Clinical trial results:
An open-label, multi-center, Phase IIIb study to assess the safety and efficacy of midostaurin (PKC412) in patients 18 years of age or older with newly diagnosed FLT3-mutated Acute Myeloid Leukemia who are eligible for “7+3” or “5+2” chemotherapy

Summary

EudraCT number	2016-004440-12
Trial protocol	SE FI CZ ES HU FR BG GR SK LT IT EE HR RO
Global end of trial date	09 July 2021

Results information

Result version number	v1 (current)
This version publication date	24 July 2022
First version publication date	24 July 2022

Trial information

Trial identification

Sponsor protocol code	CPKC412A2408

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03379727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office,, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office,, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To further assess the safety of midostaurin in induction, consolidation and maintenance therapy, including, the "7+3" regimen, daunorubicin (60-90 mg/m2/day), the substitution of daunorubicin by idarubicin (12mg/m2/day), cytarabine (100-200 mg/m2/day) and also allowing the "5+2" reduced dose regimen.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 121
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Sweden: 4
Worldwide total number of subjects	301
EEA total number of subjects	300

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	203
From 65 to 84 years	97
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in 88 investigative sites in 15 countries.

Pre-assignment

Screening details:

Investigators had to obtain locally approved FMS-like tyrosine kinase 3 (FLT3) testing results prior to informed consent form signature to allow subjects to initiate Midostaurin treatment per protocol.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Midostaurin

Arm description:

Patients went through 3 phases: Induction phase – Day (D)8 to D28 in combination with standard of care (7+3 or 5+2 chemotherapy) up to 2 cycles; Consolidation phase – D8 to D28 in combination with cytarabine up to 4 cycles; Maintenance phase – D1 to D28 up to 12 cycles

Arm type	Experimental
Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

100-200mg/m2, Days 1 - 7 in Induction phase

Investigational medicinal product name	daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

60-90mg/m2, Days 1 - 3 in Induction phase

Investigational medicinal product name	idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

12 mg/m² IV qDay over 10-15 min, Days 1 - 3 in Induction phase

Investigational medicinal product name	midostaurin
Investigational medicinal product code	PKC412
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Midostaurin 50mg (two capsules 25 mg) orally twice daily on Day 8 up to Day 28, for 1-2 cycles, consolidation with cytarabine (Days 1, 3, 5) plus midostaurin (Days 8-28) for up to 4 cycles, and

continuous dosing of midostaurin (Days 1-28) for up to 12 cycles (maintenance phase) or until relapse, unacceptable toxicity, death, physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems, pregnancy, subject withdrew consent, or until the end of study, whichever event occurred first

Number of subjects in period 1	Midostaurin
Started	301
Completed	52
Not completed	249
Adverse event, serious fatal	18
Physician decision	104
Adverse event, non-fatal	32
Patient/guardian decision	17
Lost to follow-up	1
Lack of efficacy	73
Protocol deviation	4

Baseline characteristics

Reporting groups	
Reporting group title	Midostaurin
Reporting group description:	
Patients went through 3 phases: Induction phase – Day (D)8 to D28 in combination with standard of care (7+3 or 5+2 chemotherapy) up to 2 cycles; Consolidation phase – D8 to D28 in combination with cytarabine up to 4 cycles; Maintenance phase – D1 to D28 up to 12 cycles	

Reporting group values	Midostaurin	Total	
Number of subjects	301	301	
Age categorical Units: Subjects			
Adults (18-64 years)	203	203	
From 65-84 years	97	97	
85 years and over	1	1	
Age Continuous Units: years			
arithmetic mean	55.8		
standard deviation	± 13.82	-	
Sex: Female, Male Units: participants			
Female	160	160	
Male	141	141	
Race/Ethnicity, Customized Units: Subjects			
White	225	225	
Other	18	18	
Unknown	56	56	
Missing	2	2	

End points

End points reporting groups

Reporting group title	Midostaurin

Reporting group description:

Patients went through 3 phases: Induction phase – Day (D)8 to D28 in combination with standard of care (7+3 or 5+2 chemotherapy) up to 2 cycles; Consolidation phase – D8 to D28 in combination with cytarabine up to 4 cycles; Maintenance phase – D1 to D28 up to 12 cycles

Primary: Percentage of patients with adverse events (AEs), Grade 3 & 4 AEs, serious adverse events (SAEs), AEs leading to discontinuation, and deaths up to 24 months (M24).

End point title	Percentage of patients with adverse events (AEs), Grade 3 & 4 AEs, serious adverse events (SAEs), AEs leading to discontinuation, and deaths up to 24 months (M24).[1]

End point description:

Safety of Midostaurin was represented by various types of AEs, SAEs & death up to M24. AE: the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. AE grades to characterize the severity of AEs were based on the Common Terminology Criteria for AEs ver. 4.03 with Grade (Gr) 1: mild; Gr 2: moderate; Gr 3: severe; Gr 4: life-threatening; Gr 5: death related to AE. AEs not related to hematological toxicities were generally of grade 1 or 2 severity. SAE: 1 of the following: is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant, i.e. an event that jeopardizes the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed above, requires inpatient hospitalization or prolongation of existing hospitalization with a few exceptions.

End point type	Primary

End point timeframe:

Baseline up to approximatly 24 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis were used for summarize the main information for all end points

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	301			
Units: Percentage of patients				
number (not applicable)				
Adverse events (AEs) - all grades	98.0			
Grade >=3 AEs	84.4			
Serious adverse events (SAEs) - all grades	45.5			
AEs leading to discontinuation - all grades	13.3			
Deaths	6.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as per local assessment

End point title	Percentage of patients with complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as per local assessment

End point description:

CR/CRi rate is defined as the percentage of patients with complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as per local assessment in Induction, Consolidation and Maintenance phases. CR/CRi rate was calculated based on the full analysis set (FAS).
Complete remission (CR): Bone marrow blasts <5% with spicules; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count (ANC) >1.0 x109/L; platelet count >100 x 109/L; independence of red cell transfusions.
CR with incomplete recovery (CRi): All CR criteria except for residual neutropenia (<1.0 x109/L) or thrombocytopenia (<100 x 109/L).

1 patient did not have FLT mutation, thus was not included in the efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline up to approximately 24 months

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	300			
Units: Percentage of patients				
number (not applicable)				
Complete remission (CR)	65.3			
Complete remission with incomplete recovery (CRi)	15.3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Care Resource Utilization during Maintenance Phase: Number of hospitalizations reported

End point title	Health Care Resource Utilization during Maintenance Phase: Number of hospitalizations reported

End point description:

Collection of health care resource utilization (HCRU) data focused on hospitalization e.g. reason for the hospitalization. i.e. related to Acute myeloid leukemia (AML) symptoms, adverse events (and type of adverse events) or other reason, number of hospital days by facility/ward type (e.g. hospital unit, emergency room, intensive care unit), discharge reason, and the names of concomitant medications during hospital stay. These measures were used to quantify the number of hospital day's impact of therapy during the maintenance phase and derived components of the economic impact of midostaurin during maintenance. Number of hospitalizations reported is reporting the number of participants who were hospitalized during the study. Note: Exploratory endpoints are not mandatorily required per the Novartis Standard Operating Procedures. However, since this endpoint was inadvertently registered, we are now posting the results.

End point type	Other pre-specified

End point timeframe:

During Maintenance Phase up to 12 months

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	301			
Units: hospitalizations	133			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Care Resource Utilization during Maintenance Phase: Reason for hospitalization

End point title	Health Care Resource Utilization during Maintenance Phase: Reason for hospitalization

End point description:

Collection of health care resource utilization (HCRU) data focused on hospitalization e.g. reason for the hospitalization. i.e. related to AML symptoms, adverse events (and type of adverse events) or other reason, number of hospital days by facility/ward type (e.g. hospital unit, emergency room, intensive care unit), discharge reason, and the names of concomitant medications during hospital stay. These measures were used to quantify the number of hospital day's impact of therapy during the maintenance phase and derived components of the economic impact of midostaurin during maintenance. Reason for hospitalization is reporting percentage of hospitalizations due to adverse events or not during the study. Note: Exploratory endpoints are not mandatorily required per the Novartis Standard Operating Procedures. However, since this endpoint was inadvertently registered, we are now posting the results.

End point type	Other pre-specified

End point timeframe:

During Maintenance Phase up to 12 months

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	301			
Units: Percentage of hospitalizations				
number (not applicable)				
Hospitalization due to adverse event: Yes	30.9			
Hospitalization due to adverse event: No	19.9			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Care Resource Utilization during Maintenance Phase: Length of stay

End point title	Health Care Resource Utilization during Maintenance Phase:

	Length of stay

End point description:

Collection of health care resource utilization (HCRU) data focused on hospitalization e.g. reason for the hospitalization. i.e. related to AML symptoms, adverse events (and type of adverse events) or other reason, number of hospital days by facility/ward type (e.g. hospital unit, emergency room, intensive care unit), discharge reason, and the names of concomitant medications during hospital stay. These measures were used to quantify the number of hospital day's impact of therapy during the maintenance phase and derived components of the economic impact of midostaurin during maintenance. Length of stay is the number of days participants stayed at various facilities. Note: Exploratory endpoints are not mandatorily required per the Novartis Standard Operating Procedures. However, since this endpoint was inadvertently registered, we are now posting the results.

End point type	Other pre-specified

End point timeframe:

During Maintenance Phase up to 12 months

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	301			
Units: days				
Intensive Care Unit	34			
Emergency Room	10			
General Ward	88			
Rehabilitation Unit	0			
Other Unit	27			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Care Resource Utilization during Maintenance Phase: Percentage of patients discharged

End point title	Health Care Resource Utilization during Maintenance Phase: Percentage of patients discharged

End point description:

Collection of health care resource utilization (HCRU) data focused on hospitalization e.g. reason for the hospitalization. i.e. related to AML symptoms, adverse events (and type of adverse events) or other reason, number of hospital days by facility/ward type (e.g. hospital unit, emergency room, intensive care unit), discharge reason, and the names of concomitant medications during hospital stay. These measures were used to quantify the number of hospital day's impact of therapy during the maintenance phase and derived components of the economic impact of midostaurin during maintenance. This provides the percentage of patients who were discharged to various wards. Note: Exploratory endpoints are not mandatorily required per the Novartis Standard Operating Procedures. However, since this endpoint was inadvertently registered, we are now posting the results.

End point type	Other pre-specified

End point timeframe:

During Maintenance Phase up to 12 months

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	301			
Units: Percentage of patients				
number (not applicable)				
Home	36.9			
Long-term care facility	2.0			
Hospice	0.3			
Other	6.3			
Missing	1.7			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Care Resource Utilization during Maintenance Phase: Duration of hospitalization

End point title	Health Care Resource Utilization during Maintenance Phase: Duration of hospitalization

End point description:

Collection of health care resource utilization (HCRU) data focused on hospitalization e.g. reason for the hospitalization. i.e. related to AML symptoms, adverse events (and type of adverse events) or other reason, number of hospital days by facility/ward type (e.g. hospital unit, emergency room, intensive care unit), discharge reason, and the names of concomitant medications during hospital stay. These measures were used to quantify the number of hospital day's impact of therapy during the maintenance phase and derived components of the economic impact of midostaurin during maintenance. Hospitalization duration is defined as the difference in days between admission and discharge dates. Note: Exploratory endpoints are not mandatorily required per the Novartis Standard Operating Procedures. However, since this endpoint was inadvertently registered, we are now posting the results.

End point type	Other pre-specified

End point timeframe:

During Maintenance Phase up to 12 months

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	301			
Units: days				
arithmetic mean (standard deviation)	48.9 (± 41.68)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from first dose of study treatment until end of treatment plus 30 days, up to a maximum duration of 25 months (24 months plus 1 month (30 days) post treatment).

Adverse event reporting additional description:

Adverse Events (AE): Any sign or symptom that occurs during treatment plus 30 days post treatment. Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Induction

Reporting group description:

Induction

Reporting group title	Maintenance

Reporting group description:

Maintenance

Reporting group title	Overall

Reporting group description:

Overall

Reporting group title	Consolidation

Reporting group description:

Consolidation

Serious adverse events	Induction	Maintenance	Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 301 (25.25%)	7 / 93 (7.53%)	137 / 301 (45.51%)
number of deaths (all causes)	16	0	19
number of deaths resulting from adverse events	3	0	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic infiltration pulmonary			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	3 / 301 (1.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	3 / 301 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	3 / 301 (1.00%)	0 / 93 (0.00%)	3 / 301 (1.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hypoxia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Lung infiltration			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			

subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	5 / 301 (1.66%)	0 / 93 (0.00%)	7 / 301 (2.33%)
occurrences causally related to treatment / all	2 / 5	0 / 0	4 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Product issues			
Device dislocation			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	3 / 301 (1.00%)	0 / 93 (0.00%)	3 / 301 (1.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test negative			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 301 (1.33%)	0 / 93 (0.00%)	4 / 301 (1.33%)
occurrences causally related to treatment / all	3 / 4	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Cardiac dysfunction			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Pericardial effusion			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular dysfunction			

subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral paralysis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Cytopenia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	4 / 301 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular			

coagulation			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	6 / 301 (1.99%)	0 / 93 (0.00%)	32 / 301 (10.63%)
occurrences causally related to treatment / all	6 / 8	0 / 0	25 / 45
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	5 / 301 (1.66%)	0 / 93 (0.00%)	5 / 301 (1.66%)
occurrences causally related to treatment / all	2 / 5	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Diarrhoea			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			

subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Large intestinal obstruction			
subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	2 / 301 (0.66%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			

subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis cholestatic			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal infection			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Candida infection			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium colitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related bacteraemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 93 (1.08%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			

subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic candidiasis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineal cellulitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	9 / 301 (2.99%)	1 / 93 (1.08%)	13 / 301 (4.32%)
occurrences causally related to treatment / all	9 / 10	1 / 1	12 / 14
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory moniliasis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 301 (1.33%)	0 / 93 (0.00%)	14 / 301 (4.65%)
occurrences causally related to treatment / all	3 / 4	0 / 0	10 / 16
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory tract infection fungal			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	5 / 301 (1.66%)	0 / 93 (0.00%)	11 / 301 (3.65%)
occurrences causally related to treatment / all	3 / 5	0 / 0	7 / 12
deaths causally related to treatment / all	1 / 2	0 / 0	1 / 2
Sinusitis fungal			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic candida			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic mycosis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acidosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 93 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Consolidation		

Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 210 (31.90%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemic infiltration pulmonary			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 210 (0.95%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 210 (1.43%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumothorax				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary mass				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 210 (0.95%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device dislocation				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Blood bilirubin increased				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SARS-CoV-2 test negative				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Anaphylactic transfusion reaction				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	2 / 210 (0.95%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			

Cardiac dysfunction			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stress cardiomyopathy			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			

subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular dysfunction			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral paralysis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			

Cytopenia				
subjects affected / exposed	4 / 210 (1.90%)			
occurrences causally related to treatment / all	7 / 9			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	26 / 210 (12.38%)			
occurrences causally related to treatment / all	19 / 37			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Diarrhoea				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic colitis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				

subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis cholestatic			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Acute kidney injury			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal infection			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anorectal infection			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast abscess			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Candida infection			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium colitis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Conjunctivitis			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 210 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related bacteraemia			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			

subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic candidiasis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perineal cellulitis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	3 / 210 (1.43%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia legionella				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory moniliasis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection bacterial				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	11 / 210 (5.24%)			
occurrences causally related to treatment / all	7 / 12			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection fungal				

subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	6 / 210 (2.86%)			
occurrences causally related to treatment / all	4 / 7			
deaths causally related to treatment / all	0 / 0			
Sinusitis fungal				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic candida				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Systemic mycosis				
subjects affected / exposed	1 / 210 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypernatraemia				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acidosis				
subjects affected / exposed	0 / 210 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic acidosis				

subjects affected / exposed	0 / 210 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Induction	Maintenance	Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	253 / 301 (84.05%)	48 / 93 (51.61%)	277 / 301 (92.03%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 301 (4.98%)	6 / 93 (6.45%)	32 / 301 (10.63%)
occurrences (all)	16	5	44
Platelet count decreased			
subjects affected / exposed	7 / 301 (2.33%)	3 / 93 (3.23%)	17 / 301 (5.65%)
occurrences (all)	9	3	38
Electrocardiogram QT prolonged			
subjects affected / exposed	19 / 301 (6.31%)	1 / 93 (1.08%)	24 / 301 (7.97%)
occurrences (all)	23	1	33
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 301 (2.66%)	3 / 93 (3.23%)	18 / 301 (5.98%)
occurrences (all)	9	4	27
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 301 (4.98%)	6 / 93 (6.45%)	28 / 301 (9.30%)
occurrences (all)	16	7	34
Hypotension			
subjects affected / exposed	10 / 301 (3.32%)	1 / 93 (1.08%)	24 / 301 (7.97%)
occurrences (all)	10	1	29
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 301 (7.97%)	3 / 93 (3.23%)	59 / 301 (19.60%)
occurrences (all)	28	3	118
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	34 / 301 (11.30%)	4 / 93 (4.30%)	52 / 301 (17.28%)
occurrences (all)	45	2	107
Febrile neutropenia			
subjects affected / exposed	67 / 301 (22.26%)	0 / 93 (0.00%)	88 / 301 (29.24%)
occurrences (all)	73	0	141
Neutropenia			
subjects affected / exposed	33 / 301 (10.96%)	12 / 93 (12.90%)	70 / 301 (23.26%)
occurrences (all)	37	15	152
Thrombocytopenia			
subjects affected / exposed	27 / 301 (8.97%)	6 / 93 (6.45%)	51 / 301 (16.94%)
occurrences (all)	32	6	109
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 301 (5.98%)	2 / 93 (2.15%)	30 / 301 (9.97%)
occurrences (all)	19	2	40
Oedema peripheral			
subjects affected / exposed	23 / 301 (7.64%)	3 / 93 (3.23%)	37 / 301 (12.29%)
occurrences (all)	24	3	43
Pyrexia			
subjects affected / exposed	93 / 301 (30.90%)	3 / 93 (3.23%)	139 / 301 (46.18%)
occurrences (all)	135	4	266
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	24 / 301 (7.97%)	1 / 93 (1.08%)	34 / 301 (11.30%)
occurrences (all)	24	1	41
Abdominal pain upper			
subjects affected / exposed	14 / 301 (4.65%)	1 / 93 (1.08%)	25 / 301 (8.31%)
occurrences (all)	17	1	36
Constipation			
subjects affected / exposed	32 / 301 (10.63%)	2 / 93 (2.15%)	65 / 301 (21.59%)
occurrences (all)	35	2	105
Diarrhoea			
subjects affected / exposed	97 / 301 (32.23%)	8 / 93 (8.60%)	121 / 301 (40.20%)
occurrences (all)	116	10	176
Haemorrhoids			

subjects affected / exposed	16 / 301 (5.32%)	0 / 93 (0.00%)	25 / 301 (8.31%)
occurrences (all)	18	0	31
Nausea			
subjects affected / exposed	76 / 301 (25.25%)	18 / 93 (19.35%)	121 / 301 (40.20%)
occurrences (all)	94	23	249
Vomiting			
subjects affected / exposed	57 / 301 (18.94%)	3 / 93 (3.23%)	69 / 301 (22.92%)
occurrences (all)	74	4	140
Stomatitis			
subjects affected / exposed	54 / 301 (17.94%)	0 / 93 (0.00%)	72 / 301 (23.92%)
occurrences (all)	57	0	92
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 301 (6.64%)	1 / 93 (1.08%)	27 / 301 (8.97%)
occurrences (all)	25	1	39
Epistaxis			
subjects affected / exposed	16 / 301 (5.32%)	0 / 93 (0.00%)	29 / 301 (9.63%)
occurrences (all)	25	0	47
Oropharyngeal pain			
subjects affected / exposed	6 / 301 (1.99%)	0 / 93 (0.00%)	18 / 301 (5.98%)
occurrences (all)	6	0	20
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	13 / 301 (4.32%)	0 / 93 (0.00%)	20 / 301 (6.64%)
occurrences (all)	19	0	28
Petechiae			
subjects affected / exposed	7 / 301 (2.33%)	0 / 93 (0.00%)	18 / 301 (5.98%)
occurrences (all)	7	0	22
Rash			
subjects affected / exposed	38 / 301 (12.62%)	3 / 93 (3.23%)	64 / 301 (21.26%)
occurrences (all)	40	3	80
Pruritus			
subjects affected / exposed	8 / 301 (2.66%)	0 / 93 (0.00%)	19 / 301 (6.31%)
occurrences (all)	9	0	29
Psychiatric disorders			

Insomnia			
subjects affected / exposed	14 / 301 (4.65%)	1 / 93 (1.08%)	18 / 301 (5.98%)
occurrences (all)	14	1	21
Anxiety			
subjects affected / exposed	8 / 301 (2.66%)	1 / 93 (1.08%)	16 / 301 (5.32%)
occurrences (all)	8	1	23
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 301 (1.33%)	3 / 93 (3.23%)	27 / 301 (8.97%)
occurrences (all)	4	3	30
Arthralgia			
subjects affected / exposed	2 / 301 (0.66%)	3 / 93 (3.23%)	16 / 301 (5.32%)
occurrences (all)	2	3	18
Pain in extremity			
subjects affected / exposed	9 / 301 (2.99%)	0 / 93 (0.00%)	17 / 301 (5.65%)
occurrences (all)	11	0	20
Infections and infestations			
Device related infection			
subjects affected / exposed	17 / 301 (5.65%)	0 / 93 (0.00%)	19 / 301 (6.31%)
occurrences (all)	17	0	22
Pneumonia			
subjects affected / exposed	16 / 301 (5.32%)	1 / 93 (1.08%)	27 / 301 (8.97%)
occurrences (all)	16	1	28
Oral herpes			
subjects affected / exposed	6 / 301 (1.99%)	1 / 93 (1.08%)	18 / 301 (5.98%)
occurrences (all)	7	1	21
Sepsis			
subjects affected / exposed	10 / 301 (3.32%)	0 / 93 (0.00%)	18 / 301 (5.98%)
occurrences (all)	10	0	20
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	45 / 301 (14.95%)	1 / 93 (1.08%)	58 / 301 (19.27%)
occurrences (all)	53	1	80

Non-serious adverse events	Consolidation		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	179 / 210 (85.24%)		

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 210 (8.10%)		
occurrences (all)	23		
Platelet count decreased			
subjects affected / exposed	11 / 210 (5.24%)		
occurrences (all)	26		
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 210 (2.38%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 210 (4.76%)		
occurrences (all)	14		
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 210 (4.29%)		
occurrences (all)	11		
Hypotension			
subjects affected / exposed	14 / 210 (6.67%)		
occurrences (all)	18		
Nervous system disorders			
Headache			
subjects affected / exposed	47 / 210 (22.38%)		
occurrences (all)	87		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	36 / 210 (17.14%)		
occurrences (all)	60		
Febrile neutropenia			
subjects affected / exposed	44 / 210 (20.95%)		
occurrences (all)	68		
Neutropenia			
subjects affected / exposed	50 / 210 (23.81%)		
occurrences (all)	100		
Thrombocytopenia			

subjects affected / exposed	40 / 210 (19.05%)		
occurrences (all)	71		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 210 (7.62%)		
occurrences (all)	19		
Oedema peripheral			
subjects affected / exposed	13 / 210 (6.19%)		
occurrences (all)	16		
Pyrexia			
subjects affected / exposed	72 / 210 (34.29%)		
occurrences (all)	127		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 210 (5.24%)		
occurrences (all)	16		
Abdominal pain upper			
subjects affected / exposed	13 / 210 (6.19%)		
occurrences (all)	18		
Constipation			
subjects affected / exposed	41 / 210 (19.52%)		
occurrences (all)	68		
Diarrhoea			
subjects affected / exposed	40 / 210 (19.05%)		
occurrences (all)	50		
Haemorrhoids			
subjects affected / exposed	10 / 210 (4.76%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	67 / 210 (31.90%)		
occurrences (all)	132		
Vomiting			
subjects affected / exposed	33 / 210 (15.71%)		
occurrences (all)	62		
Stomatitis			

subjects affected / exposed occurrences (all)	25 / 210 (11.90%) 35		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 9 / 210 (4.29%) 13 16 / 210 (7.62%) 22 12 / 210 (5.71%) 14		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Petechiae subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 9 / 210 (4.29%) 9 13 / 210 (6.19%) 15 29 / 210 (13.81%) 37 14 / 210 (6.67%) 20		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	 5 / 210 (2.38%) 6 11 / 210 (5.24%) 14		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 20 / 210 (9.52%) 23		

Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	11 / 210 (5.24%) 13 8 / 210 (3.81%) 9		
Infections and infestations Device related infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Sepsis subjects affected / exposed occurrences (all)	4 / 210 (1.90%) 5 11 / 210 (5.24%) 11 12 / 210 (5.71%) 13 10 / 210 (4.76%) 10		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	19 / 210 (9.05%) 26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2018	To allow the use of historical bone marrow aspiration (BMA) result performed for AML diagnosis if available within 15 days before C1D1 of the first chemotherapy, in order to limit the repetition on this invasive assessment. An adaptation of the recovery periods in Induction phase and the first cycle of consolidation based on the RATIFY study results analysis To align between Section 5.3 exclusion criteria #8 and Section 6.4.1.2 Contraceptives with midostaurin, the duration of the post study contraception to 4 months, as per approved midostaurin labeling information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported