Clinical trial results:
A Phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult subjects with EGFR mutated non-small cell lung cancer

Summary

EudraCT number	2014-000726-37
Trial protocol	DE ES FR IT
Global end of trial date	11 May 2022

Results information

Result version number	v1
This version publication date	26 January 2023
First version publication date	26 January 2023

Trial information

Trial identification

Sponsor protocol code	CINC280X2105C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02335944
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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	10 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 May 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of nazartinib in combination with capmatinib and to estimate the preliminary anti-tumor activity of nazartinib in combination with capmatinib in participants with advanced non-small cell lung cancer with documented EGFR mutation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2015
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: 8
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Singapore: 31
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	177
EEA total number of subjects	88

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)	112
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 19 investigative sites in 11 countries. Due to early study termination, Group 5 (Phase II part) was never opened

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. All screening/baseline evaluations were performed ≤ 28 days before Cycle 1 Day 1.

Period 1

Period 1 title	Treatment Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase IB part- INC280 200mg BID/ EGF816 50mg QD

Arm description:

Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Arm type	Experimental
Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 200 mg, in fasted state.

Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 50 mg, in fasted state

Arm title	Phase IB part- INC280 200mg BID/ EGF816 100mg QD

Arm description:

Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Arm type	Experimental
Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 200 mg, in fasted state.

Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

Arm title	Phase IB part- INC280 400mg BID/ EGF816 75mg QD

Arm description:

Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Arm type	Experimental
Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 75 mg, in fasted state

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

Arm title	Phase IB part- INC280 400mg BID/ EGF816 100mg QD

Arm description:

Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Arm type	Experimental
Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

Arm title	Phase IB part- INC280 400mg BID/ EGF816 150mg QD

Arm description:

Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Arm type	Experimental

Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 150 mg, in fasted state

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

Arm title	Phase II- Group 1

Arm description:

NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

Arm type	Experimental
Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

Arm title	Phase II- Group 2

Arm description:

NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

Arm type	Experimental
Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

Arm title	Phase II- Group 3

Arm description:

NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

Arm type	Experimental
Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fasted state

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fasted state.

Arm title	Phase II- Group 4

Arm description:

NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state.

Arm type	Experimental
Investigational medicinal product name	Nazartinib
Investigational medicinal product code	EGF816
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Nazartinib was administered orally, once a day, at a dose of 100 mg, in fed state

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib was administered orally, twice per day, at a dose of 400 mg, in fed state.

Number of subjects in period 1	Phase IB part- INC280 200mg BID/ EGF816 50mg QD	Phase IB part- INC280 200mg BID/ EGF816 100mg QD	Phase IB part- INC280 400mg BID/ EGF816 75mg QD
Started	4	5	3
Completed	0	0	0
Not completed	4	5	3
Physician decision	-	-	-
Adverse event, non-fatal	2	-	-
Study Terminated By Sponsor	-	-	-
Progressive Disease	2	5	2
Subject/Guardian Decision	-	-	1

Number of subjects in period 1	Phase IB part- INC280 400mg BID/ EGF816 100mg QD	Phase IB part- INC280 400mg BID/ EGF816 150mg QD	Phase II- Group 1
Started	16	5	52
Completed	1	0	2
Not completed	15	5	50
Physician decision	1	-	6
Adverse event, non-fatal	2	1	15
Study Terminated By Sponsor	1	-	3
Progressive Disease	11	4	25
Subject/Guardian Decision	-	-	1

Number of subjects in period 1	Phase II- Group 2	Phase II- Group 3	Phase II- Group 4
Started	3	47	42
Completed	0	5	6
Not completed	3	42	36
Physician decision	1	2	1
Adverse event, non-fatal	-	5	7
Study Terminated By Sponsor	-	1	1
Progressive Disease	2	30	27
Subject/Guardian Decision	-	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase IB part- INC280 200mg BID/ EGF816 50mg QD
Reporting group description:	
Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 200mg BID/ EGF816 100mg QD
Reporting group description:	
Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 75mg QD
Reporting group description:	
Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 100mg QD
Reporting group description:	
Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 150mg QD
Reporting group description:	
Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase II- Group 1
Reporting group description:	
NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state	
Reporting group title	Phase II- Group 2
Reporting group description:	
NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state	
Reporting group title	Phase II- Group 3
Reporting group description:	
NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state	
Reporting group title	Phase II- Group 4
Reporting group description:	
NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state.	

Reporting group values	Phase IB part- INC280 200mg BID/ EGF816 50mg QD	Phase IB part- INC280 200mg BID/ EGF816 100mg QD	Phase IB part- INC280 400mg BID/ EGF816 75mg QD
Number of subjects	4	5	3
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	3	5	2

>=65 years	1	0	1

Sex: Female, Male Units: Participants			
Female	4	3	1
Male	0	2	2
Race/Ethnicity, Customized Units: Subjects			
Asian	2	3	1
Caucasian	2	2	1
Missing	0	0	1
Black	0	0	0

Reporting group values	Phase IB part-INC280 400mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 150mg QD	Phase II- Group 1
Number of subjects	16	5	52
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	11	3	33
>=65 years	5	2	19
Sex: Female, Male Units: Participants			
Female	9	4	38
Male	7	1	14
Race/Ethnicity, Customized Units: Subjects			
Asian	10	4	26
Caucasian	4	1	22
Missing	2	0	3
Black	0	0	1

Reporting group values	Phase II- Group 2	Phase II- Group 3	Phase II- Group 4
Number of subjects	3	47	42
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	1	30	24
>=65 years	2	17	18
Sex: Female, Male Units: Participants			
Female	2	33	24
Male	1	14	18
Race/Ethnicity, Customized Units: Subjects			
Asian	2	30	20
Caucasian	1	16	21
Missing	0	1	1
Black	0	0	0

Reporting group values	Total		
Number of subjects	177		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	112		
>=65 years	65		
Sex: Female, Male Units: Participants			
Female	118		
Male	59		
Race/Ethnicity, Customized Units: Subjects			
Asian	98		
Caucasian	70		
Missing	8		
Black	1		

End points

End points reporting groups

Reporting group title	Phase IB part- INC280 200mg BID/ EGF816 50mg QD
Reporting group description:	
Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 200mg BID/ EGF816 100mg QD
Reporting group description:	
Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 75mg QD
Reporting group description:	
Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 100mg QD
Reporting group description:	
Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 150mg QD
Reporting group description:	
Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment	
Reporting group title	Phase II- Group 1
Reporting group description:	
NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state	
Reporting group title	Phase II- Group 2
Reporting group description:	
NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state	
Reporting group title	Phase II- Group 3
Reporting group description:	
NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state	
Reporting group title	Phase II- Group 4
Reporting group description:	
NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state.	

Primary: Phase Ib: Number of participants with dose limiting toxicities (DLTs)

End point title	Phase Ib: Number of participants with dose limiting toxicities (DLTs)[1][2]
End point description:	
Number of participants with DLTs in the Phase Ib part. A DLT is defined as an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with EGF816 in combination with INC280	

during the escalation part of the study (Phase Ib)

End point type	Primary

End point timeframe:

Up to first 28 days of treatment

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: This endpoint is only applicable for Phase Ib arms

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	1	13
Units: Participants	1	0	0	1

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 1, 2 and 3: Overall Response Rate (ORR) by investigator's assessment per RECIST 1.1

End point title	Phase II Group 1, 2 and 3: Overall Response Rate (ORR) by investigator's assessment per RECIST 1.1[3][4]

End point description:

ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) determined by investigator's assessment in accordance to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). ORR was assessed in Group 1, 2 and 3 (Phase II part). CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Primary

End point timeframe:

Up to approximately 4 years

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: This endpoint is only applicable for Phase II Groups 1, 2 and 3

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 and 3

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	3	47	
Units: Percentage of participants				
number (confidence interval 95%)	28.8 (17.1 to 43.10)	33.3 (0.8 to 90.6)	61.7 (46.4 to 75.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 4: Number of participants with Adverse Events (AEs) and Serious AEs (SAEs)

End point title	Phase II Group 4: Number of participants with Adverse Events (AEs) and Serious AEs (SAEs)[5][6]

End point description:

Number of participants in Group 4 (Phase II part) with AEs and SAEs. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. Any untoward event resulting in death, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, congenital anomaly/birth defect or any other situation according to medical or scientific judgment is categorized as SAE.

End point type	Primary

End point timeframe:

From start of treatment up to 30 days after last dose of study treatment, assessed up to 3.7 years

Notes:

[5] - 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: This endpoint is only applicable for Phase II Group 4

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Group 4

End point values	Phase II-Group 4			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Participants				
AEs	42			
SAEs	26			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 4: Number of participants with dose reductions and dose interruptions of INC280 and EGF618

End point title	Phase II Group 4: Number of participants with dose reductions and dose interruptions of INC280 and EGF618[7][8]

End point description:

Number of participants with at least one dose reduction of INC280, at least one dose interruption of INC280, at least one dose reduction of EGF816 and at least one dose interruption of EGF816 in the Group 4 (Phase II part).

End point type	Primary

End point timeframe:

From start of treatment until end of treatment, assessed up to 3.6 years

Notes:

[7] - 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: This endpoint is only applicable for Phase II Group 4

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Group 4

End point values	Phase II-Group 4			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Participants				
Dose Reduction of INC280	30			
Dose Interruption of INC280	31			
Dose Reduction of EGF816	12			
Dose Interruption of EGF816	35			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Group 4: Dose intensity

End point title	Phase II Group 4: Dose intensity[9][10]

End point description:

Dose intensity, defined as the ratio of total dose received and actual duration, for participants in Group 4 (Phase II part)

End point type	Primary

End point timeframe:

From start of treatment until end of treatment, assessed up to 3.6 years

Notes:

[9] - 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: This endpoint is only applicable for Phase II Group 4

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Group 4

End point values	Phase II-Group 4			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: milligram/day				
arithmetic mean (standard deviation)				
INC280	666.2 (± 148.97)			
EGF816	87.4 (± 14.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Number of participants with dose reductions and dose interruptions of INC280 and EGF618

End point title	Phase Ib: Number of participants with dose reductions and dose interruptions of INC280 and EGF618[11]

End point description:

Number of participants in Phase Ib with at least one dose reduction of INC280, at least one dose interruption of INC280, at least one dose reduction of EGF816 and at least one dose interruption of EGF816 .

End point type	Secondary

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 5 years

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Participants				
Dose Reduction of INC280	2	4	2	10
Dose Interruption of INC280	2	2	2	12
Dose Reduction of EGF816	2	1	1	5
Dose Interruption of EGF816	2	2	2	11

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants				
Dose Reduction of INC280	5			

Dose Interruption of INC280	5			
Dose Reduction of EGF816	3			
Dose Interruption of EGF816	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 1, 2 and 3: Number of participants with dose reductions and dose interruptions of INC280 and EGF618

End point title	Phase II Group 1, 2 and 3: Number of participants with dose reductions and dose interruptions of INC280 and EGF618[12]

End point description:

Number of participants in Groups 1, 2 and 3 (Phase II part) with at least one dose reduction of INC280, at least one dose interruption of INC280, at least one dose reduction of EGF816 and at least one dose interruption of EGF816 .

End point type	Secondary

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 4 years

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 and 3

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	3	47	
Units: Participants				
Dose Reduction of INC280	33	3	34	
Dose Interruption of INC280	31	3	39	
Dose Reduction of EGF816	17	2	23	
Dose Interruption of EGF816	34	3	40	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Dose intensity

End point title	Phase Ib: Dose intensity[13]

End point description:

Dose intensity, defined as the ratio of total dose received and actual duration, in Phase Ib participants

End point type	Secondary

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 5 years

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: milligram/day				
arithmetic mean (standard deviation)				
INC280	319.1 (± 101.09)	356.9 (± 71.14)	596.3 (± 200.24)	658.2 (± 158.18)
EGF816	40.0 (± 12.60)	89.6 (± 17.93)	60.0 (± 13.36)	85.2 (± 17.28)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: milligram/day				
arithmetic mean (standard deviation)				
INC280	463.4 (± 212.52)			
EGF816	97.7 (± 36.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 1, 2 and 3: Dose intensity

End point title	Phase II Group 1, 2 and 3: Dose intensity[14]

End point description:

Dose intensity, defined as the ratio of total dose received and actual duration, in Group 1, 2 and 3 (Phase II)

End point type	Secondary

End point timeframe:

From start of treatment until end of treatment, assessed up to approximately 4 years

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 and 3

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	3	47	
Units: milligram/day				
arithmetic mean (standard deviation)				
INC280	662.9 (± 160.73)	562.9 (± 38.36)	634.7 (± 172.33)	
EGF816	85.2 (± 18.21)	76.3 (± 15.31)	84.8 (± 15.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Overall Response Rate (ORR) per RECIST 1.1 based on investigator’s assessment

End point title	Phase Ib: Overall Response Rate (ORR) per RECIST 1.1 based on investigator’s assessment[15]

End point description:

ORR is defined as percentage of participants with best overall response of PR+CR determined by Investigator's assessment in accordance to RECIST 1.1. ORR was assessed in Phase Ib participants. CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Up to approximately 5 years

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 60.2)	40.0 (5.3 to 85.3)	33.3 (0.8 to 90.6)	50.0 (24.7 to 75.3)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Percentage of participants				
number (confidence interval 95%)	60.0 (14.7 to 94.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 4: Overall Response Rate (ORR) per RECIST 1.1 based on investigator’s assessment

End point title	Phase II Group 4: Overall Response Rate (ORR) per RECIST 1.1 based on investigator’s assessment[16]

End point description:

ORR is defined as percentage of participants with best overall response of PR+CR determined by Investigator's assessment in accordance to RECIST 1.1. ORR was assessed in Group 4 (Phase II) CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Up to approximately 4 years

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Group 4

End point values	Phase II-Group 4			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Percentage of participants				
number (confidence interval 95%)	42.9 (27.7 to 59.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Progression Free Survival (PFS) per RECIST 1.1 based on investigator’s assessment

End point title	Phase Ib: Progression Free Survival (PFS) per RECIST 1.1 based on investigator’s assessment[17]

End point description:

PFS is defined as time from date of first dose of study treatment to date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1.or death due to any cause. The PFS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, PFS is censored at the date of last adequate tumor assessment. PFS was assessed in Phase Ib participants

End point type	Secondary

End point timeframe:

From date of first dose to first documented disease progression or death, assessed up to approximately 5 years

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Months				
median (confidence interval 95%)	5.6 (3.5 to 999999)	7.4 (1.6 to 999999)	3.5 (0.8 to 999999)	5.7 (1.9 to 42.1)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Months				
median (confidence interval 95%)	14.5 (7.3 to 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Progression Free Survival (PFS) per RECIST 1.1 based on investigator's assessment

End point title	Phase II Groups 1, 2, 3 and 4: Progression Free Survival (PFS) per RECIST 1.1 based on investigator's assessment[18]

End point description:

PFS is defined as time from date of first dose of study treatment to date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1.or death due to any cause. The PFS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, PFS is censored at the date of last adequate tumor assessment. PFS was assessed in Group 1, 2, 3 and 4 (Phase II)

End point type	Secondary

End point timeframe:

From date of first dose to first documented disease progression or death, assessed up to approximately 4 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

End point values	Phase II-Group 2	Phase II-Group 3	Phase II-Group 4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	47	42	
Units: Months				
median (confidence interval 95%)	3.8 (3.7 to 999999)	10.1 (7.6 to 13.8)	10.9 (5.6 to 19.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment

End point title	Phase Ib: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment[19]

End point description:

TTR is defined as the time from the date of the first dose to the date of first documented response (CR or PR) determined by Investigator assessment in accordance to RECIST 1.1. The TTR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. TTR was assessed in Phase Ib participants.
CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From the date of the first dose to the date of first documented response, up to approximately 5 years

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Months				
median (confidence interval 95%)	999999 (999999 to 999999)	999999 (1.8 to 999999)	999999 (1.7 to 999999)	3.5 (1.6 to 999999)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Months				
median (confidence interval 95%)	4.5 (1.9 to			

	999999)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment

End point title	Phase II Groups 1, 2, 3 and 4: Time to Response (TTR) per RECIST 1.1 based on investigator's assessment[20]

End point description:

TTR is defined as the time from the date of the first dose to the date of first documented response (CR or PR) determined by Investigator assessment in accordance to RECIST 1.1. The TTR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. TTR was assessed in Group 1, 2, 3 and 4 (Phase II)
CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From the date of the first dose to the date of first documented response, up to approximately 4 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	Phase II-Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	3	47	42
Units: Months				
median (confidence interval 95%)	9999 (5.4 to 999999)	999999 (1.8 to 999999)	1.9 (1.8 to 5.9)	999999 (3.6 to 999999)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment

End point title	Phase Ib: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment[21]

End point description:

DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1 or death due to underlying cancer. The DOR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. DOR was assessed in Phase Ib participants

CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From date of first documented response to first documented disease progression or death, assessed up to approximately 5 years

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[22]	2	1	8
Units: Months				
median (confidence interval 95%)	(to)	8.8 (5.6 to 999999)	14.8 (-999999 to 999999)	25.3 (3.6 to 47.9)

Notes:

[22] - No participants had a documented response (CR or PR)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Months				
median (confidence interval 95%)	8.0 (5.4 to 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment

End point title	Phase II Groups 1, 2, 3 and 4: Duration of Response (DOR) per RECIST 1.1 based on investigator's assessment[23]

End point description:

DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression determined by Investigator assessment in accordance to RECIST 1.1 or death due to underlying cancer. The DOR distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant has not had an event, duration was censored at the date of last adequate tumor assessment. DOR was assessed in Group 1, 2, 3 and 4 (Phase II)
CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From date of first documented response to first documented disease progression or deaths, assessed up to approximately 4 years

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	Phase II-Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	1	29	18
Units: Months				
median (confidence interval 95%)	6.5 (3.7 to 10.8)	12.0 (-999999 to 999999)	11.6 (6.6 to 17.5)	14.5 (9.2 to 999999)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment

End point title	Phase Ib: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment[24]

End point description:

DCR is defined as the percentage of participants with best overall response of CR, PR, or stable disease (SD) determined by Investigator assessment in accordance to RECIST 1.1. DCR was assessed in Phase Ib participants
CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.

End point type	Secondary

End point timeframe:

Up to approximately 5 years

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Percentage of participants				
number (confidence interval 95%)	100 (39.8 to 100)	60.0 (14.7 to 94.7)	33.3 (0.8 to 90.6)	62.5 (35.4 to 84.8)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Percentage of participants				
number (confidence interval 95%)	80.0 (28.4 to 99.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Group 1, 2 3 and 4: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment

End point title	Phase II Group 1, 2 3 and 4: Disease Control Rate (DCR) per RECIST 1.1 based on investigator's assessment[25]

End point description:

DCR is defined as the percentage of participants with best overall response of CR, PR, or SD determined by Investigator assessment in accordance to RECIST 1.1. DCR was assessed in Group 1, 2, 3 and 4 (Phase II)
CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.

End point type	Secondary

End point timeframe:

Up to approximately 4 years

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2 3 and 4

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	Phase II-Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	3	47	42
Units: Percentage of participants				
number (confidence interval 95%)	59.6 (45.1 to 73.0)	100 (29.2 to 100)	93.6 (82.5 to 98.7)	81.0 (65.9 to 91.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Overall Survival (OS)

End point title	Phase Ib: Overall Survival (OS)[26]

End point description:

OS is defined as the time from first dose of the study treatment to the date of death due to any cause. The OS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant was not known to have died, survival was censored at the date of last contact. OS was assessed in Phase Ib participants

End point type	Secondary

End point timeframe:

From date of first dose to death, assessed up to approximately 5 years

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Months				
median (confidence interval 95%)	10.1 (8.1 to 999999)	56.5 (6.5 to 999999)	7.0 (1.1 to 999999)	17.2 (5.7 to 58.7)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Months				
median (confidence interval 95%)	31.5 (16.6 to 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 1, 2, 3 and 4: Overall Survival (OS)

End point title	Phase II Groups 1, 2, 3 and 4: Overall Survival (OS)[27]

End point description:

OS is defined as the time from first dose of the study treatment to the date of death due to any cause. The OS distribution was estimated using the Kaplan-Meier method and associated 95% confidence intervals were calculated. If a participant was not known to have died, survival was censored at the date of last contact. OS was assessed in Group 1, 2, 3 and 4

End point type	Secondary

End point timeframe:

From date of first dose to death, assessed up to approximately 4 years

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 1, 2, 3 and 4

End point values	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3	Phase II-Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	3	47	42
Units: Months				
median (confidence interval 95%)	18.8 (14.9 to 26.0)	5.6 (3.7 to 999999)	25.6 (18.8 to 33.0)	28.9 (20.5 to 999999)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280

End point title	Phase Ib: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280[28]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	1	12
Units: hours*nanogram/mililiter (hr*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 3 / 5 / 1 / 12 / 3)	12300 (± 4710)	10500 (± 4320)	38300 (± 999999)	22200 (± 10700)
Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2)	11600 (± 3400)	11800 (± 3360)	48800 (± 999999)	28900 (± 12700)
Cycle 2 Day 1 (n= 3 / 5 / 0 / 9 / 2)	11300 (± 4050)	11100 (± 1770)	999999 (± 999999)	21600 (± 7370)

End point values	Phase IB part-			

	INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: hours*nanogram/mililiter (hr*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 3 / 5 / 1 / 12 / 3)	23000 (± 11600)			
Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2)	23000 (± 3440)			
Cycle 2 Day 1 (n= 3 / 5 / 0 / 9 / 2)	24900 (± 5190)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Peak plasma concentration (Cmax) of INC280

End point title	Phase Ib: Peak plasma concentration (Cmax) of INC280[29]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	1	12
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3)	3630 (± 588)	2530 (± 1080)	8000 (± 999999)	5100 (± 2550)
Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2)	3070 (± 1120)	2840 (± 1350)	12000 (± 999999)	5780 (± 2640)
Cycle 2 Day 1 (N= 3 / 5 / 0 / 10 / 2)	3590 (± 1620)	2800 (± 797)	999999 (± 999999)	4830 (± 1390)

End point values	Phase IB part-INC280 400mg BID/ EGF816			

	150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3)	5930 (± 1330)			
Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2)	4350 (± 933)			
Cycle 2 Day 1 (N= 3 / 5 / 0 / 10 / 2)	6370 (± 1060)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to reach maximum concentration (Tmax) of INC280

End point title	Phase Ib: Time to reach maximum concentration (Tmax) of INC280[30]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	1	12
Units: Hours				
median (full range (min-max))				
Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3)	1.07 (1.00 to 2.00)	2.00 (1.00 to 4.00)	2.00 (2.00 to 2.00)	2.01 (1.00 to 7.67)
Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2)	1.12 (1.03 to 2.05)	2.00 (0.883 to 7.98)	1.17 (1.17 to 1.17)	1.97 (0.950 to 4.00)
Cycle 2 Day 1 (n= 3 / 5 / 0 / 10 / 2)	1.00 (1.00 to 2.00)	2.00 (1.00 to 3.83)	999999 (999999 to 999999)	1.94 (0.983 to 4.00)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			

Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
median (full range (min-max))				
Cycle 1 Day 1 (n= 4 / 5 / 1 / 12 / 3)	2.00 (1.02 to 2.13)			
Cycle 1 Day 15 (n= 3 / 5 / 1 / 11 / 2)	1.50 (1.00 to 2.00)			
Cycle 2 Day 1 (n= 3 / 5 / 0 / 10 / 2)	1.51 (1.02 to 2.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280

End point title	Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 12 hours (AUC0-12) of INC280[31]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 3 and 4

End point values	Phase II-Group 3	Phase II-Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: hours*nanogram/mililiter (hr*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 8 / 12)	22000 (± 8000)	16900 (± 7360)		
Cycle 2 Day 1 (n= 8 / 15)	19700 (± 11200)	20500 (± 7440)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of INC280

End point title	Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of

	INC280[32]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 3 and 4

End point values	Phase II-Group 3	Phase II-Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 8 / 12)	4770 (± 1460)	3420 (± 1550)		
Cycle 2 Day 1 (n= 8 / 15)	4360 (± 2060)	3940 (± 1660)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of INC280

End point title	Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of INC280[33]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 3 and 4

End point values	Phase II-Group 3	Phase II-Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: Hours				
median (full range (min-max))				
Cycle 1 Day 1 (n= 8 / 12)	1.99 (1.00 to 4.00)	2.08 (1.85 to 8.00)		

Cycle 2 Day 1 (n= 8 / 15)	1.47 (1.00 to 7.08)	3.82 (1.00 to 4.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816

End point title	Phase Ib: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816[34]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	13
Units: hours*nanogram/mililiter (hr*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 3 / 5 / 2 / 11 / 2)	3920 (± 1450)	5850 (± 4380)	4010 (± 534)	5930 (± 3600)
Cycle 1 Day 15 (n= 4 / 5 / 2 / 12 / 2)	5200 (± 2010)	9630 (± 4060)	7330 (± 108)	11100 (± 5340)
Cycle 2 Day 1 (n= 3 / 4 / 0 / 11 / 2)	4080 (± 1130)	7460 (± 2340)	999999 (± 999999)	10500 (± 7480)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: hours*nanogram/mililiter (hr*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 3 / 5 / 2 / 11 / 2)	10500 (± 3400)			

Cycle 1 Day 15 (n= 4 / 5 / 2 / 12 / 2) Cycle 2 Day 1 (n= 3 / 4 / 0 / 11 / 2)	16400 (± 5670) 11400 (± 2360)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Peak plasma concentration (Cmax) of EGF816

End point title	Phase Ib: Peak plasma concentration (Cmax) of EGF816[35]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	13
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3)	258 (± 104)	465 (± 323)	302 (± 8.49)	381 (± 231)
Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2)	361 (± 165)	677 (± 321)	517 (± 180)	595 (± 261)
Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2)	269 (± 90.8)	583 (± 261)	999999 (± 999999)	604 (± 365)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3)	777 (± 281)			
Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2)	1010 (± 354)			
Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2)	814 (± 137)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to reach maximum concentration (Tmax) of EGF816

End point title	Phase Ib: Time to reach maximum concentration (Tmax) of EGF816[36]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase Ib arms

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	13
Units: Hours (hr)				
median (full range (min-max))				
Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3)	3.03 (1.08 to 4.02)	3.90 (2.00 to 4.00)	3.00 (2.00 to 4.00)	4.00 (2.00 to 8.99)
Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2)	2.07 (2.00 to 4.05)	3.95 (2.00 to 4.00)	4.00 (2.17 to 4.05)	5.90 (2.17 to 11.9)
Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2)	4.00 (3.95 to 4.00)	4.00 (2.00 to 4.00)	999999 (999999 to 999999)	4.00 (1.98 to 7.00)

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours (hr)				
median (full range (min-max))				
Cycle 1 Day 1 (n= 4 / 5 / 2 / 13 / 3)	4.00 (2.03 to 4.02)			

Cycle 1 Day 15 (n= 3 / 5 / 3 / 12 / 2) Cycle 2 Day 1 (n= 3 / 5 / 0 / 11 / 2)	3.93 (3.83 to 4.02) 3.05 (2.10 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816

End point title	Phase II Groups 3 and 4: Area under the plasma concentration versus time curve from time 0 to 24 hours (AUC0-24) of EGF816[37]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 3 and 4

End point values	Phase II-Group 3	Phase II-Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	15		
Units: hours*nanogram/mililiter (hr*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 6 / 12) Cycle 2 Day 1 (n= 5 / 15)	6390 (± 2460) 11100 (± 2000)	3420 (± 1700) 7670 (± 3330)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of EGF816

End point title	Phase II Groups 3 and 4: Peak plasma concentration (Cmax) of EGF816[38]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1 and

Cycle 2 Day 1 (Cycle=28 days)

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 3 and 4

End point values	Phase II-Group 3	Phase II-Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	15		
Units: nanogram/mililiter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 6 / 12)	448 (± 184)	239 (± 107)		
Cycle 2 Day 1 (n= 6 / 15)	658 (± 117)	447 (± 175)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of EGF816

End point title	Phase II Groups 3 and 4: Time to reach maximum concentration (Tmax) of EGF816[39]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods. Actual time of sample collection was used (not the nominal time point as per scheduled assessment)

End point type	Secondary

End point timeframe:

Pre-dose, 0.5 hours (hr) and 1 hr, 2 hr, 4 hr, 8 hr and 12 hr and 24 hr post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 (Cycle=28 days)

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Phase II Groups 3 and 4

End point values	Phase II-Group 3	Phase II-Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	15		
Units: Hours (hr)				
median (full range (min-max))				
Cycle 1 Day 1 (n= 6 / 12)	4.00 (1.12 to 8.00)	4.00 (1.85 to 8.00)		
Cycle 2 Day 1 (n= 6 / 15)	4.00 (2.00 to 4.13)	4.00 (3.82 to 8.00)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

On-treatment deaths were collected from first dose of study medication to 30 days after the last dose of study medication for a maximum duration of approximately 5 years (Phase Ib) and 4 years (Phase II).
Post-treatment deaths were collected after 30 days post-treatment, for a maximum duration of approximately 5 years (Phase Ib) and 4 years (Phase II).
All deaths refer to the sum of on-treatment and post-treatment deaths

End point type	Post-hoc

End point timeframe:

On-treatment: up to approximately 5 years (Phase Ib) and 4 years (Phase II). Post-treatment: Up to approximately 5 years (Phase Ib) and 4 years (Phase II).

End point values	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD	Phase IB part-INC280 400mg BID/ EGF816 100mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	3	16
Units: Participants				
On-treatment deaths	0	0	1	2
Post-treatment deaths	4	3	2	9
All deaths	4	3	3	11

End point values	Phase IB part-INC280 400mg BID/ EGF816 150mg QD	Phase II-Group 1	Phase II-Group 2	Phase II-Group 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	52	3	47
Units: Participants				
On-treatment deaths	0	9	2	5
Post-treatment deaths	3	26	1	25
All deaths	3	35	3	30

End point values	Phase II-Group 4			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Participants				
On-treatment deaths	1			
Post-treatment deaths	22			
All deaths	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment until last dose of study treatment plus 30 days, up to approximately 5 years (Phase Ib) and 4 years (Phase II).

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the SAEs field "number of deaths resulting from adverse events" all those deaths, resulting from SAEs that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Phase IB part- INC280 200mg BID/ EGF816 50mg QD

Reporting group description:

Combination of INC280 200mg twice daily (BID) and EGF816 50mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Reporting group title	Phase IB part- INC280 200mg BID/ EGF816 100mg QD

Reporting group description:

Combination of INC280 200mg twice daily (BID) and EGF816 100mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 75mg QD

Reporting group description:

Combination of INC280 400mg twice daily (BID) and EGF816 75mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 100mg QD

Reporting group description:

Combination of INC280 400mg twice daily (BID) and EGF816 100mg once daily (QD) in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Reporting group title	Phase IB part- INC280 400mg BID/ EGF816 150mg QD

Reporting group description:

Combination of INC280 400mg twice daily (BID) and EGF816 150mg once daily (QD) in fasted state in NSCLC participants with previously documented EGFR mutation, who progressed on EGFR TKI treatment

Reporting group title	Phase II- Group 2

Reporting group description:

NSCLC participants harboring T790M mutation in de novo setting, irrespective of the activating mutation status who received none to 2 lines of systemic antineoplastic therapy prior to study entry, but no therapy known to inhibit EGFR. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

Reporting group title	Phase II- Group 1

Reporting group description:

NSCLC participants with previously documented activating EGFR mutation, with any T790M and MET dysregulation status, who received 1 to 3 lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

Reporting group title	Phase II- Group 4

Reporting group description:

NSCLC participants with previously documented EGFR activating mutations and any T790M and MET status who received none to 2 prior lines of systemic antineoplastic therapy prior to study entry. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fed state.

Reporting group title	Phase II- Group 3

Reporting group description:

NSCLC participants with previously documented EGFR activating mutation, T790M negative, and any MET status who never received any prior line of systemic antineoplastic therapy. Participants were treated with 400 mg twice daily for INC280 and 100 mg once daily for EGF816 in fasted state

Reporting group title	All Participants

Reporting group description:

All Participants

Serious adverse events	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	2 / 5 (40.00%)	3 / 3 (100.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Anaphylactic shock			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Apathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (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
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epilepsy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive hydrocephalus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wernicke's encephalopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purpura			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster meningitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase IB part- INC280 400mg BID/ EGF816 100mg QD	Phase IB part- INC280 400mg BID/ EGF816 150mg QD	Phase II- Group 2
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 16 (68.75%)	4 / 5 (80.00%)	2 / 3 (66.67%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (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
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Anaphylactic shock			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity pneumonitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (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
Pneumothorax			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Apathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (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
Amylase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (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

Aspartate aminotransferase increased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (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
Blood creatinine increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epilepsy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive hydrocephalus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wernicke's encephalopathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (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
Drug eruption			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purpura			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (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
Herpes zoster meningitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase II- Group 1	Phase II- Group 4	Phase II- Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 52 (55.77%)	26 / 42 (61.90%)	33 / 47 (70.21%)
number of deaths (all causes)	9	1	5
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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 pleural effusion			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Tumour associated fever			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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			
Embolism			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hypertensive crisis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Hypotension			

subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 52 (3.85%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Oedema			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Pyrexia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 42 (4.76%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	1 / 2	2 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Anaphylactic shock			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Hypersensitivity			
subjects affected / exposed	2 / 52 (3.85%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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	3 / 52 (5.77%)	2 / 42 (4.76%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Hypersensitivity pneumonitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Interstitial lung disease			
subjects affected / exposed	2 / 52 (3.85%)	3 / 42 (7.14%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 52 (3.85%)	3 / 42 (7.14%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	0 / 2	1 / 3	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Psychiatric disorders			
Apathy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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 bilirubin increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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 creatinine increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Ejection fraction decreased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Weight decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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			
Procedural pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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			
Cardiac arrest			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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

Epilepsy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive hydrocephalus			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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	2 / 52 (3.85%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Wernicke's encephalopathy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
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			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
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 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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 disorders			
Ascites			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Colitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (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
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Hiatus hernia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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			
Dermatitis allergic			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Erythema multiforme			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Purpura			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	4 / 52 (7.69%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	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 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Renal failure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
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	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 52 (1.92%)	3 / 42 (7.14%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 2	2 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Erysipelas			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster meningitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			

subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (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
Pleural infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
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	5 / 52 (9.62%)	4 / 42 (9.52%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Pneumonia chlamydial			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
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 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Soft tissue infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (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
Urosepsis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
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			
Decreased appetite			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
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	2 / 52 (3.85%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 177 (63.84%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hypertensive crisis			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	4 / 177 (2.26%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	8 / 177 (4.52%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Anaphylactic shock			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	8 / 177 (4.52%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 2		
Haemoptysis			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity pneumonitis			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	5 / 177 (2.82%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	10 / 177 (5.65%)		
occurrences causally related to treatment / all	3 / 12		
deaths causally related to treatment / all	0 / 0		

Pneumonitis			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 1		
Pneumothorax			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	7 / 177 (3.95%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	6 / 177 (3.39%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 3		
Psychiatric disorders			
Apathy			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Amylase increased			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Aspartate aminotransferase increased				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neutrophil count decreased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Procedural pain				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial ischaemia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Epilepsy			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	4 / 177 (2.26%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive hydrocephalus			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Loss of consciousness			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	7 / 177 (3.95%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Speech disorder			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			

subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Wernicke's encephalopathy				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Hypoacusis				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Visual impairment				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	5 / 177 (2.82%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug eruption			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema multiforme			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Purpura			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Rash macular			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			

subjects affected / exposed	7 / 177 (3.95%)			
occurrences causally related to treatment / all	7 / 7			
deaths causally related to treatment / all	0 / 0			
Urticaria				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	4 / 177 (2.26%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Cellulitis			
subjects affected / exposed	9 / 177 (5.08%)		
occurrences causally related to treatment / all	5 / 12		
deaths causally related to treatment / all	0 / 0		
Empyema			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster meningitis			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			

subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis aseptic				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural infection				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	10 / 177 (5.65%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 1			
Pneumonia aspiration				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia chlamydial				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	4 / 177 (2.26%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Soft tissue infection				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	3 / 177 (1.69%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase IB part-INC280 200mg BID/ EGF816 50mg QD	Phase IB part-INC280 200mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 75mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pallor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	2	3	2
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Face oedema			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	3	0	3
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	3	5	2
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Perineal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Prostatomegaly			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	2 / 3 (66.67%)
occurrences (all)	1	2	2
Dry throat			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypoxia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	2 / 4 (50.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Throat irritation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Amylase increased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	4	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Blood bilirubin increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood creatine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	6	1
Blood creatinine increased			

subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood triglycerides increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Lipase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Protein total decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Dysaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Epilepsy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Post herpetic neuralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Leukopenia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	3
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	0	2	4
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Deafness transitory			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vitreous floaters			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lip blister			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 4 (50.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	2	0	3
Odynophagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Alopecia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nail discolouration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0

Rash papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Chronic kidney disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	2	2
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tendon pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinobronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Hyperlipasaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypophagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Hypoproteinaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3

Non-serious adverse events	Phase IB part-INC280 400mg BID/ EGF816 100mg QD	Phase IB part-INC280 400mg BID/ EGF816 150mg QD	Phase II- Group 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	5 / 5 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypotension			

subjects affected / exposed	0 / 16 (0.00%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Pallor			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Thrombosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 16 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	5	0	2
Chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	3 / 16 (18.75%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Fatigue			
subjects affected / exposed	6 / 16 (37.50%)	2 / 5 (40.00%)	2 / 3 (66.67%)
occurrences (all)	10	2	3
Gait disturbance			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Oedema peripheral			

subjects affected / exposed	8 / 16 (50.00%)	4 / 5 (80.00%)	3 / 3 (100.00%)
occurrences (all)	17	8	3
Pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Pyrexia			
subjects affected / exposed	7 / 16 (43.75%)	3 / 5 (60.00%)	0 / 3 (0.00%)
occurrences (all)	11	3	0
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Perineal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Prostatomegaly			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 16 (31.25%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	10	1	3
Dry throat			

subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	4 / 16 (25.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	8	1	1
Dyspnoea exertional			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Nasal dryness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pneumothorax			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Productive cough			

subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	3 / 16 (18.75%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Throat irritation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Sleep disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 16 (12.50%)	2 / 5 (40.00%)	2 / 3 (66.67%)
occurrences (all)	2	3	2
Amylase increased			
subjects affected / exposed	8 / 16 (50.00%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	13	2	3
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	2	2	2
Blood albumin decreased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	8	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 16 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Blood creatinine increased			
subjects affected / exposed	8 / 16 (50.00%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	12	7	4
Blood glucose increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Blood potassium increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

C-reactive protein increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Haemoglobin decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	4 / 16 (25.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	6	2	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Protein total decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	3 / 16 (18.75%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Weight increased			
subjects affected / exposed	2 / 16 (12.50%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
White blood cell count decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Traumatic haematoma			

subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	4 / 16 (25.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	7	1	0
Dysaesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Epilepsy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	7 / 16 (43.75%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	12	0	1
Hypoaesthesia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Lethargy			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Neuropathy peripheral			

subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Post herpetic neuralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	2
Syncope			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	2	2
Febrile neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Deafness transitory			

subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Hypoacusis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye swelling			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eyelid oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			

subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Abdominal pain upper			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	5 / 16 (31.25%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	11	2	1
Diarrhoea			
subjects affected / exposed	6 / 16 (37.50%)	2 / 5 (40.00%)	2 / 3 (66.67%)
occurrences (all)	18	3	2
Dry mouth			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	4 / 16 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Dysphagia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Lip blister			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Lip dry			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	11 / 16 (68.75%)	5 / 5 (100.00%)	3 / 3 (100.00%)
occurrences (all)	27	5	3
Odynophagia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	3 / 16 (18.75%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	8	3	0
Toothache			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	6 / 16 (37.50%)	3 / 5 (60.00%)	1 / 3 (33.33%)
occurrences (all)	20	6	1
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Dermatitis acneiform			
subjects affected / exposed	2 / 16 (12.50%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	2	4	0
Dry skin			
subjects affected / exposed	5 / 16 (31.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	7	4	0
Eczema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ingrowing nail			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nail discolouration			

subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	5 / 16 (31.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	6	2	0
Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	1 / 16 (6.25%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Rash maculo-papular			
subjects affected / exposed	3 / 16 (18.75%)	4 / 5 (80.00%)	1 / 3 (33.33%)
occurrences (all)	5	4	1
Rash papular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chronic kidney disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	2 / 16 (12.50%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Muscular weakness			

subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Neck pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	2 / 16 (12.50%)	3 / 5 (60.00%)	0 / 3 (0.00%)
occurrences (all)	2	6	0
Tendon pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Gastroenteritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	5 / 16 (31.25%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	6	3	0
Pharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Sinobronchitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection			
subjects affected / exposed	4 / 16 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 16 (62.50%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	17	2	1
Hyperkalaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperlipasaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Hypoalbuminaemia			
subjects affected / exposed	5 / 16 (31.25%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	8	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	3	1	1
Hypomagnesaemia			

subjects affected / exposed	3 / 16 (18.75%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	16	1	1
Hyponatraemia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	9	0	0
Hypophagia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	15	1	0
Hypoproteinaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Phase II- Group 1	Phase II- Group 4	Phase II- Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 52 (98.08%)	42 / 42 (100.00%)	47 / 47 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
Hypotension			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	4 / 47 (8.51%)
occurrences (all)	1	2	5
Pallor			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 52 (11.54%)	10 / 42 (23.81%)	18 / 47 (38.30%)
occurrences (all)	12	14	22
Chest pain			

subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	3 / 52 (5.77%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	3	0	3
Face oedema			
subjects affected / exposed	2 / 52 (3.85%)	1 / 42 (2.38%)	2 / 47 (4.26%)
occurrences (all)	2	1	2
Fatigue			
subjects affected / exposed	14 / 52 (26.92%)	9 / 42 (21.43%)	9 / 47 (19.15%)
occurrences (all)	15	11	10
Gait disturbance			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	3 / 52 (5.77%)	5 / 42 (11.90%)	2 / 47 (4.26%)
occurrences (all)	4	8	3
Non-cardiac chest pain			
subjects affected / exposed	8 / 52 (15.38%)	6 / 42 (14.29%)	6 / 47 (12.77%)
occurrences (all)	9	6	8
Oedema peripheral			
subjects affected / exposed	27 / 52 (51.92%)	26 / 42 (61.90%)	31 / 47 (65.96%)
occurrences (all)	53	42	93
Pain			
subjects affected / exposed	3 / 52 (5.77%)	1 / 42 (2.38%)	2 / 47 (4.26%)
occurrences (all)	3	1	3
Peripheral swelling			
subjects affected / exposed	0 / 52 (0.00%)	3 / 42 (7.14%)	1 / 47 (2.13%)
occurrences (all)	0	4	1
Pyrexia			
subjects affected / exposed	8 / 52 (15.38%)	12 / 42 (28.57%)	11 / 47 (23.40%)
occurrences (all)	12	14	13
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0

Hypersensitivity			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Perineal pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Prostatomegaly			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 52 (19.23%)	14 / 42 (33.33%)	11 / 47 (23.40%)
occurrences (all)	20	23	13
Dry throat			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	11 / 52 (21.15%)	7 / 42 (16.67%)	13 / 47 (27.66%)
occurrences (all)	14	7	13
Dyspnoea exertional			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	4 / 47 (8.51%)
occurrences (all)	1	0	4
Haemoptysis			

subjects affected / exposed	1 / 52 (1.92%)	2 / 42 (4.76%)	0 / 47 (0.00%)
occurrences (all)	1	3	0
Hypoxia			
subjects affected / exposed	4 / 52 (7.69%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	4	0	0
Nasal discomfort			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 52 (1.92%)	5 / 42 (11.90%)	1 / 47 (2.13%)
occurrences (all)	1	5	1
Pleural effusion			
subjects affected / exposed	1 / 52 (1.92%)	3 / 42 (7.14%)	2 / 47 (4.26%)
occurrences (all)	1	3	2
Pneumothorax			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Productive cough			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences (all)	1	0	5
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 52 (3.85%)	5 / 42 (11.90%)	2 / 47 (4.26%)
occurrences (all)	3	5	2
Throat irritation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	4 / 47 (8.51%)
occurrences (all)	2	0	4

Confusional state			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
Depression			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	4 / 52 (7.69%)	4 / 42 (9.52%)	3 / 47 (6.38%)
occurrences (all)	4	5	3
Sleep disorder			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 52 (13.46%)	13 / 42 (30.95%)	13 / 47 (27.66%)
occurrences (all)	7	17	19
Amylase increased			
subjects affected / exposed	11 / 52 (21.15%)	7 / 42 (16.67%)	11 / 47 (23.40%)
occurrences (all)	35	17	23
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 52 (7.69%)	11 / 42 (26.19%)	13 / 47 (27.66%)
occurrences (all)	4	15	20
Blood albumin decreased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 52 (1.92%)	2 / 42 (4.76%)	6 / 47 (12.77%)
occurrences (all)	1	2	10
Blood bilirubin increased			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	2	1	6
Blood creatine increased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Blood creatine phosphokinase increased			

subjects affected / exposed	5 / 52 (9.62%)	6 / 42 (14.29%)	5 / 47 (10.64%)
occurrences (all)	12	10	6
Blood creatinine increased			
subjects affected / exposed	10 / 52 (19.23%)	15 / 42 (35.71%)	16 / 47 (34.04%)
occurrences (all)	14	35	30
Blood glucose increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 52 (0.00%)	2 / 42 (4.76%)	1 / 47 (2.13%)
occurrences (all)	0	2	1
Blood uric acid increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 52 (3.85%)	3 / 42 (7.14%)	1 / 47 (2.13%)
occurrences (all)	2	9	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 52 (3.85%)	5 / 42 (11.90%)	5 / 47 (10.64%)
occurrences (all)	2	9	6
Haemoglobin decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	12 / 52 (23.08%)	8 / 42 (19.05%)	7 / 47 (14.89%)
occurrences (all)	40	11	19

Lymphocyte count decreased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Protein total decreased			
subjects affected / exposed	4 / 52 (7.69%)	3 / 42 (7.14%)	0 / 47 (0.00%)
occurrences (all)	4	3	0
Weight decreased			
subjects affected / exposed	1 / 52 (1.92%)	2 / 42 (4.76%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
Weight increased			
subjects affected / exposed	3 / 52 (5.77%)	2 / 42 (4.76%)	4 / 47 (8.51%)
occurrences (all)	3	2	4
White blood cell count decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
Bradycardia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	9 / 52 (17.31%)	10 / 42 (23.81%)	11 / 47 (23.40%)
occurrences (all)	10	13	12

Dysaesthesia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Dysgeusia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	4 / 47 (8.51%)
occurrences (all)	0	1	4
Epilepsy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	7 / 52 (13.46%)	12 / 42 (28.57%)	17 / 47 (36.17%)
occurrences (all)	8	14	23
Hypoaesthesia			
subjects affected / exposed	1 / 52 (1.92%)	2 / 42 (4.76%)	3 / 47 (6.38%)
occurrences (all)	1	2	3
Lethargy			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Neuropathy peripheral			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Post herpetic neuralgia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	1	1	4
Syncope			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 52 (17.31%)	4 / 42 (9.52%)	11 / 47 (23.40%)
occurrences (all)	10	4	17
Febrile neutropenia			

subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
Lymphopenia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	4	3	2
Neutropenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Thrombocytopenia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 42 (4.76%)	3 / 47 (6.38%)
occurrences (all)	4	2	3
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
Deafness transitory			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Hypoacusis			
subjects affected / exposed	2 / 52 (3.85%)	3 / 42 (7.14%)	3 / 47 (6.38%)
occurrences (all)	2	3	3
Tinnitus			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	6 / 47 (12.77%)
occurrences (all)	1	0	6
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	1	1	3
Eye swelling			

subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 52 (1.92%)	3 / 42 (7.14%)	0 / 47 (0.00%)
occurrences (all)	1	3	0
Abdominal distension			
subjects affected / exposed	1 / 52 (1.92%)	4 / 42 (9.52%)	7 / 47 (14.89%)
occurrences (all)	1	4	7
Abdominal pain			
subjects affected / exposed	4 / 52 (7.69%)	2 / 42 (4.76%)	5 / 47 (10.64%)
occurrences (all)	6	3	5
Abdominal pain upper			
subjects affected / exposed	4 / 52 (7.69%)	7 / 42 (16.67%)	6 / 47 (12.77%)
occurrences (all)	4	7	7
Constipation			
subjects affected / exposed	4 / 52 (7.69%)	8 / 42 (19.05%)	6 / 47 (12.77%)
occurrences (all)	6	9	9
Diarrhoea			
subjects affected / exposed	20 / 52 (38.46%)	20 / 42 (47.62%)	26 / 47 (55.32%)
occurrences (all)	39	30	37
Dry mouth			
subjects affected / exposed	2 / 52 (3.85%)	3 / 42 (7.14%)	1 / 47 (2.13%)
occurrences (all)	2	3	1
Dyspepsia			
subjects affected / exposed	10 / 52 (19.23%)	6 / 42 (14.29%)	9 / 47 (19.15%)
occurrences (all)	11	6	9

Dysphagia			
subjects affected / exposed	0 / 52 (0.00%)	3 / 42 (7.14%)	2 / 47 (4.26%)
occurrences (all)	0	3	2
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 52 (3.85%)	6 / 42 (14.29%)	2 / 47 (4.26%)
occurrences (all)	2	7	2
Lip blister			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 52 (0.00%)	4 / 42 (9.52%)	4 / 47 (8.51%)
occurrences (all)	0	4	4
Nausea			
subjects affected / exposed	28 / 52 (53.85%)	19 / 42 (45.24%)	27 / 47 (57.45%)
occurrences (all)	41	31	38
Odynophagia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	5 / 52 (9.62%)	3 / 42 (7.14%)	12 / 47 (25.53%)
occurrences (all)	5	13	20
Toothache			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	1	0	2
Vomiting			
subjects affected / exposed	20 / 52 (38.46%)	11 / 42 (26.19%)	22 / 47 (46.81%)
occurrences (all)	33	12	33
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	0	1	3
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	5
Alopecia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	4 / 47 (8.51%)
occurrences (all)	0	0	4
Dermatitis acneiform			
subjects affected / exposed	2 / 52 (3.85%)	4 / 42 (9.52%)	10 / 47 (21.28%)
occurrences (all)	3	5	11
Dry skin			
subjects affected / exposed	5 / 52 (9.62%)	5 / 42 (11.90%)	7 / 47 (14.89%)
occurrences (all)	5	5	11
Eczema			
subjects affected / exposed	1 / 52 (1.92%)	6 / 42 (14.29%)	1 / 47 (2.13%)
occurrences (all)	1	8	1
Ingrowing nail			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Nail discolouration			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	6 / 52 (11.54%)	14 / 42 (33.33%)	9 / 47 (19.15%)
occurrences (all)	8	19	14
Rash			
subjects affected / exposed	7 / 52 (13.46%)	9 / 42 (21.43%)	11 / 47 (23.40%)
occurrences (all)	8	10	13
Rash macular			

subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	0	1	4
Rash maculo-papular			
subjects affected / exposed	10 / 52 (19.23%)	9 / 42 (21.43%)	14 / 47 (29.79%)
occurrences (all)	10	13	21
Rash papular			
subjects affected / exposed	0 / 52 (0.00%)	2 / 42 (4.76%)	2 / 47 (4.26%)
occurrences (all)	0	3	2
Rash pruritic			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	1	1	4
Skin hyperpigmentation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 52 (0.00%)	2 / 42 (4.76%)	2 / 47 (4.26%)
occurrences (all)	0	2	2
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Chronic kidney disease			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 52 (5.77%)	6 / 42 (14.29%)	10 / 47 (21.28%)
occurrences (all)	3	6	13
Back pain			
subjects affected / exposed	2 / 52 (3.85%)	8 / 42 (19.05%)	7 / 47 (14.89%)
occurrences (all)	2	9	8
Bone pain			
subjects affected / exposed	2 / 52 (3.85%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	2	1	8
Flank pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Joint stiffness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	4 / 52 (7.69%)	14 / 42 (33.33%)	12 / 47 (25.53%)
occurrences (all)	4	19	15
Muscular weakness			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 52 (3.85%)	2 / 42 (4.76%)	3 / 47 (6.38%)
occurrences (all)	2	2	4
Musculoskeletal pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	4 / 47 (8.51%)
occurrences (all)	0	0	4
Myalgia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences (all)	3	0	3
Neck pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)	7 / 42 (16.67%)	7 / 47 (14.89%)
occurrences (all)	4	8	8

Tendon pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 52 (3.85%)	2 / 42 (4.76%)	2 / 47 (4.26%)
occurrences (all)	2	2	4
Cellulitis			
subjects affected / exposed	1 / 52 (1.92%)	5 / 42 (11.90%)	3 / 47 (6.38%)
occurrences (all)	1	8	4
Conjunctivitis			
subjects affected / exposed	3 / 52 (5.77%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Cystitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	3 / 47 (6.38%)
occurrences (all)	1	1	3
Gastroenteritis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
Herpes zoster			
subjects affected / exposed	0 / 52 (0.00%)	3 / 42 (7.14%)	0 / 47 (0.00%)
occurrences (all)	0	4	0
Infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	5 / 52 (9.62%)	5 / 42 (11.90%)	5 / 47 (10.64%)
occurrences (all)	6	5	7
Paronychia			
subjects affected / exposed	3 / 52 (5.77%)	7 / 42 (16.67%)	7 / 47 (14.89%)
occurrences (all)	7	8	8
Pharyngitis			

subjects affected / exposed	0 / 52 (0.00%)	2 / 42 (4.76%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 42 (4.76%)	2 / 47 (4.26%)
occurrences (all)	2	2	2
Respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences (all)	1	0	4
Rhinitis			
subjects affected / exposed	2 / 52 (3.85%)	1 / 42 (2.38%)	2 / 47 (4.26%)
occurrences (all)	5	1	2
Sinobronchitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	1	1	2
Tooth infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	9 / 52 (17.31%)	6 / 42 (14.29%)	6 / 47 (12.77%)
occurrences (all)	11	10	8
Urinary tract infection			
subjects affected / exposed	5 / 52 (9.62%)	8 / 42 (19.05%)	4 / 47 (8.51%)
occurrences (all)	7	19	4
Viral infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 52 (26.92%)	9 / 42 (21.43%)	14 / 47 (29.79%)
occurrences (all)	16	11	15
Hyperkalaemia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 42 (2.38%)	0 / 47 (0.00%)
occurrences (all)	8	1	0

Hyperglycaemia			
subjects affected / exposed	0 / 52 (0.00%)	2 / 42 (4.76%)	3 / 47 (6.38%)
occurrences (all)	0	2	4
Hyperlipasaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	9 / 52 (17.31%)	7 / 42 (16.67%)	10 / 47 (21.28%)
occurrences (all)	17	9	15
Hypocalcaemia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 42 (0.00%)	3 / 47 (6.38%)
occurrences (all)	2	0	4
Hypoglycaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	1	1	2
Hypokalaemia			
subjects affected / exposed	5 / 52 (9.62%)	2 / 42 (4.76%)	4 / 47 (8.51%)
occurrences (all)	8	2	5
Hypomagnesaemia			
subjects affected / exposed	4 / 52 (7.69%)	3 / 42 (7.14%)	3 / 47 (6.38%)
occurrences (all)	7	3	5
Hyponatraemia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 42 (4.76%)	1 / 47 (2.13%)
occurrences (all)	6	3	1
Hypophagia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 42 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 52 (0.00%)	2 / 42 (4.76%)	1 / 47 (2.13%)
occurrences (all)	0	2	1
Hypoproteinaemia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 42 (2.38%)	1 / 47 (2.13%)
occurrences (all)	1	1	1

Non-serious adverse events	All Participants		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	176 / 177 (99.44%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	10 / 177 (5.65%)		
occurrences (all)	12		
Pallor			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	2		
Thrombosis			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	44 / 177 (24.86%)		
occurrences (all)	62		
Chest pain			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	7 / 177 (3.95%)		
occurrences (all)	8		
Face oedema			
subjects affected / exposed	9 / 177 (5.08%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	46 / 177 (25.99%)		
occurrences (all)	57		
Gait disturbance			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	10 / 177 (5.65%)		
occurrences (all)	15		

Non-cardiac chest pain subjects affected / exposed occurrences (all)	23 / 177 (12.99%) 26		
Oedema peripheral subjects affected / exposed occurrences (all)	103 / 177 (58.19%) 226		
Pain subjects affected / exposed occurrences (all)	6 / 177 (3.39%) 7		
Peripheral swelling subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 10		
Pyrexia subjects affected / exposed occurrences (all)	43 / 177 (24.29%) 55		
Immune system disorders Anaphylactoid reaction subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Hypersensitivity subjects affected / exposed occurrences (all)	3 / 177 (1.69%) 5		
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Perineal pain subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Prostatomegaly subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Respiratory, thoracic and mediastinal disorders			

Cough				
subjects affected / exposed	47 / 177 (26.55%)			
occurrences (all)	75			
Dry throat				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Dysphonia				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	5			
Dyspnoea				
subjects affected / exposed	40 / 177 (22.60%)			
occurrences (all)	48			
Dyspnoea exertional				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	2			
Epistaxis				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	5			
Haemoptysis				
subjects affected / exposed	4 / 177 (2.26%)			
occurrences (all)	5			
Hypoxia				
subjects affected / exposed	4 / 177 (2.26%)			
occurrences (all)	4			
Nasal discomfort				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	2			
Nasal dryness				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Oropharyngeal pain				
subjects affected / exposed	8 / 177 (4.52%)			
occurrences (all)	8			
Pleural effusion				
subjects affected / exposed	9 / 177 (5.08%)			
occurrences (all)	9			

Pneumothorax			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	5 / 177 (2.82%)		
occurrences (all)	7		
Pulmonary embolism			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	13 / 177 (7.34%)		
occurrences (all)	17		
Throat irritation			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 177 (3.39%)		
occurrences (all)	6		
Confusional state			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	12 / 177 (6.78%)		
occurrences (all)	14		
Sleep disorder			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	41 / 177 (23.16%)		
occurrences (all)	54		
Amylase increased			

subjects affected / exposed	45 / 177 (25.42%)			
occurrences (all)	103			
Aspartate aminotransferase increased				
subjects affected / exposed	34 / 177 (19.21%)			
occurrences (all)	47			
Blood albumin decreased				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	12			
Blood alkaline phosphatase increased				
subjects affected / exposed	12 / 177 (6.78%)			
occurrences (all)	18			
Blood bilirubin increased				
subjects affected / exposed	6 / 177 (3.39%)			
occurrences (all)	10			
Blood creatine increased				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	3			
Blood creatine phosphokinase increased				
subjects affected / exposed	22 / 177 (12.43%)			
occurrences (all)	42			
Blood creatinine increased				
subjects affected / exposed	56 / 177 (31.64%)			
occurrences (all)	108			
Blood glucose increased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	2			
Blood potassium increased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Blood triglycerides increased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Blood urea increased				

subjects affected / exposed	4 / 177 (2.26%)			
occurrences (all)	4			
Blood uric acid increased				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	2			
C-reactive protein increased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	7 / 177 (3.95%)			
occurrences (all)	13			
Gamma-glutamyltransferase increased				
subjects affected / exposed	16 / 177 (9.04%)			
occurrences (all)	23			
Haemoglobin decreased				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	4			
Lipase increased				
subjects affected / exposed	33 / 177 (18.64%)			
occurrences (all)	81			
Lymphocyte count decreased				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	7			
Protein total decreased				
subjects affected / exposed	8 / 177 (4.52%)			
occurrences (all)	8			
Weight decreased				
subjects affected / exposed	7 / 177 (3.95%)			
occurrences (all)	7			
Weight increased				
subjects affected / exposed	13 / 177 (7.34%)			
occurrences (all)	13			
White blood cell count decreased				
subjects affected / exposed	3 / 177 (1.69%)			
occurrences (all)	4			

Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	2		
Traumatic haematoma			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	2		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Bradycardia			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	2		
Nervous system disorders			
Amnesia			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	36 / 177 (20.34%)		
occurrences (all)	45		
Dysaesthesia			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	6 / 177 (3.39%)		
occurrences (all)	6		
Epilepsy			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	45 / 177 (25.42%)		
occurrences (all)	59		
Hypoaesthesia			
subjects affected / exposed	8 / 177 (4.52%)		
occurrences (all)	9		

Lethargy subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 4		
Neuropathy peripheral subjects affected / exposed occurrences (all)	3 / 177 (1.69%) 3		
Post herpetic neuralgia subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Seizure subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 9		
Syncope subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	30 / 177 (16.95%) 39		
Febrile neutropenia subjects affected / exposed occurrences (all)	2 / 177 (1.13%) 2		
Leukopenia subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 6		
Lymphopenia subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 11		
Neutropenia subjects affected / exposed occurrences (all)	6 / 177 (3.39%) 10		
Thrombocytopenia subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 12		
Ear and labyrinth disorders			

Deafness subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 7		
Deafness transitory subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Ear pain subjects affected / exposed occurrences (all)	2 / 177 (1.13%) 3		
Hypoacusis subjects affected / exposed occurrences (all)	9 / 177 (5.08%) 9		
Tinnitus subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 7		
Eye disorders			
Eye pruritus subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 5		
Eye swelling subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Eyelid oedema subjects affected / exposed occurrences (all)	3 / 177 (1.69%) 3		
Vision blurred subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Vitreous floaters subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 4		
Abdominal distension			

subjects affected / exposed	13 / 177 (7.34%)			
occurrences (all)	13			
Abdominal pain				
subjects affected / exposed	14 / 177 (7.91%)			
occurrences (all)	17			
Abdominal pain upper				
subjects affected / exposed	20 / 177 (11.30%)			
occurrences (all)	22			
Constipation				
subjects affected / exposed	28 / 177 (15.82%)			
occurrences (all)	42			
Diarrhoea				
subjects affected / exposed	79 / 177 (44.63%)			
occurrences (all)	132			
Dry mouth				
subjects affected / exposed	7 / 177 (3.95%)			
occurrences (all)	7			
Dyspepsia				
subjects affected / exposed	30 / 177 (16.95%)			
occurrences (all)	33			
Dysphagia				
subjects affected / exposed	8 / 177 (4.52%)			
occurrences (all)	8			
Gastrooesophageal reflux disease				
subjects affected / exposed	12 / 177 (6.78%)			
occurrences (all)	13			
Lip blister				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	2			
Lip dry				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Mouth ulceration				
subjects affected / exposed	9 / 177 (5.08%)			
occurrences (all)	9			
Nausea				

subjects affected / exposed	97 / 177 (54.80%)		
occurrences (all)	150		
Odynophagia			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	25 / 177 (14.12%)		
occurrences (all)	49		
Toothache			
subjects affected / exposed	4 / 177 (2.26%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	64 / 177 (36.16%)		
occurrences (all)	106		
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	5 / 177 (2.82%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	6		
Alopecia			
subjects affected / exposed	8 / 177 (4.52%)		
occurrences (all)	11		
Dermatitis acneiform			
subjects affected / exposed	21 / 177 (11.86%)		
occurrences (all)	26		
Dry skin			
subjects affected / exposed	23 / 177 (12.99%)		
occurrences (all)	32		
Eczema			
subjects affected / exposed	9 / 177 (5.08%)		
occurrences (all)	11		
Ingrowing nail			

subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	2			
Nail discolouration				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Night sweats				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	2			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	36 / 177 (20.34%)			
occurrences (all)	50			
Rash				
subjects affected / exposed	28 / 177 (15.82%)			
occurrences (all)	32			
Rash macular				
subjects affected / exposed	9 / 177 (5.08%)			
occurrences (all)	10			
Rash maculo-papular				
subjects affected / exposed	43 / 177 (24.29%)			
occurrences (all)	56			
Rash papular				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	6			
Rash pruritic				
subjects affected / exposed	7 / 177 (3.95%)			
occurrences (all)	9			
Skin hyperpigmentation				
subjects affected / exposed	2 / 177 (1.13%)			
occurrences (all)	2			
Urticaria				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	5			

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 177 (1.13%)		
occurrences (all)	2		
Chronic kidney disease			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Hypertonic bladder			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	3 / 177 (1.69%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 177 (14.69%)		
occurrences (all)	32		
Back pain			
subjects affected / exposed	18 / 177 (10.17%)		
occurrences (all)	20		
Bone pain			
subjects affected / exposed	6 / 177 (3.39%)		
occurrences (all)	11		
Flank pain			
subjects affected / exposed	4 / 177 (2.26%)		
occurrences (all)	4		
Joint stiffness			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	35 / 177 (19.77%)		
occurrences (all)	45		

Muscular weakness subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 8		
Musculoskeletal pain subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 4		
Myalgia subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 12		
Neck pain subjects affected / exposed occurrences (all)	2 / 177 (1.13%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	23 / 177 (12.99%) 28		
Tendon pain subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 10		
Cellulitis subjects affected / exposed occurrences (all)	12 / 177 (6.78%) 17		
Conjunctivitis subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 4		
Cystitis subjects affected / exposed occurrences (all)	2 / 177 (1.13%) 2		
Folliculitis			

subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	5			
Gastroenteritis				
subjects affected / exposed	3 / 177 (1.69%)			
occurrences (all)	3			
Herpes zoster				
subjects affected / exposed	5 / 177 (2.82%)			
occurrences (all)	6			
Infection				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	16 / 177 (9.04%)			
occurrences (all)	19			
Paronychia				
subjects affected / exposed	25 / 177 (14.12%)			
occurrences (all)	33			
Pharyngitis				
subjects affected / exposed	3 / 177 (1.69%)			
occurrences (all)	3			
Pneumonia				
subjects affected / exposed	9 / 177 (5.08%)			
occurrences (all)	9			
Respiratory tract infection				
subjects affected / exposed	4 / 177 (2.26%)			
occurrences (all)	5			
Rhinitis				
subjects affected / exposed	7 / 177 (3.95%)			
occurrences (all)	10			
Sinobronchitis				
subjects affected / exposed	1 / 177 (0.56%)			
occurrences (all)	1			
Skin infection				
subjects affected / exposed	4 / 177 (2.26%)			
occurrences (all)	5			
Tooth infection				

subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	25 / 177 (14.12%)		
occurrences (all)	34		
Urinary tract infection			
subjects affected / exposed	18 / 177 (10.17%)		
occurrences (all)	31		
Viral infection			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	50 / 177 (28.25%)		
occurrences (all)	63		
Hyperkalaemia			
subjects affected / exposed	8 / 177 (4.52%)		
occurrences (all)	14		
Hyperglycaemia			
subjects affected / exposed	6 / 177 (3.39%)		
occurrences (all)	8		
Hyperlipasaemia			
subjects affected / exposed	1 / 177 (0.56%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	34 / 177 (19.21%)		
occurrences (all)	52		
Hypocalcaemia			
subjects affected / exposed	7 / 177 (3.95%)		
occurrences (all)	10		
Hypoglycaemia			
subjects affected / exposed	4 / 177 (2.26%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	15 / 177 (8.47%)		
occurrences (all)	20		

Hypomagnesaemia subjects affected / exposed occurrences (all)	15 / 177 (8.47%) 33		
Hyponatraemia subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 19		
Hypophagia subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 22		
Hypoproteinaemia subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2014	Reduced nazartinib starting dose to 50 mg qd. Clarified the subsequent escalation of nazartinib and capmatinib doses. Revised the DLT definitions by adding Grade 2 pneumonitis as dose-limiting toxicity. Provided the latest available clinical safety and PK data for nazartinib and capmatinib tablet formulation. Provided updated hypothetical scenarios in reflection of the reduced starting dose of nazartinib and the updated priors based on the updated safety information.
24 July 2015	Introduced a formulation change for nazartinib from capsules to tablets (viable formulation for commercialization). Recommended guidelines for management and dose modification of rash/skin toxicities were provided for the nazartinib treatment. For capmatinib treatment, updated the dose modifications guideline for hepatotoxicity in regard to discontinuing study medication(s) with concurrent elevation of ALT and/or AST > 3×ULN and total bilirubin > 2×ULN with ALP < 2×ULN, in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.). Specific work-up for potential Hy's law cases had been added to the protocol. The dose modification rules and the dose limiting toxicity for liver toxicity as well as the follow-up evaluations for hepatic toxicities had also been updated accordingly. Included precautionary measures against ultraviolet exposure as capmatinib had photosensitization potential. Additionally, updated the exclusion criteria and few new exclusion criteria were added. Updated concomitant therapies, criteria for interruption and re-initiation of nazartinib and capmatinib.
01 September 2015	Provided detailed information about an urgent safety measure related to nazartinib. Excluded subjects with other malignancies, who underwent a bone marrow or solid organ transplant, with a known history of human immunodeficiency virus infection, or receiving immunosuppressive agents or chronic corticosteroids at study entry. Allowed subjects with either HBV surface antigen positive or HBV-DNA positive to enroll into the study if willing to take antiviral therapy 1-2 weeks prior to first dose of study treatment and continue antiviral therapy for at least 4 weeks after the last dose of study treatment. Allowed new subjects with negative hepatitis C antibody (HC Ab) or who were HC Ab positive but with an undetectable level of HCV-RNA into the study. Subjects with detectable HCV-RNA were not eligible to enroll into the study.

02 November 2015	Implemented a centralization of analysis for the resistance mutations EGFRT790M and MET oncogene amplification at a Novartis designated central laboratory for all subjects entering into Phase II. Introduced 50 mg dose strength of nazartinib tablets for better compliance. Optimized the subject safety and the toxicity monitoring as well as to align Novartis study protocols, the QTcF eligibility criterion and the management guidelines for pancreatic toxicity were revised. Updated the definition of the end of study to detail study continuation conditions after completion of the primary analysis until all subjects discontinued, or until another clinical trial was available for all ongoing subjects to be transferred to that clinical study and continue to receive capmatinib + nazartinib. Clarified the possibility of using bisphosphonates during the study. Detailed the use of an Interactive Response Technology system in the Phase II part of the study to specify the enrollment and the study drug dispensation tracking via the application. Modalities and conditions for subject re-screening after screen failure was introduced, together with screening assessments to be performed again during the new screening phase.
29 July 2016	Better defined the subject population to be enrolled in the Phase II part of the study (expansion phase). A new group was added (Group 3), and the sample size of Group 2 was revised. Implemented a requirement of ECOG performance status of 0-1 for all subjects to be enrolled in the study to ensure that subjects would be able to receive potential benefit from study treatment. Removed the exclusion criterion on fasting plasma glucose ≥ 160 mg/dL (≥ 8.9 mmol/L) in the absence of evidence of impact on the glycemia in light of the most recent available clinical data and according to the latest versions of capmatinib and nazartinib Investigator Brochures Introduced a new dose strength (150 mg) for capmatinib tablets. Introduced other rare EGFR activating sensitizing mutations that were also considered for enrollment onto the Phase II. These rare mutations, L861Q, G719X, and S768I, account for almost 10% of the cases whereas L858R point mutation and exon 19 deletions accounted for approximately 90% of the cases. Updated the overview of capmatinib and nazartinib according to last Investigator Brochure versions. Removed the restriction of proton pump inhibitors use during the course of the study. Clarified the conditions in which local laboratory assessments should be reported in the Case Report Form during the Phase 2 part of the trial. Clarified the time window for post-dose ECG during the visits with PK sampling. Clarified the definition of acquired resistance mechanisms and the definition of the 4 subgroups of subjects being enrolled in the Phase II Group 1. Clarified the biosample requirements for the optional biomarker assessments. Introduced the RP2D and the dose reduction steps starting from the RP2D.
11 April 2017	Added in Phase II a new group 4 of subjects (N=30) with EGFRmut, any T790M, any MET, in order to assess the safety and tolerability of the combination therapy when taken with food (unrestricted meal type). Proposed a new group 4 to administer study medication with food to improve the tolerability profile of the combination therapy, as dosing with food had been shown to improve the GI tolerability of some multi-kinase inhibitors such as imatinib (Gleevec®) and bosutinib (Bosulif®). Corrected the exclusion criterion for subjects with asymptomatic serum amylase and lipase > Grade 2, to clarify that subject now met exclusion criterion even if only one of the two parameters (asymptomatic serum amylase or lipase) was > Grade 2. Added the collection of an optional on-treatment biopsy with paired cfDNA sample to identify emergence of potential resistance markers during treatment as well as understand the correlation between tissue and plasma biomarker status. Clarified the exclusion criterion for subjects with brain metastases. Clarified the interpretation of study discontinuation after dose interruption.

20 October 2021	A new group 5 added per protocol amendment 7 will not be opened as Novartis made the decision to discontinue the study on 11-May-2022. Below are the key changes in amendment 7. As of 20-Oct-2021, a total of 177 participants have been enrolled in the study: 33 participants in Phase Ib and 144 in Phase II (Group 1 to Group 4). All participants from Phase Ib and Phase II Groups 1 to 4 had met one of the end of study completion criteria as considered under protocol amendment 6 and there were no participants receiving treatment. The main purpose of this amendment is to implement a new subject group, Phase II Group 5, to determine the efficacy and safety of capmatinib monotherapy. The rationale for this addition is based on the following: Based on evidence suggesting that MET gene amplification plays an important role as a mechanism of resistance to treatment with EGFR-TKIs in NSCLC patients carrying mutated EGFR. Furthermore, the fact that there are reports showing significant clinical antitumor activity in this subpopulation of patients when combining an EGFR-TKI with a specific cMET inhibitor (such as Capmatinib). Therefore, the contribution of capmatinib as a monodrug needs to be established. This information will pave the way for the optimal use of the combination in future trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Notes: