Clinical trial results:
Phase III study of IV vinflunine in combination with methotrexate versus methotrexate alone in patients with recurrent or metastatic squamous cell carcinoma of the head and neck previously treated with platinum-based chemotherapy (study L00070 IN 309 F0)

Summary

EudraCT number	2011-005081-38
Trial protocol	DE ES IT BE EE AT PL SK
Global end of trial date	23 November 2018

Results information

Result version number	v1 (current)
This version publication date	06 March 2019
First version publication date	06 March 2019

Trial information

Trial identification

Sponsor protocol code	L00070 IN 309 F0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02347332
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Médicament, Institut de Recherche Pierre Fabre
Sponsor organisation address	BP 13562, Toulouse, France, 31305
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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	20 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) of intravenous (IV) vinflunine (VFL) in combination with methotrexate (MTX) versus MTX alone in incurable recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) patients who have failed platinum based chemotherapy.

Futility analysis showed that the probability of demonstrating a significant benefit in OS at the time of the final analysis was very low. Consequently, the sponsor decided to end trial and limit efficacy analysis to ITT patients. At the cut-off date October 20th 2017, 3 patients were ongoing and at the time of this report 1 patient is under compassional treatment. An addendum and update of the data on safety will be made once all patients are deceased and the global end of trial is reached.

Protection of trial subjects:

The study was conducted according to Good Clinical Practices (GCPs) (CPMP/ICH/135/95), International Conference on Harmonisation (ICH) E11, the ethical principles that have their origins in the Declaration of Helsinki (1964) and its subsequent amendments. Each patient signed an Informed consent.

Background therapy:

Vinflunine (VFL) is a microtubule inhibitor of the vinca-alkaloid class. Microtubules are an important chemotherapeutic target because of the crucial role they play during mitosis, particularly for rapidly dividing cancer cells. VFL inhibits tubulin assembly by perturbing microtubule dynamics and mitotic spindles without affecting assembled microtubules. An international program of phase II studies with VFL as a single agent has been carried out in chemonaïve patients, and also as salvage therapy in order to determine the tumour response in a large spectrum of solid tumours. In a phase III study, VFL given as second-line after failure of prior platinum-based chemotherapy demonstrated a survival advantage over best supportive care in advanced transitional cell carcinoma of the urothelial tract (TCCU). In a further phase III study, VFL showed similar efficacy to docetaxel in advanced non small cell lung cancer.Vinca-alkaloids have demonstrated activity in SCCHN; single agent vinorelbine showed activity after first-line cisplatin-based chemotherapy. VFL demonstrated superior antitumour activity to vinorelbine in preclinical animal models, and has well-established efficacy in the second-line treatment of TCCU and non small cell lung cancer after platinum failure. Vinca-alkaloids have been successfully combined with MTX in a variety of solid tumours including advanced TCCU, metastatic breast cancer and malignant mesothelioma. In patients with SCCHN who had relapsed after cisplatin plus 5 FU, a regimen combining vinorelbine, bleomycin and MTX showed activity with a response rate of 27% and acceptable toxicity. Recent preliminary phase I results of the vinflunine plus methotrexate combination in SCCHN, based on a clinical review, show encouraging antitumour activity and an acceptable safety profileTherefore the combination of VFL and MTX appears a promising salvage regimen after platinum

Evidence for comparator:

For patients with incurable recurrent/metastatic SCCHN who failed platinum-based therapy, single agent MTX at a dose of 40 mg/m2/week is considered as the best available evidence-based option. Also, other trials using this comparator have demonstrated that it is generally accepted as a reasonable choice, and is often used in general practice

Actual start date of recruitment	02 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belarus: 21
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Russian Federation: 120
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	Ukraine: 53
Worldwide total number of subjects	459
EEA total number of subjects	196

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)	357
From 65 to 84 years	102
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were stratified at inclusion by the following factors: performance status (0 versus 1), refractory or resistant to platinum versus other, prior radiotherapy, treatment with anti-epidermal growth factor receptor, centre, patients were randomly assigned in a 1:1 ratio to 1 of the 2 arms.

Pre-assignment

Screening details:

Adult patients with histological or cytologically confirmed recurrent and/or metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx with a WHO performance status < 1 with adequate haematological, hepatic and renal function. Disease must have been documented as progressive during or after platinum based chemotherapy

Period 1

Period 1 title	Screening
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients randomised to Arm A received:
VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and
MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.

Arm type	Experimental
Investigational medicinal product name	Vinflunine
Investigational medicinal product code	L0070
Other name	JAVLOR, (4'R) - 20', 20'-difluoro 3'4'-dihydrovinorelbine L -(+) - tartrate (1 : 2)
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to arm A will receive vinflunine on day 1 as a 20 minute IV infusion at 280 mg/m² and methotrexate on days 1 and 8 as a bolus intravenous injection at 30 mg/m² of every three-week cycle.
The total dose to be given will be calculated according to body surface area (BSA). In calculating BSA, actual heights and weights should be used. BSA should be recalculated prior to the next cycle dosing.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

On day 1, methotrexate will be administered by direct bolus injection through the side arm of the remaining NS or 5% glucose solution bag after completion of vinflunine infusion.
On day 8, methotrexate will be administered though the side arm of a freely running NS or 5% glucose solution IV infusion.

Arm title	Arm B

Arm description:

Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through

the side arm of a freely running NS or 5% glucose solution IV infusion.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.

Number of subjects in period 1	Arm A	Arm B
Started	230	229
Completed	230	229

Period 2

Period 2 title	Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients randomised to Arm A received:
VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and
MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.

Arm type	Experimental
Investigational medicinal product name	Vinflunine
Investigational medicinal product code	L0070
Other name	JAVLOR, (4'R) - 20', 20'-difluoro 3'4'-dihydrovinorelbine L -(+) - tartrate (1 : 2)
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to arm A will receive vinflunine on day 1 as a 20 minute IV infusion at 280 mg/m² and methotrexate on days 1 and 8 as a bolus intravenous injection at 30 mg/m² of every three-week cycle.
The total dose to be given will be calculated according to body surface area (BSA). In calculating BSA, actual heights and weights should be used. BSA should be recalculated prior to the next cycle dosing.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

On day 1, methotrexate will be administered by direct bolus injection through the side arm of the remaining NS or 5% glucose solution bag after completion of vinflunine infusion.
On day 8, methotrexate will be administered though the side arm of a freely running NS or 5% glucose solution IV infusion.

Arm title	Arm B

Arm description:

Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.

Number of subjects in period 2	Arm A	Arm B
Started	230	229
Completed	0	0
Not completed	230	229
Adverse event, serious fatal	6	6
Consent withdrawn by subject	20	14
Physician decision	4	3
Adverse event, non-fatal	50	41
Progressive disease	141	159
Lost to follow-up	2	1
Protocol requirement	1	1
Switch Post study program	-	1
Protocol deviation	1	1
Patients not treated	5	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients randomised to Arm A received: VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.	
Reporting group title	Arm B
Reporting group description:	
Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	230	229	459
Age categorical Units: Subjects			
Adults (18-64 years)	182	175	357
From 65-84 years	48	54	102
85 years and over	0	0	0
Age continuous Units: years			
median	58	59	
full range (min-max)	27 to 79	34 to 79	-
Gender categorical Units: Subjects			
Female	37	35	72
Male	193	194	387

Subject analysis sets	
Subject analysis set title	ARM A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomised to Arm A received: • VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and • MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.	
Subject analysis set title	ARM B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomised to Arm B, MTX was given at a dose of 40 mg/m²/week administered by direct bolus IV injection on Days 1, 8 and 15 of every three week cycle. One cycle of MTX is defined as a three week period.	

Reporting group values	ARM A	ARM B	
Number of subjects	230	229	

Age categorical Units: Subjects			
Adults (18-64 years)	182	175	
From 65-84 years	48	54	
85 years and over	0	0	
Age continuous Units: years			
median	58	59	
full range (min-max)	27 to 79	34 to 79	
Gender categorical Units: Subjects			
Female	37	35	
Male	193	194	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Patients randomised to Arm A received:
VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and
MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.

Reporting group title	Arm B

Reporting group description:

Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.

Reporting group title	Arm A

Reporting group description:

Patients randomised to Arm A received:
VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and
MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.

Reporting group title	Arm B

Reporting group description:

Patients randomised to arm B received methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug was administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.

Subject analysis set title	ARM A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients randomised to Arm A received:
- VFL at a dose of 280 mg/m² on Day 1, over a 20 minute IV infusion, and
- MTX administered at a dose of 30 mg/m² by direct bolus IV injection on Days 1 and 8 of every three week cycle.

Subject analysis set title	ARM B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients randomised to Arm B, MTX was given at a dose of 40 mg/m²/week administered by direct bolus IV injection on Days 1, 8 and 15 of every three week cycle. One cycle of MTX is defined as a three week period.

Primary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

End point type	Primary

End point timeframe:

30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Months				
median (confidence interval 95%)	7.1 (5.7 to 8.4)	6.8 (6.1 to 8.0)		

Attachments (see zip file)	Overall Survival (ITT) in months/11_4_1_1.rtf Overall Survival (ITT) in months Fig/11_4_1_1_Fig.rtf

Statistical analyses

Statistical analysis title	Overall Survival (months) ITT
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Secondary: Progression free Survival (ITT)

End point title	Progression free Survival (ITT)

End point description:

End point type	Secondary

End point timeframe:
30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Months				
median (confidence interval 95%)	2.8 (2.6 to 3.3)	2.8 (2.1 to 3.1)		

Attachments (see zip file)	Progression Free Survival (ITT) in months)/14_2_1.rtf Progression Free Survival (ITT) in months - Fig/14_2_1_Fig.rtf

Statistical analyses

Statistical analysis title	Progression Free Survival (months) (ITT)
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided

Secondary: Objective Response Rate (ITT)	
End point title	Objective Response Rate (ITT)
End point description:	
End point type	Secondary
End point timeframe:	
30 months	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Number of patients (%)				
median (confidence interval 95%)	17.8 (13.1 to 23.4)	14.8 (10.5 to 20.1)		

Attachments (see zip file)	Objective Response Rate (ORR) [ITT]/14_2_2.rtf

Statistical analyses

Statistical analysis title	Objective Response Rate
Statistical analysis description:	
The best response designation recorded from the date of randomisation until disease progression.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Confidence interval	
level	95 %
sides	2-sided

Secondary: Disease Control Rate (DCR) (ITT)

End point title	Disease Control Rate (DCR) (ITT)

End point description:

End point type	Secondary

End point timeframe:

30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Number of patients (%)				
median (confidence interval 95%)	50.9 (44.2 to 57.5)	46.3 (39.7 to 53.0)		

Attachments (see zip file)	Disease Control Rate (DCR) [ITT]/14_2_3.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Duration Of Response (ITT)

End point title	Duration Of Response (ITT)

End point description:

End point type	Secondary

End point timeframe:

30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Months				
median (confidence interval 95%)	4.2 (2.5 to 5.6)	4.2 (2.7 to 5.1)		

Attachments (see zip file)	Duration of Response (Months) [ITT]/14_2_4.rtf Duration of Response (months) [ITT]/14_2_4_Fig.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

End point type	Secondary

End point timeframe:

30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Months				
median (confidence interval 95%)	4.4 (4.1 to 5.5)	4.2 (4.1 to 4.5)		

Attachments (see zip file)	Duration of Disease Control (months) [ITT]/14_2_5.rtf Duration of Disease Control (months) [ITT] Fig /14_2_5_Fig.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

End point type	Secondary

End point timeframe:

30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Months				
median (confidence interval 95%)	2.4 (1.7 to 2.8)	2.6 (1.6 to 2.8)		

Attachments (see zip file)	Time to Treatment Failure (months) [ITT]/14_2_6.rtf Time to Treatment Failure (months) [ITT]/14_2_6_Fig.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First response [ITT]

End point title	Time to First response [ITT]

End point description:

End point type	Secondary

End point timeframe:

30 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	229		
Units: Months				
median (confidence interval 95%)	2.0 (1.4 to 2.8)	1.5 (1.4 to 2.8)		

Attachments (see zip file)	Time to Time to First Response (months) [ITT]/14_2_7.rtf Time to First Response (months) [ITT]/14_2_7_Fig.rtf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 4 years 6 months 29 days.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19
Reporting groups	
Reporting group title	VFL + MTX
Reporting group description: -	
Reporting group title	MTX.
Reporting group description: -	

Serious adverse events	VFL + MTX	MTX.	
Total subjects affected by serious adverse events			
subjects affected / exposed	105 / 225 (46.67%)	82 / 227 (36.12%)	
number of deaths (all causes)	185	194	
number of deaths resulting from adverse events	5	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	12 / 225 (5.33%)	16 / 227 (7.05%)	
occurrences causally related to treatment / all	1 / 14	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	8 / 225 (3.56%)	10 / 227 (4.41%)	
occurrences causally related to treatment / all	1 / 11	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	5 / 225 (2.22%)	5 / 227 (2.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	22 / 225 (9.78%)	5 / 227 (2.20%)	
occurrences causally related to treatment / all	28 / 28	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	7 / 225 (3.11%)	8 / 227 (3.52%)	
occurrences causally related to treatment / all	9 / 10	10 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	10 / 225 (4.44%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	11 / 11	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	8 / 225 (3.56%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	12 / 97	3 / 90	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 225 (2.22%)	6 / 227 (2.64%)	
occurrences causally related to treatment / all	6 / 6	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	5 / 225 (2.22%)	6 / 227 (2.64%)	
occurrences causally related to treatment / all	2 / 5	1 / 6	
deaths causally related to treatment / all	2 / 5	1 / 6	
General physical health deterioration			
subjects affected / exposed	6 / 225 (2.67%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	1 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 225 (2.22%)	5 / 227 (2.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asphyxia			
subjects affected / exposed	5 / 225 (2.22%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	5 / 225 (2.22%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 225 (2.22%)	5 / 227 (2.20%)	
occurrences causally related to treatment / all	1 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 225 (3.56%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	4 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VFL + MTX	MTX.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	211 / 225 (93.78%)	213 / 227 (93.83%)	
Investigations			
Weight decreased			
subjects affected / exposed	69 / 225 (30.67%)	63 / 227 (27.75%)	
occurrences (all)	248	150	
Creatinine renal clearance decreased			
subjects affected / exposed	17 / 225 (7.56%)	10 / 227 (4.41%)	
occurrences (all)	49	28	
Weight increased			
subjects affected / exposed	12 / 225 (5.33%)	15 / 227 (6.61%)	
occurrences (all)	47	100	
Alanine aminotransferase increased			

subjects affected / exposed	11 / 225 (4.89%)	28 / 227 (12.33%)	
occurrences (all)	26	74	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	20 / 225 (8.89%)	12 / 227 (5.29%)	
occurrences (all)	58	29	
Malignant neoplasm progression			
subjects affected / exposed	12 / 225 (5.33%)	16 / 227 (7.05%)	
occurrences (all)	12	16	
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 225 (10.67%)	10 / 227 (4.41%)	
occurrences (all)	42	27	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	89 / 225 (39.56%)	71 / 227 (31.28%)	
occurrences (all)	219	190	
Anaemia			
subjects affected / exposed	82 / 225 (36.44%)	56 / 227 (24.67%)	
occurrences (all)	245	147	
Leukopenia			
subjects affected / exposed	32 / 225 (14.22%)	38 / 227 (16.74%)	
occurrences (all)	93	102	
Febrile neutropenia			
subjects affected / exposed	19 / 225 (8.44%)	1 / 227 (0.44%)	
occurrences (all)	20	1	
Thrombocytopenia			
subjects affected / exposed	19 / 225 (8.44%)	24 / 227 (10.57%)	
occurrences (all)	31	65	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	62 / 225 (27.56%)	54 / 227 (23.79%)	
occurrences (all)	181	137	
Pyrexia			
subjects affected / exposed	26 / 225 (11.56%)	24 / 227 (10.57%)	
occurrences (all)	35	27	

Fatigue			
subjects affected / exposed	24 / 225 (10.67%)	27 / 227 (11.89%)	
occurrences (all)	52	53	
Pain			
subjects affected / exposed	19 / 225 (8.44%)	17 / 227 (7.49%)	
occurrences (all)	48	55	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	56 / 225 (24.89%)	25 / 227 (11.01%)	
occurrences (all)	163	42	
Stomatitis			
subjects affected / exposed	53 / 225 (23.56%)	64 / 227 (28.19%)	
occurrences (all)	117	158	
Nausea			
subjects affected / exposed	36 / 225 (16.00%)	23 / 227 (10.13%)	
occurrences (all)	66	40	
Vomiting			
subjects affected / exposed	26 / 225 (11.56%)	13 / 227 (5.73%)	
occurrences (all)	37	20	
Diarrhoea			
subjects affected / exposed	23 / 225 (10.22%)	13 / 227 (5.73%)	
occurrences (all)	34	23	
Dysphagia			
subjects affected / exposed	18 / 225 (8.00%)	13 / 227 (5.73%)	
occurrences (all)	33	45	
Abdominal pain			
subjects affected / exposed	16 / 225 (7.11%)	2 / 227 (0.88%)	
occurrences (all)	18	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	18 / 225 (8.00%)	18 / 227 (7.93%)	
occurrences (all)	26	34	
Cough			
subjects affected / exposed	14 / 225 (6.22%)	22 / 227 (9.69%)	
occurrences (all)	32	52	
Musculoskeletal and connective tissue disorders			

Neck pain subjects affected / exposed occurrences (all)	14 / 225 (6.22%) 40	12 / 227 (5.29%) 30	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	15 / 225 (6.67%) 19	12 / 227 (5.29%) 15	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	27 / 225 (12.00%) 59	23 / 227 (10.13%) 45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2014	PA01 Three new exclusion criteria were added: • albumin level < 35 g/L, • weight loss ≥ 5% within the last 3 months, • recurrent pulmonary or upper airways infections (3 times or more in the last 3 months) requiring antibiotics and/or any infection requiring antibiotics within the last month before study entry. • Permitted the eligibility of patients who present with synchronous squamous cell carcinomas of head and neck region. • Included data from a dose-finding and pharmacokinetic phase I study (L00070 IN 117 F0) evaluating the combination of VFL with MTX. • Implemented changes in the treatment modifications guidelines. • Implemented changes on SAE reporting. • Shortened the inclusion period from 24 months to 19 months. • Increased the number of participating sites.
19 March 2014	PA04: Based on requests from the French Ethics Committee issued on 14 March 2014 that led to protocol version #4, the following modifications were implemented: • The exclusion criterion 'known hypersensitivity to vinca-alkaloids or MTX' was deleted as patients with prior treatment with vinca-alkaloids and MTX were excluded. • Mentioned that creatinine clearance is calculated by the Cockroft-Gault formula. • Specified that VFL metabolism depends on the isoform CYP3A4. • Stated that clinical data of VFL-related neurotoxicity are moderate, frequent but reversible. • Added mouthwashes as prophylaxis of oral mucositis. • Updated the references.
21 March 2014	PA05: Based on further requests from ANSM issued on 21 March 2014 leading to protocol version #5 the following modifications were implemented: • Deleted text stating that ECGs were performed in the first 40 patients who were to be analysed in the early safety analysis treated patients. • Specified the measures that were to be taken in case of QT/QTc interval > 500 msec (Grade 3).

10 April 2014	PA03: Based on the comments and requests from the French Competent Authorities (ANSM) issued on 07 March 2014 that led to protocol version #3, the following modifications were implemented: • Two new exclusion criteria were added: • serum potassium < lower limit of normal, • ECG demonstrating a QT/QTc interval > 480 msec. • ECGs would be performed throughout the study treatment to further monitor patient's safety. • Men must use adequate methods of contraception throughout the study and for up to 3 months after the study treatment if their partners were women of childbearing potential. • The exclusion criterion 'known hypersensitivity to vinca-alkaloids or MTX' was deleted as patients with prior treatment with vinca-alkaloids and MTX were excluded. • Detailed the clinical symptoms/signs and radiological features of Posterior Reversible Encephalopathy Syndrome. • Medications that prolong QT/QTc interval were to be avoided. A list of such medications was provided. • Mentioned that creatinine clearance is calculated by the Cockroft-Gault formula. • Specified that VFL metabolism depends on the isoform CYP3A4. • Stated that clinical data of VFL-related neurotoxicity are moderate, frequent but reversible. • Added mouthwashes as prophylaxis of oral mucositis.
23 November 2015	PA10: (submitted only in Belgium, France, Spain, Poland, Estonia, Russia, Belarus and Ukraine) • The results of the second interim analysis (August 2015) of efficacy of Study L00070 IN 309 F0 led the IDMC to recommend the implementation of a futility analysis of overall survival which is the primary endpoint of Study L00070 IN 309 F0. • The results of the futility analysis showed that the probability of demonstrating a significant benefit in overall survival at the time of the final analysis was very low. • As a consequence, the sponsor stopped the recruitment of study patients on 16 October 2015. • This amendment: • updated the protocol to reflect the sponsor's decision to stop study recruitment, • deleted 'adequate renal function serum creatinine ≤ ULN' in the inclusion criterion #11 in order to fulfil the SmPC of VFL.
05 February 2016	PA11 • Clarified amendment PA10 with regards to the participation of the patient after the end of treatment phase. • Modified the statistical analysis according to the PA10 amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Abbreviated CSR. Futility analysis showed that the probability of demonstrating a significant benefit in OS at the time of the final analysis was very low. Consequently, the sponsor decided to end trial and limit efficacy analysis to ITT patients.

Notes: