Clinical trial results:
A Phase Ib /II open-label, multi-center study of the combination of BYL719 plus AMG 479 (ganitumab) in adult patients with selected advanced solid tumors

Summary

EudraCT number	2012-001962-13
Trial protocol	ES BE
Global end of trial date	01 June 2017

Results information

Result version number	v1 (current)
This version publication date	16 June 2018
First version publication date	16 June 2018

Trial information

Trial identification

Sponsor protocol code	CBYL719X2105J

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01708161
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, 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	01 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase Ib
To estimate the maximum tolerated dose(s) (MTD) and/or identify the recommended phase II dose(s) (RPIID) of BYL719 in combination with ganitumab in patients with PIK3CA mutated or amplified solid tumors.
Phase II
To estimate the antitumor activity of BYL719 in combination with ganitumab in the following Phase II populations:
Arm 1: Patients with PIK3CA mutated or amplified hormone receptor positive breast cancer
Arm 2: Patients with PIK3CA mutated or amplified ovarian cancer

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	27 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	47
EEA total number of subjects	8

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	35
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with selected advanced solid tumors who had relapsed or progressed on standard therapy were treated in BYL719X2105J study with a combination of alpelisib and ganitumab. Phase I of the trial was by dose combination of the treatment. Phase II was by patients.

Period 1

Period 1 title	Overall Study (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	BYL 200mg + AMG 12mg/kg

Arm description:

BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors

Arm type	Experimental
Investigational medicinal product name	BYL719 and AMG 479
Investigational medicinal product code	
Other name	Alpelisib and Ganitumab
Pharmaceutical forms	Coated tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

BYL719 was administered orally once daily (28 day cycles) upon completion of AMG 479 intravenous infusion (every second week (Days 1 and 15 of every cycle).

Arm title	BYL 300mg + AMG 12mg/kg

Arm description:

BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors

Arm type	Experimental
Investigational medicinal product name	BYL719 and AMG 479
Investigational medicinal product code	
Other name	Alpelisib and Ganitumab
Pharmaceutical forms	Coated tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

BYL719 was administered orally once daily (28 day cycles) upon completion of AMG 479 intravenous infusion (every second week (Days 1 and 15 of every cycle).

Arm title	BYL 350mg + AMG 12mg/kg

Arm description:

BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors

Arm type	Experimental

Investigational medicinal product name	BYL719 and AMG 479
Investigational medicinal product code	
Other name	Alpelisib and Ganitumab
Pharmaceutical forms	Coated tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

BYL719 was administered orally once daily (28 day cycles) upon completion of AMG 479 intravenous infusion (every second week (Days 1 and 15 of every cycle).

Arm title	HR+BC - Phase II

Arm description:

Patients with PIK3CA mutated or amplified hormone receptor (HR) positive breast carcinoma (BC) were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg.

Arm type	Experimental
Investigational medicinal product name	BYL719 and AMG 479
Investigational medicinal product code	
Other name	Alpelisib and Ganitumab
Pharmaceutical forms	Coated tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

BYL719 was administered orally once daily (28 day cycles) upon completion of AMG 479 intravenous infusion (every second week (Days 1 and 15 of every cycle).

Arm title	Ovarian - Phase II

Arm description:

Patients with PIK3CA mutated or amplified ovarian cancer were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg

Arm type	Experimental
Investigational medicinal product name	BYL719 and AMG 479
Investigational medicinal product code	
Other name	Alpelisib and Ganitumab
Pharmaceutical forms	Coated tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

BYL719 was administered orally once daily (28 day cycles) upon completion of AMG 479 intravenous infusion (every second week (Days 1 and 15 of every cycle).

Arm title	Non-HR+BC/Ovarian - Phase II

Arm description:

Patients with other than Breast and Ovarian cancer treated in the phase II part

Arm type	Experimental
Investigational medicinal product name	BYL719 and AMG 479
Investigational medicinal product code	
Other name	Alpelisib and Ganitumab
Pharmaceutical forms	Coated tablet, Solution for injection/infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

BYL719 was administered orally once daily (28 day cycles) upon completion of AMG 479 intravenous infusion (every second week (Days 1 and 15 of every cycle).

Number of subjects in period 1	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg
Started	4	10	10
Completed	0	0	0
Not completed	4	10	10
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	1	1
Disease progression	3	5	5
Adverse event, non-fatal	1	3	4
Administrative problems	-	1	-

Number of subjects in period 1	HR+BC - Phase II	Ovarian - Phase II	Non-HR+BC/Ovarian - Phase II
Started	16	6	1
Completed	0	0	0
Not completed	16	6	1
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	-	-	-
Disease progression	13	3	-
Adverse event, non-fatal	2	3	-
Administrative problems	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	BYL 200mg + AMG 12mg/kg
Reporting group description:	
BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors	
Reporting group title	BYL 300mg + AMG 12mg/kg
Reporting group description:	
BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors	
Reporting group title	BYL 350mg + AMG 12mg/kg
Reporting group description:	
BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors	
Reporting group title	HR+BC - Phase II
Reporting group description:	
Patients with PIK3CA mutated or amplified hormone receptor (HR) positive breast carcinoma (BC) were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg.	
Reporting group title	Ovarian - Phase II
Reporting group description:	
Patients with PIK3CA mutated or amplified ovarian cancer were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg	
Reporting group title	Non-HR+BC/Ovarian - Phase II
Reporting group description:	
Patients with other than Breast and Ovarian cancer treated in the phase II part	

Reporting group values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg
Number of subjects	4	10	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	7	4
From 65-84 years	0	3	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.5	57.5	63.7
standard deviation	± 3.11	± 15.55	± 7.83
Sex: Female, Male Units: Subjects			
Female	4	7	7
Male	0	3	3

Reporting group values	HR+BC - Phase II	Ovarian - Phase II	Non-HR+BC/Ovarian - Phase II
Number of subjects	16	6	1
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	4	1
From 65-84 years	1	2	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.3	59.7	56.0
standard deviation	± 8.04	± 6.53	± 0
Sex: Female, Male Units: Subjects			
Female	15	6	1
Male	1	0	0

Reporting group values	Total		
Number of subjects	47		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	35		
From 65-84 years	12		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	40		
Male	7		

End points

End points reporting groups

Reporting group title	BYL 200mg + AMG 12mg/kg
Reporting group description:	
BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors	
Reporting group title	BYL 300mg + AMG 12mg/kg
Reporting group description:	
BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors	
Reporting group title	BYL 350mg + AMG 12mg/kg
Reporting group description:	
BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors	
Reporting group title	HR+BC - Phase II
Reporting group description:	
Patients with PIK3CA mutated or amplified hormone receptor (HR) positive breast carcinoma (BC) were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg.	
Reporting group title	Ovarian - Phase II
Reporting group description:	
Patients with PIK3CA mutated or amplified ovarian cancer were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg	
Reporting group title	Non-HR+BC/Ovarian - Phase II
Reporting group description:	
Patients with other than Breast and Ovarian cancer treated in the phase II part	
Subject analysis set title	All Patients - Phase
Subject analysis set type	Full analysis
Subject analysis set description:	
The total column “All patients” includes a patient with non-HR+BC and non-Ovarian cancer treated in the Phase II part.	
Subject analysis set title	All Patients - Phase II
Subject analysis set type	Full analysis
Subject analysis set description:	
The total column “All patients” includes a patient with non-HR+BC and non-Ovarian cancer treated in the Phase II part.	

Primary: Dose limiting toxicities (DLTs) - Phase Ib

End point title	Dose limiting toxicities (DLTs) - Phase Ib[1][2]
End point description:	
Phase lb only	
End point type	Primary
End point timeframe:	
28 days	

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: Descriptive analyses.

[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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	8	9	
Units: Participants				
Drug hypersensitivity|	0	0	1	
Hyperglycemia|	0	0	1	
Rash maculopapular|	0	1	0	
Urticaria|	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Patients with overall response rate (RECIST) based on Investigator radiology assessment for HR positive breast and ovarian cancer - Phase II

End point title	Percentage of Patients with overall response rate (RECIST) based on Investigator radiology assessment for HR positive breast and ovarian cancer - Phase II[3][4]

End point description:

The antitumor activity of alpelisib in combination with ganitumab in patients with PIK3CA mutated or amplified hormone receptor positive (HR+) breast (arm 1) or ovarian (arm 2) cancer. Overall response rate is defined as the proportion of patients who have a best overall response of complete response or partial response assessed per RECIST 1.1.

End point type	Primary

End point timeframe:

Approximately 1 year (since initiation of Phase II, Dec 2013, till Primary CSR cut off 06Jan2015)

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: Descriptive analyses.

[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: Descriptive analyses.

End point values	HR+BC - Phase II	Ovarian - Phase II	All Patients - Phase	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	6	23	
Units: Percentages of participants				
number (confidence interval 95%)	12.5 (1.6 to 38.3)	16.7 (0.4 to 64.1)	13.0 (2.8 to 33.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with best overall response (RECIST) based on investigator radiology assessment - Phase Ib

End point title	Number of Patients with best overall response (RECIST) based on investigator radiology assessment - Phase Ib[5]

End point description:

The anti-tumor activity of alpelisib and ganitumab in combination as per RECIST 1.1

End point type	Secondary

End point timeframe:

Approximately 1 year (since FPFV 27Nov2012, till MTD declaration 26Nov2013)

Notes:

[5] - 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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: Participants				
Complete response (CR)|	0	0	0	
Partial response (PR)|	0	0	3	
Stable disease (PD)|	1	3	2	
Progressive disease (PD)|	3	3	3	
Unknown|	0	4	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients with disease control rate (RECIST) based on investigator radiology assessment - Phase Ib

End point title	Percentage of Patients with disease control rate (RECIST) based on investigator radiology assessment - Phase Ib[6]

End point description:

The anti-tumor activity of alpelisib and ganitumab in combination as per RECIST 1.1

End point type	Secondary

End point timeframe:

Approximately 1 year (since FPFV 27Nov2012, till MTD declaration 26Nov2013)

Notes:

[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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: Percentages				
number (confidence interval 95%)	25.0 (0.6 to 80.6)	9.1 (6.7 to 65.2)	50.0 (18.7 to 81.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with disease control rate (RECIST) based on Investigator radiology assessment for HR positive breast and ovarian cancer - Phase II

End point title	Percentage of patients with disease control rate (RECIST) based on Investigator radiology assessment for HR positive breast and ovarian cancer - Phase II[7]

End point description:

the antitumor activity of alpelisib in combination with ganitumab in patients with PIK3CA mutated or amplified hormone receptor positive (HR+) breast (arm 1) or ovarian (arm 2) cancer. Phase II only, Cycle 1 Day 1 through Cycle 6 Day 28; assessed at baseline and every 8 weeks thereafter

End point type	Secondary

End point timeframe:

Approximately 1 year (since initiation of Phase II, Dec 2013, till Primary CSR cut off 06Jan2015)

Notes:

[7] - 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: Descriptive analyses.

End point values	HR+BC - Phase II	Ovarian - Phase II	All Patients - Phase II	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	6	23	
Units: Percentages of participants				
number (confidence interval 95%)	43.8 (19.8 to 70.1)	50.0 (11.8 to 88.2)	47.8 (26.8 to 69.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of BYL - Phase Ib

End point title	Cmax of BYL - Phase Ib[8]

End point description:

Serum concentration for BYL719 (alpelisib); cycle 1 = initial 28 days of treatment

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 15

Notes:

[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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1|	2070 (± 1040)	2620 (± 1260)	2640 (± 888)	
Cycle 1 day 15|	3080 (± 1750)	2880 (± 910)	2600 (± 1040)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under curve (AUC) 0-24 hour of BYL - Phase Ib

End point title	Area under curve (AUC) 0-24 hour of BYL - Phase Ib[9]

End point description:

Area under curve for BYL719 (Alpelisib); cycle 1 = initial 28 days of treatment

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 15

Notes:

[9] - 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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1|	19900 (± 8700)	23400 (± 10500)	25200 (± 9200)	
Cycle 1 day 15|	24000 (± 10700)	29700 (± 9170)	25200 (± 9160)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax and T half of BYL - Phase Ib

End point title	Tmax and T half of BYL - Phase Ib[10]

End point description:

Tmax and half life of BYL719 (Alpelisib); cycle 1 = initial 28 days of treatment

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 15

Notes:

[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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: hr				
median (full range (min-max))				
Tmax (Cycle 1 Day 1)|	2.78 (1.88 to 3.55)	1.97 (0.63 to 3.00)	2.36 (1.50 to 3.10)	
Tmax (Cycle 1 Day 15)|	1.57 (0.83 to 1.83)	3.01 (2.07 to 4.00)	2.02 (2.00 to 3.08)	
Thalf (Cycle 1 Day 1)|	7.78 (6.24 to 10.80)	6.06 (5.26 to 13.70)	6.86 (5.32 to 9.23)	
Thalf (Cycle 1 Day15)|	6.89 (5.94 to 9.90)	6.80 (5.82 to 8.81)	6.83 (5.19 to 13.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of AMG - Phase Ib

End point title	Cmax of AMG - Phase Ib[11]

End point description:

Serum concentration for AMG 479 (ganitumab); cycle 1 = initial 28 days of treatment

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: ng/mL				
arithmetic mean (standard deviation)	192 (± 24)	202 (± 43.3)	232 (± 59.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under curve (AUC) 0-336 hour of AMG - Phase Ib

End point title	Area under curve (AUC) 0-336 hour of AMG - Phase Ib[12]

End point description:

Area under curve for AMG 479 (ganitumab); cycle 1 = initial 28 days of treatment

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: hr*ng/mL				
arithmetic mean (standard deviation)	22900 (± 3930)	22500 (± 7040)	25200 (± 8000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax and T half of AMG - Phase Ib

End point title	Tmax and T half of AMG - Phase Ib[13]

End point description:

Tmax and half life of AMG 479 (ganitumab); cycle 1 = initial 28 days of treatment

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

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: Descriptive analyses.

End point values	BYL 200mg + AMG 12mg/kg	BYL 300mg + AMG 12mg/kg	BYL 350mg + AMG 12mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	10	10	
Units: hr				
median (full range (min-max))				
Tmax|	21.20 (1.02 to 22.70)	1.02 (1.00 to 23.10)	1.07 (1.00 to 1.77)	
Thalf|	132 (117 to 148)	117 (109 to 161)	180 (98 to 283)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	BYL 200mg + AMG 12 mg/kg

Reporting group description:

BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors.

Reporting group title	BYL 300mg + AMG 12 mg/kg

Reporting group description:

BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors.

Reporting group title	BYL 350mg + AMG 12 mg/kg

Reporting group description:

BYL719 (alpelisib) and AMG 479 (ganitumab) regimen in patients with PIK3CA mutated or amplified solid tumors

Reporting group title	HR + BC - Phase II

Reporting group description:

Patients with PIK3CA mutated or amplified hormone receptor (HR) positive breat carcinoma (BC) were treated with alpelisib 300 mg once daily and ganitumab 12 mg/kg

Reporting group title	Ovarian - Phase II

Reporting group description:

Patients with other than Breast and Ovarian cancer treated in the phase II

Serious adverse events	BYL 200mg + AMG 12 mg/kg	BYL 300mg + AMG 12 mg/kg	BYL 350mg + AMG 12 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	5 / 10 (50.00%)	5 / 10 (50.00%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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 / 10 (0.00%)	0 / 10 (0.00%)
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 / 10 (0.00%)	0 / 10 (0.00%)
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 / 10 (0.00%)	0 / 10 (0.00%)
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			
Drug hypersensitivity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (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
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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			
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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			
Fracture displacement			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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			
Neutropenia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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 retention			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (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			
Myositis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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			
Abdominal abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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%)	1 / 10 (10.00%)	0 / 10 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
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	HR + BC - Phase II	Ovarian - Phase II	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)	5 / 6 (83.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture displacement			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 16 (12.50%)	3 / 6 (50.00%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BYL 200mg + AMG 12 mg/kg	BYL 300mg + AMG 12 mg/kg	BYL 350mg + AMG 12 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	10 / 10 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	2 / 4 (50.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Peripheral venous disease			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	3	2
Axillary pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Face oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)	6 / 10 (60.00%)	8 / 10 (80.00%)
occurrences (all)	2	6	12
Feeling abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injection site rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Instillation site pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Choking			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	4 / 10 (40.00%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Laryngeal haemorrhage			

subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Paranasal sinus discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			

Agitation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	4 / 10 (40.00%)
occurrences (all)	0	1	4
Libido decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Mental status changes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Amylase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood calcium decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	3 / 4 (75.00%)	3 / 10 (30.00%)	2 / 10 (20.00%)
occurrences (all)	3	4	7
Blood magnesium decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lipase increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Neutrophil count decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Neutrophil count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	2 / 4 (50.00%)	5 / 10 (50.00%)	9 / 10 (90.00%)
occurrences (all)	2	6	10
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hip fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Infusion related reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Wound complication			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Aphonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	3 / 10 (30.00%)	3 / 10 (30.00%)
occurrences (all)	2	4	3
Dysarthria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 10 (40.00%)	4 / 10 (40.00%)
occurrences (all)	1	4	4
Headache			
subjects affected / exposed	3 / 4 (75.00%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	4	1	2
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Memory impairment			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Transient ischaemic attack			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lymph node pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ear pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hearing impaired			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eyelid ptosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Periorbital oedema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Photopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Abdominal pain lower			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Anal fissure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Anal ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Anorectal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Aphthous stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	3 / 10 (30.00%)	2 / 10 (20.00%)
occurrences (all)	0	4	2
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	5 / 10 (50.00%)	7 / 10 (70.00%)
occurrences (all)	4	10	10
Dry mouth			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	3 / 10 (30.00%)
occurrences (all)	1	2	4
Dyspepsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Flatulence			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gingival erosion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Gingival recession			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	9 / 10 (90.00%)	5 / 10 (50.00%)
occurrences (all)	0	12	7
Odynophagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sensitivity of teeth			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Small intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	3 / 4 (75.00%)	3 / 10 (30.00%)	5 / 10 (50.00%)
occurrences (all)	3	3	9
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	6 / 10 (60.00%)	4 / 10 (40.00%)
occurrences (all)	0	13	6
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blister			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Dry skin			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Onychoclasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Prurigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rash maculo-papular			

subjects affected / exposed	2 / 4 (50.00%)	2 / 10 (20.00%)	2 / 10 (20.00%)
occurrences (all)	2	2	3
Rash pruritic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin discolouration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cystitis noninfective			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hydronephrosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Micturition urgency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neurogenic bladder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Polyuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Renal failure acute			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urinary tract pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Myositis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Spinal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Trismus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Nail infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nasal herpes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Onychomycosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Periorbital cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	5 / 10 (50.00%)	6 / 10 (60.00%)
occurrences (all)	1	5	7
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	5 / 10 (50.00%)	4 / 10 (40.00%)
occurrences (all)	1	20	5
Glucose tolerance impaired			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Gout			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			

subjects affected / exposed	1 / 4 (25.00%)	7 / 10 (70.00%)	9 / 10 (90.00%)
occurrences (all)	1	11	20
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 10 (30.00%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Metabolic acidosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	HR + BC - Phase II	Ovarian - Phase II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	6 / 6 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypotension			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Peripheral venous disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 16 (18.75%)	3 / 6 (50.00%)	
occurrences (all)	4	3	
Axillary pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Catheter site pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	3 / 16 (18.75%)	1 / 6 (16.67%)	
occurrences (all)	3	2	
Face oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	7 / 16 (43.75%)	2 / 6 (33.33%)	
occurrences (all)	8	2	
Feeling abnormal			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			

subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Injection site rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Instillation site pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Localised oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	3 / 16 (18.75%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 16 (18.75%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Oedema peripheral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	4 / 16 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	4	2	
Thirst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Seasonal allergy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal dryness			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Choking			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	6 / 16 (37.50%)	2 / 6 (33.33%)	
occurrences (all)	7	3	
Dysphonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	4 / 16 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Dyspnoea exertional			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Epistaxis			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Laryngeal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 16 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Paranasal sinus discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Pneumothorax			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Productive cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Respiratory tract congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	3 / 16 (18.75%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Sinus congestion			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Confusional state			
subjects affected / exposed	2 / 16 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Depression			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Libido decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 16 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Amylase increased			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 16 (25.00%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Blood calcium decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 16 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Blood magnesium decreased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Blood phosphorus decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			

subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	2 / 16 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Neutrophil count increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	6 / 16 (37.50%)	2 / 6 (33.33%)	
occurrences (all)	6	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hip fracture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Infusion related reaction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Wound			

subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Wound complication			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	1 / 16 (6.25%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Aphonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Balance disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 16 (12.50%)	2 / 6 (33.33%)	
occurrences (all)	3	4	
Dysarthria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Headache			

subjects affected / exposed	5 / 16 (31.25%)	1 / 6 (16.67%)	
occurrences (all)	7	1	
Hypoaesthesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Presyncope			
subjects affected / exposed	0 / 16 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Somnolence			
subjects affected / exposed	0 / 16 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Transient ischaemic attack			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)	3 / 6 (50.00%)	
occurrences (all)	3	4	
Leukocytosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lymph node pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	

Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hearing impaired			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Tinnitus			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Eyelid ptosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Periorbital oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Photopsia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Abdominal distension			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			

subjects affected / exposed	3 / 16 (18.75%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Abdominal pain lower			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Anal fissure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Anal ulcer			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Anorectal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Aphthous stomatitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Chapped lips			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	4 / 16 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	10 / 16 (62.50%)	3 / 6 (50.00%)	
occurrences (all)	12	5	
Dry mouth			
subjects affected / exposed	3 / 16 (18.75%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	2 / 16 (12.50%)	3 / 6 (50.00%)	
occurrences (all)	2	3	
Dysphagia			

subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Flatulence			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Gingival bleeding			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gingival erosion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gingival recession			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	7 / 16 (43.75%)	3 / 6 (50.00%)	
occurrences (all)	10	3	
Odynophagia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oral pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Retching			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sensitivity of teeth			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Small intestinal obstruction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	6 / 16 (37.50%)	3 / 6 (50.00%)	
occurrences (all)	6	5	
Toothache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	4 / 16 (25.00%)	3 / 6 (50.00%)	
occurrences (all)	12	9	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Alopecia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Blister			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dermatitis acneiform			

subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Ingrowing nail			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nail disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Onychoclasis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Prurigo			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	4 / 16 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Rash			
subjects affected / exposed	4 / 16 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Rash erythematous			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rash macular			

subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	5 / 16 (31.25%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Rash pruritic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Skin discolouration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Cystitis noninfective			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hydronephrosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Micturition urgency			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neurogenic bladder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pollakiuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Polyuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal failure acute			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Renal impairment			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urinary tract pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 16 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Back pain			
subjects affected / exposed	3 / 16 (18.75%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Bone pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	4 / 16 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Muscular weakness			

subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 16 (18.75%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	3 / 16 (18.75%)	1 / 6 (16.67%)	
occurrences (all)	5	2	
Myositis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	5 / 16 (31.25%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Spinal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Trismus			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gingivitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Nail infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nasal herpes			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Onychomycosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Periorbital cellulitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Subcutaneous abscess			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Urinary tract infection			
subjects affected / exposed	3 / 16 (18.75%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 16 (50.00%)	6 / 6 (100.00%)	
occurrences (all)	9	6	
Dehydration			
subjects affected / exposed	4 / 16 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	8	2	
Glucose tolerance impaired			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gout			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			

subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	9 / 16 (56.25%)	4 / 6 (66.67%)	
occurrences (all)	18	12	
Hyperkalaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 6 (16.67%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolic acidosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	This amendment was to implement suggested changes from health authorities. The entry criteria were adjusted for patients with elevated blood glucose levels and for patients receiving prior platelet transfusions. Dose modification and DLT tables was amended for clarification. Storage conditions for both study treatments were included. Change was made to stagger the administration of concomitant medication affecting gastric pH relative to BYL719 administration.
11 January 2013	This amendment was to introduce local molecular pre-screening for patients whose status for PIK3CA mutation/amplification was not known. In addition, a central testing option at a Novartis designated laboratory was provided for molecular rescreening to patients with ovarian cancer enrolled in the Phase II part of the study. In addition, changes made to sampling and analyses of biomarkers were described as well.
30 May 2013	This amendment was to allow enrollment of patients who could not provide a fresh tumor biopsy at baseline into the study. Per the amendment, submission of an archival or a fresh tumor sample was acceptable. In addition, cells harvested from ascites or pleural effusions were accepted in lieu of fresh tumor samples.
26 August 2014	This amendment was released following the enrollment halt due to difficulty to enroll the patients and limited clinical activity. The protocol was amended to remove follow-up for progression and survival. Of note, there were no changes to the safety follow-up (including 30-day safety follow-up and follow-up for neutralizing antibodies).
17 December 2014	This amendment was released post recruitment halt in this study. This amendment was a consequence of an event of pneumonitis in another study with BYL719 requiring an urgent safety measure which was rolled out for all studies involving BYL719 to include guidelines for management of pneumonitis.
24 June 2016	This amendment was released after reaching the primary objective for Part Ib of the study and database lock for the primary data analysis. The purpose of the amendment was to reduce assessments for the three remaining patients while still ensuring appropriate safety monitoring. In particular, the visit evaluation schedule was modified, and no efficacy, pharmacokinetics, and biomarker assessments were collected. Only safety-related events were collected.

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 the competitive landscape for anticancer therapies in ovarian and breast cancer and given the limited clinical activity observed with the study combination treatment, Novartis decided in 2014 to halt the recruitment in the trial.

Notes: