Clinical trial results:
CHIMIOTHERAPIE AVEC OU SANS ANTICOAGULATION PREVENTIVE DANS LES CANCERS DU PANCREAS METASTATIQUES

Summary

EudraCT number	2007-002115-59
Trial protocol	FR
Global end of trial date	06 November 2012

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	D07-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00662688
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GERCOR
Sponsor organisation address	151 rue du faubourg saint Antoine, PARIS, France, 75011
Public contact	Regulatory Affairs, GERCOR, 33 1 40 29 85 00, regulatory.affairs@gercor.com.fr
Scientific contact	Regulatory Affairs, GERCOR, 33 140 29 85 00, regulatory.affairs@gercor.com.fr

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	06 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2012
Global end of trial reached?	Yes
Global end of trial date	06 November 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrated that preventive anticoagulation with dalteparin reduces the number of thromboembolic events in patients with pancreatic cancer receiving treatment with different combinations of gemcitabine and capecitabine

Protection of trial subjects:

Prior medication is not required. Antiemetic agents, anti-diarrhea and Hematopoietic growth factor may be used if necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	19
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From May 2008 to February 2011, 42 patients were enrolled in the study. the study was conducted in France, in 8 active centres: Hôpital Saint Antoine, Hôpital Pitié Salpêtrière , Hôpital Bichat (Paris) , CH Montfermeil, CH Meaux , Hôpital Foch (Suresnes), CH Draguignan, CH Antibes

Pre-assignment

Screening details:

Histologically confirmed adenocarcinoma of the pancreas, measurable disease defined as ≥ 2cm by CT scan or ≥1cm by spiral CT scan or MRI, No progressive thrombo-embolic disease, No adenocarcinoma of the biliary tract or ampulla of Vater, No known CNS mestastases.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A : Chemotherapy alone

Arm description:

Chemotherapy at the investigator's discretion

Arm type	Active comparator
Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine type Burris
ou Gemcitabine type "Tempero" modifié

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

association Gemcitabine - Tarceva according TNCD

Investigational medicinal product name	sel de platine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

oxaliplatine or cisplatine

Arm title	ARM B : Dalteparin plus chemotherapy

Arm description:

Dalteparin combinated with chemotherapy at the investigator's discretion and according to the THESAURUS National of digestive cancerology 2008 of TNCD

Arm type	Experimental

Investigational medicinal product name	DALTEPARIN
Investigational medicinal product code	
Other name	FRAGMINE
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Subcutaneous use

Dosage and administration details:

500UI/ day

Number of subjects in period 1[1]	ARM A : Chemotherapy alone	ARM B : Dalteparin plus chemotherapy
Started	22	19
Completed	22	19

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 23 patients were enrolled in arm A but 1 subject have withdraw consent after the randomization.
22 patients (arm A) were analysed

Baseline characteristics

Reporting groups	
Reporting group title	ARM A : Chemotherapy alone
Reporting group description:	
Chemotherapy at the investigator's discretion	
Reporting group title	ARM B : Dalteparin plus chemotherapy
Reporting group description:	
Dalteparin combinated with chemotherapy at the investigator's discretion and according to the THESAURUS National of digestive cancerology 2008 of TNCD	

Reporting group values	ARM A : Chemotherapy alone	ARM B : Dalteparin plus chemotherapy	Total
Number of subjects	22	19	41
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	8	19
From 65-84 years	11	11	22
85 years and over	0	0	0
Age continuous Units: years			
median	61.8	64.1	
full range (min-max)	43.6 to 76.7	46.3 to 78.6	-
Gender categorical Units: Subjects			
Female	10	8	18
Male	12	11	23
Thromboembolic history Units: Subjects			
No	22	17	39
Pulmonary embolism	0	0	0
Deep vein thrombosis	0	0	0
Others (exp. infarction, stenosis, AMI)	0	2	2
Portal vein thrombosis	0	0	0
Tumor localization Units: Subjects			
head of the pancreas	12	6	18
Body - tail of the pancreas	10	13	23
Tumor Surgery Units: Subjects			
Tumor removal	0	1	1
No surgery	22	18	40

adjuvant chemotherapy Units: Subjects			
Yes	0	1	1
No	22	18	40
Number of metastatic sites Units: Subjects			
1 site	14	10	24
2 sites	7	8	15
3 sites	0	1	1
4 sites	1	0	1
5 sites	0	0	0
Type of metastatic disease Units: Subjects			
Synchronous disease	22	18	40
Metachronous disease	0	1	1
Performans status (ECOG) Units: Subjects			
ECOG-PS 0	4	6	10
ECOG -PS 1	13	9	22
ECOG - PS 2	5	4	9
Factor II mutation Units: Subjects			
Yes	1	0	1
No	8	3	11
Unknown	13	16	29
Factor V mutation Units: Subjects			
Yes	0	0	0
No	5	3	8
Unknown	17	16	33
Activated protein C resistance Units: Subjects			
Yes	0	0	0
No	9	11	20
Unknown	13	8	21
Chemotherapy prescribed Units: Subjects			
Gemcitabine type "Burris"	4	4	8
Gemcitabine - Erlotinib	4	3	7
Gemcitabine - platinium salt	5	4	9
Gemcitabine - type "Tempero" modified	8	7	15
FOLFIRINOX	1	1	2
End of treatment reasons Units: Subjects			
Thromboembolic events	7	2	9
Toxicity	1	2	3
intercurrent medical event	1	1	2
patient choice	1	4	5
Investigator decision	2	1	3
Lost of follow-up	1	0	1

Death (due to disease progression)	7	7	14
other reason	2	1	3
Anticoagulation stop more 21 days	0	1	1
Weight			
Units: kilogram(s)			
median	64.8	69.8	
full range (min-max)	44 to 88	46 to 92	-
Height			
Units: centimetres			
median	165.7	170.4	
full range (min-max)	153 to 180	158 to 192	-
Absolute neutrophil count			
Units: /mm3			
median	6210.6	5977.7	
full range (min-max)	2661 to 12700	3314 to 9281	-
Hemoglobin			
Units: g/dL			
median	12.6	12.9	
full range (min-max)	8.5 to 15.8	9.4 to 15	-
Platelets			
Units: /mm3			
median	337454	286578	
full range (min-max)	157000 to 625000	136000 to 481000	-
Prothrobin rate			
Units: percent			
median	91.2	91.3	
full range (min-max)	72 to 100	64 to 100	-
Activated partial thromboplastin time			
Units: percent			
median	1.08	0.99	
full range (min-max)	0.9 to 1.73	0.8 to 1.3	-
Fibrinogen			
Units: g/L			
median	5.3	4.6	
full range (min-max)	2.9 to 8.4	2.4 to 7.1	-
C-reactiv protein			
Units: percent			
median	109.1	108.7	
full range (min-max)	83 to 155	64 to 154	-
Protein S			
Units: percent			
median	98.1	105.3	
full range (min-max)	66 to 165	56 to 163	-
antithrombin III			
Units: percent			
median	96.7	106.3	
full range (min-max)	60 to 125	69 to 146	-
Albuminaemia			
Units: g/L			
median	36.7	36.8	
full range (min-max)	26 to 46	24 to 49	-

Creatininemia Units: µM median full range (min-max)	 68.2 37 to 106	 77.6 45 to 116	 -
Total bilirubin Units: µM median full range (min-max)	 21.4 2 to 89.9	 11.9 3.1 to 25.7	 -
Alkaline phosphatase Units: UI/L median full range (min-max)	 258.6 64 to 796	 252.4 49 to 1447	 -
ASAT Units: UI/L median full range (min-max)	 34.3 10 to 67	 36.4 11 to 133	 -
ALAT Units: UI/L median full range (min-max)	 45.9 16 to 134	 45.4 8 to 137	 -
LDH Units: UI/L median full range (min-max)	 303.1 89 to 814	 365.9 129 to 1469	 -
Duration of exposure to dalteparin			
only bras B			
Units: day median full range (min-max)	 0 0 to 0	 286 7 to 994	 -

End points

End points reporting groups

Reporting group title	ARM A : Chemotherapy alone
Reporting group description:	
Chemotherapy at the investigator's discretion	
Reporting group title	ARM B : Dalteparin plus chemotherapy
Reporting group description:	
Dalteparin combinated with chemotherapy at the investigator's discretion and according to the THESAURUS National of digestive cancerology 2008 of TNCD	
Subject analysis set title	Clincal toxicity - grade 0
Subject analysis set type	Safety analysis
Subject analysis set description:	
The adverse events were assessed using the Terminology Criteria for Adevrse Event (CTCAE) version 3.0.	
Subject analysis set title	Clinical toxicity - grade 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
The adverse events were assessed using the Terminology Criteria for Adevrse Event (CTCAE) version 3.0.	
Subject analysis set title	Clinical toxicity - grade 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
The adverse events were assessed using the Terminology Criteria for Adevrse Event (CTCAE) version 3.0.	
Subject analysis set title	Clinical toxicity - grade 3
Subject analysis set type	Safety analysis
Subject analysis set description:	
The adverse events were assessed using the Terminology Criteria for Adevrse Event (CTCAE) version 3.0.	
Subject analysis set title	Clinical toxicty - grade 4
Subject analysis set type	Safety analysis
Subject analysis set description:	
The adverse events were assessed using the Terminology Criteria for Adevrse Event (CTCAE) version 3.0.	
Subject analysis set title	Clinical toxicity - grade Unknown
Subject analysis set type	Safety analysis
Subject analysis set description:	
The adverse events were assessed using the Terminology Criteria for Adevrse Event (CTCAE) version 3.0.	

Primary: Thromboembolic events

End point title	Thromboembolic events[1]
End point description:	
x	
End point type	Primary
End point timeframe:	
Number of thromboembolic events during anticoagulation treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The recruitment of eligible patients proved very laborious and it was decided to stop the study prematurely. 42 patients were enrolled on 136 planned.
Only the safety results (secondary end point) are presented in this report. Indeed an efficiency analysis

would not be relevant. The PAM07 study requires for a demonstration of efficacy a total of 124 evaluable patients.

End point values	ARM A : Chemotherapy alone	ARM B : Dalteparin plus chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	19		
Units: Numbers	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Tolerance analysis was performed on the population of patients who received at least one chemotherapy cycle with or without coagulation. Clinical adverse events were graded according to the NCI-CTCAE grading system version 3.0.
BRAS A:22 patients
BRAS B : 19 patients

End point type	Secondary

End point timeframe:

From randomization to end of treatment

End point values	Clincal toxicity - grade 0	Clinical toxicity - grade 1	Clinical toxicity - grade 2	Clinical toxicity - grade 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	41	41	41
Units: subjects				
Hematoma	39	0	1	0
Hemmorhage	40	0	0	0
Epitaxia	39	1	0	0
Purpura	40	1	0	0
Neutrophil count	22	5	6	5
Platelets count	11	19	5	3
Anemia	4	19	15	1
Nausea	12	13	14	1
Vomiting	18	14	7	1
diarrhea	17	16	5	2
Fever	31	6	2	1
palmar-plantar erythrodysesthesia syndrome	38	1	1	0
Mucositis	30	9	1	0
Neuropathy peripheral	24	9	4	3
Alopecia	29	9	2	0

End point values	Clinical toxicty - grade 4	Clinical toxicity - grade Unknown		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	41		
Units: subjects				
Hematoma	0	1		
Hemmorhage	0	1		
Epitaxia	0	1		
Purpura	0	1		
Neutrophil count	2	1		
Platelets count	2	1		
Anemia	1	1		
Nausea	0	1		
Vomiting	0	1		
diarrhea	0	1		
Fever	0	1		
palmar-plantar erythrodysesthesia syndrome	0	1		
Mucositis	0	1		
Neuropathy peripheral	0	1		
Alopecia	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date to randomization to the last visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	BRAS A : Chemotherapy alone
Reporting group description: -	
Reporting group title	Bras B : Dalteparin plus chemotherapy

Reporting group description: -

Serious adverse events	BRAS A : Chemotherapy alone	Bras B : Dalteparin plus chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 22 (54.55%)	8 / 19 (42.11%)	
number of deaths (all causes)	7	7	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Facial oedema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Deterioration of general status			
subjects affected / exposed	4 / 22 (18.18%)	4 / 19 (21.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Food intolerance			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastralgia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Acute cholecystitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	2 / 22 (9.09%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Femoral neck fracture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infection without neutropenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Suspicion diabetic decompensation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	BRAS A : Chemotherapy alone	Bras B : Dalteparin plus chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	19 / 19 (100.00%)	
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	0	
Epitaxy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	7 / 22 (31.82%)	9 / 19 (47.37%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Neutrophil count			
subjects affected / exposed	9 / 22 (40.91%)	9 / 19 (47.37%)	
occurrences (all)	0	0	
Platelet count			

subjects affected / exposed	12 / 22 (54.55%)	17 / 19 (89.47%)	
occurrences (all)	0	0	
Anemia			
subjects affected / exposed	19 / 22 (86.36%)	17 / 19 (89.47%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	5 / 22 (22.73%)	4 / 19 (21.05%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 22 (68.18%)	17 / 19 (89.47%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	11 / 22 (50.00%)	11 / 19 (57.89%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	12 / 22 (54.55%)	11 / 19 (57.89%)	
occurrences (all)	0	0	
mucositis			
subjects affected / exposed	5 / 22 (22.73%)	5 / 19 (26.32%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 22 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	0	
Alopecia			
subjects affected / exposed	5 / 22 (22.73%)	6 / 19 (31.58%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2008	The 2008 update of the TNCD no longer recommends the combination of Gemcitabine plus Capecitabine as a therapeutic option given the lack of confirmation of the data presented in 2005. Thus, we propose to modify the PAM 07 protocol by allowing the investigator to choose the chemotherapy regimen based on the updated version of the TNCD: - Gemcitabine of the Burris type, - gemcitabine-erlotinib - Gemcitabine-Platinum Salts (oxaliplatin or cisplatin) for patients with IP = 0, - Gemcitabine FDR of type Tempero
27 March 2009	List of investigators modified
28 September 2010	List of investigators modified

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2011	Due to a very low inclusion rate, GERCOR have concluded to stop the study.	-

Notes:

Limitations and caveats

None reported