Clinical trial results:
Randomised Phase II Study comparing, as first-line chemotherapy, single-agent Oral Vinorelbine administered with two different schedules (metronomic and weekly schedules) in patients with Advanced Breast Cancer.

Summary

EudraCT number	2014-003860-19
Trial protocol	PT ES AT HU RO CZ DE
Global end of trial date	28 September 2020

Results information

Result version number	v1 (current)
This version publication date	03 October 2021
First version publication date	03 October 2021

Trial information

Trial identification

Sponsor protocol code	PM0259CA233B0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Médicament
Sponsor organisation address	45 place Abel Gance, Boulogne , France, 92100
Public contact	Christine TA THANH MINH, PIERRE FABRE MEDICAMENT, +33 (0)149108121, christine.ta.thanh.minh@pierre-fabre.com
Scientific contact	Christine TA THANH MINH, PIERRE FABRE MEDICAMENT, +33 (0)149108121, christine.ta.thanh.minh@pierre-fabre.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	07 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the Disease Control Rate (CR + PR + SD) in both arms (metronomic and weekly schedules) assessed during study treatments.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonisation Good Clinical practice (ICH GCP) and applicable regulatory requirements. The study was conducted in compliance with the protocol. The protocol, amendments, the subject information leaflet and the subject informed consent were approved by the appropriate independent Ethics Committee(s) in the involved countries prior to implementation.

Background therapy:

Preventive medication with an oral 5-HT3 antagonist was recommended before each oral vinorelbine administration. The primary prophylactic use of Colony Stimulating Factor (CSF) was allowed during the treatment period. Granulocyte stimulating growth factors were permitted for patients experiencing febrile neutropenia, Grade 4 asymptomatic neutropenia or neutropenic infection, according to institutional rules. Pre-menopausal patients were allowed to receive LHRH analogues in order to block ovarian functions. Patients received full supportive care throughout the study, including treatment when required with antibiotics, anti-diarrhoeals, analgesics, antiemetics, and transfusion of blood products, according to local guidelines and the investigator’s opinion. Treatment with a bisphosphonate was allowed during the study period.

Evidence for comparator:

This study evaluated two schedules of administration of oral vinorelbine: the metronomic and the weekly schedules.The currently registered and approved regimen of Oral Vinorelbine delivered in a weekly schedule was used as reference arm.

Actual start date of recruitment	03 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 3

Country: Number of subjects enrolled	Hungary: 9
Worldwide total number of subjects	163
EEA total number of subjects	163

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)	76
From 65 to 84 years	83
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 43 centres in 10 countries screened 218 hormone-receptor-positive (HRc) and HER2 negative patients with advanced breast cancer between the 22 of December 2015 and the 13 of December 2017. Of these 218 patients, 164 patients were randomised and 163 patients received at least one dose of study drug.

Pre-assignment

Screening details:

A 28-day screening period was planned before randomisation and screened HRc-positive and HER2 negative patients with advanced breast cancer. Once the screening period was successfully completed, patients who fulfilled the eligibility criteria were randomised in a 1:1 ratio in the 2 arms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: metronomic schedule

Arm description:

Patients received Oral Vinorelbine at metronomic schedules, i.e. three times weekly.

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

Dosage and administration details:

Patients received a fixed dose of 50 mg of Oral Vinorelbine (one capsule of 20mg plus one of 30mg) three times weekly (on Mondays, Wednesdays and Fridays or Tuesdays, Thursdays and Saturdays) continuously until disease progression, unacceptable toxicity, patient’s refusal or investigator’s decision. Each 3 weeks of treatment was considered as a separate cycle, therefore in Treatment Arm A, a cycle consisted of 9 fixed doses of 50 mg at days 1, 3, 5, 8, 10, 12, 15, 17 and 19.

Arm title	Arm B: weekly schedule

Arm description:

Patients received Oral Vinorelbine at weekly schedules, i.e. once a week.

Arm type	Active comparator
Investigational medicinal product name	Oral vinorelbine
Investigational medicinal product code	
Other name	Navelbine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received Oral Vinorelbine at the dose of 60 mg/m² on day 1, day 8 and day 15 of the first cycle. At the second and following cycles, the day 1, day 8 and day 15 were increased to 80 mg/m², according to haematological tolerance. The dosage was calculated according to BSA, using the Dubois and Dubois formula. Treatment was administered until disease progression, unacceptable toxicity, patient’s refusal or investigator’s decision. Each 3 weeks of treatment was considered a cycle, therefore in Treatment Arm B a cycle consisted of 3 doses at days 1, 8 and 15.

Number of subjects in period 1	Arm A: metronomic schedule	Arm B: weekly schedule
Started	82	81
Completed	0	2
Not completed	82	79
Physician decision	2	4
Adverse event, non-fatal	7	10
Other	5	3
Progressive disease	68	57
Withdrawal by subject	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: metronomic schedule
Reporting group description: Patients received Oral Vinorelbine at metronomic schedules, i.e. three times weekly.	
Reporting group title	Arm B: weekly schedule
Reporting group description: Patients received Oral Vinorelbine at weekly schedules, i.e. once a week.	

Reporting group values	Arm A: metronomic schedule	Arm B: weekly schedule	Total
Number of subjects	82	81	163
Age categorical Units: Subjects			
[redacted]			
Age continuous Units: years median full range (min-max)	 64 42 to 89	 66 38 to 87	 -
Gender categorical Units: Subjects			
Female	82	81	163
Male	0	0	0
Karnofsky performance status (KPS) Units: Subjects			
70%	5	4	9
80%	22	18	40
90%	22	27	

IIA	15	16	31
IIB	16	19	35
IIIA	15	10	25
IIIB	3	5	8
IIIC	6	7	13
IV	17	12	29
Missing	3	2	5
Primary tumor site Units: Subjects			
Right breast	44	41	85
Left breast	35	37	72
Bilateral breast	3	3	6
Histological grade at first diagnosis Units: Subjects			
SBR I	7	6	13
SBR II	31	33	64
SBR III	18	12	30
Unknown	26	30	56
Body mass index Units: kg/m^2			
arithmetic mean	27.3	27.3	
standard deviation	± 5.25	± 5.17	-
Time between diagnosis and randomisation Units: months			
median	67.65	78.00	
full range (min-max)	2.4 to 321.1	2.0 to 327.5	-

End points

End points reporting groups

Reporting group title	Arm A: metronomic schedule
Reporting group description:	
Patients received Oral Vinorelbine at metronomic schedules, i.e. three times weekly.	
Reporting group title	Arm B: weekly schedule
Reporting group description:	
Patients received Oral Vinorelbine at weekly schedules, i.e. once a week.	

Primary: Disease control rate (DCR)

End point title	Disease control rate (DCR)[1]
End point description:	
DCR, defined as the sum of CR, PR and SD rates was observed in 52/82 patients (63.4% [95% CI: 52.0, 73.8]) in Arm A and 59/81 patients (72.8% [95% CI: 61.8, 82.1]) in Arm B.	
End point type	Primary
End point timeframe:	
DCR according to investigator was calculated among the BOCR responders in the ITT analysis set on the treatment period (from the date of randomisation until the documentation of progression or death due to any cause.	

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: The study was designed to evaluate the disease control rate in each arm of oral vinorelbine but not to compare the two schedules (metronomic / weekly). No statistical analysis was performed on the primary efficacy endpoint

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: percentage				
number (confidence interval 95%)	63.4 (52.0 to 73.8)	72.8 (61.8 to 82.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control

End point title	Duration of disease control
End point description:	
Overall, for patients who achieved PR or SD (no CR was observed in any arm), 43 (82.7%) patients in Arm A and 44 (74.6%) patients in Arm B experienced disease progression or death. The median time to disease progression or death was 6.9 months (95% CI: 4.2, 8.6) in Arm A and 7.9 months (95% CI: 5.7, 10.0) in Arm B. The distribution of DCR was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.	
End point type	Secondary

End point timeframe:

Duration of disease control was defined as the period from the date of randomisation until date of PD or death from any cause, whichever occurred first. Only responders (patients with BOCR of CR or PR) and stable patients were included in the analysis.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	59		
Units: months				
median (confidence interval 95%)	6.9 (4.2 to 8.6)	7.9 (5.7 to 10.0)		

Attachments (see zip file)	Duration of disease control (months)/14_2_1_1_FIG.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: DCR without grade 3-4 toxicity

End point title	DCR without grade 3-4 toxicity

End point description:

DCR without grade 3-4 toxicity, defined as the sum of CR, PR and SD without grade 3-4 toxicity rates, was observed in 24/82 patients (29.3% [95% CI: 19.7, 40.4]) in Arm A and 18/81 patients (22.2% [95% CI: 13.7, 32.8]) in Arm B.

End point type	Secondary

End point timeframe:

DCR without grade 3-4 toxicity was calculated among the BOCR responders and stable patients without grade 3-4 toxicity in the ITT population from the date of randomisation until the documentation of progression or death or first grade 3 or 4 AE.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: percent				
number (confidence interval 95%)	29.3 (19.7 to 40.4)	22.2 (13.7 to 32.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: DCR without grade 3-4 neutropenia

End point title	DCR without grade 3-4 neutropenia

End point description:

DCR without grade 3-4 neutropenia, defined as the sum of CR, PR and SD without grade 3-4 neutropenia rates, was observed in 35/82 patients (42.7% [95% CI: 31.8, 54.1]) in Arm A and 25/81 patients (30.9% [95% CI: 21.1, 42.1]) in Arm B.

End point type	Secondary

End point timeframe:

DCR without grade 3-4 neutropenia was calculated among the BOCR responders and stable patients without grade 3-4 neutropenia in the ITT population from the date of randomisation until the documentation of progression, first grade 3-4 neutropenia or death.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: percent				
number (confidence interval 95%)	42.7 (31.8 to 54.1)	30.9 (21.1 to 42.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR, defined as the sum of CR and PR rates, was observed in 14/82 patients (17.1% [95% CI: 9.7, 27.0]) in Arm A and 17/81 patients (21.0% [95% CI: 12.7, 31.5]) in Arm B.

End point type	Secondary

End point timeframe:

ORR according to investigator was calculated among the BOCR responders (CR and PR) in the ITT population from the date of randomisation until the documentation of progression or death.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: percent				
number (confidence interval 95%)	17.1 (9.7 to 27.0)	21.0 (12.7 to 31.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR without grade 3-4 toxicity

End point title	ORR without grade 3-4 toxicity

End point description:

ORR without grade 3-4 toxicity, defined as the sum of CR and PR without grade 3-4 toxicity rates, was observed in 8/82 patients (9.8% [95% CI: 4.3, 18.3]) in Arm A and 6/81 patients (7.4% [95% CI: 2.8, 15.4]) in Arm B.

End point type	Secondary

End point timeframe:

ORR without grade 3-4 toxicity was calculated among the BOCR responders (CR and PR) who had not experienced grade 3-4 toxicity in the ITT population from the date of randomisation until the documentation of progression, first grade 3 or 4 AE or death.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: percent				
number (confidence interval 95%)	9.8 (4.3 to 18.3)	7.4 (2.8 to 15.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR without grade 3-4 neutropenia

End point title	ORR without grade 3-4 neutropenia

End point description:

ORR without grade 3-4 neutropenia, defined as the sum of CR and PR without grade 3-4 neutropenia rates, was observed in 10/82 patients (12.2% [95% CI: 6.0, 21.3]) in Arm A and 6/81 patients (7.4% [95% CI: 2.8, 15.4]) in Arm B.

End point type	Secondary

End point timeframe:

ORR without grade 3-4 neutropenia was calculated among the BOCR responders (CR and PR) who hadn't experienced grade 3-4 neutropenia in the ITT population from the date of randomisation until the documentation of PD, first grade 3-4 neutropenia or death

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: percent				
number (confidence interval 95%)	12.2 (6.0 to 21.3)	7.4 (2.8 to 15.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

Overall, for patients who achieved PR (no CR was observed in any arm), 12 (85.7%) patients in Arm A and 10 (58.8%) patients in Arm B experienced disease progression or death. The median DOR was 8.5 months (95% CI: 4.2, 11.4) in Arm A and 9.3 months (95% CI: 6.8, 19.2) in Arm B. The distribution of duration of response was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

Duration of response was calculated among the BOCR responders (CR and PR) in the ITT population from the date of randomisation until the documentation of progression or death from any cause, whichever occurred first.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: months				
median (confidence interval 95%)	8.5 (4.2 to 11.4)	9.3 (6.8 to 19.2)		

Attachments (see zip file)	Duration of response (months) (ITT analysis set)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response

End point title	Time to first response

End point description:

Overall, 14 patients in Arm A and 17 patients in Arm B achieved a PR (no CR). The median Time to first

response was 2.8 months (95% CI: 1.3, 3.9) in Arm A and 2.8 months (95% CI: 1.4, 4.2) in Arm B. The distribution of Time to first response was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

Time to first response, defined as the time from the date of randomisation to the date of first CR or PR after randomisation, whichever occurred first was measured until the documentation of progression or death from any cause, whichever occurred first.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: month				
median (confidence interval 95%)	2.8 (1.3 to 3.9)	2.8 (1.4 to 4.2)		

Attachments (see zip file)	Time to first response (months) (ITT analysis set)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease

End point title	Duration of stable disease

End point description:

A total of 38 patients in Arm A and 42 patients in Arm B achieved SD. Of these, 31 (81.6%) patients in Arm A and 34 (81.0%) patients in Arm B experienced disease progression or death. The median duration of SD was 4.2 months (95% CI: 4.0, 6.7) in Arm A and 5.7 months (95% CI: 5.0, 7.8) in Arm B. The distribution of duration of stable disease was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

Duration of Stable Disease was measured from the date of randomisation until the date of PD or death from any cause, whichever occurred first.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	42		
Units: month				
median (confidence interval 95%)	4.2 (4.0 to 6.7)	5.7 (5.0 to 7.8)		

Attachments (see zip file)	Duration of stable disease (months) (ITT analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Overall, disease progression or death was reported in 80/82 (97.6%) patients in Arm A and 73/81 (90.1%) patients in Arm B. The median PFS was 4.0 months (95% CI: 2.8, 5.4) in Arm A and 5.6 months (95% CI: 4.4, 7.8) in Arm B. The distribution of progression-free survival was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

The progression-free survival (PFS) was measured from randomisation until the first radiographically documented progression of disease or death from any cause, whichever occurred first.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: month				
median (confidence interval 95%)	4.0 (2.8 to 5.4)	5.6 (4.4 to 7.8)		

Attachments (see zip file)	PFS (months) (ITT analysis set)/14_2_5_1_FIG.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival without grade 3-4 toxicity

End point title	Progression-free survival without grade 3-4 toxicity

End point description:

Overall, grade 3-4 toxicity, disease progression or death was reported in 77 (93.9%) patients in Arm A and 74 (91.4%) patients in Arm B. The median PFS without grade 3-4 toxicity was 1.7 months (95% CI: 1.4, 2.8) in Arm A and 1.4 months (95% CI: 1.3, 2.1) in Arm B. The distribution of Progression-free survival without grade 3-4 toxicity was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

PFS without grade 3-4 toxicity was measured from randomisation until the first radiographically documented progression of disease, first AE with grade 3 or 4 toxicity or death from any cause, whichever occurred first.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: month				
median (confidence interval 95%)	1.7 (1.4 to 2.8)	1.4 (1.3 to 2.1)		

Attachments (see zip file)	PFS without grade 3-4 toxicity (months)/14_2_6_1_FIG.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival without grade 3-4 neutropenia

End point title	Progression-free survival without grade 3-4 neutropenia

End point description:

Overall, grade 3-4 neutropenia, disease progression or death was reported in 76 (92.7%) patients in Arm A and 70 (86.4%) patients in Arm B. The median PFS without grade 3-4 neutropenia was 2.7 months (95% CI: 1.4, 3.9) in Arm A and 2.1 months (95% CI: 1.4, 2.6) in Arm B. The distribution of Progression-free survival without grade 3-4 neutropenia was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

PFS without grade 3-4 neutropenia was measured from randomisation until the first radiographically documented progression of disease, first grade 3 or 4 neutropenia or death from any cause, whichever occurred first.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: month				
median (confidence interval 95%)	2.7 (1.4 to 3.9)	2.1 (1.4 to 2.6)		

Attachments (see zip file)	Progression-free survival without grade 3-4

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Death was reported in 50 (61.0%) patients in Arm A and 42 (51.9%) patients in Arm B. Median OS were 22.3 months (95% CI: 19.0, 27.3) in Arm A and 26.7 months (95% CI: 22.2, 37.8) in Arm B. The distribution of Overall Survival was described by treatment arm using Kaplan-Meier methods, reporting estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points.

End point type	Secondary

End point timeframe:

Overall survival was measured from the date of randomisation until the date of death, regardless of the cause of death.

End point values	Arm A: metronomic schedule	Arm B: weekly schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: month				
median (confidence interval 95%)	22.3 (19.0 to 27.3)	26.7 (22.2 to 37.8)		

Attachments (see zip file)	Overall survival (months) (ITT analysis set)/14_2_9_1_FIG.rtf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any AE that first occurred during the treatment period (i.e. from first study treatment administration date up to last administration date + 30 days) was recorded in the CRF and included in the analysis of AEs (on-study AE).

Adverse event reporting additional description:

At the cut-off date (07-NOV-2019), 2 patients were still on treatment. Death was reported for 88 patients, while 60 patients were still being followed for survival. Four patients were lost to follow-up. All patients in the safety analysis set received at least one cycle with a median number of cycle of 4.0 (1-41) in Arm A and 7.0 (1-45) in Arm B.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Arm A: metronomic schedule (Safety analysis set)

Reporting group description:

All patients who received at least one dose of study drug and with at least one post-baseline safety data were included in the safety analysis set. A total of 82 patients were included in the safety analysis set.

Reporting group title	Arm B: weekly schedule (Safety analysis set)

Reporting group description:

All patients who received at least one dose of study drug and with at least one post-baseline safety data were included in the safety analysis set. A total of 80 patients were included in the safety analysis set.

Serious adverse events	Arm A: metronomic schedule (Safety analysis set)	Arm B: weekly schedule (Safety analysis set)	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 82 (26.83%)	13 / 80 (16.25%)	
number of deaths (all causes)	50	42	
number of deaths resulting from adverse events	2	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			

subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 82 (1.22%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	1 / 82 (1.22%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			

subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Neuroglycopenia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 82 (0.00%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 82 (2.44%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Intestinal obstruction			
subjects affected / exposed	2 / 82 (2.44%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Mastitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 82 (3.66%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: metronomic schedule (Safety analysis set)	Arm B: weekly schedule (Safety analysis set)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 82 (96.34%)	78 / 80 (97.50%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	1	5	
Weight decreased			
subjects affected / exposed	28 / 82 (34.15%)	35 / 80 (43.75%)	
occurrences (all)	37	57	
Weight increased			
subjects affected / exposed	3 / 82 (3.66%)	5 / 80 (6.25%)	
occurrences (all)	3	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 82 (6.10%)	4 / 80 (5.00%)	
occurrences (all)	6	4	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 82 (1.22%)	5 / 80 (6.25%)	
occurrences (all)	1	6	
Headache			
subjects affected / exposed	3 / 82 (3.66%)	9 / 80 (11.25%)	
occurrences (all)	3	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 82 (6.10%)	4 / 80 (5.00%)	
occurrences (all)	5	14	

Neutropenia			
subjects affected / exposed	28 / 82 (34.15%)	57 / 80 (71.25%)	
occurrences (all)	64	175	
Thrombocytopenia			
subjects affected / exposed	1 / 82 (1.22%)	4 / 80 (5.00%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 82 (19.51%)	26 / 80 (32.50%)	
occurrences (all)	38	57	
Fatigue			
subjects affected / exposed	13 / 82 (15.85%)	11 / 80 (13.75%)	
occurrences (all)	17	15	
Mucosal inflammation			
subjects affected / exposed	2 / 82 (2.44%)	6 / 80 (7.50%)	
occurrences (all)	2	8	
Pyrexia			
subjects affected / exposed	6 / 82 (7.32%)	9 / 80 (11.25%)	
occurrences (all)	7	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 82 (9.76%)	8 / 80 (10.00%)	
occurrences (all)	10	14	
Abdominal pain upper			
subjects affected / exposed	7 / 82 (8.54%)	9 / 80 (11.25%)	
occurrences (all)	9	11	
Constipation			
subjects affected / exposed	14 / 82 (17.07%)	14 / 80 (17.50%)	
occurrences (all)	16	17	
Diarrhoea			
subjects affected / exposed	23 / 82 (28.05%)	30 / 80 (37.50%)	
occurrences (all)	30	91	
Dyspepsia			
subjects affected / exposed	5 / 82 (6.10%)	3 / 80 (3.75%)	
occurrences (all)	7	3	
Nausea			

subjects affected / exposed	27 / 82 (32.93%)	44 / 80 (55.00%)	
occurrences (all)	55	99	
Vomiting			
subjects affected / exposed	8 / 82 (9.76%)	31 / 80 (38.75%)	
occurrences (all)	14	46	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 82 (3.66%)	4 / 80 (5.00%)	
occurrences (all)	3	5	
Dyspnoea			
subjects affected / exposed	8 / 82 (9.76%)	4 / 80 (5.00%)	
occurrences (all)	17	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 82 (3.66%)	9 / 80 (11.25%)	
occurrences (all)	4	14	
Rash			
subjects affected / exposed	0 / 82 (0.00%)	4 / 80 (5.00%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 82 (6.10%)	6 / 80 (7.50%)	
occurrences (all)	5	6	
Back pain			
subjects affected / exposed	8 / 82 (9.76%)	5 / 80 (6.25%)	
occurrences (all)	11	6	
Bone pain			
subjects affected / exposed	7 / 82 (8.54%)	7 / 80 (8.75%)	
occurrences (all)	10	8	
Pain in extremity			
subjects affected / exposed	2 / 82 (2.44%)	5 / 80 (6.25%)	
occurrences (all)	2	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 82 (3.66%)	5 / 80 (6.25%)	
occurrences (all)	3	6	

Respiratory tract infection			
subjects affected / exposed	6 / 82 (7.32%)	1 / 80 (1.25%)	
occurrences (all)	7	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 82 (1.22%)	6 / 80 (7.50%)	
occurrences (all)	1	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 82 (10.98%)	16 / 80 (20.00%)	
occurrences (all)	12	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2019	Considering all data collected during the time period of the study, the sponsor decided to anticipate the end of study and to proceed with the final statistical analysis earlier. This decision was based on the following considerations observed on September 10th, 2019: • After 45 months of study duration, among the 165 randomised patients (164 treated), 152 events (progression or death) were observed. For 12 randomised patients, neither disease progression nor death were recorded (1 patient never received the study drug, 3 patients did not yet progress, 4 drop out patients and 4 patients with only non-radiological progression), and 1 patient was removed from clinical database (no local data privacy form available). • The maturity of PFS data could thus be considered as being reached. • 85 deaths were observed, and it was estimated that maturity of OS data (i.e. at least 80% of events) would not be reached by the end-of-study (with the current definition in the protocol). The study was not designed to get mature OS data, however the median OS was reached.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported