Clinical trial results:
INTERNATIONAL RANDOMIZED PHASE II TRIAL OF THE COMBINATION OF VINCRISTINE AND IRINOTECAN WITH OR WITHOUT TEMOZOLOMIDE (VI OR VIT) IN CHILDREN AND ADULTS WITH REFRACTORY OR RELAPSED RHABDOMYOSARCOMA

Summary

EudraCT number	2010-023135-42
Trial protocol	FR NL ES GB IT
Global end of trial date	25 June 2019

Results information

Result version number	v1 (current)
This version publication date	10 May 2024
First version publication date	10 May 2024

Trial information

Trial identification

Sponsor protocol code	VIT-0910

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	VHP: 201116, ClinicalTrials.gov: NCT01355445

Notes:

Sponsors

Sponsor organisation name	Centre Oscar Lambret
Sponsor organisation address	3 rue Frédéric Combemale – BP307, LILLE, France, 59020
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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	12 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2018
Global end of trial reached?	Yes
Global end of trial date	25 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of the combination of temozolomide with vincristine and irinotecan in children and adult patients with refractory or relapsed rhabdomyosarcoma as assessed by confirmed objective tumor response after 2 courses

Protection of trial subjects:

This study will be conducted in accordance with the ethical principles of the 1964 Helsinki declaration, revised in 2013 in Fortaleza, with the rules of Good Clinical Practice (GCP) defined by the International Conference on Harmonization (ICH-E6, 17/7/96). The clinical trial may not begin before approval of the Ethics Committees and authorization by competent authorities concerned is obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2011
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	Netherlands: 16
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	120
EEA total number of subjects	86

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)	2
Children (2-11 years)	60

Adolescents (12-17 years)	32
Adults (18-64 years)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was opened in 37 centres, from five countries (France, United Kingdom, Netherland, Italy, Spain). 120 patients were enrolled from 14.03.2012 to 06.04.2018.

Pre-assignment

Screening details:

Firstly, 80 patients were included between 14.03.2012 and 19.06.2014. As preliminary results indicated that more precision was needed, 40 additional patients in the relapse status have been enrolled between 17.06.2016 and 06.04.2018, up to 120 patients (60 patients in the VI arm and 60 patients in the VIT arm).

Period 1

Period 1 title	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 VI

Arm description:

The treatment was given every 3 weeks.
Vincristine was given by intravenous infusion on day 1 and day 8 of each course before irinotecan
Irinotecan was given by intravenous infusion on day 1 and day 5 of each course.

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

1.5 mg/m² or 0.05 mg/kg for patient ≤ 10 kg (maximum 2.0 mg) on day 1 and 8 of each course (every 3 weeks)

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

50 mg/m²/day given intravenously infusion over 1 hour on days 1-5 of each course (every 3 weeks)

Arm title	Arm VIT

Arm description:

The treatment was given every 3 weeks.
Vincristine was given by intravenous infusion on day 1 and day 8 of each course before irinotecan
Irinotecan was given by intravenous infusion on day 1 and day 5 of each course, one hour following the administration of temozolide (TMZ).
TMZ was given orally, prior to vincristine and irinotecan, on days 1-5 repeated.

Arm type	Experimental

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

1.5 mg/m² or 0.05 mg/kg for patient ≤ 10 kg (maximum 2.0 mg) on day 1 and 8 of each course (every 3 weeks)

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

50 mg/m²/day given intravenously infusion over 1 hour on days 1-5 of each course (every 3 weeks), one hour following the administration of temozolide (TMZ).

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

Dosage and administration details:

The starting dose of TMZ was 125 mg/m²/day. The dose of TMZ was to be escalated to 150 mg/m²/day at cycle 2 for patients who did not experience > grade 3 toxicity of any kind. The dose of TMZ was rounded to the nearest 5 mg. TMZ was given orally, on an empty stomach, prior to vincristine and irinotecan, on days 1-5 repeated every 3-weeks. If the patient vomited within 20 minutes after TMZ, the dose had to be re-administered.

Number of subjects in period 1	Arm VI	Arm VIT
Started	60	60
Completed	58	60
Not completed	2	0
Patient decision	1	-
patient ineligible after amendment	1	-

Baseline characteristics

Reporting groups

Reporting group title	Arm VI

Reporting group description:

The treatment was given every 3 weeks.
Vincristine was given by intravenous infusion on day 1 and day 8 of each course before irinotecan
Irinotecan was given by intravenous infusion on day 1 and day 5 of each course.

Reporting group title	Arm VIT

Reporting group description:

The treatment was given every 3 weeks.
Vincristine was given by intravenous infusion on day 1 and day 8 of each course before irinotecan
Irinotecan was given by intravenous infusion on day 1 and day 5 of each course, one hour following the administration of temozolide (TMZ).
TMZ was given orally, prior to vincristine and irinotecan, on days 1-5 repeated.

Reporting group values	Arm VI	Arm VIT	Total
Number of subjects	60	60	120
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	2	2
Children (2-11 years)	33	27	60
Adolescents (12-17 years)	15	17	32
Adults (18-64 years)	12	14	26
Age continuous Units: years			
median	10.5	12	
full range (min-max)	3 to 45	1 to 45	-
Gender categorical Units: Subjects			
Female	18	28	46
Male	42	32	74

End points

End points reporting groups

Reporting group title	Arm VI

Reporting group description:

The treatment was given every 3 weeks.
Vincristine was given by intravenous infusion on day 1 and day 8 of each course before irinotecan
Irinotecan was given by intravenous infusion on day 1 and day 5 of each course.

Reporting group title	Arm VIT

Reporting group description:

The treatment was given every 3 weeks.
Vincristine was given by intravenous infusion on day 1 and day 8 of each course before irinotecan
Irinotecan was given by intravenous infusion on day 1 and day 5 of each course, one hour following the administration of temozolide (TMZ).
TMZ was given orally, prior to vincristine and irinotecan, on days 1-5 repeated.

Primary: Objective response rate (ORR) after 2 courses of treatment in each arm (VI, VIT)

End point title	Objective response rate (ORR) after 2 courses of treatment in each arm (VI, VIT)

End point description:

The primary efficacy endpoint is defined as the documented objective response, i.e. complete or partial response, after the first 2 cycles of treatment, based on central radiological review. Responses have been evaluated using the three-dimension WHO response criteria for the primary lesions and according to RECIST 1.1 criteria for metastatic sites. Patients who had a clinical progression reported before 2 cycles with no radiological confirmation of the progression were counted as progressions (all of them died shortly after the diagnosis of progression). A radiological review by the independent radiological experts' committee has been done for 88 cases. For the others, evaluation from the center has been taking into account.

End point type	Primary

End point timeframe:

From start of treatment to 2 courses of treatment

End point values	Arm VI	Arm VIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	55		
Units: Number of participants	18	24		

Statistical analyses

Statistical analysis title	ORR between two arms

Statistical analysis description:

A multivariate logistic regression gives the adjusted odds ratio of treatment failure (no objective response) for the VIT arm compared to the VI arm. Model is adjusted on possible confounding factors in the treatment arm effect estimate: histology (non-alveolar vs alveolar), disease staging at study entry (metastatic vs loco-regional) and disease status (refractory vs relapse).

Comparison groups	Arm VIT v Arm VI
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.09
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.12

Notes:

[1] - bilateral test

Secondary: Best overall response over the treatment duration in each arm (VI, VIT)

End point title	Best overall response over the treatment duration in each arm (VI, VIT)

End point description:

Best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started) over the whole treatment duration, using the three-dimension WHO response criteria for the primary lesions and according to RECIST 1.1 criteria for metastatic sites, based on central radiological review when available, and excluding response related to local treatment. Objective response as best response includes complete response and partial response as best response.

End point type	Secondary

End point timeframe:

Start of treatment to end of treatment (before local treatment if any)

End point values	Arm VI	Arm VIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: Number of participants				
Objective Response	22	33		
Complete Response	4	9		
Partial Response	18	24		
Minor Partial Response	1	3		
Stable Disease	16	13		
Progressive Disease	19	9		

Statistical analyses

Statistical analysis title	Best overall response between two arms

Statistical analysis description:

A multivariate logistic regression gives the adjusted odds ratio of non-objective response for the best overall response for the VIT arm compared to the VI arm. Model is adjusted on possible confounding factors in the treatment arm effect estimate: histology (non-alveolar vs alveolar), disease staging at

study entry (metastatic vs loco-regional) and disease status (refractory vs relapse).

Comparison groups	Arm VI v Arm VIT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.023
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.88

Notes:

[2] - bilateral

Secondary: Duration of treatment response in each arm (VI, VIT)

End point title	Duration of treatment response in each arm (VI, VIT)

End point description:

Overall, 55 patients (22 VI and 33 VIT) had achieved an objective response under study treatment and before local treatment, and are thus evaluable for the duration of response. Duration of response defined as the time from first documentation of objective tumour response to the first objective or clinical documentation of progression, as defined by the radiological review committee when available, based on the information from the treating centre in the other cases. Patients without progression will be censored at the date of death or at the date of last news.

End point type	Secondary

End point timeframe:

From first documentation of objective tumour response to date of last news.

End point values	Arm VI	Arm VIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	33		
Units: Months				
median (confidence interval 95%)	8.8 (2.5 to 20.1)	12.3 (2.9 to 20.9)		

Statistical analyses

Statistical analysis title	Treatment response between two arms

Statistical analysis description:

A multivariate Cox model gives the adjusted hazard ratio of progression after objective response under treatment for the VIT arm compared to the VI arm. Model is adjusted on possible confounding factors in the treatment arm effect estimate: histology (non-alveolar vs alveolar), disease staging at study entry (metastatic vs loco-regional) and disease status (refractory vs relapse).

Comparison groups	Arm VI v Arm VIT

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.282
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.35

Notes:

[3] - bilateral test

Secondary: Progression-free survival (PFS) in each arm (VI, VIT)

End point title	Progression-free survival (PFS) in each arm (VI, VIT)

End point description:

Progression-free survival defined as the time interval from the date of first treatment administration (or date of randomization for untreated patients) to the date of first objective or clinical documentation of tumour progression or death due to any cause. Patients alive without progression will be censored at the date of last news. Progression was defined according to WHO criteria for the primary tumour and RECIST 1.1 criteria for metastatic sites, based on central review when available, on the evaluation from the treating centre in the other cases. Patients who had a clinical progression according to the treating physician with no radiological confirmation of the progression but who died shortly after the diagnosis of progression were counted as progressions at the corresponding date.

End point type	Secondary

End point timeframe:

Start of treatment (or date of randomization for untreated patients) to date of last news.

End point values	Arm VI	Arm VIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Months				
median (confidence interval 95%)	3.2 (2.4 to 6.7)	4.7 (4.1 to 8.5)		

Statistical analyses

Statistical analysis title	PFS between two arms

Statistical analysis description:

A multivariate Cox model gives the adjusted hazard ratio of progression for the VIT arm compared to the VI arm. Model is adjusted on possible confounding factors in the treatment arm effect estimate: histology (non-alveolar vs alveolar), disease staging at study entry (metastatic vs loco-regional) and disease status (refractory vs relapse).

Comparison groups	Arm VIT v Arm VI

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.036
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.97

Notes:

[4] - bilateral test

Secondary: Time to treatment failure in each arm (VI, VIT)

End point title	Time to treatment failure in each arm (VI, VIT)

End point description:

Time to treatment failure defined as the time interval from the date of first treatment administration to the first documentation of treatment failure, defined as tumour progression, discontinuation of study treatment before one year, or death, whichever occurs first. Data of patients still on-treatment at last follow-up were censored at the date of last treatment administration.

End point type	Secondary

End point timeframe:

Start of treatment (or date of randomization for untreated patients) to date of last news before one year.

End point values	Arm VI	Arm VIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Months				
median (confidence interval 95%)	2.8 (1.64 to 3.21)	3.99 (2.99 to 4.40)		

Statistical analyses

Statistical analysis title	Treatment failure between two arms

Statistical analysis description:

A multivariate Cox model gives the adjusted hazard ratio of treatment failure for the VIT arm compared to the VI arm. Model is adjusted on possible confounding factors in the treatment arm effect estimate: histology (non-alveolar vs alveolar), disease staging at study entry (metastatic vs loco-regional) and disease status (refractory vs relapse).

Comparison groups	Arm VIT v Arm VI

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0391
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.24

Notes:

[5] - bilateral test

Secondary: Overall survival (OS) failure in each arm (VI, VIT)

End point title	Overall survival (OS) failure in each arm (VI, VIT)

End point description:

Overall survival defined as the time interval from the date of first treatment administration (or date of randomization for untreated patients) to date of death from any cause. Patients alive will be censored at the date of last news.

End point type	Secondary

End point timeframe:

Start of treatment (or date of randomization for untreated patients) to date of last news.

End point values	Arm VI	Arm VIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: Months				
median (confidence interval 95%)	10.0 (7.1 to 12.6)	15.0 (10.0 to 21.2)		

Statistical analyses

Statistical analysis title	OS between two arms

Statistical analysis description:

A multivariate Cox model gives the adjusted hazard ratio of death for the VIT arm compared to the VI arm. Model is adjusted on possible confounding factors in the treatment arm effect estimate: histology (non-alveolar vs alveolar), disease staging at study entry (metastatic vs loco-regional) and disease status (refractory vs relapse).

Comparison groups	Arm VI v Arm VIT

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.53
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.83

Notes:

[6] - bilateral test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period begins upon signature of the informed consent form by the study subject and ends 30 days after last study treatment dose.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Arm VI
Reporting group description: -	
Reporting group title	Arm VIT

Reporting group description: -

Serious adverse events	Arm VI	Arm VIT	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 54 (42.59%)	28 / 58 (48.28%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Investigations			
NEUTROPENIA	Additional description: NEUTROPENIA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN	Additional description: TUMOUR PAIN		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM	Additional description: EMBOLISM		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
APHASIA	Additional description: APHASIA		

subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF CONSCIOUSNESS	Additional description: DEPRESSED LEVEL OF CONSCIOUSNESS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HEADACHE	Additional description: HEADACHE		
subjects affected / exposed	2 / 54 (3.70%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDROCEPHALUS	Additional description: HYDROCEPHALUS		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCLONIC	Additional description: MYOCLONIC		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL NEUROPATHY	Additional description: PERIPHERAL NEUROPATHY		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE	Additional description: SEIZURE		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE	Additional description: SYNCOPE		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

ANOREXIA	Additional description: ANOREXIA		
subjects affected / exposed	0 / 54 (0.00%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHENIA	Additional description: ASTHENIA		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION	Additional description: GENERAL PHYSICAL HEALTH DETERIORATION		
subjects affected / exposed	2 / 54 (3.70%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HYPERTHERMIA	Additional description: HYPERTHERMIA		
subjects affected / exposed	2 / 54 (3.70%)	4 / 58 (6.90%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN, OTHER	Additional description: PAIN, OTHER		
subjects affected / exposed	2 / 54 (3.70%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED	Additional description: WEIGHT DECREASED		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
subjects affected / exposed	2 / 54 (3.70%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES	Additional description: ASCITES		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

COLITIS	Additional description: COLITIS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CONSTIPATION	Additional description: CONSTIPATION		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

DIARRHOEA	Additional description: DIARRHOEA		
subjects affected / exposed	4 / 54 (7.41%)	10 / 58 (17.24%)	
occurrences causally related to treatment / all	4 / 6	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	

INTUSSUSCEPTION	Additional description: INTUSSUSCEPTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

LARGE INTESTINE PERFORATION	Additional description: LARGE INTESTINE PERFORATION		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NAUSEA	Additional description: NAUSEA		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

PANCREATITIS	Additional description: PANCREATITIS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SMALL INTESTINAL OBSTRUCTION	Additional description: SMALL INTESTINAL OBSTRUCTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

VOMITING	Additional description: VOMITING

subjects affected / exposed	4 / 54 (7.41%)	10 / 58 (17.24%)	
occurrences causally related to treatment / all	3 / 4	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLESTASIS	Additional description: CHOLESTASIS		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER DISORDER	Additional description: LIVER DISORDER		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA	Additional description: DYSPNOEA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BACTERIAL INFECTION, NOS	Additional description: BACTERIAL INFECTION, NOS		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS INFECTIVE	Additional description: CHOLECYSTITIS INFECTIVE		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS	Additional description: CLOSTRIDIUM DIFFICILE COLITIS		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION	Additional description: DEVICE RELATED INFECTION		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
subjects affected / exposed	3 / 54 (5.56%)	3 / 58 (5.17%)	
occurrences causally related to treatment / all	1 / 4	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
FUNGIC INFECTION	Additional description: FUNGIC INFECTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS	Additional description: SEPSIS		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION	Additional description: VIRAL INFECTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION	Additional description: WOUND INFECTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION	Additional description: DEHYDRATION		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA	Additional description: HYPOKALAEMIA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA	Additional description: HYPONATRAEMIA		

subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm VI	Arm VIT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)	58 / 58 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN	Additional description: TUMOUR PAIN		
subjects affected / exposed	4 / 54 (7.41%)	2 / 58 (3.45%)	
occurrences (all)	5	2	
Vascular disorders			
EPISTAXIS	Additional description: EPISTAXIS		
subjects affected / exposed	1 / 54 (1.85%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
HAEMATOMA	Additional description: HAEMATOMA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
HOT FLUSH	Additional description: HOT FLUSH		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
HYPERTENSION	Additional description: HYPERTENSION		
subjects affected / exposed	2 / 54 (3.70%)	2 / 58 (3.45%)	
occurrences (all)	2	2	
HYPOTENSION	Additional description: HYPOTENSION		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
MENO/METRORRHAGIA	Additional description: MENO/METRORRHAGIA		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	2	
PURPURA	Additional description: PURPURA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions			
ANOREXIA	Additional description: ANOREXIA		
subjects affected / exposed	8 / 54 (14.81%)	15 / 58 (25.86%)	
occurrences (all)	9	24	
ASTHENIA	Additional description: ASTHENIA		
subjects affected / exposed	16 / 54 (29.63%)	29 / 58 (50.00%)	
occurrences (all)	27	52	
FACE OEDEMA	Additional description: FACE OEDEMA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
HYPERTHERMIA	Additional description: HYPERTHERMIA		
subjects affected / exposed	6 / 54 (11.11%)	4 / 58 (6.90%)	
occurrences (all)	12	5	
MALAISE	Additional description: MALAISE		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
OEDEMA PERIPHERAL	Additional description: OEDEMA PERIPHERAL		
subjects affected / exposed	2 / 54 (3.70%)	1 / 58 (1.72%)	
occurrences (all)	4	1	
PAIN, OTHER	Additional description: PAIN, OTHER		
subjects affected / exposed	7 / 54 (12.96%)	8 / 58 (13.79%)	
occurrences (all)	8	9	
WEIGHT DECREASED	Additional description: WEIGHT DECREASED		
subjects affected / exposed	8 / 54 (14.81%)	10 / 58 (17.24%)	
occurrences (all)	9	14	
Immune system disorders			
CHOLINERGIC SYNDROME	Additional description: CHOLINERGIC SYNDROME		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
DERMATITIS ALLERGIC	Additional description: DERMATITIS ALLERGIC		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
HYPERSENSITIVITY	Additional description: HYPERSENSITIVITY		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
SEASONAL ALLERGY	Additional description: SEASONAL ALLERGY		

subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
subjects affected / exposed	6 / 54 (11.11%)	6 / 58 (10.34%)	
occurrences (all)	8	9	
DYSPNOEA	Additional description: DYSPNOEA		
subjects affected / exposed	3 / 54 (5.56%)	1 / 58 (1.72%)	
occurrences (all)	3	1	
NASAL DISCOMFORT	Additional description: NASAL DISCOMFORT		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
THROAT IRRITATION	Additional description: THROAT IRRITATION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
Psychiatric disorders			
AFFECT LABILITY	Additional description: AFFECT LABILITY		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
AGITATION	Additional description: AGITATION		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	2	
ANXIETY	Additional description: ANXIETY		
subjects affected / exposed	2 / 54 (3.70%)	4 / 58 (6.90%)	
occurrences (all)	2	4	
DELIRIUM	Additional description: DELIRIUM		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
DEPRESSION	Additional description: DEPRESSION		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
INSOMNIA	Additional description: INSOMNIA		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
SLEEP TERROR	Additional description: SLEEP TERROR		

subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Investigations			
ANAEMIA	Additional description: ANAEMIA		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	4	
HYPOALBUMINEMIA	Additional description: HYPOALBUMINEMIA		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	4	
HYPOKALAEMIA	Additional description: HYPOKALAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
HYPONATRAEMIA	Additional description: HYPONATRAEMIA		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
HYPOPHOSPHATAEMIA	Additional description: HYPOPHOSPHATAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
LEUKOPENIA	Additional description: LEUKOPENIA		
subjects affected / exposed	4 / 54 (7.41%)	6 / 58 (10.34%)	
occurrences (all)	17	15	
LYMPHOCYTOSIS	Additional description: LYMPHOCYTOSIS		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	2	
LYMPHOPENIA	Additional description: LYMPHOPENIA		
subjects affected / exposed	3 / 54 (5.56%)	4 / 58 (6.90%)	
occurrences (all)	12	5	
NEUTROPENIA	Additional description: NEUTROPENIA		
subjects affected / exposed	8 / 54 (14.81%)	15 / 58 (25.86%)	
occurrences (all)	27	31	
THROMBOCYTOPENIA	Additional description: THROMBOCYTOPENIA		
subjects affected / exposed	2 / 54 (3.70%)	2 / 58 (3.45%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			

INFUSION RELATED REACTION	Additional description: INFUSION RELATED REACTION		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
INJURY	Additional description: INJURY		
subjects affected / exposed	0 / 54 (0.00%)	4 / 58 (6.90%)	
occurrences (all)	0	4	
Cardiac disorders			
BRADYCARDIA	Additional description: BRADYCARDIA		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
PALPITATIONS	Additional description: PALPITATIONS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
TACHYCARDIA	Additional description: TACHYCARDIA		
subjects affected / exposed	2 / 54 (3.70%)	3 / 58 (5.17%)	
occurrences (all)	2	3	
Nervous system disorders			
AGEUSIA	Additional description: AGEUSIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
CRANIAL NERVE DISORDER	Additional description: CRANIAL NERVE DISORDER		
subjects affected / exposed	2 / 54 (3.70%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
DEPRESSED LEVEL OF CONSCIOUSNESS	Additional description: DEPRESSED LEVEL OF CONSCIOUSNESS		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
DIZZINESS	Additional description: DIZZINESS		
subjects affected / exposed	1 / 54 (1.85%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
DYSGEUSIA	Additional description: DYSGEUSIA		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	3	
HEADACHE	Additional description: HEADACHE		
subjects affected / exposed	6 / 54 (11.11%)	10 / 58 (17.24%)	
occurrences (all)	7	19	
HEMIPLEGIA	Additional description: HEMIPLEGIA		

subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
HYPOAESTHESIA	Additional description: HYPOAESTHESIA		
subjects affected / exposed	2 / 54 (3.70%)	1 / 58 (1.72%)	
occurrences (all)	2	2	
MEMORY IMPAIRMENT	Additional description: MEMORY IMPAIRMENT		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
MONOPLEGIA	Additional description: MONOPLEGIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
NEURALGIA	Additional description: NEURALGIA		
subjects affected / exposed	2 / 54 (3.70%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
NEUROTOXICITY, NOS	Additional description: NEUROTOXICITY, NOS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
PERIPHERAL NEUROPATHY	Additional description: PERIPHERAL NEUROPATHY		
subjects affected / exposed	8 / 54 (14.81%)	16 / 58 (27.59%)	
occurrences (all)	9	22	
PSYCHOMOTOR HYPERACTIVITY	Additional description: PSYCHOMOTOR HYPERACTIVITY		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
SEIZURE	Additional description: SEIZURE		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
SYNCOPE	Additional description: SYNCOPE		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
TREMOR	Additional description: TREMOR		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
ANAEMIA	Additional description: ANAEMIA		
subjects affected / exposed	54 / 54 (100.00%)	58 / 58 (100.00%)	
occurrences (all)	1479	1609	

LEUKOPENIA	Additional description: LEUKOPENIA		
subjects affected / exposed	9 / 54 (16.67%)	14 / 58 (24.14%)	
occurrences (all)	18	25	
LYMPHOPENIA	Additional description: LYMPHOPENIA		
subjects affected / exposed	7 / 54 (12.96%)	9 / 58 (15.52%)	
occurrences (all)	17	14	
NEUTROPENIA	Additional description: NEUTROPENIA		
subjects affected / exposed	54 / 54 (100.00%)	58 / 58 (100.00%)	
occurrences (all)	360	476	
THROMBOCYTOPENIA	Additional description: THROMBOCYTOPENIA		
subjects affected / exposed	5 / 54 (9.26%)	5 / 58 (8.62%)	
occurrences (all)	8	6	
Ear and labyrinth disorders			
DEAFNESS UNILATERAL	Additional description: DEAFNESS UNILATERAL		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
Eye disorders			
DIPLOPIA	Additional description: DIPLOPIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
DRY EYE	Additional description: DRY EYE		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
EYE DISORDER	Additional description: EYE DISORDER		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
EYELID OEDEMA	Additional description: EYELID OEDEMA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
PAPILLOEDEMA	Additional description: PAPILLOEDEMA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
PHOTOPHOBIA	Additional description: PHOTOPHOBIA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
VISUAL IMPAIRMENT	Additional description: VISUAL IMPAIRMENT		

subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
ABDOMINAL DISTENSION	Additional description: ABDOMINAL DISTENSION		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
subjects affected / exposed	20 / 54 (37.04%)	29 / 58 (50.00%)	
occurrences (all)	29	58	
ANAL HAEMORRHAGE	Additional description: ANAL HAEMORRHAGE		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
ANAL INCONTINENCE	Additional description: ANAL INCONTINENCE		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
ANORECTAL DISORDER	Additional description: ANORECTAL DISORDER		
subjects affected / exposed	1 / 54 (1.85%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
CONSTIPATION	Additional description: CONSTIPATION		
subjects affected / exposed	10 / 54 (18.52%)	22 / 58 (37.93%)	
occurrences (all)	12	30	
DIARRHOEA	Additional description: DIARRHOEA		
subjects affected / exposed	43 / 54 (79.63%)	48 / 58 (82.76%)	
occurrences (all)	107	162	
DYSPEPSIA	Additional description: DYSPEPSIA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	2	
GASTROOESOPHAGEAL REFLUX DISEASE	Additional description: GASTROOESOPHAGEAL REFLUX DISEASE		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
NAUSEA	Additional description: NAUSEA		
subjects affected / exposed	24 / 54 (44.44%)	34 / 58 (58.62%)	
occurrences (all)	47	77	
OESOPHAGITIS	Additional description: OESOPHAGITIS		

subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
PANCREATITIS	Additional description: PANCREATITIS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
SALIVARY HYPERSECRETION	Additional description: SALIVARY HYPERSECRETION		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
STOMATITIS	Additional description: STOMATITIS		
subjects affected / exposed	3 / 54 (5.56%)	10 / 58 (17.24%)	
occurrences (all)	3	17	
VOMITING	Additional description: VOMITING		
subjects affected / exposed	35 / 54 (64.81%)	44 / 58 (75.86%)	
occurrences (all)	90	132	
Hepatobiliary disorders			
BLOOD ALKALINE PHOSPHATASE INCREASED	Additional description: BLOOD ALKALINE PHOSPHATASE INCREASED		
subjects affected / exposed	3 / 54 (5.56%)	2 / 58 (3.45%)	
occurrences (all)	4	4	
GAMMA-GLUTAMYLTRANSFERASE INCREASED	Additional description: GAMMA-GLUTAMYLTRANSFERASE INCREASED		
subjects affected / exposed	3 / 54 (5.56%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
HEPATIC FAILURE	Additional description: HEPATIC FAILURE		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
LIVER DISORDER	Additional description: LIVER DISORDER		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
TRANSAMINASES INCREASED	Additional description: TRANSAMINASES INCREASED		
subjects affected / exposed	9 / 54 (16.67%)	13 / 58 (22.41%)	
occurrences (all)	28	25	
Skin and subcutaneous tissue disorders			
ALOPECIA	Additional description: ALOPECIA		
subjects affected / exposed	10 / 54 (18.52%)	13 / 58 (22.41%)	
occurrences (all)	14	17	
DECUBITUS ULCER	Additional description: DECUBITUS ULCER		

subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
DRY SKIN	Additional description: DRY SKIN		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
ECZEMA	Additional description: ECZEMA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
PRURITUS	Additional description: PRURITUS		
subjects affected / exposed	1 / 54 (1.85%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
RADIODERMATITIS	Additional description: RADIODERMATITIS		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
RASH	Additional description: RASH		
subjects affected / exposed	6 / 54 (11.11%)	7 / 58 (12.07%)	
occurrences (all)	8	11	
SKIN EXFOLIATION	Additional description: SKIN EXFOLIATION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
SKIN LESION, NOS	Additional description: SKIN LESION, NOS		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
Renal and urinary disorders			
BLOOD CREATININE INCREASED	Additional description: BLOOD CREATININE INCREASED		
subjects affected / exposed	5 / 54 (9.26%)	1 / 58 (1.72%)	
occurrences (all)	8	1	
BLOOD UREA INCREASED	Additional description: BLOOD UREA INCREASED		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
MICTURITION URGENCY	Additional description: MICTURITION URGENCY		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
URINARY RETENTION	Additional description: URINARY RETENTION		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	

Musculoskeletal and connective tissue disorders			
MUSCLE FATIGUE	Additional description: MUSCLE FATIGUE		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	2	
MUSCLE HAEMORRHAGE	Additional description: MUSCLE HAEMORRHAGE		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
MUSCLE SPASMS	Additional description: MUSCLE SPASMS		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
MUSCLE SPASTICITY	Additional description: MUSCLE SPASTICITY		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
MUSCLE TWITCHING	Additional description: MUSCLE TWITCHING		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
MUSCULOSKELETAL PAIN	Additional description: MUSCULOSKELETAL PAIN		
subjects affected / exposed	12 / 54 (22.22%)	15 / 58 (25.86%)	
occurrences (all)	15	27	
TRISMUS	Additional description: TRISMUS		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
CONJUNCTIVITIS	Additional description: CONJUNCTIVITIS		
subjects affected / exposed	1 / 54 (1.85%)	4 / 58 (6.90%)	
occurrences (all)	1	4	
DEVICE RELATED INFECTION	Additional description: DEVICE RELATED INFECTION		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
EAR INFECTION	Additional description: EAR INFECTION		
subjects affected / exposed	2 / 54 (3.70%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
subjects affected / exposed	6 / 54 (11.11%)	10 / 58 (17.24%)	
occurrences (all)	8	12	
FUNGIC INFECTION	Additional description: FUNGIC INFECTION		

subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
GASTROENTERITIS	Additional description: GASTROENTERITIS		
subjects affected / exposed	2 / 54 (3.70%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
INFECTION, NOS	Additional description: INFECTION, NOS		
subjects affected / exposed	0 / 54 (0.00%)	4 / 58 (6.90%)	
occurrences (all)	0	5	
INFLUENZA LIKE ILLNESS	Additional description: INFLUENZA LIKE ILLNESS		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
LOWER RESPIRATORY TRACT INFECTION	Additional description: LOWER RESPIRATORY TRACT INFECTION		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	3	
PARONYCHIA	Additional description: PARONYCHIA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
PNEUMONIA	Additional description: PNEUMONIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
SEPSIS	Additional description: SEPSIS		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
UPPER RESPIRATORY TRACT INFECTION	Additional description: UPPER RESPIRATORY TRACT INFECTION		
subjects affected / exposed	5 / 54 (9.26%)	6 / 58 (10.34%)	
occurrences (all)	5	12	
URINARY TRACT INFECTION	Additional description: URINARY TRACT INFECTION		
subjects affected / exposed	3 / 54 (5.56%)	3 / 58 (5.17%)	
occurrences (all)	4	3	
VIRAL INFECTION	Additional description: VIRAL INFECTION		
subjects affected / exposed	3 / 54 (5.56%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			

DEHYDRATION	Additional description: DEHYDRATION		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
HYPERCALCAEMIA	Additional description: HYPERCALCAEMIA		
subjects affected / exposed	0 / 54 (0.00%)	1 / 58 (1.72%)	
occurrences (all)	0	1	
HYPERGLYCAEMIA	Additional description: HYPERGLYCAEMIA		
subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
HYPERKALAEMIA	Additional description: HYPERKALAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
HYPERMAGNESAEMIA	Additional description: HYPERMAGNESAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
HYPOALBUMINEMIA	Additional description: HYPOALBUMINEMIA		
subjects affected / exposed	3 / 54 (5.56%)	0 / 58 (0.00%)	
occurrences (all)	5	0	
HYPOCALCAEMIA	Additional description: HYPOCALCAEMIA		
subjects affected / exposed	2 / 54 (3.70%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
HYPOKALAEMIA	Additional description: HYPOKALAEMIA		
subjects affected / exposed	2 / 54 (3.70%)	2 / 58 (3.45%)	
occurrences (all)	2	3	
HYPOMAGNESAEMIA	Additional description: HYPOMAGNESAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
HYPONATRAEMIA	Additional description: HYPONATRAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	
occurrences (all)	1	3	
HYPOPHOSPHATAEMIA	Additional description: HYPOPHOSPHATAEMIA		
subjects affected / exposed	1 / 54 (1.85%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
MALNUTRITION	Additional description: MALNUTRITION		
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2011	International amendment n°1 of 15-July-2011 (VHP procedure: the date refers to the date of preparation of the text submitted to VHP): 1. As requested by the National Cancer Research Network (NCRN), several clarifications and modifications that could impact directly on patient safety have been added on the protocol. 2. Removal of the pharmacogenetic study, mainly due to lack of funding 3. Update of international trial site list
28 February 2012	International amendment n°2 of 4-May-2012 (VHP procedure): Changes in the protocol: - addition of a selection criteria and dose adjustments required in case of bone marrow disease - new instructions about the management of vincristine : definition of the dose level -1 (-50%), and dose reduction to be respected in case of grade 3 or 4 peripheral neurotoxicity - introduction of country-specific guidelines which describe the management of temozolomide and Cefixime in The Netherlands, and the administration of temozolomide to patients from UK who have difficulties swallowing capsules - changes in SAE reporting (all SAE should be reported to the sponsor, and pregnancies should be reported immediately as SAE to the sponsor during treatment and up to 6 months after the last administration, a period during which a method of contraception is required)
30 January 2014	International amendment n°3 of 30-Jan-2014 (VHP procedure): 1. Update of the safety reference document (SPC) of temozolomide 2. Changes in of the protocol: addition of recommendations in case of liver abnormalities according to the new version of the SPC of temozolomide
27 January 2015	International amendment n°4 of 27-Jan-2015 (VHP procedure): Changes in the protocol: - an interim analysis was performed on 80 patients being treated or on follow-up, and preliminary results about efficacy and safety have been presented to an Independent Data Monitoring Committee (IDMC) and to the Steering Committee (SC) who both recommended to continue the trial and to increase the number of subjects by 40 extra patients with recurrent RMS. This amendment was submitted to follow this recommendation, and to randomize additional patients according to prior radiotherapy (yes vs no), country and recurrence (metastatic vs locoregional) due to the importance of these factors on the PFS curve
09 July 2018	International amendment n°5 of 9 July 2018 (non-VHP procedure, the date refers to the date of preparation of the text submitted to all national coordinating centres): 1. Update of the safety reference documents (SPC) of Vincristine an irinotecan ; with changes having an impact on the conduct of the study and the safety of patients 2. Changes in the protocol: - addition of a secondary objective to estimate the relative treatment effect of VIT compared to VI in terms of objective response rate (ORR), PFS and OS, in order to anticipate the future design of FarRMS trial ; statistical considerations are updated according to this new objective - update of the protocol to make it compliant with the new safety reference documents of vincristine and irinotecan - update of Pharmacovigilance guidelines according to the recent french legislation (SAE must be reported immediately) and new sponsor procedures

24 June 2019	International amendment n°6 of 24-June-2019 (non-VHP procedure): Changes in the protocol: - Removal of a withdrawal criterion: "Local therapy after 2nd cycle of study treatment", in line with Steering Committee recommendations to perform analysis on local treatment received after VI/VIT, in order to explain the much larger effect of VIT compared to VI on overall survival than progression-free survival. - Clarification of the Last Visit of the Last Subject (LVLS) timepoint, defined as the last VI/VIT administration followed by 6 months to have relevant data in terms of response after 2 cycles ; in this way, the study end date corresponds to the last database export, and is the same all across countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34343032