR): Phase 1b

End point title	Objective Response Rate (ORR): Phase 1b

End point description:

ORR was defined as the percentage of subjects with a best overall response of CR or PR. As per RECIST v1.1, CR was defined as complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must have a reduction in short axis <10 mm. PR was defined as >= 30 % decrease under baseline of sum of diameters of all target lesions taking as reference the baseline sum of

diameters. FAS included all subjects who received at least one dose of LGX818 or MEK162 or LEE011.

End point type	Secondary

End point timeframe:

Phase 1b: From Day 1 of dosing till complete response or partial response achieved (maximum exposure of treatment in Phase 1b was 118.3 months)

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: Percentage of subjects				
number (confidence interval 95%)	66.7 (22.3 to 95.7)	40.0 (5.3 to 85.3)	25.0 (0.6 to 80.6)	40.0 (5.3 to 85.3)

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Percentage of subjects				
number (confidence interval 95%)	53.8 (25.1 to 80.8)	25.0 (3.2 to 65.1)	50.0 (11.8 to 88.2)	75.0 (19.4 to 99.4)

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Percentage of subjects				
number (confidence interval 95%)	60.0 (14.7 to 94.7)	66.7 (22.3 to 95.7)	66.7 (22.3 to 95.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR): Phase 2

End point title	Time to Response (TTR): Phase 2

End point description:

TTR was defined as the time from the first dose of study treatment to the first documentation of objective tumor response documented in subject with confirmed objective response (CR or PR). As per RECIST v1.1, CR was defined as complete disappearance of all target lesions and non-target disease. All

nodes, both target and non-target, must have a reduction in short axis <10 mm. PR was defined as >= 30 % decrease under baseline of sum of diameters of all target lesions taking as reference the baseline sum of diameters. Kaplan-Meier method was used for analysis. Here "Number of Subjects Analyzed" signifies the number of subjects who were confirmed responders and were evaluable for this endpoint measure.

End point type	Secondary

End point timeframe:

Phase 2: From date of start of treatment until date of first documentation of objective tumor response (maximum exposure of treatment in Phase 2 was 111.5 months)

End point values	Phase 2: Arm1 (mCRC):Enco+ Bini	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	11	28	25
Units: Months				
median (confidence interval 95%)	2.6 (1.6 to 3.6)	1.8 (1.0 to 5.6)	1.0 (1.0 to 1.8)	1.9 (1.8 to 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR): Phase 2

End point title	Duration of Response (DOR): Phase 2

End point description:

DOR was defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to underlying cancer, whichever occurred first in subjects with confirmed objective response (CR or PR). As per RECIST v1.1, CR was defined as complete disappearance of all target lesions and non-target disease. All nodes, both target and non-target, must have a reduction in short axis <10 mm. PR was defined as >= 30 % decrease under baseline of sum of diameters of all target lesions taking as reference the baseline sum of diameters. Kaplan-Meier method was used for analysis. FAS evaluated. Here "Number of Subjects Analyzed" signifies the number of subjects who were confirmed responders and were evaluable for this endpoint measure. 99999 signifies data could not be calculated due to insufficient number of subjects.

End point type	Secondary

End point timeframe:

Phase 2: From date of first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to underlying cancer, whichever occurred first (maximum exposure of treatment in Phase 2 was 111.5 months)

End point values	Phase 2: Arm1 (mCRC):Enco+ Bini	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	11	28	25
Units: Months				

median (confidence interval 95%)	7.1 (3.8 to 99999)	3.8 (2.9 to 12.9)	10.9 (6.5 to 19.5)	7.5 (5.6 to 25.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Molecular Alterations of Tumor Tissues Using Potential Predictive Markers: Phase 1b

End point title	Number of Subjects With Molecular Alterations of Tumor Tissues Using Potential Predictive Markers: Phase 1b

End point description:

Molecular alterations of tumor tissues was determined using the following potential predictive markers: Biomarkers like V-raf murine sarcoma viral oncogene homolog B1 (BRAF),V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), Phosphatase and tensin homolog (PTEN), Phosphatidylinositol 3' kinase catalytic alphapolypeptide (PIK3CA), Epidermal growth factor receptor (EGFR). FAS included all subjects who received at least one dose of LGX818 or MEK162 or LEE011.

End point type	Secondary

End point timeframe:

Phase 1b: Baseline

End point values	Phase 1b: Encorafenib 50 mg+Binimetinib 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg	Phase 1b: Enco 400 mg+Bini 45 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	4	5
Units: Subjects				
BRAF	5	4	3	4
KRAS	1	0	0	0
PTEN	0	1	0	0
PIK3CA	0	1	0	0
EGFR	0	0	0	0

End point values	Phase 1b: Enco 450 mg+Bini 45 mg	Phase 1b: Enco 600 mg+Bini 45 mg	Phase 1b: Enco 800 mg+Bini 45 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	6	4
Units: Subjects				
BRAF	7	7	3	3
KRAS	0	0	0	0
PTEN	1	2	1	0
PIK3CA	0	1	0	0
EGFR	2	0	0	0

End point values	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 200 mg	Phase 1b:Enco 200 mg+Bini 45 mg+Ribo 400 mg	Phase 1b: Enco 200 mg+Bini 45 mg+Ribo 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	6	6	
Units: Subjects				
BRAF	4	5	4	
KRAS	0	0	0	
PTEN	0	0	1	
PIK3CA	0	0	0	
EGFR	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): Phase 2

End point title	Overall Survival (OS): Phase 2

End point description:

OS was defined as the time from date of randomization/start of treatment to date of death due to any cause. If a subject was not known to have died, survival was censored at the date of last contact. Analysis was performed using Kaplan-Meier method. FAS included all subjects who received at least one dose of LGX818 or MEK162 or LEE011. 99999 signifies data could not be calculated due to insufficient number of subjects.

End point type	Secondary

End point timeframe:

Phase 2: From date of start of study treatment until date of death or censoring date (maximum exposure of treatment in Phase 2 was 111.5 months)

End point values	Phase 2: Arm1 (mCRC):Enco+ Bini	Phase 2: Arm 2 (prior BRAFi melanoma):En co+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):En co+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):En co+Bini+Ribo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	26	42	42
Units: Months				
median (confidence interval 95%)	9.5 (7.7 to 27.2)	11.4 (5.9 to 20.7)	23.1 (17.3 to 99999)	21.8 (14.8 to 35.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Molecular Alterations of Tumor Tissues Using Potential Predictive Markers:Phase 2

End point title	Number of Subjects With Molecular Alterations of Tumor Tissues Using Potential Predictive Markers:Phase 2

End point description:

Molecular alterations of tumor tissues was determined using the following potential predictive markers: BRAF, HRAS, KRAS, Neuroblastoma RAS viral oncogene homolog (NRAS), PTEN, PIK3CA, Mitogen-activated protein kinase 1 (MAP2K1), Mitogen-activated protein kinase 2 (MAP2K2), EGFR.FAS included all subjects who received at least one dose of LGX818 or MEK162 or LEE011.

End point type	Secondary

End point timeframe:

Phase 2: Baseline

End point values	Phase 2: Arm1 (mCRC):Enco+Bini	Phase 2: Arm 2 (prior BRAFi melanoma):Enco+Bini	Phase 2: Arm 3 (BRAFi-naïve melanoma):Enco+Bini	Phase 2: Arm A (BRAFi-naïve melanoma):Enco+Bini+Ribo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	26	42	42
Units: Subjects				
BRAF	4	15	20	30
HRAS	0	0	0	0
KRAS	2	0	0	0
NRAS	0	2	0	0
PTEN	1	6	5	5
PIK3CA	2	0	0	2
MAP2K1	0	3	1	0
MAP2K2	0	0	0	0
ARAF	0	0	0	0
EGFR	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 of dosing up to 30 days after last dose (maximum treatment exposure for Phase 1b was 118.3 months, Phase 2 was 111.5 months)

Adverse event reporting additional description:

Same event may appear as both non-SAE and SAE, but what is presented are distinct events. An event may be categorised as serious in 1 subject and non-serious in other subject, or a subject may have experienced both SAE and non-SAE. Safety analysis set was evaluated.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Phase 1b: Enco 800 mg + Bini 45 mg

Reporting group description:

Subjects received Encorafenib 800 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 600 mg + Bini 45 mg

Reporting group description:

Subjects received Encorafenib 600 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 450 mg+ Bini 45 mg

Reporting group description:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 400 mg + Bini 45 mg

Reporting group description:

Subjects received Encorafenib 400 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 200 mg + Bini 45 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 100 mg+ Bini 45 mg

Reporting group description:

Subjects received Encorafenib 100 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 50 mg + Bini 45 mg

Reporting group description:

Subjects received Encorafenib 50 mg QD and Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks.

Reporting group title	Phase 1b: Enco 200 mg+ Bini 45 mg + Ribo 600 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD, Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule.

Reporting group title	Phase 1b: Enco 200 mg+ Bini 45 mg+ Ribo 400 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD, Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks and Ribociclib 400 mg QD orally for 3 weeks on, 1 week off schedule.

Reporting group title	Phase 1b: Enco 200 mg+ Bini 45 mg+ Ribo 200 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD, Binimetinib 45 mg BID orally on a schedule of continuous 4

weeks and Ribociclib 200 mg QD orally for 3 weeks on, 1 week off schedule.

Reporting group title	Phase 1b: Enc 200 mg+ Bini 45 mg+ Ribo 100 mg

Reporting group description:

Subjects received Encorafenib 200 mg QD, Binimetinib 45 mg BID orally on a schedule of continuous 4 weeks and Ribociclib 100 mg QD orally for 3 weeks on, 1 week off schedule.

Reporting group title	Phase 2: Arm 3 (BRAFi-naïve melanoma): Enco+ Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks.

Reporting group title	Phase 2: Arm 2 (prior BRAFi melanoma): Enco+ Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks.

Reporting group title	Phase 2: Arm A (BRAFi-naïve melanoma): Enco+ Bini+ Ribo

Reporting group description:

Subjects received Encorafenib 200 mg QD (MTD), Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks, and Ribociclib 600 mg QD orally for 3 weeks on, 1 week off schedule.

Reporting group title	Phase 2: Arm 1 (mCRC): Enco+ Bini

Reporting group description:

Subjects received Encorafenib at MTD (600 mg QD, permitted dose reduction to 450 mg QD) and Binimetinib 45 mg BID orally on a continuous schedule of 4 weeks.

Serious adverse events	Phase 1b: Enco 800 mg + Bini 45 mg	Phase 1b: Enco 600 mg + Bini 45 mg	Phase 1b: Enco 450 mg+ Bini 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	4 / 8 (50.00%)	5 / 13 (38.46%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Lymphadenectomy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Troponin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinoscopy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy hypertensive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pharyngeal abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatininaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1b: Enco 400 mg + Bini 45 mg	Phase 1b: Enco 200 mg + Bini 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	2 / 4 (50.00%)	2 / 5 (40.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to central nervous system			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Troponin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinoscopy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy hypertensive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Detachment of retinal pigment epithelium			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pharyngeal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Post procedural infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatininaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1b: Enco 50 mg + Bini 45 mg	Phase 1b: Enco 200 mg+ Bini 45 mg + Ribo 600 mg	Phase 1b: Enco 200 mg+ Bini 45 mg+ Ribo 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	3 / 6 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Lymphadenectomy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Troponin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinoscopy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Balance disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy hypertensive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pharyngeal abscess			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatininaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1b: Enco 200 mg+ Bini 45 mg+ Ribo 200 mg	Phase 1b: Enc 200 mg+ Bini 45 mg+ Ribo 100 mg	Phase 2: Arm 3 (BRAFi-naïve melanoma): Enco+ Bini
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	2 / 4 (50.00%)	18 / 42 (42.86%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			

subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Troponin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinoscopy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo positional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy hypertensive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pharyngeal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatininaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Arm 2 (prior BRAFi melanoma): Enco+ Bini	Phase 2: Arm A (BRAFi-naïve melanoma): Enco+ Bini+ Ribo	Phase 2: Arm 1 (mCRC): Enco+ Bini
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 26 (50.00%)	21 / 42 (50.00%)	5 / 11 (45.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 26 (3.85%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Troponin increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinoscopy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Traumatic haematoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac mass			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy hypertensive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blindness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haematemesis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	2 / 11 (18.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 26 (11.54%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 26 (11.54%)	3 / 42 (7.14%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 3	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			

subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 42 (2.38%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			

subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 26 (0.00%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pharyngeal abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatininaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 26 (0.00%)	1 / 42 (2.38%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 1b: Enco 800 mg + Bini 45 mg	Phase 1b: Enco 600 mg + Bini 45 mg	Phase 1b: Enco 450 mg+ Bini 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	8 / 8 (100.00%)	13 / 13 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cancer pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	1	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	3 / 13 (23.08%)
occurrences (all)	0	1	9
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Hot flush			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	2	3	1
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	1	1	1

Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	3 / 8 (37.50%)	7 / 13 (53.85%)
occurrences (all)	7	7	16
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	2	2	2
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	3 / 13 (23.08%)
occurrences (all)	1	2	6
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	4 / 13 (30.77%)
occurrences (all)	0	1	16
Peripheral swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	3 / 8 (37.50%)	1 / 13 (7.69%)
occurrences (all)	1	3	1
Cough			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	1	1	5
Wheezing			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	1	2	2
Respiratory tract congestion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	3	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	4 / 13 (30.77%)
occurrences (all)	0	0	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 8 (37.50%)	2 / 13 (15.38%)
occurrences (all)	3	17	4
Lipase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	3 / 13 (23.08%)
occurrences (all)	1	1	6
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 6 (16.67%)	3 / 8 (37.50%)	1 / 13 (7.69%)
occurrences (all)	3	11	1
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	9	8	17
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 6 (83.33%)	2 / 8 (25.00%)	3 / 13 (23.08%)
occurrences (all)	12	7	5
Dysgeusia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	1	0	2
Dizziness			
subjects affected / exposed	2 / 6 (33.33%)	2 / 8 (25.00%)	2 / 13 (15.38%)
occurrences (all)	3	2	4
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Visual field defect			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	3	0	3
Memory impairment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Presyncope			
subjects affected / exposed	2 / 6 (33.33%)	2 / 8 (25.00%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Disturbance in attention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 8 (37.50%)	1 / 13 (7.69%)
occurrences (all)	0	7	1

Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	5
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Chorioretinopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	0	1	3
Retinal detachment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Macular oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Subretinal fluid			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	4 / 13 (30.77%)
occurrences (all)	4	6	12
Vision blurred			

subjects affected / exposed	3 / 6 (50.00%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	3	2	1
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	3 / 13 (23.08%)
occurrences (all)	1	1	3
Cataract			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	1 / 6 (16.67%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	1	5	1
Retinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	0	2	3
Retinal degeneration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	1	2	2
Vitreous detachment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Vitreous floaters			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	2	1	2
Uveitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	7 / 8 (87.50%)	7 / 13 (53.85%)
occurrences (all)	11	12	18
Constipation			
subjects affected / exposed	4 / 6 (66.67%)	3 / 8 (37.50%)	4 / 13 (30.77%)
occurrences (all)	4	8	5
Abdominal pain upper			
subjects affected / exposed	3 / 6 (50.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	3	1	1

Abdominal pain			
subjects affected / exposed	3 / 6 (50.00%)	2 / 8 (25.00%)	4 / 13 (30.77%)
occurrences (all)	5	2	6
Dry mouth			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	2	0	3
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	3 / 8 (37.50%)	7 / 13 (53.85%)
occurrences (all)	5	5	14
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	5 / 8 (62.50%)	7 / 13 (53.85%)
occurrences (all)	17	8	13
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Mouth ulceration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	4	3	1
Hyperkeratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	4
Dry skin			
subjects affected / exposed	3 / 6 (50.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	3	0	2
Pruritus			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	2	4	2
Alopecia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	2	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	3 / 13 (23.08%)
occurrences (all)	2	1	5
Palmoplantar keratoderma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	3
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Vitiligo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	4
Actinic keratosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	5
Dermatitis acneiform			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	1	2	2
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	1	0	3
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	7	6	4
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 8 (25.00%)	2 / 13 (15.38%)
occurrences (all)	1	5	2
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	3 / 6 (50.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	6	2	2
Myalgia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 8 (25.00%)	2 / 13 (15.38%)
occurrences (all)	3	2	2
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	1	0	4
Arthritis			

subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	3 / 13 (23.08%)
occurrences (all)	0	4	3
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Joint stiffness			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Infections and infestations			
Oral herpes			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	2	4	0
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	2	1	3
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	3 / 6 (50.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	3	2	0
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	0	2	3
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypercreatininaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	22
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Iron deficiency			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1b: Enco 400 mg + Bini 45 mg	Phase 1b: Enco 200 mg + Bini 45 mg	Phase 1b: Enco 100 mg+ Bini 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	4 / 4 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cancer pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Seborrhoeic keratosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	4
Flushing			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1

Fatigue			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	7	0	4
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Peripheral swelling			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	2
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Cough			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	3 / 5 (60.00%)
occurrences (all)	4	0	5
Wheezing			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	7	3	0
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	11
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	8	2	0
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
Dysgeusia			

subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Visual field defect			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	2	8

Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Chorioretinopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Retinal detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Macular oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Subretinal fluid			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vision blurred			

subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	2	2
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Retinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Retinal degeneration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vitreous floaters			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	3	1	2
Constipation			
subjects affected / exposed	2 / 5 (40.00%)	2 / 4 (50.00%)	3 / 5 (60.00%)
occurrences (all)	2	3	6
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Abdominal pain			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	2	0	4
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	0	1	3
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	4 / 4 (100.00%)	1 / 5 (20.00%)
occurrences (all)	4	6	3
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	2 / 4 (50.00%)	4 / 5 (80.00%)
occurrences (all)	7	4	6
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	3	2	1
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 4 (50.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	3
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Palmoplantar keratoderma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Actinic keratosis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Dermatitis acneiform			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 5 (60.00%)
occurrences (all)	0	0	3
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	1	2	6
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	2 / 4 (50.00%)	1 / 5 (20.00%)
occurrences (all)	1	3	1
Myalgia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Arthritis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Flank pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Conjunctivitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	3
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	0	1	3
Metabolism and nutrition disorders			
Hypertriglyceridaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypercreatininaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Iron deficiency			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1b: Enco 50 mg + Bini 45 mg	Phase 1b: Enco 200 mg+ Bini 45 mg + Ribo 600 mg	Phase 1b: Enco 200 mg+ Bini 45 mg+ Ribo 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	5 / 6 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cancer pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Seborrhoeic keratosis			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	7	1
Fatigue			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	6	5	1
Oedema peripheral			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	4	6	1
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	7	1	3
Peripheral swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Cough			

subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	17	1	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	6	3
Lipase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	5	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	21
Blood creatine phosphokinase increased			

subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	74	9	28
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	8	4
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	14	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	4	25	0
Dysgeusia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Dizziness			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Paraesthesia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Visual field defect			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Memory impairment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	5	5	3
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	16	0
Neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	51	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	4	2
Retinopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Photophobia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chorioretinopathy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Retinal detachment			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Macular oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	6	5

Subretinal fluid			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	3	5
Vision blurred			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	9	0	0
Visual impairment			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Retinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Retinal degeneration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	5	5	9
Constipation			

subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	7	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	6	3	5
Dry mouth			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Flatulence			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Abdominal distension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	4	4	0
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	6	4	0
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperkeratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	5	3	0
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Palmoplantar keratoderma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin lesion			

subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vitiligo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Actinic keratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Muscular weakness			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Myalgia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Flank pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Joint stiffness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Influenza			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0

Nasopharyngitis			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypercreatininaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1b: Enco 200 mg+ Bini 45 mg+ Ribo 200 mg	Phase 1b: Enc 200 mg+ Bini 45 mg+ Ribo 100 mg	Phase 2: Arm 3 (BRAFi-naïve melanoma): Enco+ Bini
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	4 / 4 (100.00%)	39 / 42 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4
Basal cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4
Cancer pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	9 / 42 (21.43%)
occurrences (all)	0	0	26
Flushing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	3	0	5
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	2 / 4 (50.00%)	12 / 42 (28.57%)
occurrences (all)	2	2	23
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	7 / 42 (16.67%)
occurrences (all)	0	3	9
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	7 / 42 (16.67%)
occurrences (all)	0	0	10
Pyrexia			
subjects affected / exposed	3 / 5 (60.00%)	2 / 4 (50.00%)	14 / 42 (33.33%)
occurrences (all)	5	2	24
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Dyspnoea			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	7 / 42 (16.67%)
occurrences (all)	0	2	8
Cough			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	11 / 42 (26.19%)
occurrences (all)	2	0	15
Wheezing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	8
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	11 / 42 (26.19%)
occurrences (all)	2	1	40
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	14 / 42 (33.33%)
occurrences (all)	0	0	28
Haemoglobin decreased			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Blood creatinine increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	7 / 42 (16.67%)
occurrences (all)	0	0	11
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 5 (60.00%)	1 / 4 (25.00%)	15 / 42 (35.71%)
occurrences (all)	35	4	64
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	12 / 42 (28.57%)
occurrences (all)	2	1	34
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	6 / 42 (14.29%)
occurrences (all)	0	0	35
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	9
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	6 / 42 (14.29%)
occurrences (all)	0	0	10
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	9
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	5 / 42 (11.90%)
occurrences (all)	0	0	6
Injury, poisoning and procedural complications			

Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	8 / 42 (19.05%)
occurrences (all)	1	1	11
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	9 / 42 (21.43%)
occurrences (all)	0	0	13
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	5 / 42 (11.90%)
occurrences (all)	0	0	5
Visual field defect			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Presyncope			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	7 / 42 (16.67%)
occurrences (all)	1	1	23
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	2 / 5 (40.00%)	3 / 4 (75.00%)	5 / 42 (11.90%)
occurrences (all)	3	4	9
Retinopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	6 / 42 (14.29%)
occurrences (all)	0	0	10
Photophobia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Chorioretinopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Retinal detachment			

subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Macular oedema			
subjects affected / exposed	2 / 5 (40.00%)	3 / 4 (75.00%)	3 / 42 (7.14%)
occurrences (all)	9	5	15
Subretinal fluid			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	9 / 42 (21.43%)
occurrences (all)	3	1	21
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	12 / 42 (28.57%)
occurrences (all)	0	0	12
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	1 / 5 (20.00%)	2 / 4 (50.00%)	3 / 42 (7.14%)
occurrences (all)	3	2	3
Retinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Retinal degeneration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	20 / 42 (47.62%)
occurrences (all)	1	0	65
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	2 / 4 (50.00%)	13 / 42 (30.95%)
occurrences (all)	0	3	21
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	11 / 42 (26.19%)
occurrences (all)	0	2	23
Dry mouth			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	2	0	4
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	7 / 42 (16.67%)
occurrences (all)	0	4	8
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Abdominal distension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	0 / 4 (0.00%)	14 / 42 (33.33%)
occurrences (all)	5	0	24
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	2 / 4 (50.00%)	20 / 42 (47.62%)
occurrences (all)	2	4	38
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	5 / 42 (11.90%)
occurrences (all)	0	0	9
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	11 / 42 (26.19%)
occurrences (all)	0	0	12
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	12 / 42 (28.57%)
occurrences (all)	1	0	16
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	8 / 42 (19.05%)
occurrences (all)	1	0	8
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Hair texture abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Rash			
subjects affected / exposed	1 / 5 (20.00%)	2 / 4 (50.00%)	8 / 42 (19.05%)
occurrences (all)	2	2	12
Palmoplantar keratoderma			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Actinic keratosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 5 (60.00%)	2 / 4 (50.00%)	15 / 42 (35.71%)
occurrences (all)	4	3	27
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	8 / 42 (19.05%)
occurrences (all)	1	0	12
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Pain in extremity			

subjects affected / exposed	0 / 5 (0.00%)	2 / 4 (50.00%)	5 / 42 (11.90%)
occurrences (all)	0	2	11
Myalgia			
subjects affected / exposed	3 / 5 (60.00%)	2 / 4 (50.00%)	7 / 42 (16.67%)
occurrences (all)	4	2	13
Musculoskeletal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	1	0	4
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	2 / 4 (50.00%)	7 / 42 (16.67%)
occurrences (all)	0	2	12
Flank pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	3 / 42 (7.14%)
occurrences (all)	2	3	6
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	7
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	4 / 42 (9.52%)
occurrences (all)	1	1	4
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Hypercholesterolaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	6 / 42 (14.29%)
occurrences (all)	0	0	8
Hypercreatininaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	6
Hyperphosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Hypokalaemia			

subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	5
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	5
Iron deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4

Non-serious adverse events	Phase 2: Arm 2 (prior BRAFi melanoma): Enco+ Bini	Phase 2: Arm A (BRAFi-naïve melanoma): Enco+ Bini+ Ribo	Phase 2: Arm 1 (mCRC): Enco+ Bini
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	42 / 42 (100.00%)	11 / 11 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Basal cell carcinoma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cancer pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)	9 / 42 (21.43%)	1 / 11 (9.09%)
occurrences (all)	7	27	1
Flushing			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Hot flush			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 26 (11.54%)	9 / 42 (21.43%)	7 / 11 (63.64%)
occurrences (all)	3	22	10
Fatigue			
subjects affected / exposed	10 / 26 (38.46%)	14 / 42 (33.33%)	2 / 11 (18.18%)
occurrences (all)	12	26	2
Oedema peripheral			
subjects affected / exposed	4 / 26 (15.38%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	4	5	0
Influenza like illness			
subjects affected / exposed	2 / 26 (7.69%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	2	4	0
Chills			
subjects affected / exposed	5 / 26 (19.23%)	4 / 42 (9.52%)	2 / 11 (18.18%)
occurrences (all)	5	6	2
Pyrexia			
subjects affected / exposed	4 / 26 (15.38%)	12 / 42 (28.57%)	6 / 11 (54.55%)
occurrences (all)	4	18	12
Peripheral swelling			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	3 / 11 (27.27%)
occurrences (all)	2	0	5
Oropharyngeal pain			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	3
Dyspnoea			
subjects affected / exposed	1 / 26 (3.85%)	5 / 42 (11.90%)	0 / 11 (0.00%)
occurrences (all)	1	6	0
Cough			
subjects affected / exposed	6 / 26 (23.08%)	3 / 42 (7.14%)	3 / 11 (27.27%)
occurrences (all)	6	3	3
Wheezing			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 26 (19.23%)	11 / 42 (26.19%)	1 / 11 (9.09%)
occurrences (all)	16	52	3
Lipase increased			
subjects affected / exposed	1 / 26 (3.85%)	4 / 42 (9.52%)	1 / 11 (9.09%)
occurrences (all)	1	13	1
Haemoglobin decreased			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 26 (3.85%)	9 / 42 (21.43%)	1 / 11 (9.09%)
occurrences (all)	1	16	3
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 26 (23.08%)	11 / 42 (26.19%)	0 / 11 (0.00%)
occurrences (all)	24	20	0
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 26 (23.08%)	10 / 42 (23.81%)	1 / 11 (9.09%)
occurrences (all)	11	29	3
Neutrophil count decreased			
subjects affected / exposed	0 / 26 (0.00%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	0	15	0
Weight increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Amylase increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
White blood cell count decreased			
subjects affected / exposed	2 / 26 (7.69%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	2	7	0
Platelet count decreased			
subjects affected / exposed	0 / 26 (0.00%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	0	6	0
Weight decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	5
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 26 (3.85%)	10 / 42 (23.81%)	1 / 11 (9.09%)
occurrences (all)	1	15	1
Dysgeusia			
subjects affected / exposed	1 / 26 (3.85%)	6 / 42 (14.29%)	1 / 11 (9.09%)
occurrences (all)	1	7	1
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	2
Paraesthesia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	2
Hypoaesthesia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Somnolence			

subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 26 (23.08%)	11 / 42 (26.19%)	1 / 11 (9.09%)
occurrences (all)	19	30	10
Lymphopenia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	6	0
Leukopenia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	11	0
Neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	17 / 42 (40.48%)	0 / 11 (0.00%)
occurrences (all)	0	114	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	7 / 26 (26.92%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences (all)	10	2	0
Retinopathy			
subjects affected / exposed	4 / 26 (15.38%)	9 / 42 (21.43%)	7 / 11 (63.64%)
occurrences (all)	4	14	13
Photophobia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Chorioretinopathy			

subjects affected / exposed	3 / 26 (11.54%)	0 / 42 (0.00%)	2 / 11 (18.18%)
occurrences (all)	5	0	3
Retinal detachment			
subjects affected / exposed	0 / 26 (0.00%)	5 / 42 (11.90%)	0 / 11 (0.00%)
occurrences (all)	0	6	0
Macular oedema			
subjects affected / exposed	4 / 26 (15.38%)	5 / 42 (11.90%)	1 / 11 (9.09%)
occurrences (all)	6	7	1
Subretinal fluid			
subjects affected / exposed	4 / 26 (15.38%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	4	5	0
Vision blurred			
subjects affected / exposed	5 / 26 (19.23%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	7	0	3
Dry eye			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	4 / 26 (15.38%)	6 / 42 (14.29%)	0 / 11 (0.00%)
occurrences (all)	5	7	0
Retinal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Retinal degeneration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Uveitis			

subjects affected / exposed	0 / 26 (0.00%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	0	9	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 26 (53.85%)	18 / 42 (42.86%)	8 / 11 (72.73%)
occurrences (all)	23	49	14
Constipation			
subjects affected / exposed	5 / 26 (19.23%)	12 / 42 (28.57%)	4 / 11 (36.36%)
occurrences (all)	6	20	6
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	5 / 42 (11.90%)	0 / 11 (0.00%)
occurrences (all)	0	6	0
Abdominal pain			
subjects affected / exposed	2 / 26 (7.69%)	6 / 42 (14.29%)	0 / 11 (0.00%)
occurrences (all)	2	8	0
Dry mouth			
subjects affected / exposed	1 / 26 (3.85%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	1	4	0
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Flatulence			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	3 / 26 (11.54%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	9 / 26 (34.62%)	16 / 42 (38.10%)	7 / 11 (63.64%)
occurrences (all)	16	30	15
Nausea			
subjects affected / exposed	11 / 26 (42.31%)	17 / 42 (40.48%)	6 / 11 (54.55%)
occurrences (all)	19	30	11
Abdominal discomfort			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Mouth ulceration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 26 (0.00%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 26 (0.00%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	0	8	0
Hyperkeratosis			
subjects affected / exposed	3 / 26 (11.54%)	5 / 42 (11.90%)	1 / 11 (9.09%)
occurrences (all)	3	5	1
Dry skin			
subjects affected / exposed	4 / 26 (15.38%)	5 / 42 (11.90%)	1 / 11 (9.09%)
occurrences (all)	5	9	1
Pruritus			
subjects affected / exposed	3 / 26 (11.54%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	4	4	0
Alopecia			
subjects affected / exposed	1 / 26 (3.85%)	3 / 42 (7.14%)	1 / 11 (9.09%)
occurrences (all)	1	3	1
Erythema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Hair texture abnormal			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rash			

subjects affected / exposed	9 / 26 (34.62%)	7 / 42 (16.67%)	0 / 11 (0.00%)
occurrences (all)	10	11	0
Palmoplantar keratoderma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Actinic keratosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 26 (26.92%)	6 / 42 (14.29%)	4 / 11 (36.36%)
occurrences (all)	11	8	5
Back pain			
subjects affected / exposed	5 / 26 (19.23%)	7 / 42 (16.67%)	4 / 11 (36.36%)
occurrences (all)	5	13	7
Muscular weakness			

subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	5 / 26 (19.23%)	8 / 42 (19.05%)	1 / 11 (9.09%)
occurrences (all)	5	12	1
Myalgia			
subjects affected / exposed	2 / 26 (7.69%)	4 / 42 (9.52%)	1 / 11 (9.09%)
occurrences (all)	2	6	1
Musculoskeletal pain			
subjects affected / exposed	1 / 26 (3.85%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	1	4	0
Arthritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 26 (0.00%)	4 / 42 (9.52%)	1 / 11 (9.09%)
occurrences (all)	0	6	2
Flank pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 26 (0.00%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
Conjunctivitis			
subjects affected / exposed	0 / 26 (0.00%)	4 / 42 (9.52%)	0 / 11 (0.00%)
occurrences (all)	0	5	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	2 / 42 (4.76%)	0 / 11 (0.00%)
occurrences (all)	0	5	0

Influenza			
subjects affected / exposed	0 / 26 (0.00%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	4 / 26 (15.38%)	0 / 42 (0.00%)	4 / 11 (36.36%)
occurrences (all)	5	0	5
Nasopharyngitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	1 / 26 (3.85%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	1	4	0
Hyperkalaemia			
subjects affected / exposed	1 / 26 (3.85%)	3 / 42 (7.14%)	0 / 11 (0.00%)
occurrences (all)	1	6	0
Decreased appetite			
subjects affected / exposed	1 / 26 (3.85%)	8 / 42 (19.05%)	4 / 11 (36.36%)
occurrences (all)	1	11	6
Dehydration			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Hypercholesterolaemia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Hypercreatininaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	3 / 11 (27.27%)
occurrences (all)	1	0	6
Hyperglycaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	3 / 26 (11.54%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Hypocalcaemia			

subjects affected / exposed	3 / 26 (11.54%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	2 / 26 (7.69%)	5 / 42 (11.90%)	1 / 11 (9.09%)
occurrences (all)	2	5	6
Hypomagnesaemia			
subjects affected / exposed	3 / 26 (11.54%)	0 / 42 (0.00%)	2 / 11 (18.18%)
occurrences (all)	5	0	4
Hyponatraemia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Iron deficiency			
subjects affected / exposed	2 / 26 (7.69%)	0 / 42 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2012	Amendment 1: Addressed the enhanced safety measures to be implemented in order to minimize risks to subjects to be treated in this study.
26 July 2012	Amendment 2: Introduced a third arm in the Phase 2 part of the study to enroll 40 subjects with locally advanced or metastatic BRAF V600 mutant melanoma who were naïve to previous treatment with a selective BRAF inhibitor.
26 November 2012	Amendment 3: Production of the original MEK162 tablet used in this study will cease and two new MEK162 tablet variants have been developed. One variant is a modified formulation of the MEK162 drug product and the other variant has the same formulation but contains drug substance from a new manufacturer.
21 May 2013	Amendment 4: To allow for reduction of the MEK162 dose in case of MEK162 related toxicities.
25 July 2013	Amendment 5: To add LEE011 to the LGX818 and MEK162 combination treatment in order to explore safety and preliminary efficacy of this triple combination in subjects with BRAF V600-dependent advanced solid tumors.
03 January 2014	Amendment 6: To modify existing safety monitoring for visual toxicities.
24 March 2014	Amendment 7: Based on Urgent Safety Measures.
30 September 2015	Amendment 8: Addressed recently observed safety findings from subjects treated with LEE011 (Ribociclib) in other clinical trials.
15 November 2018	Amendment 9: Definition of end of study, disease progression follow-up period, and survival follow-up period and dose limiting toxicities was updated.
15 March 2021	Amendment 10: To modify the frequency of assessments to allow for subjects still on treatment to be monitored in a manner that is consistent with local standard-of-care practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported