Clinical trial results:
Randomized Phase II study comparing single agent oral vinorelbine administered with two different schedules in patients with Advanced Non Small Cell Lung Cancer unfit for a platinum-based chemotherapy

Summary

EudraCT number	2014-003859-61
Trial protocol	ES PL HU CZ DE AT FR GR IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	28 October 2019
First version publication date	28 October 2019

Trial information

Trial identification

Sponsor protocol code	PM0259CA232J1

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, Boulgone-Billancourt, France, 92654
Public contact	Director of medical affairs department, DENJEAN François, MD, +33 149108058, francois.denjean@pierre-fabre.com
Scientific contact	Director of medical affairs department, DENJEAN François, MD, +33 149108058, francois.denjean@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	Interim
Date of interim/final analysis	15 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the Progression Free Survival (PFS) without Grade 4 toxicity (G4PFS) in both arms. This composite endpoint considers the first occurrence of either of the following:
- Grade 4 toxicity (lower grade AEs are not considered),
- Disease Progression or Death.

Protection of trial subjects:

This study was conducted in accordance with the Institut de Recherche Pierre Fabre (IRPF) Clinical Standard Operating Procedures, the ethical principles that have their origin in the Declaration of Helsinki and subsequent amendments that are consistent with the International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) (CPMP/ICH/135/95) and related national regulations. Written informed consent was obtained from the patient before any study specific procedures
were undertaken. Patients were informed about the study, both verbally and through their review of the Subject Information Leaflet (SIL) and ICF. The information in the SIL was based on the elements defined in the Declaration of Helsinki and the ICH GCP Guideline. The SIL also described the measures taken to safeguard the patient’s privacy and protection of personal data, according to the European General Data Protection Regulation (2016/679).

Background therapy:

Preventative treatment with an oral 5HT3 antagonist was recommended before each oral vinorelbine (OV) administration.

Evidence for comparator:

Chemotherapy with a single agent is an appropriate therapeutic option, suitable for a large number of patients with advanced NSCLC unfit for receiving a platinum-based chemotherapy (ie patients with creatinine clearance decrease, poor Performance Status (PS), co-morbidities, cardio-vascular problems and, in some cases, age, when it is correlated with functional impairment).

Actual start date of recruitment	26 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 67

Worldwide total number of subjects	165
EEA total number of subjects	165

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)	9
From 65 to 84 years	149
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

34 opened sites across nine countries randomised 167 patients. Of the 167 patients randomised, two patients were not treated, one because of disease progression and the other because of the delay between randomisation and start of study treatment.

Pre-assignment

Screening details:

An initial screening assessment within 28 days prior to the first dose of study treatment was planned before randomisation and screened 225 patients for NSCLC stage IIIB or stage IV. of the 225 screened patients, 167 were randomised.

Period 1

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

Blinding implementation details:

This was an open-label study and neither the investigators nor the participants were blinded to the randomisation allocation.

Arms

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

Arm description:

Oral vinorelbine: 50 mg (one capsule of 20 mg plus one of 30 mg) three times weekly

Arm type	Experimental
Investigational medicinal product name	Oral Vinorelbine
Investigational medicinal product code	NVBO
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral vinorelbine: 50 mg (one capsule of 20 mg plus one of 30 mg) three times weekly on Monday, Wednesday and Friday.
NB: for practical reasons, the same schedule could be adapted to Tuesday/Thursday/Saturday.
A cycle is a treatment period between 9 administrations of oral vinorelbine (3 administrations on Monday, Wednesday and Friday during 3 weeks).
Treatment should be administered until documented disease progression, unacceptable toxicity, patient’s refusal or investigator’s decision.
Treatment will be modified in case of dose limiting haematological and/or non haematological toxicity.
Dose adjustment and/or treatment delay are to be made according to the body system showing the greatest degree of toxicity.

Arm title	Arm B: weekly schedules

Arm description:

Oral vinorelbine: 60 mg/m2 weekly, for cycle 1, then 80 mg/ m2 weekly for subsequent cycles according to haematological tolerance and investigator’s decision.

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

Dosage and administration details:

Oral vinorelbine will be administered at a weekly dose of 60 mg/m2 at the first cycle (1 cycle = 3 weeks of treatment) and then at weekly dose of 80 mg/m² at cycle 2 and subsequent cycles according to haematological tolerance, until disease progression, unacceptable toxicity, patient's refusal or investigator's decision. A cycle is a treatment period between 3 administrations of weekly oral vinorelbine (Day 1, day 8 and day 15). First study drug administration is to begin within 7 days after randomisation.

Number of subjects in period 1	Arm A: metronomic schedules	Arm B: weekly schedules
Started	83	82
Completed	2	0
Not completed	81	82
Adverse event, serious fatal	5	9
Consent withdrawn by subject	6	2
Physician decision	-	3
Adverse event, non-fatal	14	19
Other	-	2
Progressive disease	56	47

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: metronomic schedules
Reporting group description:	
Oral vinorelbine: 50 mg (one capsule of 20 mg plus one of 30 mg) three times weekly	
Reporting group title	Arm B: weekly schedules
Reporting group description:	
Oral vinorelbine: 60 mg/m2 weekly, for cycle 1, then 80 mg/ m2 weekly for subsequent cycles according to haematological tolerance and investigator's decision.	

Reporting group values	Arm A: metronomic schedules	Arm B: weekly schedules	Total
Number of subjects	83	82	165
Age categorical Units: Subjects			
Adults (18-64 years)	5	4	9
From 65-84 years	74	75	149
85 years and over	4	3	7
Age continuous Units: years			
arithmetic mean	76.1	75.9	
standard deviation	± 6.39	± 6.19	-
Gender categorical Units: Subjects			
Female	21	19	40
Male	62	63	125
ECOG performance at baseline Units: Subjects			
0-1	55	51	106
02	28	31	59
>2	0	0	0
Smoking history at baseline Units: Subjects			
Never smoked	7	6	13
Stopped smoking >=10 years ago	44	28	72
Stopped smoking <10 years ago	22	33	55
Smoker	10	15	25
Cancer stage at first diagnosis Units: Subjects			
IA	1	4	5
IB	3	2	5
IIA	6	1	7
IIB	4	5	9
IIIA	7	9	16
IIIB	9	7	16
IV	53	54	107
Histological type at first diagnosis Units: Subjects			

Squamous cell or epidermoid carcinoma	30	33	63
Adenocarcinoma	45	40	85
Large cell carcinoma	3	1	4
Bronchial-alveolar carcinoma	1	3	4
Giant cell carcinoma	0	0	0
Adenoid-cystic carcinoma	0	0	0
Clear cell carcinoma	0	0	0
Scar cancer	0	0	0
Not otherwise specified	4	5	9
Other rare histological NSCLC	0	0	0
Unknown	0	0	0
Number of organs involved Units: Subjects			
One	6	4	10
Two	28	29	57
>=3	49	49	98
BSA at baseline Units: m^2			
arithmetic mean	1.81	1.77	
standard deviation	± 0.176	± 0.212	-
Time between diagnosis and randomization (months) Units: months			
arithmetic mean	7.65	11.54	
standard deviation	± 15.563	± 22.234	-
Time between first relapse and diagnosis Units: months			
arithmetic mean	17.03	27.30	
standard deviation	± 23.409	± 31.290	-

End points

End points reporting groups

Reporting group title	Arm A: metronomic schedules
Reporting group description:	
Oral vinorelbine: 50 mg (one capsule of 20 mg plus one of 30 mg) three times weekly	
Reporting group title	Arm B: weekly schedules
Reporting group description:	
Oral vinorelbine: 60 mg/m2 weekly, for cycle 1, then 80 mg/ m2 weekly for subsequent cycles according to haematological tolerance and investigator’s decision.	

Primary: Progression-free survival (PFS) without grade 4 toxicity (G4PFS)

End point title	Progression-free survival (PFS) without grade 4 toxicity (G4PFS)
End point description:	
G4PFS, defined as the time from randomisation until the first radiographically documented progression of disease, first AE with grade 4 toxicity or death from any cause, whichever occurs first, was estimated on the ITT population (all treated patients) using Kaplan Meier curves and Confidence intervals on the median PFS were calculated using the Brookmeyer and Crowley method. Patients who had radiographically documented disease progression, had an adverse event with grade 4 toxicity or died from any cause are considered as having an event. Clinical progression with no radiological evidence of progression not considered as event. The clinical response was determined using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines Version 1.1. Tumor assessments of the same sites that were assessed at baseline were performed every 6 weeks until disease progression. At DCO or last contact, death was reported for 142 patients, while 25 were still alive.	
End point type	Primary
End point timeframe:	
Progression-free survival without G4 toxicity (G4PFS) will be calculated from the date of randomisation until the date of progression or the date of G4 toxicity or the date of death due to any cause whichever occurs first.	

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	4.0 (2.6 to 4.3)	2.2 (1.5 to 2.9)		

Attachments (see zip file)	G4PFS (Intent-to-treat analysis set)/G4PFS.jpg

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Comparison groups	Arm B: weekly schedules v Arm A: metronomic schedules

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.88

Secondary: Disease control rate (DCR) without Grade 4 Toxicity

End point title	Disease control rate (DCR) without Grade 4 Toxicity

End point description:

DCR without grade 4 toxicity is defined as the sum of CR, PR and SD rates in patients without grade 4 toxicity. Only responders (patients with BOCR of CR or PR) and stable patients (patients with BOCR of SD) will be included in the analysis of duration of disease control without grade 4 toxicity. DCR was observed in 38/83 (45.8%) patients in arm A [95% CI: 34.8%; 57.1%] and 22/82 (26.8%) patients in arm B [95% CI: 17.6%; 37.8%]. 95% confidence intervals are computed using the Clopper-Pearson approach. Clinical progression with no radiological evidence of progression are not taken into account for establishing best overall confirmed response.

End point type	Secondary

End point timeframe:

DCR according to Investigator was calculated among the BOCR responders and stable patients without gr4 toxicity in the ITT population from the date of randomisation until the documentation of progression or grade 4 toxicity or death due to any cause.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: pourcentage				
number (confidence interval 95%)	45.8 (34.8 to 57.1)	26.8 (17.6 to 37.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

DCR, defined as the sum of confirmed CR, PR and SD rates, was observed in 53/83 (63.9%) patients in arm A [95% CI: 52.6%; 74.1%] and 52/82 (63.4%) patients in arm B [95% CI: 52.0%; 73.8%]. 95%

confidence intervals are computed using the Clopper-Pearson approach. Clinical progression with no radiological evidence of progression are not taken into account for establishing best overall confirmed response.

End point type	Secondary

End point timeframe:

DCR according to Investigator was calculated among the BOCR responders (CR and PR) and stable patients in the ITT population on the study period from the date of randomisation until the documentation of progression or death due to any cause.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: pourcentage				
number (confidence interval 95%)	63.9 (52.6 to 74.1)	63.4 (52.0 to 73.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control without grade 4 toxicity

End point title	Duration of disease control without grade 4 toxicity

End point description:

Duration of disease control without grade 4 toxicity is defined as the period from the date of randomisation until date of progressive disease, first AE with grade 4 toxicity or death from any cause, whichever occurs first. Only responders (patients with BOCR of CR or PR) and stable patients (patients with BOCR of SD) will be included in the analysis. Medians are based upon Kaplan-Meier approach. 95% CI for median duration of disease control without grade 4 toxicity are calculated using the Brookmeyer and Crowley method. Patients who are lost to follow-up without progression or gr4 toxicity or reach the time point of analysis without a known record of progression or gr4 toxicity or death will have the duration of disease control censored at the date of last tumour assessment or last contact of a follow-up showing no progression or gr4 toxicity, whichever occur last. Patients who received a new anti-tumoral treatment before their progression will be censored at the start of treatment

End point type	Secondary

End point timeframe:

Duration of disease control without grade 4 toxicity will be calculated among the responders and stable patients from the date of randomisation until the documentation of progression or grade 4 toxicity or death due to any cause whichever occurs first.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	4.8 (4.2 to 6.5)	3.3 (2.5 to 3.8)		

Attachments (see zip file)	Duration of disease control without grade 4 tox/Duration of

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control

End point title	Duration of disease control

End point description:

The disease control rate (sum of confirmed CR, confirmed PR and stabilisation rate) were evaluated for the ITT population. Medians are based upon Kaplan-Meier approach. 95% CI for median duration of disease control are calculated using the Brookmeyer and Crowley method. Patients who are lost to follow-up without progression, or reach the time point of analysis without a known record of progression or death will have the duration of disease control censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occur last. Patients who received a new anti-tumoral treatment, whatever the type of treatment, before their disease progression will be censored at the start date of this new anti-tumoral treatment.

End point type	Secondary

End point timeframe:

The duration of disease control (CR, PR and stabilization of at least 24 weeks) was measured from the date of registration until the criteria for disease progression is met or the date of death or start of new anticancer therapy.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	5.4 (4.5 to 7.0)	5.8 (4.3 to 6.8)		

Attachments (see zip file)	Duration of disease control/duration of disease control2.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate Without Grade 4 Toxicity

End point title	Objective Response Rate Without Grade 4 Toxicity

End point description:

Objective response rate without grade 4 toxicity is defined as the sum of CR and PR rate in patients without grade 4 toxicity. ORR without grade 4 toxicity was evaluated in the ITT population. CR and PR are based on best overall confirmed response. Patients with at least one grade 4 or 5 adverse event are

flagged as having grade 4 toxicity. Four (4.8%) patients in Arm A and 2 (2.4%) patients in Arm B achieved ORR without Grade 4 toxicity.

End point type	Secondary

End point timeframe:

ORR without grade 4 toxicity was evaluated from the date of randomisation until end of study treatment period.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: pourcentage				
number (confidence interval 95%)	4.8 (1.3 to 11.9)	2.4 (0.3 to 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was defined as the sum of CR and PR rate and evaluated on the whole study treatment period in the ITT population. Five (6.0%) patients in Arm A and 5 (6.1%) patients in Arm B achieved ORR.

End point type	Secondary

End point timeframe:

ORR was evaluated from the date of randomisation until end of study treatment period.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: pourcentage				
number (confidence interval 95%)	6.0 (2.0 to 13.5)	6.1 (2.0 to 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response

End point title	Time to first response

End point description:

Time to first response is defined as the time from date of randomisation to the date of first CR or PR after randomisation, whichever occurs first. Only responders (patients with BOCR of CR or PR) will be included in the analysis of time to first response.

End point type	Secondary

End point timeframe:

Time to first response will be calculated among the responders (i.e. confirmed CR and PR) from the date of randomisation up to the first report of documented response.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	1.6 (1.4 to 7.1)	2.6 (1.1 to 4.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease

End point title	Duration of stable disease

End point description:

Duration of stable disease is defined as the period from the date of randomisation until date of progressive disease or death from any cause, whichever occurs first. Only stable patients (patients with BOCR of SD) will be included in the analysis of duration of stable disease. Patients who are lost to follow-up, or reach the time point of analysis without a known record of progression or death will have the duration of stable disease censored at the date of last tumor assessment or last contact of a follow-up showing no progression, whichever occur last. Patients who received a new anti-tumoral treatment, whatever the type of treatment, before their disease progression will be censored at the start date of this new anti-tumoral treatment.

End point type	Secondary

End point timeframe:

Duration of stable disease according to investigator will be calculated among the stable patients from the date of randomisation until the documentation of progression or death due to any cause in the ITT population.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	5.3 (4.3 to 6.3)	5.7 (4.1 to 6.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Time to treatment failure is defined as the period from the date of randomisation up to the date of failure (disease progression, relapse, death or withdrawal due to adverse event, patient's refusal, lost to follow-up or start of new anti-cancer therapy, whichever occurs first). Patients who reach the time point of analysis without failure as defined above will have the time to treatment failure censored at the date of last tumor assessment or last contact of a follow-up not showing progression. Patients who discontinued treatment for other reason and who are lost to follow-up will be censored at the date of last contact.

End point type	Secondary

End point timeframe:

Time-to-treatment failure will be calculated from the date of randomisation up to the date of failure (progression, relapse, death or withdrawal due to adverse event, patient's refusal, lost to follow-up or start of new anticancer therapy).

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	2.6 (2.1 to 3.9)	3.1 (2.3 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

The progression-free survival (PFS) is defined as the time from randomisation until the first radiographically documented progression of disease or death from any cause, whichever occurs first. Patients who are lost to follow-up, or reach the time point of analysis without a known record of progression or death will have the progression-free survival censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occur last.

End point type	Secondary

End point timeframe:

Progression-free survival will be calculated from the date of randomisation until the date of progression or the date of death due to any cause if no progression was recorded before in the ITT population.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	4.3 (3.3 to 5.1)	3.9 (2.8 to 5.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the period from the date of randomisation up to the date of death, regardless of cause of death. Patients alive at the time of the analysis will have the overall survival censored at the date of last tumor assessment or last contact, whichever occur last. For patients with no post baseline tumor assessment a censored overall survival at day 1 will be considered.

End point type	Secondary

End point timeframe:

Overall survival is measured from the date of randomisation up to death or last follow-up.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	7.1 (5.3 to 8.5)	7.6 (5.2 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival Without Grade 2-3-4 Toxicity

End point title	Progression-free Survival Without Grade 2-3-4 Toxicity

End point description:

The progression-free survival without grade 2-3-4 toxicity (G2PFS) is defined as the time from randomisation until the first radiographically documented progression of disease, first AE with grade 2, 3 or 4 toxicity or death from any cause, whichever occurs first. Patients who are lost to follow-up, or reach the time
point of analysis without a known record of progression or date of G2-3-4 toxicity or death will have the

G2PFS censored at the date of last tumour assessment or last contact of a follow-up showing no progression, whichever occur last. Patients who received a new anti-tumoral treatment, whatever the type of treatment, before their disease progression will be censored at the start date of this new anti-tumoral treatment.

End point type	Secondary

End point timeframe:

Progression-free survival without G2-3-4 toxicity (G2PFS) will be calculated from the date of randomisation until the date of progression or the date of G2-3-4 toxicity or the date of death due to any cause whichever occurs first.

End point values	Arm A: metronomic schedules	Arm B: weekly schedules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: months				
median (confidence interval 95%)	1.2 (0.8 to 1.5)	0.6 (0.5 to 0.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event occuring during the study period (treatment period + follow-up) and all SAEs occuring after signing the ICF and up top 30 days after the last study administration were recorded in the CRF.

Adverse event reporting additional description:

At the cutoff date (15 October 2018) or last contact, death was reported for 142 patients, while 25 were still alive. 2 patients remained on treatment, 18 in follow-up period and 5 were lost top follow-up. The median RDI was 85.02% for Arm A and 68.76% in Arm B. The median number of cycles was 4.0 in each arm respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Arm A Safety Set

Reporting group description:

The Safety Set includes all patients randomized who received at least one dose of study drug. 83 patients in the Arm A were included in the Safety Set

Reporting group title	Arm B Safety Set

Reporting group description:

The Safety Set includes all patients randomized who received at least one dose of study drug. 81 patients in the Arm B were included in the Safety Set

Serious adverse events	Arm A Safety Set	Arm B Safety Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 83 (44.58%)	42 / 81 (51.85%)	
number of deaths (all causes)	72	69	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	7 / 83 (8.43%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 6	0 / 7	
Tumour pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	2 / 83 (2.41%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 83 (1.20%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 83 (0.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	10 / 83 (12.05%)	6 / 81 (7.41%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 6	1 / 4	
Pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	2 / 83 (2.41%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	2 / 83 (2.41%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pleural effusion			
subjects affected / exposed	2 / 83 (2.41%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 83 (1.20%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	2 / 83 (2.41%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (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			
Hip fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pulmonary embolism			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 83 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardio-respiratory arrest			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 83 (3.61%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 83 (3.61%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 83 (1.20%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 83 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 83 (1.20%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (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 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	3 / 83 (3.61%)	5 / 81 (6.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Septic shock			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A Safety Set	Arm B Safety Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 83 (90.36%)	80 / 81 (98.77%)	
Investigations			
Weight decreased			
subjects affected / exposed	22 / 83 (26.51%)	24 / 81 (29.63%)	
occurrences (all)	25	29	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	8 / 83 (9.64%)	12 / 81 (14.81%)	
occurrences (all)	15	13	
Malignant neoplasm progression			
subjects affected / exposed	7 / 83 (8.43%)	7 / 81 (8.64%)	
occurrences (all)	7	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 83 (8.43%)	8 / 81 (9.88%)	
occurrences (all)	12	11	
Febrile neutropenia			
subjects affected / exposed	3 / 83 (3.61%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Neutropenia			
subjects affected / exposed	14 / 83 (16.87%)	42 / 81 (51.85%)	
occurrences (all)	16	98	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 83 (32.53%)	40 / 81 (49.38%)	
occurrences (all)	50	85	
Fatigue			
subjects affected / exposed	13 / 83 (15.66%)	16 / 81 (19.75%)	
occurrences (all)	28	37	
General physical health deterioration			
subjects affected / exposed	15 / 83 (18.07%)	11 / 81 (13.58%)	
occurrences (all)	18	12	
Oedema peripheral			

subjects affected / exposed	5 / 83 (6.02%)	7 / 81 (8.64%)	
occurrences (all)	6	7	
Pyrexia			
subjects affected / exposed	9 / 83 (10.84%)	10 / 81 (12.35%)	
occurrences (all)	15	28	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 83 (4.82%)	5 / 81 (6.17%)	
occurrences (all)	6	7	
Abdominal pain upper			
subjects affected / exposed	2 / 83 (2.41%)	8 / 81 (9.88%)	
occurrences (all)	3	8	
Constipation			
subjects affected / exposed	13 / 83 (15.66%)	21 / 81 (25.93%)	
occurrences (all)	13	27	
Diarrhoea			
subjects affected / exposed	21 / 83 (25.30%)	27 / 81 (33.33%)	
occurrences (all)	51	66	
Nausea			
subjects affected / exposed	21 / 83 (25.30%)	31 / 81 (38.27%)	
occurrences (all)	36	62	
Stomatitis			
subjects affected / exposed	11 / 83 (13.25%)	7 / 81 (8.64%)	
occurrences (all)	14	9	
Vomiting			
subjects affected / exposed	7 / 83 (8.43%)	15 / 81 (18.52%)	
occurrences (all)	10	20	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 83 (15.66%)	9 / 81 (11.11%)	
occurrences (all)	20	9	
Dyspnoea			
subjects affected / exposed	21 / 83 (25.30%)	22 / 81 (27.16%)	
occurrences (all)	27	35	
Haemoptysis			

subjects affected / exposed	9 / 83 (10.84%)	4 / 81 (4.94%)	
occurrences (all)	14	4	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	7 / 83 (8.43%)	3 / 81 (3.70%)	
occurrences (all)	9	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 83 (4.82%)	5 / 81 (6.17%)	
occurrences (all)	4	6	
Pneumonia			
subjects affected / exposed	3 / 83 (3.61%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 83 (16.87%)	19 / 81 (23.46%)	
occurrences (all)	27	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2016	Local Amendment Germany In the current protocol, the pelvic CT scan is asked to be performed at Baseline for tumour assessment among others. However in Germany, pelvic CT scan will lead to an over-exposure of radiation as defined by the Bundesamt für Strahlenschutz. To fulfil this requirement, the pelvic CT scan / MRI will be optional. Moreover, the sponsor's personnel list is updated.
02 February 2017	PM 0259 CA 232 J1 is a prospective study which aims to assess an alternative schedule of treatment with oral vinorelbine for a category of advanced NSCLC (non-small cell lung cancer) whose medical conditions makes the use of intensive doublet not suitable. This study compares the use of oral vinorelbine as single agent in first-line treatment using a fractionated administration (metronomic) approach versus the approved dosing scheme of oral vinorelbine in patients considered as unfit for a platinum-based regimen. As planned per protocol, an interim analysis of safety was performed after the first 40 patients (20 in each arm) enrolled. All safety data were reviewed by the Data Monitoring Committee (DMC). Further to this review the DMC has issued the following recommendations regarding the conduct of the trial: To implement in both arms standard practice for infection prevention in these high-risk patients unfit for platinum-based chemotherapy, as the study protocol is addressed to patients more likely to have comorbidities that significantly expose them to infection.; To perform a second interim analysis of safety when accrual of 40 additional patients would have been reached (in total 80 patients enrolled, 40 patients in each arm). Furthermore several additional changes were implemented: -An harmonization of the definition of febrile neutropenia in accordance with NCI-CTC v.4 in use in this trial; -A clarification of the definition of " G4PFS" (progression-free survival without Grade 4 Toxicity), of " G2PFS" (progression-free survival without Grade 2 Toxicity); addition of definition of progression-free survival (PFS); -An update of the list of Sponsor's representatives.

14 September 2018	As of today, 167 patients have been randomized in the study, two patients (1 patient in Greece & 1 patient in Poland), both randomized in metronomic arm, are still receiving study medication and 27 other patients are still alive in Follow-up period. The final analysis requires the confirmation of at least 143 events (Grade 4 toxicity, Disease Progression or Death) and 162 events have been documented so far in the study. The statistical power needed to perform the final analysis of the study primary endpoint and the maturity of data of the secondary endpoints have been achieved. Therefore, to proceed with the final analysis earlier as planned per protocol, this amendment aims to modify the end of study definition as follows: The end of study is defined as: 30 days following the last study drug administration of the last patient. No additional information will be collected from 30 days following the last study drug administration. A data cut-off date for final analysis is fixed on 15-Oct-2018. Statistical analysis will contain all data generated up to 15-Oct-2018 inclusive or the end of study, whichever occurs first. • For patients having discontinued the study at the data cut-off date (15-Oct-2018), only data generated up to 15-Oct-2018 inclusive will be collected into e-CRF and analysed. • Patients who remain on study treatment at the data cut-off date (15-Oct-2018) may continue to benefit receiving treatment in the study until documented progressive disease, unacceptable toxicity, patient's refusal, or investigator's discretion for subject's interest as defined in the study protocol. Study procedures during treatment period will remain unchanged except the completion of the Quality of Life questionnaire (EORTC QLQ C30) which will not be longer required to decrease the burden of patients in the study. Pierre Fabre Medicament will supply study drug, free of charge to each centre. The efficacy and safety reporting will be maintained as per protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported