EU Results Form

Trial Information

A. Trial Identification

Full title of the trial

BYLieve: A phase II, multicenter, open-label, three-cohort, non- comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with PIK3CA mutant, hormone receptor (HR) positive, HER2-negative advanced breast cancer (aBC), who have progressed on or after prior treatments

EudraCT Number

Sponsor Protocol Code	CBYL719X2402
ISRCTN Number	
ClinicalTrials.gov identifier (NCT Number)	NCT03056755
WHO Universal Trial Reference Number (UTRN)	

Other trial identifiers

Other identifier name	Other identifier code

B. Paediatric Regulatory Details

Is the trial part of an agreed Paediatric Investigation Plan (PIP)?	No
Paediatric Investigation Plan(s) **Enter the EMA paediatric Investigation plan number(s) (PIP) using the following format: EMEA-999999-PIP99-99, where 9 is a number (0-9 inclusive).**	EMA Decision number of Paediatric Investigation Plan(s)
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

C. Sponsor Details

Name	Scientific Contact	Public Contact
Organisation name: Novartis Pharma AG **Street Address:** Lichtstrasse 35 **Town/City:** Basel **Country:** Switzerland	**Functional contact name:** Clinical Disclosure Office **Organisation name:** Novartis Pharma AG **Country code:** 41 **Phone Number:** 613241111	**Functional contact name:** Clinical Disclosure Office **Organisation name:** Novartis Pharma AG **Country code:** 41 **Phone Number:** 613241111

Name	Scientific Contact	Public Contact
Post code: 4056	**Email address:** novartis.email@novartis.com	**Email address:** novartis.email@novartis.com

D. Results Analysis Stage

Analysis Stage	Final
Date of interim/Final Analysis	2024-11-12
Is this the analysis of the primary completion data?	No
Primary completion date	
Global end of trial date reached?	Yes
Global end of trial date	2024-11-12
Was the trial ended prematurely?	No

E. General Information About Trial

Main objective of Trial

The primary objective is to assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 in Cohort A (alpelisib in combination with fulvestrant) and Cohort B (alpelisib in combination letrozole) among patients with Hormone Receptor Positive (HR+), Human Epidermal Growth Factor Receptor 2 negative (HER2-) Advanced Breast Cancer (aBC) harboring a PIK3CA mutation whose disease had progressed on or after Cyclin-Dependent Kinases 4 and 6 (CDK 4/6) inhibitor combination with an aromatase inhibitor (AI) or fulvestrant.

The actual start date of recruitment must be the current date or a date in the past.

Actual Start date of Recruitment	2017-08-29
Long term follow up planned?	No
Long term follow up rationale	
Long term follow up duration	
Independent data monitoring committee (IDMC) involvement?	No

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 of comparator(s)

F. Population of Trial Subjects

Subject number per country

Country	Actual number of subjects enrolled
Argentina	19
Belgium	18
Canada	22
Chile	13
Denmark	5
France	52
Germany	17
India	6
Israel	13
Italy	32
Japan	1
Korea, Republic of	16
Mexico	3
Netherlands	6
Singapore	5
Taiwan	10
United Kingdom	9
United States	80
Spain	52
Total: worldwide	379
Total: EEA	182

Age group breakdown for Trial

Age Range	Actual number of subjects enrolled
In Utero	0
Pre-term newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	258
From 65 years	
Elderly (From 65-84 years)	121

Age Range	Actual number of subjects enrolled
Elderly 85 years and over	0
Total	379

Subject Disposition

Subject Disposition

Recruitment Details

This study was conducted in 92 centers across 19 countries

Pre-Assignment

Screening Details

Screening assessments occurred before 21 days of the start of treatment.

Pre-Assignment Period

Periods

Core Phase

Blinding Implementation Details:

Is this the baseline period? true

Mutually exclusive arms? true

Non-Mutual Exclusive Number of Subjects:

Allocation: Non-Randomised-Controlled

Blinding Used: Not-blind

Roles Blinded:

Started

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
127	126	126	379 *(calculated)*

Completed

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI)	Total *(=sum per row)*

will receive alpelisib + fulvestrant	will receive alpelisib + letrozole	as immediate prior treatment will receive alpelisib + fulvestrant.	
1	0	10	11 *(calculated)*

Reasons Not Completed

Adverse event, non-fatal

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
20	14	13	47 *(calculated)*

Physician Decision

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
7	13	5	25 *(calculated)*

Adverse event, serious fatal

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
3	2	4	9 *(calculated)*

Other Reason: Progressive disease

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
89	88	90	267 *(calculated)*

Other Reason: Subject/guardian decision

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI)	Total *(=sum per row)*

will receive alpelisib + fulvestrant	will receive alpelisib + letrozole	as immediate prior treatment will receive alpelisib + fulvestrant.	
5	8	4	17 *(calculated)*

Other Reason: Protocol deviation

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
1	1	0	2 *(calculated)*

Other Reason: Technical problems

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
1	0	0	1 *(calculated)*

Reasons Joined

Products

Arm	Product Name	Product Code	Product Other Name	Dosage and Administration Details	Pharmaceutical Forms	Routes of Administration
Cohort A: Pre-treated with CDK 4/6i + AI	Alpelisib		BYL719	300 mg of alpelisib film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort A: Pre-treated with CDK 4/6i + AI	Fulvestrant			500 mg of fulvestrant via intramuscular injection administered on Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter. Cycle=28 days	Concentrate for solution for injection, Solution for injection	Intramuscular use
Cohort A: Pre-treated with CDK 4/6i + AI	Goserelin			3.6 mg of goserelin via injectable subcutaneous implant administered every 28 days. Only for men in Cohort B and premenopausal women.	Implant	Subcutaneous use
Cohort A: Pre-treated with CDK 4/6i + AI	Leuprolide			7.5 mg of leuprolide via injectable intramuscular depot administered every 28 days. Only for men in cohort B and premenopausal women.	Solution for injection	Subcutaneous use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Letrozole			2.5 mg of letrozole film-coated tablets	Film-coated tablet	Oral use

Arm	Product Name	Product Code	Product Other Name	Dosage and Administration Details	Pharmaceutical Forms	Routes of Administration
				administered orally once daily		
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Alpelisib		BYL719	300 mg of alpelisib film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Goserelin			3.6 mg of goserelin via injectable subcutaneous implant administered every 28 days. Only for men in Cohort B and premenopausal women.	Implant	Subcutaneous use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Leuprolide			7.5 mg of leuprolide via injectable intramuscular depot administered every 28 days. Only for men in cohort B and premenopausal women.	Solution for injection	Subcutaneous use
Cohort C: Pre-treated with systemic chemotherapy or ET	Alpelisib		BYL719	300 mg of alpelisib film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort C: Pre-treated with systemic chemotherapy or ET	Fulvestrant			500 mg of fulvestrant via intramuscular injection administered on Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter. Cycle=28 days	Concentrate for solution for injection, Solution for injection	Intramuscular use
Cohort C: Pre-treated with systemic chemotherapy or ET	Goserelin			3.6 mg of goserelin via injectable subcutaneous implant administered every 28 days. Only for men in Cohort B and premenopausal women.	Implant	Subcutaneous use
Cohort C: Pre-treated with systemic chemotherapy or ET	Leuprolide			7.5 mg of leuprolide via injectable intramuscular depot administered every 28 days. Only for men in cohort B and premenopausal women.	Solution for injection	Subcutaneous use

Extension phase

Blinding Implementation Details:

Is this the baseline period? false

Mutually exclusive arms? false

Non-Mutual Exclusive Number of Subjects:

Allocation: Non-Randomised-Controlled

Blinding Used: Not-blind

Roles Blinded:

Started

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as	Total *(=sum per row)*

any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	
1	0	10	11 *(calculated)*

Completed

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
0	0	5	5 *(calculated)*

Reasons Not Completed

Adverse event, non-fatal

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
0	0	1	1 *(calculated)*

Physician Decision

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
1	0	3	4 *(calculated)*

Other Reason: Subject/guardian decision

Cohort A: Pre-treated with CDK 4/6i + AI (Experimental) Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	Cohort B: Pre-treated with CDK 4/6i + fulvestrant (Experimental) Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	Cohort C: Pre-treated with systemic chemotherapy or ET (Experimental) Participants who received systemic chemotherapy or endocrine therapy (ET) (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	Total *(=sum per row)*
0	0	1	1 *(calculated)*

Reasons Joined

Products

Arm	Product Name	Product Code	Product Other Name	Dosage and Administration Details	Pharmaceutical Forms	Routes of Administration
Cohort A: Pre-treated with CDK 4/6i + AI	Alpelisib		BYL719	300 mg of alpelisib film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort A: Pre-treated with CDK 4/6i + AI	Fulvestrant			500 mg of fulvestrant via intramuscular injection administered on Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter. Cycle=28 days	Concentrate for solution for injection, Solution for injection	Intramuscular use
Cohort A: Pre-treated with CDK 4/6i + AI	Goserelin			3.6 mg of goserelin via injectable subcutaneous implant administered every 28 days. Only for men in Cohort B and premenopausal women.	Implant	Subcutaneous use
Cohort A: Pre-treated with CDK 4/6i + AI	Leuprolide			7.5 mg of leuprolide via injectable intramuscular depot administered every 28 days. Only for men in cohort B and premenopausal women.	Solution for injection	Subcutaneous use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Letrozole			2.5 mg of letrozole film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Alpelisib		BYL719	300 mg of alpelisib film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Goserelin			3.6 mg of goserelin via injectable subcutaneous implant administered every 28 days. Only for men in Cohort B and premenopausal women.	Implant	Subcutaneous use
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Leuprolide			7.5 mg of leuprolide via injectable intramuscular depot administered every 28 days. Only for men in cohort B and premenopausal women.	Solution for injection	Subcutaneous use
Cohort C: Pre-treated with systemic chemotherapy or ET	Alpelisib		BYL719	300 mg of alpelisib film-coated tablets administered orally once daily	Film-coated tablet	Oral use
Cohort C: Pre-treated with systemic chemotherapy or ET	Fulvestrant			500 mg of fulvestrant via intramuscular injection administered on Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter. Cycle=28 days	Concentrate for solution for injection, Solution for injection	Intramuscular use

Arm	Product Name	Product Code	Product Other Name	Dosage and Administration Details	Pharmaceutical Forms	Routes of Administration
Cohort C: Pre-treated with systemic chemotherapy or ET	Goserelin			3.6 mg of goserelin via injectable subcutaneous implant administered every 28 days. Only for men in Cohort B and premenopausal women.	Implant	Subcutaneous use
Cohort C: Pre-treated with systemic chemotherapy or ET	Leuprolide			7.5 mg of leuprolide via injectable intramuscular depot administered every 28 days. Only for men in cohort B and premenopausal women.	Solution for injection	Subcutaneous use

Baseline Characteristics

Baseline Characteristics Information

The baseline Period is : Core Phase

How are baseline characteristics being reported?

Per Arm in the baseline period

Subject Analysis Sets

Subject Analysis Set Title	Number of subjects	Description	Type	Options
All Patients in Extension Phase	11	Patients with clinical benefit in Extension Phase	Sub-group analysis	

Reporting Groups

Reporting Group Title	Number of subjects	Description	Options
Cohort A: Pre-treated with CDK 4/6i + AI	127	Participants who received any CDK 4/6i plus AI as immediate prior treatment will receive alpelisib + fulvestrant	
Cohort B: Pre-treated with CDK 4/6i + fulvestrant	126	Patients who received any CDK 4/6i plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole	
Cohort C: Pre-treated with systemic chemotherapy or ET	126	Participants who received systemic chemotherapy or ET (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.	

Age Characteristics

Title: Age Categorical

Description:

Unit: Participants

Reporting Group Values	Cohort A: Pre-treated with CDK 4/6i + AI	Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Cohort C: Pre-treated with systemic chemotherapy or ET	Total
Overall number of baseline subjects	127	126	126	379 (calculated)
<=18 years	0	0	0	0
Between 18 and 65 years	95	80	83	258
>=65 years	32	46	43	121
Total	127 (calculated)	126 (calculated)	126 (calculated)	379 (calculated)

Age Categorical	All Patients in Extension Phase
Overall number of baseline subjects	11
<=18 years	
Between 18 and 65 years	
>=65 years	

Title: Age continuous

Description:

Unit:

Central Tendency Type:

Dispersion Type:

Reporting Group Values	Cohort A: Pre-treated with CDK 4/6i + AI		Cohort B: Pre-treated with CDK 4/6i + fulvestrant		Cohort C: Pre-treated with systemic chemotherapy or ET	
Unit of measure ()		Low () High ()		Low () High ()		Low () High ()

Age Continuous Values	All Patients in Extension Phase	
Unit of measure ()		Low () High ()

Gender Characteristics

Title: Sex: Female, Male

Description:

Unit: Participants

Reporting Group Values	Cohort A: Pre-treated with CDK 4/6i + AI	Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Cohort C: Pre-treated with systemic chemotherapy or ET	Total
Overall number of baseline subjects	127	126	126	379

Reporting Group Values	Cohort A: Pre-treated with CDK 4/6i + AI	Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Cohort C: Pre-treated with systemic chemotherapy or ET	Total
Female	127	126	125	378
Male	0	0	1	1

Gender Categorical Values	All Patients in Extension Phase
Overall number of baseline subjects	11
Female	
Male	

Study Categorical Characteristics

Title: Race/Ethnicity, Customized

Description:

Unit: Participants

Reporting Group Values	Cohort A: Pre-treated with CDK 4/6i + AI	Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Cohort C: Pre-treated with systemic chemotherapy or ET	Total
Overall number of baseline subjects	127	126	126	379 (calculated)
Caucasian	81	85	83	249
Unknown	23	24	11	58
Asian	12	8	28	48
Black	6	1	1	8
Other	3	7	3	13
Pacific islander	1	0	0	1
Missing	1	1	0	2

Study Categorical Values	
Race/Ethnicity, Customized	All Patients in Extension Phase
Overall number of baseline subjects	11
Caucasian	
Unknown	
Asian	
Black	
Other	
Pacific islander	
Missing	

Study Continuous Characteristics

End Points

Reporting Groups

Periods	Arms
Core Phase	Cohort A: Pre-treated with CDK 4/6i + AI
	Cohort B: Pre-treated with CDK 4/6i + fulvestrant
	Cohort C: Pre-treated with systemic chemotherapy or ET
Extension phase	Cohort A: Pre-treated with CDK 4/6i + AI
	Cohort B: Pre-treated with CDK 4/6i + fulvestrant
	Cohort C: Pre-treated with systemic chemotherapy or ET

Subject Analysis Set Title	Number of subjects	Description	Type	Options
All Patients in Extension Phase	11	Patients with clinical benefit in Extension Phase	Sub-group analysis	

End Points

Primary: Core Phase: Percentage of participants who were alive without disease progression at 6 months

Countable or measurable? Measurable

Description: Percentage of participants who were alive without disease progression at 6-month follow-up based on local investigator assessment per RECIST v1.1 in Cohort A, Cohort B and Cohort C. Participants who progressed, died, or discontinued study before 6 months were counted as a failure.

Time Frame: At 6 months

Measure Type: Number

Precision/Dispersion Type: Confidence Interval

Units: Percentage of participants

Percentage: 95

Arm Reporting Groups			
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI	Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET
Number of subjects that started the Arm:	127	126	126
Number of Subjects Analyzed:	119	114	115
Comment: (The comment is mandatory when the number of subjects analysed is zero)			

	Number	Confidence Interval (95%)	Number	Confidence Interval (95%)	Number	Confidence Interval (95%)
	53.8	44.41 to 62.96	46.5	37.10 to 56.07	53.0	43.51 to 62.41

Secondary: Core Phase: Progression free survival (PFS)

Countable or measurable? Measurable

Description: PFS is defined as the time from the date of first dose of study medication to the date of the first documented progression or death due to any cause occurring in the study. PFS was assessed based on local investigator's assessment according to RECIST v1.1. PFS was censored if no PFS event was observed before the cut-off date. The censoring date was the date of last adequate tumor assessment before the cut-off date. If a PFS event was observed after two or more missing or non-adequate tumor assessments, then PFS was censored at the last adequate tumor assessment. PFS was estimated using the Kaplan-Meier method.

Time Frame: From date of first dose to date of first documented progression or death, up to 46 months

Measure Type: Median

Precision/Dispersion Type: Confidence Interval

Units: Months

Percentage: 95

Arm Reporting Groups						
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI		Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant		Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET	
Number of subjects that started the Arm:	127		126		126	
Number of Subjects Analyzed:	119		114		115	
Comment: (The comment is mandatory when the number of subjects analysed is zero)						
	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)
	8.0	5.6 to 8.6	5.6	3.7 to 7.1	5.6	5.4 to 8.1

Secondary: Core Phase: Progression free survival on next line treatment (PFS2)

Countable or measurable? Measurable

Description: PFS2 is defined as time from the date of first dose of study medication to the date of first documented progression on next-line therapy or death from any cause. The first documented progression on next-line treatment is based on investigator assessment of progressive disease. PFS2 was estimated using the Kaplan-Meier method.

Time Frame: From date of first dose to date of first documented progression on next-line therapy or death, up to approximately 55 months

Measure Type: Median

Precision/Dispersion Type: Confidence Interval

Units: Months

Percentage: 95

Arm Reporting Groups						
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI		Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant		Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET	
Number of subjects that started the Arm:	127		126		126	
Number of Subjects Analyzed:	119		114		115	
Comment: (The comment is mandatory when the number of subjects analysed is zero)						
	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)
	15.2	11.4 to 21.7	13.0	10.2 to 13.9	13.5	11.5 to 17.3

Secondary: Core Phase: Overall response rate (ORR)

Countable or measurable? Measurable

Description: ORR is defined as the percentage of participants with best overall response (BOR) of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST v1.1 in each cohort. CR: Disappearance of all non-nodal target lesions and all non-target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm and all lymph nodes assigned as non-target lesions must be non-pathological in size (<10 mm short axis) PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

Time Frame: Up to 46 months

Measure Type: Number

Precision/Dispersion Type: Confidence Interval

Units: Percentage of participants

Percentage: 95

Arm Reporting Groups			
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI	Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET
Number of subjects that started the Arm:	127	126	126
Number of Subjects Analyzed:	119	114	115
Comment: (The comment is mandatory when the number of			

subjects analysed is zero)						
	Number	Confidence Interval (95%)	Number	Confidence Interval (95%)	Number	Confidence Interval (95%)
	19.3	12.7 to 27.6	17.5	11.1 to 25.8	25.2	17.6 to 34.2

Secondary: Core Phase: Clinical benefit rate (CBR)

Countable or measurable? Measurable

Description: CBR is defined as the percentage of participants with a BOR of CR or PR or an overall lesion response of stable disease (SD) or Non-CR/ Non-PD lasting ≥ 24 weeks based on local investigator's assessment according to RECIST v1.1. CR: Disappearance of all non-nodal target lesions and all non-target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm and all lymph nodes assigned as non-target lesions must be non-pathological in size (<10 mm short axis) PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease.

Time Frame: Up to 46 months

Measure Type: Number

Precision/Dispersion Type: Confidence Interval

Units: Percentage of participants

Percentage: 95

Arm Reporting Groups						
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI		Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant		Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET	
Number of subjects that started the Arm:	127		126		126	
Number of Subjects Analyzed:	119		114		115	
Comment: (The comment is mandatory when the number of subjects analysed is zero)						
	Number	Confidence Interval (95%)	Number	Confidence Interval (95%)	Number	Confidence Interval (95%)
	46.2	37.0 to 55.6	35.1	26.4 to 44.6	38.3	29.4 to 47.8

Secondary: Core Phase: Duration of response (DOR)

Countable or measurable? Measurable

Description: DOR is the time from the date of first documented response (confirmed CR or PR based on local investigator's assessment according to RECIST v1.1) to the date of first documented progression or death due to underlying cancer. Subjects continuing without progression or death due to underlying cancer were censored at the date of their last adequate tumor assessment. DOR was estimated using the Kaplan-Meier method.

Time Frame: From date of first documented response to first documented progression or death, up to 33.3 months

Measure Type: Median

Precision/Dispersion Type: Confidence Interval

Units: Months

Percentage: 95

Arm Reporting Groups						
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI		Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant		Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET	
Number of subjects that started the Arm:	127		126		126	
Number of Subjects Analyzed:	23		20		29	
Comment: (The comment is mandatory when the number of subjects analysed is zero)						
	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)
	13.8	5.5 to 19.4	6.5	5.4 to 9.4	16.5	8.3 to 22.2

Secondary: Core Phase: Overall Survival (OS)

Countable or measurable? Measurable

Description: OS is defined as the time of start of treatment to date of death or lost to follow-up. If a subject was not known to have died, then the OS data was censored at the date of the last known alive status for the patient.

Time Frame: From date of first dose and up to approximately 55 months

Measure Type: Median

Precision/Dispersion Type: Confidence Interval

Units: Months

Percentage: 95

Arm Reporting Groups			
	Core Phase Cohort A: Pre-treated with CDK 4/6i + AI	Core Phase Cohort B: Pre-treated with CDK 4/6i + fulvestrant	Core Phase Cohort C: Pre-treated with systemic chemotherapy or ET
Number of subjects that started the Arm:	127	126	126
Number of Subjects Analyzed:	119	114	115
Comment: (The comment is mandatory when the number of			

subjects analysed is zero)						
	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)	Median	Confidence Interval (95%)
	27.3	21.3 to 32.7	29.0	24.5 to 34.8	20.7	16.9 to 28.1

Secondary: Extension Phase: Percentage of participants with clinical benefit as assessed by the Investigator during the Extension Phase

Countable or measurable? Countable

Description: Clinical Benefit Rate, as assessed by the Investigator during the Extension Phase, was defined as the proportion of patients with a best overall response of Complete Response (CR) or Partial Response (PR), or an overall lesion response of Stable Disease (SD) or non-complete response/non-progressive disease that lasted at least 24 weeks, based on the local investigator's assessment according to Response Evaluation Criteria in Solid Tumors version 1.1.

Time Frame: Day 1 of each extension cycle up to Cycle 29 (each cycle lasting 28 days); median duration of exposure to study treatment (alpelisib or fulvestrant) = 41 months

Units: Participants

Percentage:

Arm Reporting Groups
Number of subjects that started the Arm:
Number of Subjects Analyzed:
Comment: (The comment is mandatory when the number of subjects analysed is zero)
Extension Cycle 1 Day 1
Extension Cycle 2 Day 1
Extension Cycle 3 Day 1
Extension Cycle 4 Day 1
Extension Cycle 5 Day 1
Extension Cycle 6 Day 1
Extension Cycle 7 Day 1
Extension Cycle 8 Day 1
Extension Cycle 9 Day 1
Extension Cycle 10 Day 1
Extension Cycle 11 Day 1
Extension Cycle 12 Day 1
Extension Cycle 13 Day 1
Extension Cycle 14 Day 1
Extension Cycle 15 Day 1
Extension Cycle 16 Day 1
Extension Cycle 17 Day 1
Extension Cycle 18 Day 1
Extension Cycle 19 Day 1

Extension Cycle 20 Day 1
Extension Cycle 21 Day 1
Extension Cycle 22 Day 1
Extension Cycle 23 Day 1
Extension Cycle 24 Day 1
Extension Cycle 25 Day 1
Extension Cycle 26 Day 1
Extension Cycle 27 Day 1
Extension Cycle 28 Day 1
Extension Cycle 29 Day 1

Subject Analysis Sets	
	All Patients in Extension Phase
Number of subjects in the subject analysis set:	11
Number of Subjects Analyzed:	11
Comment: (The comment is mandatory when the number of subjects analysed is zero)	
	Countable
Extension Cycle 1 Day 1	8
Extension Cycle 2 Day 1	7
Extension Cycle 3 Day 1	7
Extension Cycle 4 Day 1	6
Extension Cycle 5 Day 1	8
Extension Cycle 6 Day 1	7
Extension Cycle 7 Day 1	7
Extension Cycle 8 Day 1	6
Extension Cycle 9 Day 1	7
Extension Cycle 10 Day 1	5
Extension Cycle 11 Day 1	4
Extension Cycle 12 Day 1	7
Extension Cycle 13 Day 1	4
Extension Cycle 14 Day 1	5
Extension Cycle 15 Day 1	4
Extension Cycle 16 Day 1	3
Extension Cycle 17 Day 1	3
Extension Cycle 18 Day 1	3
Extension Cycle 19 Day 1	3
Extension Cycle 20 Day 1	3
Extension Cycle 21 Day 1	3
Extension Cycle 22 Day 1	3

Extension Cycle 23 Day 1	3
Extension Cycle 24 Day 1	2
Extension Cycle 25 Day 1	2
Extension Cycle 26 Day 1	2
Extension Cycle 27 Day 1	2
Extension Cycle 28 Day 1	2
Extension Cycle 29 Day 1	1

Adverse Events

Adverse Events

Adverse Events Information

Timeframe for adverse event reporting

Adverse Events (AEs) were collected from first dose of study medication until end of post-treatment follow-up (efficacy or survival) (end of study), assessed up to approximately 86 months.

Adverse events reporting additional description

Core phase (up to 19 months post last subject's first treatment (LSFT)) and Extension phase (thereafter) are reported separately. No patient from Cohort B entered Extension Phase.

Assessment Type	Systematic
Frequency threshold for reporting non-serious adverse events:	5
Dictionary name	MedDRA
Dictionary name - if other	
Dictionary version	27.1

Adverse Events Reporting Groups

Reporting Group Totals	**CORE PHASE@Cohort A** CORE PHASE@Cohort A	**CORE PHASE@Cohort B** CORE PHASE@Cohort B	**CORE PHASE@Cohort C** CORE PHASE@Cohort C	**EXTENSION PHASE@Cohort A** EXTENSION PHASE@Cohort A
Total # Subjects Exposed	127	126	126	1
Total # Subjects Affected by Serious Adverse Events	37	48	38	0
Total # Subjects Affected by Non Serious Adverse Events	126	126	124	1

Reporting Group Totals	**CORE PHASE@Cohort A** CORE PHASE@Cohort A	**CORE PHASE@Cohort B** CORE PHASE@Cohort B	**CORE PHASE@Cohort C** CORE PHASE@Cohort C	**EXTENSION PHASE@Cohort A** EXTENSION PHASE@Cohort A
Total # of Deaths (all causes)	78	76	67	0
Total # of Deaths Resulting From Adverse Events	0	0	1	0

Reporting Group Totals	**EXTENSION PHASE@Cohort C** EXTENSION PHASE@Cohort C
Total # Subjects Exposed	10
Total # Subjects Affected by Serious Adverse Events	3
Total # Subjects Affected by Non Serious Adverse Events	10
Total # of Deaths (all causes)	1
Total # of Deaths Resulting From Adverse Events	0

Serious Adverse Events

Reporting Groups:	**CORE PHASE@Cohort A**	**CORE PHASE@Cohort B**	**CORE PHASE@Cohort C**	**EXTENSION PHASE@Cohort A**	**EXTENSION PHASE@Cohort C**
Blood and lymphatic system disorders					
Anaemia *Systematic*					
# of subjects affected	1	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	1	0	0
# of occurrences causally related to treatment	0	1	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0
Febrile neutropenia *Systematic*					
# of subjects affected	1	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0

# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Cardiac disorders					
Acute myocardial infarction *Systematic*					
# of subjects affected	1	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	1	0	0
# of occurrences causally related to treatment	0	0	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pericardial effusion *Systematic*					
# of subjects affected	1	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Supraventricular tachycardia *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Eye disorders					
Vision blurred *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0

# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Gastrointestinal disorders					
Abdominal pain *Systematic*					
# of subjects affected	2	4	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	4	0	0	0
# of occurrences causally related to treatment	0	2	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Ascites *Systematic*					
# of subjects affected	0	1	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	2	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Colitis *Systematic*					
# of subjects affected	1	2	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	2	0	0	0
# of occurrences causally related to treatment	1	2	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Colitis ulcerative *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	2
# of occurrences causally related to treatment	0	0	0	0	1
# of fatalities	0	0	0	0	0

# of fatalities causally related to treatment	0	0	0	0	0

Diarrhoea *Systematic*					
# of subjects affected	1	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	0
# of occurrences causally related to treatment	1	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Duodenal obstruction *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Dysphagia *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Enteritis *Systematic*					
# of subjects affected	0	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	0
# of occurrences causally related to treatment	0	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Enterocolitis
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Erosive oesophagitis
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Haematemesis
Systematic

# of subjects affected	2	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Intestinal perforation
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Mesenteric artery thrombosis
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Nausea *Systematic*					
# of subjects affected	0	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	0
# of occurrences causally related to treatment	0	1	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Subileus *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Vomiting *Systematic*					
# of subjects affected	0	2	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	2	0	0
# of occurrences causally related to treatment	0	1	2	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

General disorders and administration site conditions					
Asthenia *Systematic*					
# of subjects affected	1	1	0	0	0

# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	0
# of occurrences causally related to treatment	1	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Fatigue *Systematic*					
# of subjects affected	0	2	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

General physical health deterioration *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	2	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Influenza like illness *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Performance status decreased *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0

# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pyrexia *Systematic*					
# of subjects affected	1	2	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	2	2	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Sudden death *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	1	0	0
# of fatalities	0	0	1	0	0
# of fatalities causally related to treatment	0	0	1	0	0

Hepatobiliary disorders					
Biliary obstruction *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hepatic failure *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0

# of fatalities	0	0	1	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Immune system disorders					
Anaphylactic reaction *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hypersensitivity *Systematic*					
# of subjects affected	0	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	0
# of occurrences causally related to treatment	0	1	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Infections and infestations					
Bacterial infection *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

COVID-19 *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0

# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Device related infection *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Escherichia urinary tract infection *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Meningitis *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pharyngitis *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pneumonia
Systematic

# of subjects affected	1	4	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	4	2	0	0
# of occurrences causally related to treatment	1	1	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pyelonephritis
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pyelonephritis acute
Systematic

# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	5	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Sepsis
Systematic

# of subjects affected	0	2	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	2	0	0
# of occurrences causally related to treatment	0	1	0	0	0
# of fatalities	0	0	1	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Septic shock
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	1	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Urinary tract infection *Systematic*					
# of subjects affected	0	0	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	3	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Wound infection *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Injury, poisoning and procedural complications					
Ankle fracture *Systematic*					
# of subjects affected	0	1	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	1
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hip fracture *Systematic*					
# of subjects affected	0	1	0	0	0

# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Procedural pneumothorax *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Thoracic vertebral fracture *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Toxicity to various agents *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Investigations					
Alanine aminotransferase increased *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10

# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Aspartate aminotransferase increased
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Blood alkaline phosphatase increased
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Blood bilirubin increased
Systematic

# of subjects affected	0	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Blood creatine phosphokinase increased
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0

# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Laboratory test abnormal *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Liver function test abnormal *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Metabolism and nutrition disorders					
Dehydration *Systematic*					
# of subjects affected	1	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	1	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hypercalcaemia *Systematic*					
# of subjects affected	0	2	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	2	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0

# of fatalities causally related to treatment	0	0	0	0	0

Hyperglycaemia *Systematic*					
# of subjects affected	7	3	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	7	4	2	0	0
# of occurrences causally related to treatment	7	4	2	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hypokalaemia *Systematic*					
# of subjects affected	0	0	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	2	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hyponatraemia *Systematic*					
# of subjects affected	1	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	0
# of occurrences causally related to treatment	1	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Musculoskeletal and connective tissue disorders					
Arthralgia *Systematic*					
# of subjects affected	1	3	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	3	1	0	0
# of occurrences causally related to treatment	0	1	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Back pain
Systematic

# of subjects affected	0	0	3	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	4	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Musculoskeletal chest pain
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Myalgia
Systematic

# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Osteonecrosis of jaw
Systematic

# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Spinal pain
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Angiosarcoma
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Cancer pain
Systematic

# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Malignant pleural effusion
Systematic

# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Small cell lung cancer
Systematic

# of subjects affected	0	1	0	0	0

# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Tumour associated fever *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Nervous system disorders					
Cerebral ischaemia *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	1	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Cerebrovascular accident *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Migraine with aura *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10

# of occurrences (all)	0	0	1	0	1
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Monoparesis *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Psychiatric disorders					
Confusional state *Systematic*					
# of subjects affected	0	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Psychotic disorder *Systematic*					
# of subjects affected	1	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Suicidal ideation *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0

# of occurrences causally related to treatment	0	0	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Renal and urinary disorders					
Acute kidney injury *Systematic*					
# of subjects affected	0	3	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	3	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hydronephrosis *Systematic*					
# of subjects affected	0	1	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Nephrolithiasis *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Urinary retention *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0

# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Urinary tract obstruction *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Respiratory, thoracic and mediastinal disorders					
Acute respiratory failure *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	1	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Atelectasis *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Dyspnoea *Systematic*					
# of subjects affected	3	2	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	2	2	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0

# of fatalities causally related to treatment	0	0	0	0	0

Haemothorax *Systematic*					
# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Hypoxia *Systematic*					
# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pleural effusion *Systematic*					
# of subjects affected	3	2	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	2	2	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pneumonitis *Systematic*					
# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pneumothorax
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Pulmonary embolism
Systematic

# of subjects affected	0	0	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	1	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Respiratory failure
Systematic

# of subjects affected	0	2	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Skin and subcutaneous tissue disorders

Drug reaction with eosinophilia and systemic symptoms
Systematic

# of subjects affected	1	0	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	0
# of occurrences causally related to treatment	1	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Rash
Systematic

# of subjects affected	1	1	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	2	2	0	0
# of occurrences causally related to treatment	1	2	2	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Rash maculo-papular
Systematic

# of subjects affected	3	2	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	2	1	0	0
# of occurrences causally related to treatment	3	2	1	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Skin ulcer
Systematic

# of subjects affected	0	2	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Vascular disorders

Deep vein thrombosis
Systematic

# of subjects affected	0	1	0	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	0	0	0
# of occurrences causally related to treatment	0	0	0	0	0
# of fatalities	0	0	0	0	0
# of fatalities causally related to treatment	0	0	0	0	0

Non Serious Adverse Events

Threshold for non-serious adverse event reporting is: **5%**

Reporting Groups:	CORE PHASE@Cohort A	CORE PHASE@Cohort B	CORE PHASE@Cohort C	EXTENSION PHASE@Cohort A	EXTENSION PHASE@Cohort C
Blood and lymphatic system disorders					
Anaemia *Systematic*					
# of subjects affected	11	9	9	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	17	10	10	0	0
Neutropenia *Systematic*					
# of subjects affected	5	3	7	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	10	4	8	0	0
Cardiac disorders					
Angina pectoris *Systematic*					
# of subjects affected	1	0	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	2	0	1
Atrial fibrillation *Systematic*					
# of subjects affected	0	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	1
Pericardial effusion *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1
Tachycardia *Systematic*					
# of subjects affected	2	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	1	1	0	1
Ear and labyrinth disorders					
Cerumen impaction *Systematic*					

# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Eye disorders					
Dry eye *Systematic*					
# of subjects affected	7	6	5	1	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	9	8	6	1	1

Eye oedema *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Eye pruritus *Systematic*					
# of subjects affected	0	1	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	3	0	1

Eye swelling *Systematic*					
# of subjects affected	0	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	0	0	1

Lacrimation increased *Systematic*					
# of subjects affected	1	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	1	0	3

Vision blurred *Systematic*					
# of subjects affected	10	4	6	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	11	4	6	0	0

Gastrointestinal disorders

Abdominal distension *Systematic*					
# of subjects affected	3	3	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	3	3	0	1

Abdominal pain *Systematic*					
# of subjects affected	17	21	10	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	22	27	17	0	2

Abdominal pain upper *Systematic*					
# of subjects affected	16	17	6	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	22	18	7	0	2

Anal fissure *Systematic*					
# of subjects affected	0	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	1

Anal incontinence *Systematic*					
# of subjects affected	0	1	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	2	0	1

Anal inflammation *Systematic*					
# of subjects affected	0	1	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	2	0	1

Colitis ulcerative *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	5	0	6

Constipation *Systematic*					
# of subjects affected	12	16	15	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	12	18	15	0	1

Diarrhoea *Systematic*					
# of subjects affected	82	86	68	1	7
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	155	151	103	6	12

Dry mouth *Systematic*					
# of subjects affected	11	10	11	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	11	11	12	0	0

Dyspepsia *Systematic*					
# of subjects affected	19	13	13	1	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	21	16	14	1	3

Eructation *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Faeces soft *Systematic*					
# of subjects affected	1	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	5	1	0	1

Flatulence *Systematic*					
# of subjects affected	1	3	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	3	3	0	2

Gastrointestinal oedema *Systematic*					
# of subjects affected	0	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	0	0	1

Gastrointestinal pain *Systematic*					
# of subjects affected	2	0	0	1	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	0	0	1	0

Gingival pain *Systematic*					
# of subjects affected	0	1	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	2	0	1

Glossodynia *Systematic*					
# of subjects affected	1	0	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	4	0	1

Hyperchlorhydria *Systematic*					
# of subjects affected	1	0	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	3	0	1

Lip dry *Systematic*					
# of subjects affected	1	0	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	2	0	1

Mouth ulceration *Systematic*					
# of subjects affected	2	1	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	1	3	0	1

Mucous stools *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Nausea *Systematic*					
# of subjects affected	59	68	51	1	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	66	101	67	2	6

Oral pain *Systematic*					
# of subjects affected	2	0	4	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	0	6	0	3

Periodontal disease *Systematic*					
# of subjects affected	1	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	1

Proctalgia *Systematic*					
# of subjects affected	1	0	2	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	2	0	2

Stomatitis *Systematic*					
# of subjects affected	34	43	38	1	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	52	52	49	1	4

Vomiting *Systematic*					
# of subjects affected	31	31	31	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	45	43	47	0	4

General disorders and administration site conditions

Asthenia *Systematic*					
# of subjects affected	24	27	15	1	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	27	34	19	3	2

Chest pain *Systematic*					
# of subjects affected	1	1	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	1

Facial pain *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Fatigue *Systematic*					
# of subjects affected	39	38	44	0	5
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	42	42	60	0	5

Influenza like illness *Systematic*					
# of subjects affected	5	2	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	2	2	0	1

Non-cardiac chest pain *Systematic*					
# of subjects affected	5	6	5	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	6	5	0	2

Oedema peripheral *Systematic*					
# of subjects affected	10	12	8	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	12	15	11	0	1

Pain *Systematic*					
# of subjects affected	5	3	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	4	3	0	1

Pyrexia *Systematic*					
# of subjects affected	17	19	19	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	23	28	29	0	1

Thirst *Systematic*					
# of subjects affected	2	2	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	2	3	0	1

Xerosis *Systematic*					
# of subjects affected	2	2	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	2	0	0	1

Immune system disorders					
Food allergy *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Hypersensitivity *Systematic*					
# of subjects affected	1	4	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	4	0	0	2

Seasonal allergy *Systematic*					
# of subjects affected	0	2	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	1	0	1

Infections and infestations					
Bronchitis *Systematic*					
# of subjects affected	1	2	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	2	1	0	1
Conjunctivitis *Systematic*					
# of subjects affected	1	2	7	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	2	9	0	4
COVID-19 *Systematic*					
# of subjects affected	3	1	5	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	1	6	0	3
Cystitis *Systematic*					
# of subjects affected	4	3	4	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	3	10	0	8
Erysipelas *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1
Herpes zoster *Systematic*					
# of subjects affected	0	3	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	3	2	0	1
Influenza *Systematic*					
# of subjects affected	2	3	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	3	1	0	1

Mastitis *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Nasal herpes *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Nasopharyngitis *Systematic*					
# of subjects affected	9	4	3	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	10	4	4	0	5

Pneumonia *Systematic*					
# of subjects affected	2	3	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	3	2	0	1

Rhinitis *Systematic*					
# of subjects affected	2	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	1	1	0	1

Upper respiratory tract infection *Systematic*					
# of subjects affected	5	8	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	6	8	2	0	1

Urinary tract infection *Systematic*					
# of subjects affected	14	11	15	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	17	13	21	0	9

Injury, poisoning and procedural complications

Contusion
Systematic

# of subjects affected	3	3	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	4	2	0	1

Infusion related reaction
Systematic

# of subjects affected	0	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	0	0	1

Skin graft failure
Systematic

# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Sunburn
Systematic

# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Investigations

Alanine aminotransferase increased
Systematic

# of subjects affected	13	13	18	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	16	15	19	0	3

Aspartate aminotransferase increased
Systematic

# of subjects affected	17	11	15	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	21	12	15	0	0

Blood alkaline phosphatase increased
Systematic

# of subjects affected	5	7	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	8	3	0	1

Blood calcium increased *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Blood cholesterol increased *Systematic*					
# of subjects affected	1	1	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	3	0	4

Blood creatine increased *Systematic*					
# of subjects affected	0	0	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	2	0	1

Blood creatine phosphokinase increased *Systematic*					
# of subjects affected	4	2	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	8	2	3	0	1

Blood creatinine increased *Systematic*					
# of subjects affected	15	12	8	1	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	19	17	10	1	2

Blood glucose increased *Systematic*					
# of subjects affected	2	1	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	1	4	0	2

Blood thyroid stimulating hormone increased *Systematic*					
# of subjects affected	1	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	0	0	1

Blood triglycerides increased *Systematic*					
# of subjects affected	1	0	2	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	2	0	2

Eosinophil count increased *Systematic*					
# of subjects affected	0	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	1

Gamma-glutamyltransferase increased *Systematic*					
# of subjects affected	7	7	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	7	7	2	0	0

Glycosylated haemoglobin increased *Systematic*					
# of subjects affected	3	8	2	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	10	2	0	0

Lymphocyte count decreased *Systematic*					
# of subjects affected	4	2	4	1	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	7	2	4	3	0

Weight decreased *Systematic*					
# of subjects affected	18	19	23	1	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	19	19	24	1	2

Metabolism and nutrition disorders					
Decreased appetite *Systematic*					
# of subjects affected	37	56	42	0	4
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	41	70	50	0	4

Hyperglycaemia *Systematic*					
# of subjects affected	76	81	85	1	6
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	140	125	141	3	14

Hypocalcaemia *Systematic*					
# of subjects affected	2	1	5	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	1	5	0	1

Hypoglycaemia *Systematic*					
# of subjects affected	1	1	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	1

Hypokalaemia *Systematic*					
# of subjects affected	10	12	8	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	17	14	10	0	1

Hyponatraemia *Systematic*					
# of subjects affected	9	3	1	0	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	13	3	1	0	0

Polydipsia *Systematic*					
# of subjects affected	4	3	5	1	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	3	5	2	0

Musculoskeletal and connective tissue disorders					
Arthralgia *Systematic*					
# of subjects affected	19	21	14	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	24	25	16	0	4

Back pain *Systematic*					
# of subjects affected	10	14	12	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	13	16	13	0	2

Bone pain *Systematic*					
# of subjects affected	6	5	8	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	6	5	8	0	1

Joint stiffness *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Muscle spasms *Systematic*					
# of subjects affected	14	15	14	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	14	18	32	0	22

Musculoskeletal chest pain *Systematic*					
# of subjects affected	8	3	6	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	8	4	6	0	1

Myalgia *Systematic*					
# of subjects affected	10	6	5	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	13	6	7	0	2

Neck pain *Systematic*					
# of subjects affected	2	1	4	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	1	5	0	2

Pain in extremity *Systematic*					
# of subjects affected	5	7	7	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	7	7	0	1

Plantar fasciitis *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Nervous system disorders					
Balance disorder *Systematic*					
# of subjects affected	0	0	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	3	0	1

Dizziness *Systematic*					
# of subjects affected	8	9	7	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	9	10	10	0	2

Dysgeusia *Systematic*					
# of subjects affected	18	21	8	1	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	19	22	9	1	1

Headache *Systematic*					
# of subjects affected	28	25	21	0	4
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	34	41	32	0	17

Lethargy *Systematic*					
# of subjects affected	1	1	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	3	0	1

Memory impairment *Systematic*					
# of subjects affected	0	1	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	3	0	1

Muscle spasticity *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Psychiatric disorders					
Depressed mood *Systematic*					
# of subjects affected	0	2	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	2	1	0	1

Depression *Systematic*					
# of subjects affected	6	3	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	6	3	1	0	1

Insomnia *Systematic*					
# of subjects affected	6	3	9	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	6	4	11	0	1

Renal and urinary disorders					
Pollakiuria *Systematic*					
# of subjects affected	2	4	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	4	2	0	1

Urinary incontinence *Systematic*					
# of subjects affected	2	0	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	0	2	0	1

Reproductive system and breast disorders					
Dyspareunia *Systematic*					
# of subjects affected	1	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	1	0	1

Vulvovaginal dryness *Systematic*					
# of subjects affected	2	1	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	1	2	0	1

Respiratory, thoracic and mediastinal disorders					
Cough *Systematic*					
# of subjects affected	14	9	13	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	14	9	16	0	7

Dyspnoea *Systematic*					
# of subjects affected	19	14	7	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	19	14	8	0	2

Dyspnoea exertional *Systematic*					
# of subjects affected	2	2	5	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	2	5	0	1

Lung opacity *Systematic*					
# of subjects affected	0	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	0	0	1

Oropharyngeal pain *Systematic*					
# of subjects affected	6	5	7	0	2
# of subjects exposed	127	126	126	1	10

# of occurrences (all)	6	5	11	0	4

Pleural effusion *Systematic*					
# of subjects affected	1	1	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	0	0	2

Pneumonitis *Systematic*					
# of subjects affected	1	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	0	1	0	1

Rhinalgia *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Skin and subcutaneous tissue disorders					
Alopecia *Systematic*					
# of subjects affected	17	20	19	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	18	21	27	0	4

Dermal cyst *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Dermatitis *Systematic*					
# of subjects affected	0	0	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	2	0	1

Dermatitis acneiform *Systematic*					
# of subjects affected	1	1	2	0	1
# of subjects exposed	127	126	126	1	10

# of occurrences (all)	1	1	2	0	1

Dermatitis bullous *Systematic*					
# of subjects affected	0	0	0	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	0	0	1

Dry skin *Systematic*					
# of subjects affected	22	24	16	1	4
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	26	26	20	2	5

Erythema *Systematic*					
# of subjects affected	9	7	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	9	7	1	0	1

Erythema nodosum *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	2	0	2

Nail disorder *Systematic*					
# of subjects affected	1	1	5	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	1	5	0	2

Nail toxicity *Systematic*					
# of subjects affected	0	1	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	1	1	0	2

Palmar-plantar erythrodysaesthesia syndrome *Systematic*					
# of subjects affected	8	1	3	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	9	1	3	0	1

Pruritus
Systematic

# of subjects affected	20	13	29	0	3
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	31	18	37	0	4

Rash
Systematic

# of subjects affected	39	39	51	1	4
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	55	44	75	1	11

Rash maculo-papular
Systematic

# of subjects affected	16	20	9	1	0
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	26	31	11	1	0

Skin fragility
Systematic

# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Skin toxicity
Systematic

# of subjects affected	1	2	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	1	3	1	0	1

Skin ulcer
Systematic

# of subjects affected	3	2	2	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	3	2	2	0	1

Urticaria
Systematic

# of subjects affected	5	1	5	0	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	5	1	5	0	2

Vascular disorders

Capillary fragility *Systematic*					
# of subjects affected	0	0	1	0	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	0	0	1	0	1

Hypertension *Systematic*					
# of subjects affected	9	11	8	1	2
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	12	15	8	1	2

Lymphoedema *Systematic*					
# of subjects affected	2	2	3	1	1
# of subjects exposed	127	126	126	1	10
# of occurrences (all)	2	2	3	1	1

More Information

More Information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Amendment Date	Description
30-Jan-2018	Amendment 1: 1) Guidance for the management of skin and subcutaneous reactions was updated to include further detailed dose modification and follow-up management guidelines in case of severe cutaneous reactions. 2) Allowed for premenopausal women to be included in the study as long as they were receiving concomitant ovarian suppression with LHRH agonist. 3) Planned an interim analysis after at least 20 subjects receiving alpelisib + fulvestrant (Cohort A) had at least 6 months of follow-up
02-May-2018	Amendment 2: Clarified the use of goserelin or leuprolide (LHRH agonists) as study treatment for premenopausal women (as applicable) and men (Cohort B)
30-Jan-2019	Amendment 3: 1) Added a new cohort (Cohort C). 2) Increased the total number of subjects to approximately 340 for this study. 3) Added a second interim analysis to report preliminary efficacy (overall response rate (ORR) and clinical benefit rate (CBR)) and key safety data.
31-Oct-2019	Amendment 4: 1) Allowed analyses of the primary endpoint for each cohort independent of the other cohorts. Following this update, the primary analysis for each cohort was planned to be performed 6 months after the start of treatment by the last subject. 2) Inclusion/exclusion criteria were updated: (a) Prior therapy for Cohort C was clarified (inclusion criterion). (b) Updated total serum bilirubin criteria for inclusion. (c) Revision/correction of previous exclusion criteria + 1 new exclusion criteria: “subjects with unresolved osteonecrosis of the jaw” based on observations within SOLAR-1 data”. 3) Updated permitted concomitant medications to be used with caution, prohibited medications and the use of bisphosphonates/denosumab. 4) Updated guidance of dose interruption/modifications, management of AEs associated with the use of alpelisib, and guidance for follow-up on toxicities.
14-Jan-2022	Amendment 5: 1) Added an extension phase (for up to 12 months). The study now consisted of two phases: the Core Phase and the Extension Phase. 2) Revised to align with the alpelisib protocol/IB standard language based on other studies in the BYL719 development program
28-Mar-2023	Amendment 6: 1) Updated the duration of the Extension Phase from up to 12 months to up to 36 months. Consent information for the increased Extension Phase was also updated. 2) Revised to align with the alpelisib protocol/IB standard

Amendment Date	Description
	language based on other studies in the BYL719 development program. 3) Updated text regarding monitoring and management of AEs

Interruptions (globally)

For any interruption, the restart date must not be before the interruption date.

Were there any global interruptions to the trial? No

Interruption Date	Description	Restart Date

Limitations and caveats

Limitations and caveats applicable to this summary of the results

Online References

Provide identifiers to retrieve publications of interest in regards to the results of this clinical trial. **Enter PubMed Identifier (PMID)**

CTIS

Data fields displayed on this tab are specific to CTIS and are not included in EudraCT Results Submissions.

CTIS

CTIS ID 2023-509167-24-00

Additional Results Analysis Information

Additional Information about the clinical trial