# Randomized Phase II Study of Weekly ABI-007 plus Gemcitabine or Simplified LV5FU2 as First-line Therapy in Patients with Metastatic Pancreatic Cancer.

**CLINICAL STUDY PROTOCOL**
**D12-2 (AFUGEM)**

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| **EudraCT Number** | 2013-001463-23 |
| **Product Name** | ABI-007 |
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| **Original Protocol** | **Version 2.1** | **18SEPTEMBER-2013** |

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## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | adverse event |
| AEPM | adverse event with pre-specified monitoring |
| ASCO | American Society of Clinical Oncology |
| BSA | body surface area |
| BSC | best supportive care |
| CNS | central nervous system |
| CR | complete response |
| CRF | case report form |
| CSR | clinical study report |
| CT | computerized tomography |
| DI | dose-intensity |
| DMC | data monitoring committee |
| DRF | discrepancy resolution form |
| EC | executive committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOI | end of infusion |
| FA | folinic acid |
| FU | fluorouracil |
| GCP | good clinical practice |
| HR | hazard ratio |
| HRQL | health-related quality of life |
| IA | interim analysis |
| IB | Investigator's brochure |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |
| IRR | Infusion Related Reaction |
| ITT | intent-to-treat |
| IV | intra venous |
| LDH | lactico deshydrogenase |
| LLN | lower limit normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPC | Metastatic Pancreatic Cancer |
| MR | Minor Response |
| MRI | magnetic resonance imaging |
| MTD | Maximal Tolerated Dose |
| NCI-CTC | National Cancer Institute Common Terminology Criteria |
| OS | overall survival |
| PAC | pancreatic adenocarcinoma |
| PD | progressive disease |
| PFS | progression-free survival |
| PI | package insert |
| PK | pharmacokinetics |
| PR | partial response |
| Q1w | every week |
| Q2w | every 2 weeks |
| RECIST | response evaluation criteria in solid tumors |
| RR | response rate |
| SAE | serious adverse event |
| SD | stable disease |
| SmPC | summary of product characteristics |
| ULN | upper limit normal |

## SYNOPSIS

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|---|---|
| **STUDY NUMBER**<br>**EUDRACT NUMBER** | **GERCOR STUDY D12-2 – "AFUGEM"**<br>2013-001463-23 |
| **TITLE** | Randomized Phase II Study of Weekly ABI-007 plus Gemcitabine or Simplified LV5FU2 as First-line Therapy in Patients with Metastatic Pancreatic Cancer. |
| **COORDINATOR INVESTIGATOR** | Dr Jean-Baptiste Bachet (Hôpital La Pitié-Salpêtrière, Paris, France) Pr Christophe Louvet (Institut Mutualiste Montsouris, Paris, France) |
| **INVESTIGATIONAL DRUG** | ABI-007 – Paclitaxel albumin-bound particles |
| **STUDY OBJECTIVE(S)** | **Primary Objective**<br>To evaluate the efficacy of weekly ABI-007 in combination with weekly gemcitabine or with fortnightly simplified LV5FU2 regimen in terms of progression-free survival in patients with previously untreated metastatic pancreatic cancer<br>**Secondary Objective(s)**<br>To evaluate tumor Response Rate (RR) according to RECIST v1.1 guidelines<br>To evaluate the duration of response,<br>To evaluate the duration of disease control,<br>To evaluate Overall Survival (OS)<br>To assess health related Quality of life (EORTC QLQ C-30)<br>To evaluate the safety profile of ABI-007 in combination with sLV5FU2 (NCI CTCAE v4.0)<br>To assess the prognostic and predictive value of SPARC expression when feasible in both arms, hENT1 and dCK expressions in arm 1, and TS expression in arm 2. |

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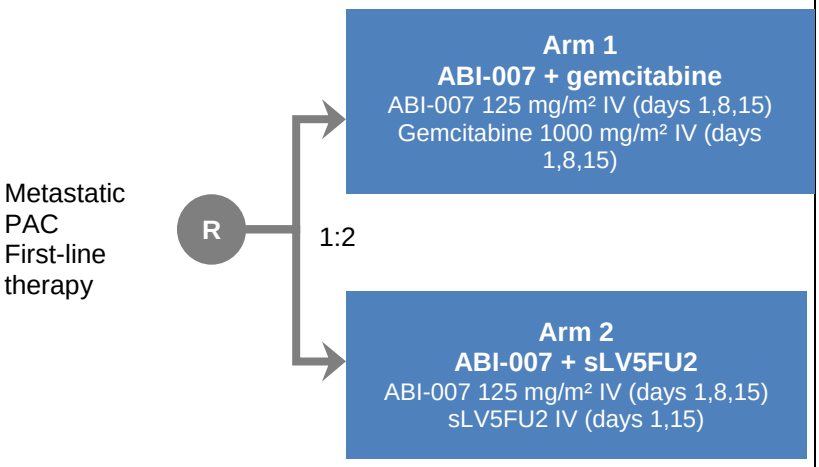
| **STUDY DESIGN** | This is a randomized (ratio 1:2), multicentre, open-label phase II study. Randomization with stratification on center and ECOG performance status.<br>  |
| **STUDY POPULATION**<br><br>**Main selection criteria:** | **Inclusion Criteria:**<br><br>1. Signed and dated informed consent, and willing and able to comply with protocol requirements,<br><br>2. Histologically or cytologically proven adenocarcinoma of the pancreas,<br><br>3. Metastatic disease confirmed (stage IV),<br><br>4. No prior therapy for metastatic disease (in case of previous adjuvant therapy, interval from end of chemotherapy and relapse must be >12 months),<br><br>5. At least one measurable or evaluable lesion as assessed by CT-scan or MRI (Magnetic Resonance Imaging) according to RECIST v1.1 guidelines,<br><br>6. Age ≥18 years,<br><br>7. ECOG Performance status (PS) 0-2,<br><br>8. Hematological status: neutrophils (ANC) >1.5x$10^9$/L; platelets >100x$10^9$/L; haemoglobin ≥9g/dL,<br><br>9. Adequate renal function: serum creatinine level <150µM,<br><br>10. Adequate liver function: AST (SGOT) and ALT (SGPT) ≤2.5xULN (≤5xULN in case of liver metastases)<br><br>11. Total bilirubin ≤1.5 x ULN, albumin ≥25g/L<br><br>12. Baseline evaluations performed before randomization: clinical and blood evaluations no more |

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| | than 2 weeks (14 days) prior to randomization, tumor assessment (CT-scan or MRI, evaluation of non-measurable lesions) no more than 3 weeks (21 days) prior to randomization,<br><br>13. Female patients must be surgically sterile, or be postmenopausal, or must commit to using reliable and appropriate methods of contraception during the study and during at least six months after the end of study treatment (when applicable). All female patients with reproductive potential must have a negative pregnancy test (β HCG) within 72 hours prior to starting ABI-007 treatment. Breastfeeding is not allowed. Male patients must agree to use effective contraception in addition to having their partner use a contraceptive method as well during the trial and during at least six months after the end of the study treatment,<br><br>14. Registration in a national health care system (CMU included for France).<br><br>**Exclusion Criteria:**<br><br>1. History or evidence upon physical examination of CNS metastasis unless adequately treated (e.g. non irradiated CNS metastasis, seizure not controlled with standard medical therapy)<br><br>2. Local or locally advanced disease (stage I to III),<br><br>3. Patient uses warfarin,<br><br>4. Uncontrolled hypercalcemia,<br><br>5. Pre-existing permanent neuropathy (NCI grade ≥2),<br><br>6. Known dihydropyrimidine dehydrogenase (DPD) deficiency,<br><br>7. Concomitant unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy),<br><br>8. Treatment with any other investigational medicinal product within 28 days prior to study entry,<br><br>9. Other serious and uncontrolled non-malignant disease (eg. active infection requiring systemic therapy, coronary stenting or myocardial infarction or stroke in the past 6 months), |

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| | 10. Known or historical active infection with HIV, or known active infection untreated with hepatitis B or hepatitis C.<br>11. History or active interstitial lung disease (ILD),<br>12. Other concomitant or previous malignancy, except: i/ adequately treated in-situ carcinoma of the uterine cervix, ii/ basal or squamous cell carcinoma of the skin, iii/ cancer in complete remission for >5 years,<br>13. Patients with known allergy to any excipient of study drugs,<br>14. Concomitant administration of live, attenuated virus vaccine such as yellow fever vaccine and concomitant administration of prophylactic phenytoin |
| **Total expected number of patients:** | 114 patients (arm 1: N=38; arm 2: N=76) |
| **Regimens:** | **ARM 1 (CONTROL) : <u>ABI-007 + Gemcitabine</u>**<br>▪ ABI-007 : 125 mg/m² IV /30min (day 1, day 8, day 15)<br>▪ Gemcitabine 1000 mg/m² IV /30min (day 1, day 8, day 15)<br>One cycle every four weeks<br>Treatment until progression or limiting toxicity<br><br>**ARM 2 (INVESTIGATIONAL) : <u>ABI-007 + simplified LV5FU2</u>**<br>▪ ABI-007 : 125 mg/m² IV/30 min (day 1, day 8, day 15)<br>▪ Folinic acid: 400 mg/m² IV /2h (day 1, day 15)<br>▪ Bolus 5-FU: 400 mg/m² IV /15min (day 1, day 15)<br>▪ 5-FU infusion: 2400 mg/m² IV /46h (day 1-2, day 15-16)<br>One cycle every four weeks<br>Treatment until progression or limiting toxicity |

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| **ASSESSMENT SCHEDULE** | ▪ Screening visit (V1) : day≤ 21<br>▪ Eligibility visit (V2): day≤ 14<br>▪ Start of study treatment: day 1 (within 7 days of randomization)<br>▪ Tumor evaluations visits (V3): every 2 months (RECIST 1.1)<br>▪ End of study treatment visit (V4)<br>▪ Follow-up visit (V5) |
| **STATISTICAL CONSIDERATIONS** | **Total number of patients: 114 to be randomized (ratio 1:2)**<br>▪ Accrual time: 18 months (7 patients per month)<br>▪ Follow-up time for primary endpoint: follow-up for the last patient-in 4 months from randomization<br>**Fleming 2-stage design**<br>▪ Null hypothesis (H0): 4-month PFS=35%<br>▪ Alternative hypothesis (H1): 4-month PFS=50%<br>▪ One-sided type I error (α): 5%,<br>▪ Type II error (ß): 20% (power 80%),<br>▪ Expected drop-out patients: 5%<br>**Randomization**<br>Randomization by minimization technique, ratio 1:2<br>Stratification criteria:<br>- Center,<br>- ECOG PS (0-1 versus 2) |
| **DURATION OF STUDY PERIOD** | Expected monthly accrual: 7 patients<br>Estimated accrual duration: 18 months<br>Estimated minimal follow-up for last included patient for primary objective : 4 months from randomization<br>Estimated mean treatment duration per patient: 6 months<br>Estimated trial duration: 30 months |
| **PLANNED DATES OF BEGINNING AND END OF STUDY** | Date of beginning of study: 4Q 2013 (First patient in).<br>Date of end of study: 2Q 2016 (Last patient out) |
| **TRANSLATIONAL SUB-STUDY** | Collection of paraffin embedded tumor tissue to assess biomarkers<br>SPARC when feasible, in both arms<br>hENT1, dCK in Arm 1<br>TS in Arm2 |

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## STUDY PLAN TABLE

| | Prior to randomization | | Treatment phase (until disease progression or toxicity) | | Post-treatment | |
|---|---|---|---|---|---|---|
| | Screening Visit Day-21 | Eligibility Visit Day-14 | Start of Study Treatment[1] | Treatment Visit (prior to each scheduled dosing: D1, D8, D15 of each cycle ) | End of Treatment Visit 28 Days post study treatment | Standard Follow-up |
| | V1 | V2 | **Day 1** | V3 | V4 | |
| **Informed consent** | X | | | | | |
| **Eligibility criteria** | X | X | | | | |
| **Demographic data/ Medical history** | X | | | | | |
| **Histology reports review for inclusion** | X | | | | | |
| **Physical examination** | X | X | | X | X | |
| **Vital signs** | X | X | | X | X | |
| **12 lead-ECG**[2] | X | | | | | |
| **Diagnostic Imaging** | X | | | | | |
| **Tumor evaluation -CT scan or MRI**[3] | | | | Every 8 weeks | | |
| | | | | | | |
| **Biopsy-Surgical specimen collection**[4] | X | | | | | |
| **Laboratory tests** | | | | | | |
| Biochemistry (total bilirubin, AST, ALT……..) | | X | | X | X | |
| Haematology (WBC, …..) | | X | | X | X | |
| Albumin plasma level | | X | | Every 8 weeks | X | |
| β-HCG Pregnancy test (blood or urinary test) | X[5] | | | | | |
| **Plasma biomarkers** (CA19-9, CEA) | X | | | Every 8 weeks | X | |
| **Adverse event collection** | X | X | | X | X | X |
| **Quality of life questionnaire** | | X | | at D1 of each cycle | X | |
| **Prior treatment / concomitant treatment** | X | X | | X | X | |
| **Follow-up information** | | | | | | X[6] |

[1] Eligible patients must start study treatment within 7 days of **randomisation;** [2] performed within 2 months before randomization; [3] unscheduled CT scan for suspected progression can be performed at anytime; [4] Biopsy is off protocol, performed as part of the standard practice to confirm diagnosis [5] Within 72 hours of starting ABI-007 treatment; [6] Data collected as part of the standard patient follow-up: Date of progression if the patient withdrew due to other reason than progression, Date of initiation and type of new therapy: second-line and the eventual other(s) line(s) if administered, Date of death

# 1. INTRODUCTION AND BACKGROUND INFORMATION

## 1.1. PANCREATIC CANCER

The incidence of pancreatic adenocarcinoma (PAC) increases regularly in most of the western countries and this cancer ranks as the fourth cause of death by cancer [1]. Considering all stages, five years survival is less than 5% [2,3]. At diagnosis, 50% to 60% of patients have distant metastases: of the 10% of patients who undergo a curative resection, many will relapse with metastases.

In patients with resectable PAC, adjuvant chemotherapy improves the 5 years survival rate from about 10% with surgery alone up to 20% [4-7]. 5-Fluorouracil (5-FU) based chemotherapy was as efficient as gemcitabine monotherapy in the ESPAC-3 adjuvant trial [7]. Thus, gemcitabine or 5FU are today the drugs of choice for adjuvant chemotherapy which is indicated in all patients after resection of the primary tumor.

In metastatic PAC, monotherapy with gemcitabine remained the main therapeutic option during more than 10 years [8]. In phase III studies, many different combinations of drugs and new targeted therapies have been tested with gemcitabine. Unfortunately, most of these studies were negative and failed to confer any added benefit on overall survival (OS) in comparison to gemcitabine alone. Combinations of gemcitabine with fluoropyrimidine or derivative platinum were only associated with a significant OS improvement in meta-analyses [9-11]. Recently, the triplet combination of 5FU, irinotecan and oxaliplatin (FOLFIRINOX) has shown a significant benefit on progression-free survival (PFS) and OS in comparison with gemcitabine alone [12]. Nevertheless, only patients with a performance status of 0-1 and normal total bilirubin level were included in this study [12].

The taxanes, docetaxel and paclitaxel have been tested in patients with pancreatic cancer with variable and non reproducible results. Docetaxel has demonstrated variable activity in pancreatic cancer patients with response rates ranging from 0% to28%, and reported median survivals of 6 months or more were reported [13-16]. Docetaxel has been combined with gemcitabine in multiple studies. Gemcitabine was given weekly at the standard dose of 1,000 mg/m$^2$, and docetaxel doses ranged from 75-100 mg/m$^2$ every 3 weeks. Response rates ranged from 7.4% to33%, and the best median survival was 7

months [17,18]. In a Phase II trial paclitaxel also has been evaluated as a single agent in metastatic pancreatic cancer; the response rate was 8% and the median survival was 5 months [19].

Recently, a combination of gemcitabine plus docetaxel plus capecitabine (GTX) was tested by Fine and colleagues [20]. The response rate of such a combination was 47% partial response (PR), and 31% minor response (MR) with activity observed even in patients with previous progression on gemcitabine (10% complete response [CR], 20% PR). A recent study showed increased survival time compared to standard therapy in locally advanced or metastatic pancreatic adenocarcinoma patients treated with gemcitabine plus EndoTAG-1, a cationic lipid-complexed paclitaxel particle [21]. Therefore, combinations of gemcitabine plus a taxane remain of interest.

## 1.2. ABI-007: PACLITAXEL ALBUMIN-BOUND PARTICLES

### 1.2.1. *THE INVESTIGATIONAL PRODUCT*

ABI-007 is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm. Each 50 ml vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin, as a white to yellow sterile lyophilized powder for reconstitution with 20 ml of 0.9% Sodium Chloride Injection.

ABI-007 is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. ABI-007 has been developed to reduce the toxicities associated with paclitaxel injection (in which paclitaxel - from the native crystalline form – is formulated with Cremophor EL/ethanol as the solvent) while maintaining or improving its chemotherapeutic effect.

Additional information can be found in the Investigator's Brochure (IB).

### 1.2.2. *RATIONALE OF THE CLINICAL STUDY*

ABI-007 has been approved for commercialization in 38 countries, including the US, Canada, the EU, Australia, China, India and Korea for the treatment of women with

metastatic breast cancer. ABI-007 alone and in combination is being evaluated in a number of cancers, including metastatic melanoma, non-small cell lung cancer, pancreatic cancer, and other solid tumors. Conditions which are responsive to paclitaxel such as non-hematological solid tumor malignancies are good clinical candidates for treatment with ABI-007.

### 1.2.3. *PRE-CLINICAL STUDIES*

A range of preclinical studies in the appropriate species have been completed with ABI-007 including single and repeat-dose toxicity studies, carcinogenicity evaluations, reproductive toxicity assessments, and mutagenicity and toxicity studies. A thorough discussion of these is included in the IB.

Preclinical studies comparing ABI-007 to paclitaxel demonstrated lower toxicities, with a MTD approximately 50% higher for ABI-007 compared to paclitaxel. At equitoxic doses of paclitaxel, ABI-007 was found to be markedly more efficacious in these animal models than paclitaxel [22].

### 1.2.4. *PREVIOUS CLINICAL STUDIES*

Combination of ABI-007 plus gemcitabine

The regimen of *nab*-paclitaxel (ABI-007) plus gemcitabine showed promising antitumor activity and tolerable adverse effects in a phase I/II trial [23]. The safety results of this study reported few grade 3-4 adverse events at the exception of grade 3-4 neutropenia (67%) [23]. Using a systematic Granulocyte colony stimulating factor (G-CSF) prophylaxis, this toxicity profile may allow to prescribe this combination in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2. The results of the randomized phase III study evaluating the *nab*-paclitaxel plus gemcitabine combination in comparison to gemcitabine alone have been recently presented [24]. The overall survival (median: 8.5 months vs 6.7 months; $p<0.0001$), the progression-free survival (median: 5.5 months vs 3.7 months; $p<0.0001$) and the response rate (23% vs 7%; $p<0.0001$) were significantly increased in the *nab*-paclitaxel plus gemcitabine arm. The safety results were in concordance with those of the phase II. The most common grade 3-4 adverse events in

the combination arm and the gemcitabine arm were, respectively, neutropenia (38% vs 27%), fatigue (17% vs 7%) and neuropathy (17% vs 1%) [24].

Combination of ABI-007 plus fluoropyrimidine

For many years, 5-fluorouracil is known as an efficient cytotoxic in pancreatic adenocarcinoma, when used alone in adjuvant setting or in combination with cisplatin or oxaliplatin and/or irinotecan in metastatic setting [7,12,25-27]. *Nab*-paclitaxel can be associated with fluoropyrimidine with tolerable adverse effects. The combination of *nab*-paclitaxel plus capecitabine is currently assessed in an adjuvant randomized phase II/III study in patients with an increased risk of relapse of a primary breast carcinoma (ICE II/GBG 52 trial).

In the two randomized trials comparing capecitabine to 5-fluorouracil bolus, capecitabine had a better toxicity profile [28, 29]. Indeed capecitabine led to significantly lower incidences of grade 3-4 neutropenia and stomatitis but to an increased incidence of grade 3 hand-foot syndrome.

To our knowledge, no randomized studies have compared capecitabine to LV5FU2 regimen. However, LV5FU2 regimen has a better toxicity profile than 5-fluorouracil bolus with less neutropenia, diarrhea and stomatitis [30]. Thus, the toxicity profile of the LV5FU2 regimen appears to be closer to the one of capecitabine than of 5-fluorouracil bolus.

When analyzing the randomized studies comparing XELOX to FOLFOX4 or FOLFOX6 in patients with metastatic colorectal cancer, a cross-trial comparison between capecitabine and LV5FU2 regimen is possible. In these studies, the XELOX arm was systematically associated with less grade 3-4 neutropenia but more grade 3-4 diarrhea and grade 3 hand-foot syndrome [31-33]. Thus, in comparison to capecitabine, the option of LV5FU2 regimen combined to *nab*-paclitaxel could be associated with more grade 3-4 neutropenia but probably less diarrhea and hand-foot syndrome.

In clinical practice, diarrhea is frequent in patients with pancreatic adenocarcinoma. In addition, peritoneal carcinomatosis is a frequent metastatic site in this disease and can limit oral administration of medication and increase the risk of digestive toxicity. The hand-

foot syndrome is not easy to manage and requires frequently a dose-reduction of chemotherapy. Neutropenia is also a limiting toxicity. Nevertheless, the use of G-CSF (Granulocyte colony stimulating factor) may help in reducing the rate of such a toxicity and in using a high chemotherapy dose-intensity. For these reasons, the LV5FU2 regimen in combination with *nab*-paclitaxel will probably be better tolerated than capecitabine. In this study, the use of systematic prophylaxis with G-CSF in both arms is expected to limit the rate of grade 3-4 neutropenia and to ease prescription this combination in patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 2. The prescription of G-CSF will be made as recommended by the EORTC [34].

### 1.2.5. *POTENTIAL RISKS WITH ABI-007*

ABI-007 is not formulated in Cremophor and thus the risk of hypersensitivity reactions is much less than that of paclitaxel. The major risks of ABI-007 have been assessed in clinical trials in patients with a variety of malignances and reflect the known toxicities of paclitaxel. See the IB for a complete description of all toxicities reported in conjunction with ABI-007 administration.

The most common toxicities reported following ABI-007 administration are:

• *Myelosuppression, predominantly neutropenia*. Grade 4 neutropenia was reported and typically resolved in <7 days.

• *Peripheral neuropathy, predominantly sensory*. Grade 3 peripheral neuropathy was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the ABI-007 dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart ABI-007 dosing at a lower dose level.

• *Nausea and vomiting*. Nausea and vomiting were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens.

• *Myalgia and arthralgia*. Myalgia and arthralgia were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication.

• *Mucositis*. Mucositis was reported typically Grade 1 or 2. It was not dose limiting.

• *Alopecia*. Alopecia was reported by most patients and was similar to that seen with paclitaxel.

## 1.3. RATIONALE OF THE TRANSLATIONAL STUDY

For 10 years, an increasing number of translational studies in PAC have been published on potential prognostic and/or predictive biomarkers. As more options are currently available in PAC treatment, identification of robust markers should be a priority. It may help in choosing the best option(s) for each patient and to therefore improve overall survival. Identification of biomarkers could help in predicting treatment efficacy or in personalizing the choice of chemotherapy.

The high expression of SPARC by peritumoral fibroblasts has been described as a negative prognostic biomarker after curative surgery in patients with PAC [35]. Such high expression of SPARC was observed in about 30% of cases [35]. At the opposite, in patients treated with gemcitabine plus ABI-007 regimen, SPARC level was a significant predictor of overall survival in multivariate analysis and seems to be a promising biomarker of ABI-007 efficacy [23].

The understanding of the intracellular uptake and metabolism of gemcitabine led to investigate how the expression of the major players in these pathways may affect gemcitabine benefit in adjuvant setting. Among these candidate biomarkers, the human equilibrative nucleoside transporter 1 (hENT1) evaluation has the strongest pre-clinical mechanistic support, and the strongest clinical dataset to suggest a meaningful role as a predictive marker able to guide treatment decisions [36-38]. Interestingly, both hENT1 and deoxycitydine kinase (dCK) expression provide additional information as compared to the isolated analysis of hENT1 [38].

Considering that the predictive values of SPARC for ABI-007 and hENT1 and dCK for gemcitabine will be probably confirmed in a near future, the ABI-007 plus gemcitabine regimen could be an option in the sub-group of patients with those predictive biomarkers. However, about 40% of patients only had high hENT1 expression in studies which evaluated it [36-38], and, consequently, a non-gemcitabine regimen could be preferred in

about 60% of patients with metastatic PAC. As we know, no studies have evaluated a possible correlation between SPARC and hENT1 expressions.

Numerous mechanisms are involved in the antitumor effect of 5FU. Among them, competitive inhibition of thymidylate synthase (TS) is one of the mains, and the predictive value of TS expression on 5FU sensitivity has been well described in vitro [39, 40]. In vivo, a large meta-analysis in colorectal cancer has reported that a high level of TS was a worse predictive marker of overall survival in metastatic colorectal cancer [HR=1.74; 95% CI: 1.34-2.26] as in adjuvant setting [HR=1.35; 95% CI: 1.07-1.80] [41]. Thus, TS expression could be assessed in pancreatic tumors using immunohistochemistry. To our knowledge, no studies have evaluated the predictive value of TS expression in PAC.

## 2. STUDY OBJECTIVES

### 2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the PFS rate at 4 months in both arms: ABI-007 plus gemcitabine and ABI-007 plus simplified LV5FU2.

### 2.2. SECONDARY OBJECTIVES

- To evaluate the tumor response rate according to RECIST 1.1 guidelines,
- To evaluate the duration of response,
- To evaluate the duration of disease control,
- To evaluate overall survival,
- To characterize the safety profile of ABI-007 in combination with sLV5FU2,
- To assess health related quality of life using QLQ C-30 questionnaire,
- To assess the prognostic and predictive value of SPARC expression when feasible, in both arms, hENT1 and dCK expressions in arm 1, and TS expression in arm 2.

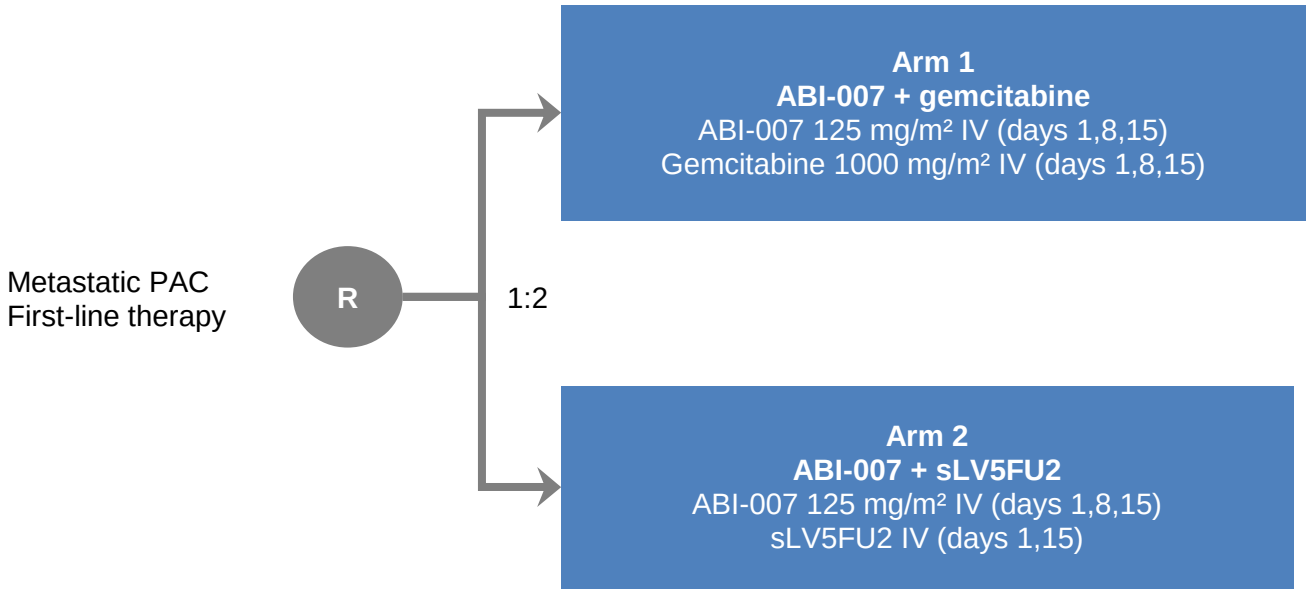
# 3. DESCRIPTION OF THE STUDY

## 3.1. DESIGN

The study is an open-label, randomized, multicenter, phase II trial conducted in France to evaluate the efficacy of weekly ABI-007 with gemcitabine or simplified LV5FU2 in terms of progression-free survival (PFS) in patients with previously untreated metastatic PAC.

One hundred fourteen patients will be randomized to each treatment regimen in a 1:2 ratio.

Randomization will be performed using a minimization technique. Stratification criteria are centre and ECOG performance status (0-1 versus 2).




## 3.2. DURATION AND PLANNED DATES OF THE STUDY

The duration of the study is expected to be 26 months, beginning with the first patient's first visit anticipated to occur in 4Q 2013, and ending with the last patient's visit by 2Q 2016.

# 4. STUDY POPULATION

## 4.1. ELIGIBILITY CRITERIA

Before any study-related procedure is undertaken, written informed consent must be obtained (see sample of information to patient and consent in Appendix 17.1)

To be eligible, all of the inclusion criteria and none of the exclusion criteria must be met.

### 4.1.1. *INCLUSION CRITERIA*

1. Signed and dated informed consent, and willing and able to comply with protocol requirements,
2. Histologically or cytologically proven adenocarcinoma of the pancreas,
3. Metastatic disease confirmed (stage IV),
4. No prior therapy for metastatic disease (in case of previous adjuvant therapy, interval from end of chemotherapy and relapse must be >12 months),
5. At least one measurable or evaluable lesion as assessed by CT-scan or MRI (Magnetic Resonance Imaging) according to RECIST v1.1 guidelines,
6. Age ≥18 years,
7. ECOG Performance status (PS) 0-2,
8. Haematological status: neutrophils (ANC) >1.5x$10^9$/L; platelets >100x$10^9$/L; haemoglobin ≥9g/dL,
9. Adequate renal function: serum creatinine level <150µM,
10. Adequate liver function: AST (SGOT) and ALT (SGPT) ≤2.5xULN (≤5xULN in case of liver metastases)
11. Total bilirubin ≤1.5 x ULN, albumin ≥25g/L

12. Baseline evaluations performed before randomization: clinical and blood evaluations no more than 2 weeks (14 days) prior to randomization, tumor assessment (CT-scan or MRI, evaluation of non-measurable lesions) no more than 3 weeks (21 days) prior to randomization,
13. Female patients must be surgically sterile, or be postmenopausal, or must commit to using reliable and appropriate methods of contraception during the study and during at least six months after the end of study treatment (when applicable). All female patients with reproductive potential must have a negative pregnancy test (β HCG) within 72 hours days prior to starting ABI-007 treatment. Breastfeeding is not allowed. Male patients must agree to use effective contraception in addition to having their partner use a contraceptive method as well during the trial and during at least six months after the end of the study treatment,
14. Registration in a national health care system (CMU included for France).

### 4.1.2. *EXCLUSION CRITERIA*

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. History or evidence upon physical examination of CNS metastasis unless adequately treated (e.g. non irradiated CNS metastasis, seizure not controlled with standard medical therapy)
2. Local or locally advanced disease (stage I to III),
3. Patient uses warfarin,
4. Uncontrolled hypercalcemia,
5. Pre-existing permanent neuropathy (NCI grade ≥2),
6. Known dihydropyrimidine dehydrogenase (DPD) deficiency,
7. Concomitant unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy),

8. Treatment with any other investigational medicinal product within 28 days prior to study entry,
9. Other serious and uncontrolled non-malignant disease (eg. active infection requiring systemic therapy, coronary stenting or myocardial infarction or stroke in the past 6 months),
10. Known or historical active infection with HIV, or known active infection untreated with hepatitis B or hepatitis C.
11. History or active interstitial lung disease (ILD),
12. Other concomitant or previous malignancy, except: i/ adequately treated in-situ carcinoma of the uterine cervix, ii/ basal or squamous cell carcinoma of the skin, iii/ cancer in complete remission for >5 years,
13. Patients with known allergy to any excipient of study drugs,
14. Concomitant administration of live, attenuated virus vaccine such as yellow fever vaccine and concomitant administration of prophylactic phenytoin

## 4.2. DURATION OF PATIENT PARTICIPATION

For each patient, the participation will last approximately 12 months, i.e. a 3-week screening period, an anticipated 6-month mean treatment period, an evaluation at 1 month post treatment , and a follow-up period until death or of at least 12 months from randomization whichever occurs last.

## 4.3. PREMATURE DISCONTINUATION CRITERIA

If a patient is prematurely withdrawn from the study treatment, the Investigator should document the date and reason by means of a narrative description.

The study treatment may be interrupted or stopped at the discretion of the investigator if this is considered to be in the best interest of the patient. An attempt to obtain all end-of-study evaluations is expected.

The criteria could include treatment-limiting toxicity, intercurrent medical problem, non-compliance with study procedure, voluntary withdrawal, investigator's decision.

A patient may be discontinued from the study at any time for one or more of the following reasons:

1. Protocol deviation that could invalidate the interpretation of the results
2. Dose interruption longer than 21 days for acute toxicity
3. Withdrawal of consent for any reason, at any time,
4. Lost to follow-up,
5. Pregnancy.

### 4.4. LOST TO FOLLOW-UP

Investigators should make every effort to minimise the number of patients lost to follow-up and to obtain a maximum of information on patients lost to follow-up. All attempts will be documented in the patient's medical records.

## 5. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

### 5.1. DESCRIPTION

ABI-007 is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm. Each 50 ml vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin, as a white to yellow sterile lyophilized powder for reconstitution with 20 ml of 0.9% Sodium Chloride Injection. Further details are available in the investigator's brochure (IB).

The investigational medicinal product (IMP) ABI-007 will be packaged and labelled for clinical trial use by Celgene, under GERCOR responsibility. For reconstitution of the IMP before administration, instructions in section 6.6 of the SmPC should be followed.

The labels will carry required regulatory mentions.

### 5.1.1. *SHIPMENT AND RECEIPT*

The frequency at which the IMP will be supplied to each individual centre will be adapted according to the enrolment rate of the centre, to the actual duration of the treatment of the randomized patients and will take into consideration the expiry date of the IMP**.** The IMP will be shipped to the Hospital Pharmacist in accordance with local requirements. Upon receipt of treatment supplies, the Pharmacist will inventory the study treatment and complete the shipping form. Should any abnormality of the supply boxes be observed, the Investigator or Pharmacist must immediately inform the Monitor/Sponsor.

### 5.1.2. *STORAGE REQUIREMENTS*

The IMP should be stored at room temperature in a secured limited-access area. Unreconstituted ABI-007 should be stored in accordance with the vial label. Reconstituted ABI-007 should be used immediately. If not used immediately, the vial of reconstituted ABI-007 must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

The Hospital Pharmacist will be responsible for the appropriate storage of the IMP at the study centre, and must immediately inform the Monitor/Sponsor of non respect of the required storage conditions.

### 5.1.3. *IMP RETURN, DESTRUCTION AND RECALL*

When closing the investigational centre, all unused IMP containers will be destroyed on site.

The Pharmacist must not destroy the used/unused treatment without written authorisation from the Sponsor.

If an IMP batch is suspected to be defective, Celgene will immediately inform the Sponsor so that the Hospital Pharmacist can immediately get the appropriate information.

The Hospital Pharmacist will organise the destruction of the concerned batch(es) after sponsor’s approval and new batch(es) will be sent to the investigational centre when appropriate.

## 5.2. TREATMENT OF PATIENTS

### 5.2.1. *DISPENSING*

Treatment will be assigned to eligible patients according to the randomization system including stratification, integrated into the electronic CRF.

Under no circumstances will the Investigator allow the IMP to be used other than as directed in the protocol.

### 5.2.2. *PREMEDICATION*

ABI-007 premedication

Patients do not require premedication prior to ABI-007 administration, as hypersensitivity reactions are not expected, though initial antiemetic prophylaxis is recommended due to administration of gemcitabine following ABI-007 treatment. If a hypersensitivity reaction occurs, the infusion should be stopped and not restarted. If felt to be in the patient's best interests, at the investigator's discretion, treatment may continue on subsequent cycles using the premedication regimen the institution typically uses for Taxol®.

Gemcitabine and 5-fluorouracil premedication

See gemcitabine and 5-fluorouracil Summary Product Characteristics for recommended premedication strategies.

### 5.2.3. *ADMINISTRATION*

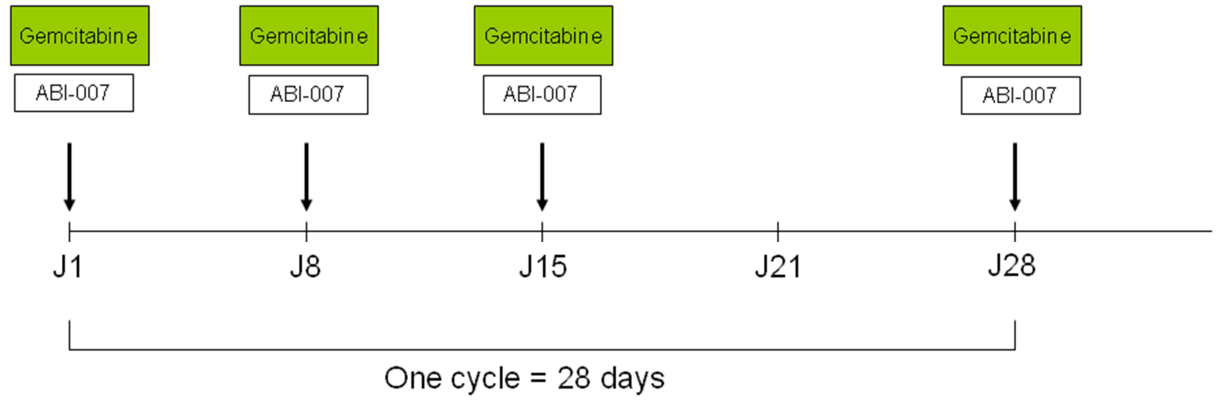
Patients will be treated on an outpatient basis with ABI-007 plus gemcitabine or ABI-007 plus sLV5FU2.

Treatment dose and schedule:

| **Cycle** | | **#1** | | | | **#2** | | | | **#3** |
|---|---|---|---|---|---|---|---|---|---|---|
| Day | | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | |
| Week | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Arm 1 | ABI-007 | × | × | × | - | × | × | × | - | … |
| | Gemcitabine | × | × | × | - | × | × | × | - | … |
| Arm 2 | ABI-007 | × | × | × | - | × | × | × | - | … |
| | sLV5FU2 | × | - | × | - | × | - | × | - | … |

Arm 1 : ABI-007 + gemcitabine regimen

| | | |
|---|---|---|
| H0 | Day 1, 8, 15 | **ABI-007** 125 mg/m², 30 min IV infusion (maximum infusion time not to exceed 40 minutes) |
| H+0.5 | Day 1, 8, 15 | **Gemcitabine** 1000 mg/m² as a 30-min IV infusion |



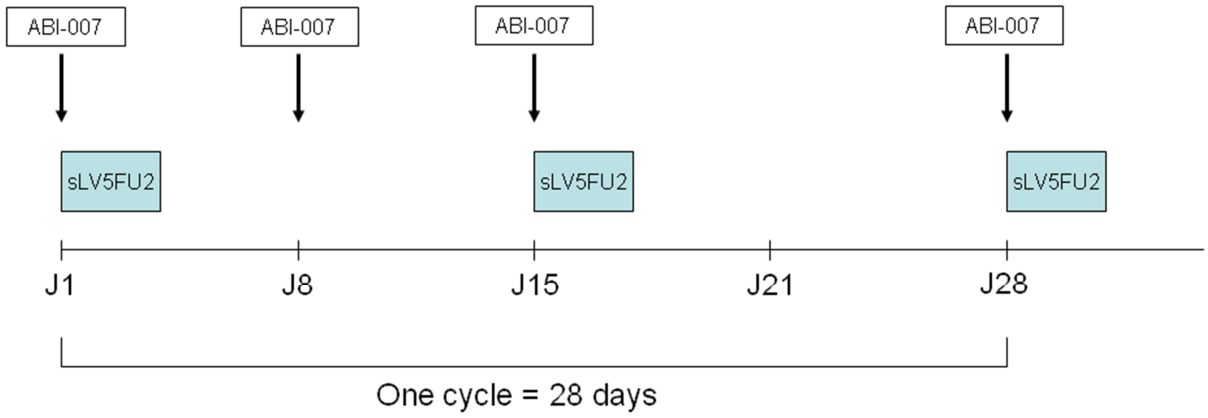

Treatment administration will be given at day 1, 8 and 15 followed by a week of rest until disease progression or limiting toxicity.

**IMPORTANT:**

- If gemcitabine must be early interrupted because of adverse events, ABI-007 must be continued until progression.
- If ABI-007 must be early interrupted because of adverse events, gemcitabine must be continued until progression.
- If both gemcitabine and ABI-007 must be early interrupted because of adverse events, a complete break in therapy will be allowed until disease progression.

Arm 2: ABI-007 + sLV5FU2 regimen

| | | |
|---|---|---|
| H0 | Day 1, 8, 15 | **ABI-007** 125 mg/m², 30 min IV infusion (maximum infusion time not to exceed 40 minutes) |
| H+0.5 | Day 1, 15 | **Folinic acid** 400 mg/m² (leucovorin, *l* + d racemic form, or *l* form 200mg/m²) in 250 ml glucose 5% solution, 2-h IV infusion |
| H + 2.5 | Day 1, 15 | **5-FU bolus** 400 mg/m² in 100 ml glucose 5% solution, 15 min IV infusion |
| H+ 3 | Days 1-2, 15-16 | **5-FU continuous infusion** 2400 mg/m², 46-h IV infusion |



Treatment administration will be given at day 1, 8 and 15 followed by a week of rest for ABI-007, and at day 1 and 15 for sLV5FU2 until disease progression or limiting toxicity.

**IMPORTANT:**

- If sLV5FU2 must be early interrupted because of adverse events, ABI-007 must be continued until progression.
- If ABI-007 must be early interrupted because of adverse events, sLV5FU2 must be continued until progression.
- If both sLV5FU2 and ABI-007 must be early interrupted because of adverse events, a complete break in therapy will be allowed until disease progression.

A systematic primary G-CSF prophylaxis is recommended in patients with an ECOG performance status of 2 in both arms. After a previous episode of febrile neutropenia, a secondary G-CSF prophylaxis is recommended in patients with an ECOG performance status of 0-1 in both arms according to EORTC guidelines. The type of G-CSF and treatment duration will be determined according to local standard of care in each center. An administration of lenograstim or filgrastim is commonly recommended: one injection daily from J9 to J14 of each cycle, or an administration of pegfilgrastim, one single injection at J9 of each cycle.

### 5.2.4. *RULES FOR DOSE OMISSIONS AND MODIFIED SCHEDULES*

If the dose held or missed was to be given on Day 1, 8 or 15 of the cycle, this dose will be considered as canceled and will not be shifted; i.e.:

- normal administration: 1-2-3-Rest-1-2-3-Rest, etc
- cancellation of day 1: 1-2-3-Rest-X-2-3-Rest, etc
- cancellation of day 8: 1-2-3-Rest-1-X-3-Rest, etc
- cancellation of day 15: 1-2-X-Rest-1-2-3-Rest, etc

The time period between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days in case of acute toxicity (except in case of peripheral neuropathy; see Section 5.2.6).

### 5.2.5. *DOSE ADJUSTMENT OF FIRST CYCLE*

Doses of the first cycle will be adapted according to the ECOG PS at inclusion.

- Patients with an ECOG PS of 0 or 1 at inclusion will receive a full dose for the first cycle.

- Patients with an ECOG PS of 2 at inclusion will receive a level -1 of dose for the first cycle. In absence of grade 2 or more toxicity during the first cycle, patients with an ECOG PS of 2 at inclusion will receive a full dose from the second cycle.

| Dose Level | ABI-007 (mg/m²) | Gemcitabine (mg/m²) | 5-FU bolus (mg/m²) | 5-FU infusion (mg/m²) |
|---|---|---|---|---|
| Study dose | 125 | 1000 | 400 | 2400 |
| Level -1 | 100 | 1000 | 400 | 2400 |

### 5.2.6. *DOSE ADJUSTMENT WITHIN A TREATMENT CYCLE AND AFTER FIRST CYCLE*

Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.0. Alopecia will not generate dose reduction during the study.

Two dose modifications are permitted in the ABI-007 + gemcitabine arm and in the ABI-007 + sLV5FU2 arm according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either drug, further treatment should be discontinued.

| Dose Level | ABI-007 (mg/m²) | Gemcitabine (mg/m²) | 5-FU bolus (mg/m²) | 5-FU infusion (mg/m²) |
|---|---|---|---|---|
| Study dose | 125 | 1000 | 400 | 2400 |
| Level -1 | 100 | 1000 | 400 | 2400 |
| Level -2 | 75 | 800 | - | 2000 |

Patients experiencing study drug-related toxicities that require a delay in scheduled ABI-007, gemcitabine or sLV5FU2 dosing for >21 days will be discontinued from further treatment in this study (except for peripheral neuropathy; see Section 5.2.6). In case of dose interruption longer than 21 days for other medical reasons (such as biliary obstruction), additional time can be discussed with the coordinator and the patient remained in the study. When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment.

DOSE ADJUSTMENTS BEFORE A TREATMENT CYCLE

If dose modifications are required at the beginning of a cycle due to hematologic or non hematologic toxicities, doses of ABI-007, of gemcitabine and of sLV5FU2 may be adjusted as detailed below.

| Toxicity | Timing and dose modifications |
|---|---|
| Hematologic | |
| ANC ≥ 1500 AND Platelets ≥ 100,000 | Day 1 on time |
| ANC < 1500 OR Platelets < 100,000 | Day 1 is delayed until recovery |
| Non Hematologic | |
| Grade 0-1 | Day 1 on time |
| Grade 2 | Day 1 is delayed until recovery |
| Grade 3 | Day 1 is delayed until recovery and decrease dose level to next lower[a] |
| Grade 4[b] | End of study treatment[b] |

[a] If the toxicity only affects neuropathy, then only ABI-007 should be reduced (please see Section PERIPHERAL NEUROPATHY).
[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section PULMONARY EMBOLISM).

DOSE ADJUSTMENTS WITHIN A TREATMENT CYCLE

If patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up.

Dose modifications due to hematologic toxicity within a treatment cycle should be adjusted as described below.

| **Day 8** | | **Day 15** | | **Any Day** |
|---|---|---|---|---|
| Blood counts | Dose modifications | Blood counts | Dose modifications | Dose modifications |
| ANC ≥1000 AND Platelets ≥75,000 | Same dose, Day 8 on time | ANC ≥1000 AND Platelets ≥75,000 | Same dose, Day 15 on time | |
| | | ANC 500-1000 OR Platelets 50,000-<75,000 | Lower level, Day 15 on time | |
| | | ANC <500 OR Platelets <50,000 | Hold | |
| ANC 500-1000 OR Platelets 50,000-<75,000 | Lower level, Day 8 on time | ANC ≥1000 AND Platelets ≥75,000 | Same dose, Day 15 on time | |
| | | ANC 500-1000 OR Platelets 50,000-<75,000 | Lower level, Day 15 on time | |
| | | ANC <500 OR Platelets <50,000 | Hold | |
| ANC <500 OR Platelets <50,000 | Hold | ANC ≥1000 AND Platelets ≥75,000 | Lower level, Day 15 on time | |
| | | ANC 500-1000 OR Platelets 50,000-<75,000 | Lower level, Day 15 on time | |
| | | ANC <500 OR Platelets <50,000 | Hold | |
| Febrile neutropenia (Grade 3-4) | | | | Hold. Decrease to next lower level and do not re-escalate during treatment. |

Dose modifications due to non-hematologic toxicity within a treatment cycle should be adjusted as described below.

| Non Hematologic Toxicity | Dose modifications* |
|---|---|
| Grade 0-1 | Day 8 or 15 on time |
| Grade 2 | Day 8 or 15 is cancelled |
| Grade 3 | Day 8 or 15 is cancelled, and Decrease dose lower level[a] |
| Grade 4[b] | End of study treatment |

[a] If the toxicity only affects neuropathy, then only ABI-007 should be reduced (please see Section PERIPERAL NEUROPATHY).
[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section PULMONARY EMBOLISM).
* dose modifications for both drugs, ABI-007 + gemcitabine or ABI-007 + sLV5FU2

PERIPHERAL NEUROPATHY

ABI-007 treatment should be withheld in patients who experience ≥Grade 3 peripheral neuropathy. Gemcitabine or sLV5FU2 administration can continue during this period. ABI-007 treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤Grade 1. Patients experiencing peripheral neuropathy that requires a postponement in scheduled ABI-007 dosing for ≥21 days will discontinue ABI-007 but will remain in the study and will continue Gemcitabine or sLFVFU2. The time to resolution to Grade ≤1 should be the adverse event duration used for adverse event reporting.

CUTANEOUS TOXICITY

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level for both drugs. If the patient still experiences such an event despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

PULMONARY EMBOLISM

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions are not expected with either ABI-007 or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy.

Patients who develop a severe hypersensitivity reaction should not be re-challenged.

# 6. PRIOR AND CONCOMITANT MEDICATION

## 6.1. PRIOR MEDICATION

The term ‘prior medication’ refers to any medication given before study entry, i.e. before informed consent was signed.

All relevant prior medication taken within 1 month before entering the study must be recorded in the patient’s medical records and documented as appropriate in the CRF.

## 6.2. CONCOMITANT MEDICATION

Concomitant medication should be kept to a minimum during the study. However, if it is considered to be necessary for the patient’s welfare or well-being and is unlikely to interfere with the study assessments, it may be given at the discretion of the Investigator, preferably after consultation with the Sponsor.

Concomitant treatment with warfarin is an exclusion criterion. However, low-molecular weight heparin (LMWH) is permitted.

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. ketoconazole and other imidazole, antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, cabamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

A systematic primary G-CSF prophylaxis is recommended in patients with an ECOG performance status of 2 in both arms. After a previous episode of febrile neutropenia, a secondary G-CSF prophylaxis is recommended in patients with an ECOG performance status of 0-1 in both arms according to EORTC guidelines.

The decision to withdraw a patient on the basis of concomitant medication should preferably be made jointly by the Sponsor and the Investigator.

All concomitant medication must be recorded in the patient's medical records and documented as appropriate in the CRF.

## 6.3. MANAGEMENT OF ADVERSE EVENTS

### 6.3.1. *NAUSEA, VOMITING*

Premedication for acute nausea and vomiting including NK1 inhibitors, 5-HT3 inhibitors and/or steroids are allowed, during chemotherapy and at home.

### 6.3.2. *DIARRHEA*

To avoid complications of diarrhea such as electrolyte imbalance, dehydration, and renal dysfunction, early intervention with loperamide should be started for diarrhea grade ≥1. Treatment of diarrhea should follow local guidance however the maximum daily dose of loperamide should not exceed 16mg.

### 6.3.3. *NEUTROPENIA*

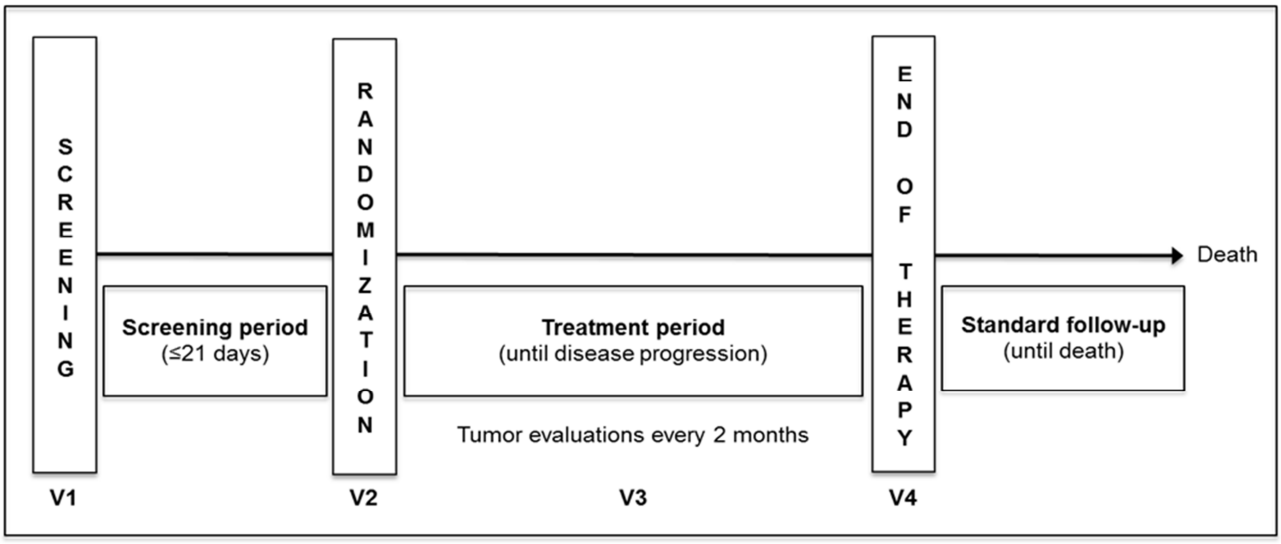
Hematopoietic growth factors (i.e. G- or GM-CSF) are recommended as prophylaxis treatment. Use of any growth factors must be documented in the patient record.

### 6.3.4. *INFUSION RELATED REACTION*

If an infusion related reaction (IRR) develops, the infusion should be temporarily slowed down or interrupted. The patient should be monitored until complete resolution of the symptoms and treated as clinically indicated. Treatment may include acetaminophen/paracetamol, antihistamine, IV saline, oxygen, bronchodilatators, corticosteroids and vasopressors depending on the symptoms.

## 7. STUDY PLAN

The study plan could be summarized as follows:




The first administration of the study treatment should occur within 7 days after randomization.

A study plan table outlining the study requirements by visit is presented at the end of the section.

## 7.1. SCHEDULE OF VISITS

### 7.1.1. *SCREENING - VISIT (V1) – DAY ≤21*

Patient's informed consent:

The Investigator or a formal designee should provide each patient, and/or a legal representative, with relevant, comprehensive, verbal and written information regarding the objectives and procedures of the study as well as the possible risks involved.

If possible, the patient should have enough time and opportunity to inquire about study details. All his/her questions should be answered in a satisfying manner. The patient must be informed about his/her right to withdraw from the study at any time.
Signed informed consent must be obtained from the patient, and/or a legal representative, prior to undertaking any study-related procedure.

A copy of the informed consent form, signed and dated by both the patient (or the designated person as described above) and the Investigator, should be given to the patient (or the designated person as described above). The process for obtaining consent will be documented in the patient's file.

All subjects entered into the study will receive a unique subject identification number. This number will be used to identify the subject throughout the clinical study and must be used on all study-related documents. The subject identification number must remain constant throughout the clinical study.

Results of the following assessments must be available:

- Demographics, medical history with prior medication
- Cancer and treatment history
- Physical examination including weight, height, ECOG-PS, and vital signs (temperature, blood pressure, heart rate)
- Existing signs and symptoms (pain, jaundice, ascites)
- Standard resting supine 12-lead-ECG (performed within 2 months before randomization),
- Histopathology report.

Assessment of tumor response:

Tumor response will be assessed using RECIST version 1.1. Tumor response will be measured using chest-abdominal CT-scan (or MRI). For each patient, the same method of assessment and the same technique must be used to evaluate each lesion throughout the entire treatment period. If more than one method is used, select the most accurate method according to RECIST version 1.1 when recording data. Baseline total tumor burden must be assessed within a maximum of 21 days before randomization and within a maximum of 28 days before starting study treatment.

### 7.1.2. *ELIGIBILITY - VISIT 2 - DAY ≤ 14*

Results of the following assessments must be available:

- Physical examination, weight, blood pressure, ECOG PS, neurological examination
- Hematology
- Coagulation
- BiochemistryCA 19-9 and CEA Radiological tumor assessment according to RECIST 1.1 guidelines
- Health related quality of life questionnaire (EORTC QLQ C-30)
- Serum pregnancy test in women of childbearing potential done within 72 hours prior to starting ABI-007 treatment
- Inclusion and exclusion criteria
- If the patient is eligible, to secure paraffin embedded tumor tissue

A central allocation by electronic CRF (e-CRF™) will provide patient's number as soon as eligibility criteria are fulfilled. The confirmation of patient's allocation will be immediately sent by e-mail to the investigator.

All eligible patients must start study treatment within 7 days of randomization.

### 7.1.3. *STUDY TREATMENT PERIOD – VISIT 3*

Prior to the schedule dosing (<48h):

- Concomitant treatment,
- Complete physical examination including : weight, blood pressure, ECOG PS
- Hematology : complete blood count and differential counts, haemoglobin, platelets, serum creatinine, liver function tests (LFTs) : total and indirect bilirubin, AST, ALT and alkaline phosphatase
- Health related quality of life questionnaire (EORTC QLQ C-30) at J1 of each cycle,
- Adverse event collection.

Tumor evaluation (every 2 months):

- complete physical examination including : weight, blood pressure, ECOG PS
- Radiological tumor assessment according to RECIST 1.1 guidelines
- Hematology : complete blood count and differential counts, haemoglobin, platelets,
- Biochemistry : , Albumin plasma level
- CA 19-9 and CEA
- Adverse event and concomitant medication collection.

Post-baseline tumor assessments are to be performed every 2 months. If there is a suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. All tumor assessments after baseline will be done within +/-7 days of the scheduled visit. If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, this patient may continue treatment until the next assessment, and an unscheduled assessment should be planned as soon as possible.

### 7.1.4. *END OF TREATMENT VISIT 4*

The end of strategy visit should be performed 28 days after the last dose of any study drug. A +/- 3 day window is allowed.

- Date and reason for end of study treatment,
- Complete physical examination including: weight, blood pressure, ECOG performance status (Appendix 17.3),
- Hematology: complete blood count and differential counts (including neutrophils, lymphocytes and monocytes), haemoglobin, platelets,
- Biochemistry: Albumin plasma level
- Health-related quality of life questionnaire (EORTC QLQ C-30),
- Adverse events and concomitant medication.

### 7.1.5. *FOLLOW-UP*

Patients will be followed-up every 2 months as part of their standard follow-up and the following information will be collected:

- Date of progression if the patient withdrew due to other reason than progression

- Date of initiation and type of new therapy: second-line and the eventual other(s) line(s) if administered

- Date of death

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**Table 1 :** STUDY PLAN TABLE

| | Prior to randomization | | Treatment phase (until disease progression or toxicity) | | Post-treatment | |
|---|---|---|---|---|---|---|
| | Screening Visit Day-21 | Eligibility Visit Day-14 | Start of Study Treatment[1] | Treatment Visit (prior to each scheduled dosing: D1, D8, D15 of each cycle ) | End of Treatment Visit 28 Days post study treatment | Standard Follow-up |
| | V1 | V2 | **Day 1** | V3 | V4 | |
| **Informed consent** | X | | | | | |
| **Eligibility criteria** | X | X | | | | |
| **Demographic data/ Medical history** | X | | | | | |
| **Histology reports review for inclusion** | X | | | | | |
| **Physical examination** | X | X | | X | X | |
| **Vital signs** | X | X | | X | X | |
| **12 lead-ECG**[2] | X | | | | | |
| **Diagnostic Imaging** | X | | | | | |
| **Tumor evaluation -CT scan or MRI**[3] | | | | Every 8 weeks | | |
| | | | | | | |
| **Biopsy-Surgical specimen collection**[4] | X | | | | | |
| **Laboratory tests** | | | | | | |
| Biochemistry (total bilirubin, AST, ALT……..) | | X | | X | X | |
| Haematology (WBC, …..) | | X | | X | X | |
| Albumin plasma level | | X | | Every 8 weeks | X | |
| β-HCG Pregnancy test (blood or urinary test) | X[5] | | | | | |
| **Plasma biomarkers** (CA19-9, CEA) | X | | | Every 8 weeks | X | |
| **Adverse event collection** | X | X | | X | X | X |
| **Quality of life questionnaire** | | X | | at D1 of each cycle | X | |
| **Prior treatment / concomitant treatment** | X | X | | X | X | |
| **Follow-up information** | | | | | | X[6] |

[1] Eligible patients must start study treatment within 7 days of **randomisation;** [2] performed within 2 months before randomization; [3] unscheduled CT scan for suspected progression can be performed at anytime; [4] Biopsy is off protocol, performed as part of the standard practice to confirm diagnosis [5] Within 72 hours of starting ABI-007 treatment; [6] Data collected as part of the standard patient follow-up: Date of progression if the patient withdrew due to other reason than progression, Date of initiation and type of new therapy: second-line and the eventual other(s) line(s) if administered, Date of death

## 7.2. TRANSLATIONAL STUDY

Biomarkers in tissues may be obtained from paraffin embedded material taken prior treatment. If paraffin-embedded (PE) histological or cytological material is available, and informed consent has been obtained, tumor samples will be submitted for immunohistochemistry analysis. All tissue samples for immunohistochemistry analysis will be run blinded with respect to the treatment assignment and to the patient response to treatment. PE tumor samples will be collected centrally to assess the expressions of hENT1 dCK and TS in the tumor. The levels of expressions of hENT1, dCK and TS will be determined in immunohistochemistry in using the same scores as previously reported [35-38, 41]. Analysis of SPARC expression in immunohistochemistry will be done if feasible.

PE will be centralized at Institut Mutualiste Montsouris (IMM), Paris, France. Immunohistochemistry (IHC) will be performed in IMM for hENT1, dCK and TS analysis. Tissue samples will be shipped as PE sections on slides. At least, 5 slides (1 section per slide) should be prepared using super frost plus slides and left to AIR DRY. Thickness of the sections should be at 4-5 micron.

## 7.3. COMPLIANCE WITH THE STUDY PLAN

The Investigator should make every effort to comply with the study plan. If the Investigator encounters difficulties in complying with the study plan, e.g. with regard to the schedule of visits or the required procedures, he/she must alert the Sponsor. The Sponsor may consider it relevant to generate an amendment.

The Investigator should make every effort to avoid the occurrence of deviations from the study plan. If deviations occur or if the Investigator knows that a deviation will occur, he/she must promptly inform the Sponsor to determine how to manage the deviation.

The Investigator can delegate tasks to the research team but he/she remains responsible for coordinating and informing his/her staff about the protocol and the possible changes in the study. The Investigator should maintain a list of appropriately qualified persons to whom significant study-related duties will be delegated.

# 8. SAFETY

## 8.1. SAFETY REFERENCE DOCUMENT

In this trial, the Investigator's Brochure will be considered as the Safety Reference Document, based on which evaluation of adverse events will be performed, in particular regarding their expectedness, severity and outcome.

## 8.2. BENEFIT / RISK INFORMATION

This study is a randomized phase II study in patients routinely managed for metastatic pancreatic adenocarcinoma.

All patients that will be included in this study will receive *nab*-paclitaxel in combination with gemcitabine or 5-fluorouracil. The *nab*-paclitaxel plus gemcitabine combination has recently proved its superiority compared to gemcitabine alone in a large phase III study in patients with metastatic pancreatic adenocarcinoma. The 5-fluorouracil is a component of several therapeutic protocols used in such an indication. The efficacy of 5-fluorouracil alone has been shown similar to the one of gemcitabine alone in adjuvant setting, after curative surgical resection.

Adverse events reported with the three drugs used in this study have been well described and are routinely managed in the investigational sites that will take part in the study. Patients will be informed of the adverse events that may occur.
Patients will be followed-up as recommended in this disease, including an evaluation every 8 weeks and regular biological exams before each cycle of chemotherapy.It is not anticipated that the study will modify the benefit risk ratio for the patient.

## 8.3. DEFINITION AND REPORTING OF (SERIOUS) ADVERSE EVENTS

### 8.3.1. *DEFINITION OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT*

**An adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign, including an abnormal clinically significant laboratory finding or ECG, any symptom, syndrome or disease temporally associated with the use of a medicinal product, whether or not related to the IMP that can be new or exacerbated by the deterioration of a pre-existing condition.

**A Serious Adverse Event (SAE)** is an AE that, at any time, fulfils one or more of the following criteria:

- **results in death,**
- **is life threatening**, i.e. the patient was at immediate risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe,
- **requires in-patient hospitalisation or prolongation of existing hospitalisation**, i.e. hospitalisation signifies that the patient has been detained, usually involving at least an overnight stay,
- **results in persistent or significant disability/incapacity,** i.e. substantial disruption of a person's ability to carry out normal life functions,
- **is a congenital anomaly/birth defect,**
- **is any important medical event** that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may endanger the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

- **Occurrence of IMP overdose, abuse/misuse, or drug dependency**, whether or not clinical signs or symptoms are present, should be reported as an SAE to the sponsor. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

- **Events initially reported as an AE may become serious**. For example, diarrhoea may become debilitating and require hospitalisation or prolongation of hospitalisation and is then reported as SAE.

- **Distinction should be made between serious and severe AEs.** Severity is a measure of intensity whereas seriousness is based on the seriousness criteria described above. The severity/intensity of AEs will be graded upon the subject's symptoms according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

### 8.3.2. *CONSIDERATIONS SPECIFIC TO THE STUDY*

- Hospitalisation for planned surgical measures permitted or requested by the protocol, as well as the condition leading to these measures, if the condition was known before the start of study treatment, should not be considered as adverse events.

- hospitalisation to simplify treatment or procedures should not be considered as adverse event/ SAE
- hospitalisation for pre-existing conditions that have not been exacerbated by study treatment should not be considered as adverse event/ SAE
- A progression or worsening of the disease investigated in this study protocol will be recorded as appropriate, but will not be reported as an adverse event/serious adverse event

### 8.3.3. *PERIOD OF ADVERSE EVENT COLLECTION*

In order to ensure complete safety data collection, the period of observation for this study is from signature of informed consent (visit 1) to 28 days after the last administration of the investigational product. SAEs occurring beyond these 28 days, if assessed as related to study treatment, should also be notified to Sponsor.

### 8.3.4. *RECORDING OF (SERIOUS) ADVERSE EVENT*

Apart from adverse events clinically observed by the Investigator, the patient will be given the opportunity to report adverse events spontaneously. A general prompt will also be given to detect adverse events, e.g. “Did you notice anything unusual about your health since your last visit?”

It is the responsibility of the Investigator to record all the relevant information regarding the event.

The Investigator is requested to assess the relationship between the investigational product and the occurrence of each (S)AE. The Investigator will use clinical judgment to determine the relationship. Alternatives causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated.

### 8.3.5. *PROCEDURE FOR REPORTING SERIOUS ADVERSE EVENT*

The Investigator must forward to the Sponsor **within 24 hours** a duly completed “SERIOUS ADVERSE EVENT NOTIFICATION FORM” provided by the Sponsor. The SAE

form is incorporated into the electronic CRF and can be printed-out. The SAE is to be reported even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusion:

- identification of the notifying person,
- identification of the clinical study (that identifies the product),
- identification of a patient (patient number and/or initials),
- description of the SAE and causality.

When applicable the Investigator will ensure a follow-up of an initial SAE with further investigations as may be indicated to elucidate the nature, the outcome or the causality of the SAE. This may include additional lab tests, histo-pathological examinations, and consultations with other healthcare professionals or any post mortem findings. This follow-up information should be provided to the Sponsor within 24 hours as of its availability.
In case of a follow-up of an SAE, for which additional information/modification are provided, the follow-up will be reported on a new “SERIOUS ADVERSE EVENT NOTIFICATION FORM", with the box "follow-up" being ticked.

The SAE report should be sent by fax

| |
|---|
| TO: **GERCOR within 24 hours**<br>FAX NUMBER:**+33 (*0)1.40.29.85.08***|

In rare circumstances, when fax transmission is not possible, notification by telephone is acceptable. But this should be followed with a completed “SERIOUS ADVERSE EVENT NOTIFICATION FORM” signed and faxed by the investigator as soon as possible.

Please make an immediate call to +33 (*0)1.40.29.85.00* in case of death or a life threatening reaction.

### 8.4. PREGNANCY

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in patients (or partners of patients) while the patient is still treated with the IMP, or within 28 days of the subject’s last dose of the IMP, must be

reported immediately. In case of pregnancies and suspected pregnancies in study patients, the IMP is to be discontinued immediately and the subject instructed to return any unused portion of the IMP to the Investigator. The patient should be withdrawn from the study. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately to the Sponsor using the GERCOR Pregnancy Reporting Form. The exposure of any pregnant female (e.g. caregiver, pharmacist) to the IMP is also an immediately reportable event.

If a female partner of a male subject taking the IMP becomes pregnant, the male subject taking the IMP should notify the Investigator, and the pregnant female partner should be advised to call the healthcare provider immediately.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IMP should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Any congenital anomaly detected in an aborted fetus should be reported.

The Sponsor/Coordinating Investigator shall be responsible for any decision regarding the continued participation in the Study of Patients who after an initial positive pregnancy diagnosis appear to be no longer pregnant.

## 8.5. REGULATORY SAFETY REQUIREMENTS

The Sponsor will report to Health Authorities, i.e. ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) and to Ethics Committee, new events, i.e. any serious unexpected related event that is not mentioned or that is of a different nature, intensity or frequency than that found in the Investigator's Brochure according to local regulations. "Unexpected" refers to an adverse drug experience that has not been previously observed.

The Sponsor will ensure that the Investigators, and all other appropriate persons, are informed in a timely manner of findings that could adversely affect the safety of patients.
During the course of the study, the GERCOR will submit to the Health Authorities once a year or upon request a Safety report describing concisely all relevant new findings related to the safety of the subjects throughout the reporting period.

# 9. DATA MANAGEMENT

## 9.1. CRF COMPLETION GUIDELINES

For each study patient, the data to be reported to the Sponsor will be entered in English in the electronic Case Report Forms (CRFs) via Internet. The CRFs must be completed by the Investigator or any study centre staff designated by the Investigator.
The Investigator is responsible for ensuring that data recorded in the CRFs are complete, accurate and legible. The CRFs should be completed before review by the Monitor.

All data in the CRFs must come from and be consistent with the source documents, i.e. patient's file or medical records.
Any discrepancy between the data in the CRF and those in the source documents should be documented by the Investigator.
No data field will be left blank. The Investigator should make every effort to provide the information required. Abbreviations will be avoided since they are often ambiguous.

Patient names must be kept confidential and should not appear on any CRF page or study-specific documents.

## 9.2. CRF AND DATA HANDLING

The Monitor, who is mandated by the Sponsor, must ensure that the study is conducted in accordance with Good Clinical Practice guidelines and all applicable local laws, and that the rights, the security and the well-being of the patients are respected.
The Monitor will perform source document verification and validation and request clarification to ensure the accuracy, completeness and reliability of data.

The Investigator and the relevant personnel should be available during monitoring visits and ensure that sufficient time is devoted to the process.
The Investigator guarantees the Sponsor or its representative direct access to source documents.

Throughout the study, data electronically captured via e-CRF will be regularly checked for consistency, and queries on data clarification will be generated through e-CRF. Queries must be answered by the investigator (or an authorized staff member) and could be resolved by phone if needed. The database will then be updated accordingly.

At the end of the data handling process, a data review meeting will be held in order to prepare the database lock. After database lock, data will be transferred into SAS format for the production of statistical analyses.

# 10. STATISTICS

## 10.1. SAMPLE SIZE DETERMINATION

The primary objective of this phase II, randomized, prospective, multicenter trial is to evaluate the PFS rate at 4 months of patients with metastatic pancreatic cancer treated with either ABI-007 plus gemcitabine (arm 1) or ABI-007 plus simplified LV5FU2 (arm 2).

According to Fleming 2-stage design with a one-sided 5% type I error and power of 80%, 72 patients in arm 2 (ABI-007 + sLV5FU2) will need to be randomized in order to test the following hypotheses:

- H0 (null): a PFS rate at 4 months of 35% (uninteresting to pursue any further investigation)

- H1 (alternative): a PFS rate at 4 months of 50% (warrants further investigation in a phase III trial).

The hypotheses regarding an anticipated PFS rate at 4 months of 50% and an uninteresting rate of 35% is based on the observed PFS in metastatic pancreatic cancer treated with gemcitabine first-line therapy.

- 37% of patients free of progression at 4 months in patients with metastatic disease, ECOG PS 0-2 (Louvet et al, J Clin Oncol 2005)
- 37% of patients free of progression at 4 months in patients with metastatic disease, ECOG PS 0-1 (Conroy et al, NEJM 2011)

The control arm will serve as calibration that the populations in the two arms are similar: no statistical comparison is planned between the two arms.

Stage 1:

In arm 2, after recruitment of the first 15 patients with a 4-month follow-up from randomization:

- if 1 or less than 1 alive patient is free of progression at 4 months (6.7%), the treatment could be declared uninteresting. No more additional patient will be included in this arm and the study will be stopped. Standard treatment (at the investigator's discretion) should be given to the potential 1 patient free of progression from this arm
- if 2 to 12 alive patients are free of progression at 4 months, 57 additional patients will be randomized to arm 2;
- if 13 or more than 13 alive patients are free of progression at 4 months (86.7%), the treatment could be declared interesting for further phase III evaluation, however we will pursue with 57 additional patients allocated to arm 2.

The probability to conclude for efficacy at the end of stage 1 whereas p=35.0% is $\alpha 1=0\%$.

This early look interim analysis is planned to look for an early efficacy and safety data.

Stage 2:

In arm 2, after recruitment of 72 patients with a follow-up of 4 months from randomization:

- if 32 or less than 32 patients are free of progression at 4 months (≤44.4%), the treatment will be declared uninteresting,
- if 33 or more than 33 patients are free of progression at 4 months (≥45.8%) are observed, the treatment will be regarded as interesting for further evaluation in a phase III trial.

The probability to conclude for inefficacy at the end of stage 1 whereas p=50.0% is β2=20.4%.

The probability to conclude for efficacy at the end of stage 1 whereas p=35.0% is α2=3.7%.

**With an expected 5% rate of patients not evaluable at 4 months or drop out patients, it will be necessary to include a total of 114 patients (arm 1: N=38; arm 2: N=76).**

The primary analysis will be on modified intention-to-treat (mITT) population, i.e. including all evaluable randomized patients regardless of their eligibility and treatment received. The results will be reported according to the randomized treatment.

Confirmative analyses will be conducted firstly in the ITT population (not assessable patients and patients with drop out between randomization and 4 months will be considered as progressive) and secondly, in the Per Protocol population defined as patients who have received at least one dose of allocated treatment and presenting no major deviations from the protocol.

Analyses of tolerance will be conducted in all patients who have received at least one dose of allocated treatment.

### 10.2. RANDOMIZATION

Randomization will take place, after assessment of eligibility and signing of informed consent form.

Randomization will be performed through an electronic CRF, using a minimization technique with a 1:2 ratio, stratifying patients according to the following parameters:

- Center,
- ECOG Performance status (Appendix 17.3) : 0-1 versus 2

The minimization algorithm takes into account the patients already randomized in order to allocate the subsequent treatment. The subgroup of patients who present the same stratification variables that the patient to be randomized is isolated. The total number of patient in that subgroup is counted by stratification variables and by treatment group. The treatment group that is the less represented is selected by the system and attributed to the patient. The randomization result provided by the system is attributed in 80% of the cases; otherwise the other treatment is attributed.

## 10.3. PROTOCOL DEVIATIONS AND ANALYSIS SETS

Prior to locking the database, a data review meeting will be planned in order to review individual data and validate the Statistical Analysis Plan (SAP).

All the deviations from protocol definitions (if any) will be listed and defined as major or minor deviations in the SAP.

With regard to the safety evaluation, the analysis will be performed in the Total Treated Set in order to document the safety when the treatment is actually received. Total Treated Set is defined as all patients who received at least one administration of IMP.

## 10.4. ENDPOINTS

*Progression-free survival (PFS)*

PFS is defined as the time interval from randomization to the date of first documented disease progression or death from any cause, whichever occurs first. Alive patients without progression will be censored at the last tumor assessment, either during study treatment period or during follow-up period.

*Tumor response*

Tumor response will be assessed using RECIST version 1.1.

Overall survival

Overall survival is defined as the time interval from randomization to the date of death from any cause. Alive patients will be censored at the last date known to be alive, either during study treatment period or during follow-up period.

*Time to QoL score deterioration for targeted dimensions*

QoL will be considered to be improved if at least one time to QoL score deterioration (Five targeted dimensions) will be significantly longer without a significant shorter time to QoL score dimensions for other 4 targeted dimensions.

## 10.5. STUDY POPULATION

**modified intention-to-treat (mITT) population, i.e. including all evaluable randomized patients regardless of their eligibility and treatment received. The results will be reported according to the randomized treatment.**

**Intent-to-treat (ITT) population**

The ITT population includes all randomized patients whatever eligibility criteria were fulfilled and study treatment received.

**Modified Intent-to-treat (mITT2) population for QoL analyses**

The mITT population includes all randomized patients whatever eligibility criteria were fulfilled and study treatment received with at least one QoL questionnaire completed at baseline.

**Per protocol (PP) population**

The PP population includes all evaluable randomized patients according to the treatment group allocated by randomization, and fulfilling the following criteria:

- All eligibility criteria are fulfilled,

- The patient received at least one dose of allocated treatment,

**Safety population**

All patients who received at least one dose of any study treatment.

**Evaluable populations**

The following evaluable patient populations are defined for some selected endpoints.

- Tumor response will be evaluated in randomized patients with measurable disease at baseline.
- CA 19-9 response will be evaluated in randomized patients with available CA 19-9 assessment at baseline.

## 10.6. ANALYSIS

A final statistical plan will be written before data frozen. A specific statistical plan dedicated to QoL analyses will be also written before data frozen.

Statistical analyses will be performed using CRF data collected until a clinical cut-off date that is defined when the number of events required for the interim and final analysis of the efficacy variables will be achieved.

The mITT population will be used for the analyses of all efficacy endpoints. mITT2 population will be used for QoL analyses. The safety population will be used for reporting of safety data and treatment exposure data.

Selected efficacy analyses will be repeated for the ITT, PP population and for subgroups.

Unless otherwise indicated all analyses will present data by treatment arm.

**Continuous Variables**

Continuous variables will be summarized using descriptive statistics, i.e. number of patients with available data (N), mean, median, standard deviation (S.D.), 25% - 75% quartile (Q1-Q3), minimum, and maximum. Continuous variables could be transformed to

categorical variables using the median or using conventional cut-offs from bibliography or clinical practice.

**Categorical Variables**

Frequencies in tables will be presented by arm and total frequency and percentages and missing modality. Qualitative variables will be summarized by means of counts and percentages. Unless otherwise stated the calculation of proportions will based on the sample size of the population of interest. 95% confidence interval (CI) will be calculated for the 4-months PFS rate

**Time to Event Variables**

Kaplan Meier curves will be used to describe event-free rates over time. Median event-free times by treatment arm will be reported with 95% CI, if the number of events allows the estimation of the median. The confidence interval for the median survival time will be calculated according to Brookmeyer, R. and Crowley, J. (1982) Event rates at specified time points will be estimated from the Kaplan-Meier curve. The standard error will be estimated by the Greenwood formula and the log-log transformation will be used to compute confidence intervals.

**Follow-up**

Follow-up will be estimated using the reverse Kaplan-Meier method, and will be described using the median with its 95% CI.

**Survival**

Survival will be estimated using the Kaplan-Meier method, and will be described using the median with its 95% CI.

**Analyses of baseline and demographic data**

Clinical and demographic data will be described using rules form. The statistical parameters mean, median, SD, interquartile range and range will be presented for continuous baseline variables. For categorical baseline variables, corresponding frequencies (n, %) will be calculated. All baseline variables listed below will be summarized by treatment arm.

**Treatment exposure analysis**

These analyses will be done in mITT population. The dose-intensity (DI) of a drug is calculated based on the number of cycles actually received by the patient. The relative DI is calculated as the ratio of the DI to the DI indicated in the protocol. The DI indicated in the protocol is obtained as the dose specified per cycle ($mg/m^2$).

## 11. STUDY REPORT

A clinical study report will be prepared by the Sponsor in collaboration with the coordinating Investigator.

Within 1 year after the end of the study, the Sponsor will provide the Health Authorities with the full study report or summary. Only the Sponsor is entitled to make the study report available to the Authorities.

Neither the complete report nor any part of the study report may be used without the approval of the Sponsor.

Information on the overall results of the study

Pursuant to the French “Patient’s rights” law adopted on 9 August 2004, the Investigator must provide any patient who requests it with the overall results of the study. The Sponsor will provide the Investigator with the overall results beforehand.

The Investigator should document in the patient’s file the fact that the information has been provided.

## 12. CONFIDENTIALITY AND PUBLICATION

### 12.1. PATIENT CONFIDENTIALITY

Patient data will be kept strictly confidential and patient anonymity will be protected by using number codes and /or initials.

The Sponsor or its representative(s) and the Health Authorities are obligated to respect medical secrecy and to refrain from divulging any personal patient information they might fortuitously be aware of.

### 12.2. USE OF INFORMATION

The Investigator is obligated to provide the Sponsor with complete test results and all data derived from the study.

The Investigator shall not divulge unpublished data or information related to the study provided by the Sponsor, including but not limited to the study product characteristics, the Investigator brochure if applicable, the study protocol, case report forms, assay methods and scientific data, to any third party without written approval from the Sponsor.

In addition, any new information that may become available during the course of the study shall be considered as confidential and shall not be used for any purpose other than the performance of the clinical study.

The study data are the property of the Sponsor. The Investigator and any of the research staff shall obtain written approval from the Sponsor prior to the publication/communication of the results of any work carried out during or in relation to the study.

Publication and/or communication of the results of the clinical study will be of a cooperative nature involving authors representing the Sponsor, the Investigators.

Authorship of any publication related to the study and the order of presentation of the authors' names shall be approved by the Sponsor. The Sponsor shall not use an Investigator's name in any publication without his/her written permission and vice versa.

## 13. ARCHIVING

The Investigators should retain all essential study-related documents, i.e. documents which permit evaluation of the conduct of a study and the quality of the data produced, in accordance with the applicable regulatory requirements of his/her country. These essential documents include but are not limited to signed protocol, Investigator Brochure when applicable, print-out of CRFs or CRFs on CR-roms, medical records, laboratory reports, informed consent forms, drug disposition records, safety reports, information regarding participants who discontinued, and other relevant documents and data.

The study-related documents should be kept together in the Investigator site file provided to the Investigator by the Sponsor.

Sufficient information about the identity of all study patients, e.g. name, medical records number, patient number and study number, should be retained by the Investigator so that any Sponsor representatives, auditors or inspectors may access this information when required.

The Investigator must retain all records for 15 years or longer if required by specific local requirements.

The Investigator will contact the Sponsor for authorization prior to the destruction of any study record or in the event of accidental loss or destruction of any of them.

The Investigator will also notify the Sponsor should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's Study Master File.

All records should be kept in a secure area however, in case of audit or inspection they should be rapidly made available.

## 14. ETHICS AND REGULATORY CONSIDERATIONS

The current study is to be conducted in accordance with globally accepted standards of Good Clinical Practice (ICH-E6), European Directive 2001/20/EC, and the revised version of the Declaration of Helsinki set out in the European Directive, as well as with the CSP specific to France.

The protocol will be submitted to the Health Authorities and a properly constituted Ethics Committee (EC) for formal approval of the study conduct in accordance with local regulations. The study will not begin until the protocol has received written approvals, including the list of declared investigational sites.

**Personal Data Protection Committee**

For biomedical research in France: The Sponsor attests his conformity regarding the Personal Data Protection French requirements ("Méthodologie de Réference MR001" dated 5 january 2006).

**Insurance**

The Sponsor will contract civil liability insurance to provide patients with compensation for any injury, including the consequences of administration of the investigational product and of the study procedures: insurance certificate is available in appendix 17.2.

**Indemnity**

Participation in this study will not entail any financial compensation to patient.

**Changes to the protocol**

The Sponsor will not assume any responsibility or liability resulting from implementation of unapproved deviations or changes.

## 15. AUDIT AND INSPECTION

An audit/inspection may be carried out by qualified Sponsor staff, by subcontracted auditors or by representatives of national or foreign Health Authorities to ensure that the study is conducted as per protocol and in accordance with regulatory requirements, and to ensure the validity of the data.

Participation in this study implies acceptance to cooperate in any potential audit/inspection.

The audit/inspection may consist of an inspection of the premises and equipment together with verification of the study documents and data.

The investigational team must be available for inspection or audit.

When the Sponsor or the Investigator is informed that an inspection is to be performed, the other party must be informed immediately.

Audits/inspection may take place after the end of the study.

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# 17. APPENDICES

## 17.1. INFORMED CONSENTS

### 17.1.1 INFORMED CONSENT FOR THE CLINICAL STUDY version 1.1 dated 18-09-2013

# LETTRE D'INFORMATION AU PATIENT

**ETUDE AFUGEM– ABI -007 (Paclitaxel-Albumine)**

ETUDE RANDOMISEE DE PHASE II D'UNE CHIMIOTHERAPIE DE PREMIERE LIGNE ASSOCIANT ABI-007(PACLITAXEL-ALBUMINE) ET GEMCITABINE OU LV5FU2 SIMPLIFIE, CHEZ DES PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

Madame, Monsieur,

Vous êtes invité(e) à prendre part à une recherche biomédicale ou étude clinique menée par le Docteur..... .

Le promoteur de cette étude est le GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie, Paris).

Avant de décider de prendre part à cette recherche, il est important que vous preniez le temps de lire et de comprendre les informations suivantes concernant son déroulement. Elles décrivent l'objectif, les procédures, les bénéfices et les risques éventuels ainsi que vos droits par rapport à cette étude.

S'il y a quoi que ce soit dans ce document que vous ne comprenez pas, veuillez demander à votre médecin ("investigateur") de vous l'expliquer. Prenez votre temps pour décider si vous souhaitez ou non participer à cette étude ; parlez-en avec vos amis ou vos proches.

Si vous prenez part à cette étude, vous contribuerez aux efforts de la recherche, lesquels permettront peut-être d'améliorer nos traitements et d'aider d'autres patients à l'avenir. Si vous choisissez de participer, il vous sera demandé de signer ce formulaire, dont un exemplaire vous sera remis. Si vous refusez de prendre part à l'étude, ceci n'aura pas de conséquence sur votre prise en charge médicale.

Vous disposez du délai de réflexion que vous jugerez nécessaire pour décider de participer ou non à cette étude.

Cette lettre d'information et ce formulaire de consentement éclairé, ainsi que l'étude elle-même, ont été appréciés par le Comité de Patients pour la Recherche Clinique en Cancérologie (CPRCC), et ont été examinés et approuvés par le Comité de Protection des Personnes (CPP) Ile de France VI (Groupe Hospitalier Pitié Salpêtrière, Paris).

En cas de problème ou de question, votre médecin est à votre disposition.

Nom du médecin : ……

Hôpital : ……..

Téléphone : |__|__|__|__|__|__|__|__|__|__|

**Quel est l'objectif de cette étude clinique ?**

Votre médecin a diagnostiqué un cancer du pancréas métastatique, c'est à dire qu'il a envahi d'autres organes sous la forme d'une ou plusieurs métastases. Le traitement de référence actuel est une chimiothérapie dite de première ligne utilisant gemcitabine seule ou le schéma FOLFIRINOX utilisant une combinaison de 5FU (5-Fluorouracile), irinotecan et oxaliplatine. Votre médecin vous propose de participer à l'étude de recherche clinique **AFUGEM**. Cette recherche a pour but d'évaluer si l'association de ABI-007 (Abraxane®) soit à gemcitabine, soit à une fluoropyrimidine (5-Fluorouracile) et acide folinique (schéma appelé LV5FU2 simplifié), est efficace pour bloquer la croissance tumorale.

Au total 114 patients participeront à cette recherche. La durée de participation à l'essai sera d'environ 12 mois.

Les patients seront répartis en deux groupes et le traitement sera décidé par tirage au sort (randomisation) :

- Les patients du premier groupe recevront ABI-007 associé à gemcitabine
- Les patients du second groupe recevront ABI-007 associé à LV5FU2

Chaque patient recevra donc ABI-007, quel que soit le groupe attribué.

**Le médicament ABI-007 a-t-il déjà été administré ?**

ABI 007 est une nouvelle forme pharmaceutique de paclitaxel (Taxol®) attaché à une protéine humaine appelée albumine. Paclitaxel agit en bloquant la multiplication des cellules cancéreuses. Il bloque les cellules en cours de réplication cellulaire, en empêchant la division de l'ADN et entraine la mort de la cellule cancéreuse. ABI007 administré seul ou en association a déjà été étudié dans de nombreux types de cancers. Dans le cancer du pancréas, l'association de ABI007 à gemcitabine a déjà été rapportée comme supérieure à gemcitabine seule dans une grande étude internationale.

**Que devrez-vous faire si vous participez à cette étude?**

Au cours de la période du traitement, vous ne pourrez participer à aucune autre étude clinique évaluant un médicament ou un matériel médical.

Tant que vous serez traité(e), vous ne pourrez pas prendre d'autres traitements spécifiques pour votre cancer, du type chimiothérapie, ou toute autre thérapie.

Par ailleurs les traitements concomitants à base de Warfarine (Coumadine®) vous seront interdits pendant votre participation à l'étude. Si vous prenez actuellement ce type de traitement, votre médecin vous prescrira un autre traitement anticoagulant.

**Quels types d'examens ou de procédures cette étude clinique va-t-elle comporter ?**

**<u>Phase de sélection du patient avant début du traitement</u>:**

Avant la mise en œuvre de toute procédure liée à la recherche, vous aurez donné votre accord de participation (en datant et signant le présent formulaire d'information et de consentement éclairé). Vous passerez ensuite une visite médicale pour déterminer si vous pouvez participer à l'étude. Cette phase de sélection comporte les examens suivants.

- Recueil de données démographiques (date de naissance, sexe), antécédents médicaux et traitements antérieurs et actuels,
- Examen clinique incluant la mesure de la taille, du poids, des signes vitaux (pression artérielle, température, pouls), vos symptômes et l'évaluation de votre état général,
- Prise de sang (20 ml) vous seront prélevés au total) en vue d'examens biochimiques, hématologiques,
- Electrocardiogramme (ECG),
- Scanner (ou IRM) thoraco-abdomino-pelvien,
- Test sanguin de grossesse pour les femmes susceptibles d'être enceintes. Il est important de noter que si votre test de grossesse est positif, vous ne pourrez pas participer à cette recherche.

Tous ces examens sont ceux qui sont habituellement effectués même si vous ne participez pas à cette recherche.
En plus de ces examens de routine, nous vous demanderons de remplir un questionnaire de qualité de vie.

Pour les femmes : Vous ne pourrez pas participer à cette étude si vous êtes enceinte ou si vous allaitez.
Compte tenu des risques possibles pour le fœtus, si vous êtes une femme susceptible d'être enceinte, vous devrez faire un test de grossesse au cours des 72 heures précédant le début du traitement à l'étude.
Si vous décidez de participer à cette étude, vous devrez accepter d'utiliser une méthode de contraception approuvée par un médecin pendant toute la durée de l'étude et pendant 6 mois après la dernière dose du traitement à l'étude.
Si vous devenez enceinte au cours de l'étude, vous devrez en informer immédiatement le médecin de l'étude. Si cela se produit, votre participation à cette étude sera arrêtée. Si vous tombez enceinte au cours des 6 mois suivant la prise de votre dernière dose, vous devrez en informer immédiatement le médecin de l'étude. Le médecin de l'étude continuera à vous suivre vous et votre grossesse jusqu'à l'accouchement.

Pour les hommes : si votre partenaire est une femme en âge de procréer, vous devrez accepter d'utiliser une méthode de contraception approuvée par un médecin pendant toute la durée de l'étude et pendant 6 mois après la dernière dose du traitement à l'étude et d'éviter de concevoir un enfant pendant 6 mois après la prise de votre

dernière dose. Si votre partenaire devient enceinte au cours de l'étude ou au cours des 6 mois suivant la prise de votre dernière dose du traitement à l'étude, vous devrez en informer immédiatement le médecin de l'étude.

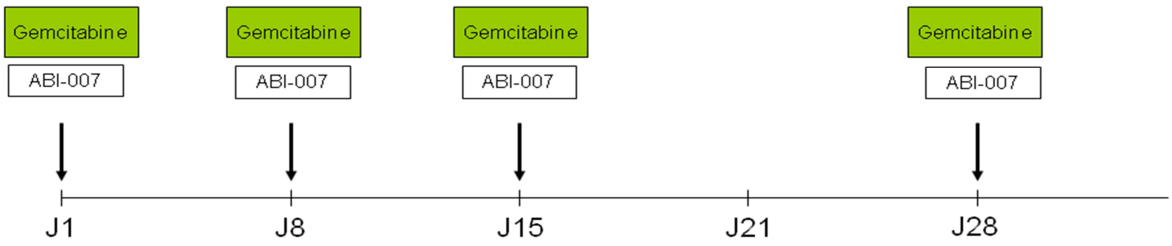
Avant de commencer le traitement par Paclitaxel-albumine, il est conseillé aux hommes de se renseigner sur les procédures de conservation du sperme en raison du risque potentiel de stérilité irréversible lié au traitement.

**Phase de traitement :**

ABI-007, gemcitabine et LV5FU2 sont administrés par voie intraveineuse. Les traitements seront interrompus en cas de progression de la maladie ou en cas d'intolérance.

Si vous présentez les caractéristiques nécessaires pour participer à cette recherche, vous recevrez alors le traitement selon les séquences suivantes :

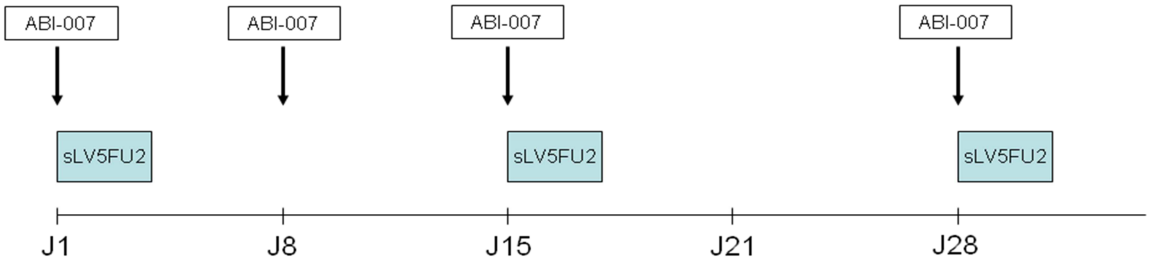
- **Pour les patients du groupe ABI-007+ Gemcitabine**




Un cycle = 28 jours (Par exemple : Jour 1= lundi semaine 1 ; Jour 8 = lundi semaine 2 ; Jour 15 = lundi semaine 3)
Le J28 correspond au J1 du cycle suivant.

Pour chaque cycle, le traitement vous sera administré en perfusion intraveineuse sur trente minutes, aux jours 1, 8 et 15, suivi d'une semaine d'interruption, et ceci jusqu' à la progression de la maladie ou intolérance.

- **Pour les patients du groupe ABI-007+LV5FU2**




Un cycle = 28 jours (Par exemple : Jour 1= lundi semaine 1 ; Jour 8 =lundi semaine 2 ; Jour 15= lundi semaine 3).
Le J28 correspond au J1 du cycle suivant.

Pour chaque cycle, ABI-007 vous sera administré aux jours 1, 8 et 15, suivi d'une semaine d'interruption. LV5FU2 vous sera administré au jour 1 et 15, et ceci jusqu'à la progression de la maladie ou intolérance.

Vous recevrez le traitement sur deux jours. Le premier jour de chaque cycle vous recevrez ABI007 puis l'acide folinique en perfusion intraveineuse sur deux heures (au jour 1 et 15). Ensuite le 5-FU vous sera administré (aux jours 1 et 15) sous forme d'une perfusion rapide de 15 minutes puis plus lente sur 46 heures.

Vous pourrez recevoir d'autres médicaments avant ou après les perfusions afin de réduire les éventuels effets secondaires tels que nausées, vomissements.

Il pourra être nécessaire occasionnellement de différer votre traitement afin d'améliorer votre tolérance au traitement et de limiter les effets secondaires.
La dose de chaque médicament sera ajustée en fonction de la façon dont vous le tolérez. Votre médecin vous en informera.

Si en cours d'étude vous ou votre partenaire êtes ou pensez être enceinte, vous devrez en informer immédiatement votre médecin. En cas de grossesse, le traitement devra être arrêté. Si vous ou votre partenaire décidiez de poursuivre votre grossesse, celle-ci sera suivie jusqu'à terme, ainsi que le développement de votre enfant pendant la première année.

**Suivi du traitement :**

Avant chaque administration de chimiothérapie, vous devrez réaliser une prise de sang pour vérification de vos paramètres biologiques et vous serez systématiquement examiné par un médecin pour évaluation des éventuels effets secondaires. On vous demandera de signaler tout effet indésirable que vous ressentiriez, et tout médicament que vous prendriez, prescrits ou non par un médecin. En cas de paramètre biologique satisfaisant et en l'absence d'effet secondaire non contrôlé, la chimiothérapie sera administrée. Dans les autres cas, la dose de chimiothérapie pourra être réduite et/ou l'injection décalée dans le temps.
Vous aurez une consultation tous les deux cycles (tous les deux mois) de chimiothérapie avec votre médecin-investigateur afin de s'assurer de la bonne tolérance et de l'efficacité du traitement. Lors de ces consultations d'évaluation vous aurez :

- une mesure des signes vitaux et du poids,
- une prise de sang (20 ml, prélevés à chaque cycle) en vue d'examens biochimiques et hématologiques pour évaluer la tolérance de votre traitement et mesurer les marqueurs tumoraux,
- questionnaire de qualité de vie, un scanner (ou IRM) thoraco-abdomino-pelvien sera effectué pour surveiller l'évolution de votre maladie.

**Fin de traitement :**

Une visite avec votre médecin-investigateur sera effectuée à la fin de votre traitement de l'étude (et ce quel que soit le moment), pour l'évaluation de l'efficacité et de la tolérance du traitement. Lors de cette visite, les examens et procédures suivants seront réalisés :

- Examen clinique incluant la mesure du poids, des signes vitaux (pression artérielle, température, pouls), vos symptômes avec le recueil des effets secondaires éventuels et l'évaluation de votre état général par un questionnaire de qualité de vie,
- Prise de sang (15 ml) en vue d'examens biochimiques, hématologiques,
- Scanner (ou IRM) thoraco-abdomino-pelvien afin d'évaluer votre maladie,

**Tableau récapitulatif des examens et procédures :**

| Procedures requises | Phase de sélection | Phase de traitement | | Fin de traitement |
|---|---|---|---|---|
| | | Avant chaque administration de traitement | Tous les 2 mois | |
| **Examen Clinique** | X | X | X | X |
| **Electrocardiogramme** | X | | | |
| **Imagerie scanner ou IRM** | X | | X | |
| **test de grossesse (si applicable)** | X | | | |
| **prise de sang pour examens hématologiques biochimiques** | X | X | X | X |
| **Marqueurs tumoraux (ACE et Ca 19-9)** | X | | X | X |
| **Questionnaire Qualité de vie** | X | X* | X | X |
| **recueil des traitements** | X | X | X | X |

*Le premier jour de chaque cycle

**Quand prendra fin ma participation à cette recherche ?**

Votre participation à cette recherche pourra se terminer quand votre médecin décidera, dans votre intérêt, de ne plus poursuivre le traitement à l'étude. Votre médecin vous proposera alors un autre traitement adapté à votre situation et vous continuerez à bénéficier pleinement de sa compétence.

Le traitement pourra se poursuivre aussi longtemps qu'il se montrera efficace.

Si dans un premier temps vous acceptez de participer à cette étude et qu'ensuite vous changez d'avis, vous êtes libre de retirer votre consentement et d'interrompre votre participation à tout moment sans aucun préjudice.

**Quelles sont les alternatives thérapeutiques ?**

Si vous décidez de ne pas participer à cette étude, vous pourrez alors parler avec votre médecin des autres options thérapeutiques possibles pour vous.

**Quels sont les possibles effets indésirables?**

Les différents traitements que vous serez amené(e) à recevoir peuvent engendrer des effets secondaires. Ils varient selon les médicaments utilisés et les personnes, mais sont généralement réversibles.

Leur survenue ne signifie pas que votre traitement est inefficace.

Risques liés au médicament à l'étude :

**ABI-007 (paclitaxel-albumine) :**

Il est possible que vous présentiez des effets indésirables pendant votre participation à l'étude, mais le médecin de l'étude vous surveillera attentivement et adaptera le traitement en conséquence. Il est possible que des risques ou des effets indésirables associés au médicament de l'étude soient inconnus à ce jour. Il sera important que vous signaliez au médecin ou au personnel de l'étude toute préoccupation ou effet indésirable que vous pourriez éprouver, même si vous pensez qu'il n'est pas lié au médicament à l'étude.

Vous trouverez ci-dessous une liste des effets indésirables les plus médicalement significatifs ou les plus fréquents, rapportés dans des études aujourd'hui terminées, considérés comme imputables au paclitaxel/albumine. Dans certains cas, les effets indésirables peuvent être graves, durables, voire même entraîner le décès. Certains effets indésirables peuvent disparaître rapidement après l'arrêt de la prise du médicament ou de la thérapie et certains ne jamais disparaître. Le médecin de l'étude pourra modifier le dosage de paclitaxel albumine ou vous donner des médicaments pour contribuer à diminuer les effets indésirables. Il ne s'agit pas d'une liste exhaustive de tous les effets indésirables susceptibles de se produire. Pour plus d'informations sur les risques et les effets indésirables, veuillez consulter le médecin de l'étude.

**Très fréquent (10 % ou plus de possibilités que cet effet se produise)**

- Anémie (diminution du nombre de globules rouges qui peut se traduire par une sensation de faiblesse ou de fatigue)
- Faible nombre de globules blancs avec ou sans fièvre (qui vous rend plus sensible aux infections)
- Diminution du nombre de plaquettes, cellules qui aident votre sang à coaguler (peut mener à des saignements inhabituels ou ecchymoses sous la peau)
- Constipation
- Diarrhée
- Nausée
- Vomissement
- Douleur, gonflement ou plaies à l'intérieur de la bouche
- Sensation de fatigue ou de faiblesse
- Douleur (y compris muscles, articulations et douleur dans la poitrine)
- Gonflement causé par une accumulation de fluide dans les tissus, particulièrement dans les chevilles, pieds ou doigts
- Fièvre
- Diminution de l'appétit
- Neuropathie, trouble nerveux pouvant causer picotement ou engourdissement, avec faiblesse ou diminution de sensation ou mouvement
- Toux
- Essoufflement
- Perte de cheveux
- Eruption cutanée

**Fréquents (de 1 % à moins de 10 % de possibilités que cet effet se produise) :**

- Accélération des battements du cœur
- Yeux larmoyants
- Vision floue
- Douleur au niveau de l'estomac
- Indigestion ou maux d'estomac
- Trouble de la déglutition
- Perturbation des résultats biologiques sanguins
- Inflammation des voies pulmonaires
- Infections y compris pneumonie ou infection urinaire (qui peuvent être bactériales, fongiques ou virales)
- Anomalies des résultats des tests de la fonction hépatique
- Perte de poids
- Déshydratation
- Etourdissement
- Modification du goût
- Maux de tête
- Difficulté à dormir

- Saignement du nez
- Crachement de sang
- Fluide dans la cavité thoracique
- Caillot de sang dans les poumons
- Modification des ongles, incluant une décoloration
- Démangeaison
- Rougeurs de la peau
- Pression sanguine élevée
- Pression sanguine basse

Peu fréquents (de 0.1% à moins de 1 % de possibilités que cet effet se produise):

- Diminution des fonctions de la moelle osseuse entraînant (à peu près au même moment) une diminution sévère des globules rouges, blancs et des plaquettes et pouvant provoquer faiblesse, contusions ou pouvant augmenter les risques d'infection
- Battements cardiaques irréguliers ou ralentis
- Diminution de la capacité du cœur à envoyer le sang dans toutes les parties du corps et possible insuffisance cardiaque
- Arrêt cardiaque
- Irritation et rougeur de la fine membrane recouvrant l'œil
- Inflammation de la cornée
- Modifications de la vision
- Sensation de malaise
- Réactions au site d'injection (décrites comme sensation d'inconfort, saignement, ou contusion/gonflement à l'endroit où l'aiguille est insérée et dans certains cas infection ou fuite de liquide à l'extérieur des vaisseaux sanguins)
- Envie de dormir
- Réaction allergique (pouvant inclure inflammation de la peau, éruption cutanée, difficulté respiratoire, difficulté pour parler, fièvre, et/ou diarrhée) parfois fatale
- Infection grave du sang qui peut inclure une diminution de la pression sanguine
- Anomalie des résultats des tests de la fonction rénale
- Excès de fluide dans le corps
- Epaississement, inflammation ou tissu cicatriciel dans les poumons qui peut entraîner essoufflement et toux
- Peau écailleuse ou qui se desquame
- Urticaires

D'autres effets indésirables ont été observés dans le cadre de la surveillance après mise sur le marché du produit, parmi lesquels:

- Œdème/gonflement et formation de kyste dans la région maculaire de la rétine
- Perte de fonction nerveuse dans les muscles du visage

- Manque de mouvement dans les cordes vocales avec possible modification de la voix
- “Syndrome main-pied” impliquant rougeur, gonflement, engourdissement et desquamation des paumes de la main et des plantes des pieds
- Sensibilité de la peau au soleil
- Eruption cutanée avec apparition de cloques, mettant potentiellement la vie en danger
- La peau et les tissus ayant été endommagés par une radiothérapie antérieure peuvent être endommagés à nouveau suite à une chimiothérapie. Ceci est une réaction de rappel à la radiothérapie qui peut impliquer rougeur, desquamation, douleur et gonflement. Des modifications de la peau ont été observées allant d’une rougeur légère jusqu’à la mort des tissus. La réaction de rappel à la radiothérapie peut également avoir lieu dans les poumons et dans d’autres organes internes.

**Toxicités liées au LV5FU2s, et à Gemcitabine**

La chimiothérapie n'étant pas spécifique des cellules cancéreuses, elle peut également affecter des cellules saines. Cet inconvénient est à l'origine d’effets secondaires communs à tout type de chimiothérapie :

Toxicités hématologiques : baisse des globules du sang (globules blancs, globules rouges), et des plaquettes.

Toxicités digestives : nausées, vomissements, diarrhées, constipation, douleurs abdominales, perte ou diminution de l’appétit. Aphtes, perte modérée de cheveux.

Autres toxicités : fatigue, infection, fièvre, douleur et/ou rougeur au point d’injection, réaction cutanée, syndrome main-pied (rougeur et sensibilité des paumes des mains et des plantes des pieds).

**Quels sont les bénéfices thérapeutiques attendus de l’étude ?**

Dans le cadre de cette étude, vous allez bénéficier d'un nouveau traitement, ABI007 qui vient de démontrer son efficacité dans le cancer du pancréas métastatique.

Un autre avantage de votre participation à cette étude est–que vous pourriez contribuer à améliorer la prise en charge des patients atteints d’un cancer du pancréas.

A l’issue de la recherche, vous serez informé (e) si vous le souhaitez, des résultats globaux de cette étude. Si vous le désirez, le Dr ……. vous communiquera et vous expliquera ces résultats lorsque ces derniers seront disponibles.

**Coûts potentiels et remboursement-Assurance**

Vous n’aurez pas de frais supplémentaires liés à la recherche si vous participez à cette étude clinique, y compris les frais liés aux examens supplémentaires et à la prise en charge des effets secondaires, et vous accéderez gratuitement aux produits de l’étude.

Toutefois, pour pouvoir participer à cette recherche vous devez être affilié(e) ou bénéficier d'un régime de sécurité sociale (*incluse la Couverture Médicale Universelle – CMU)*

Le GERCOR, qui organise cette recherche biomédicale en qualité de promoteur, a contracté une assurance conformément aux dispositions législatives, garantissant sa responsabilité civile et celle de tout intervenant auprès de la compagnie ACE European Group Limited, n°FRCAN12107.

**Comment la confidentialité de votre dossier sera-t-elle préservée ?**

Votre participation à cette étude figurera dans votre dossier médical. La confidentialité de votre dossier médical sera préservée dans les limites prévues par la loi.

L'accès direct à votre dossier médical par des personnes désignées par le GERCOR sera nécessaire à la vérification des données collectées pour l'étude. Les données collectées demeureront strictement confidentielles. La confidentialité de votre dossier médical sera maintenue dans les limites prévues par la loi. Si les résultats de l'étude sont publiés, votre identité demeurera confidentielle.

Les données et informations recueillies au cours de l'étude seront analysées et pourront être transmises dans les conditions définies dans le formulaire de consentement. Elles feront également l'objet d'un traitement informatique, par le GERCOR ou pour son compte, dans les conditions définies dans ce formulaire dans le respect des dispositions de la loi n°78-17 du 6 janvier 1978, telle que modifiée. Les données relatives aux effets indésirables éventuels liés à l'utilisation du médicament étudié pourront également, dans des conditions assurant leur confidentialité, être transmises aux titulaires de l'autorisation de mise sur le marché du médicament, en France ou à l'étranger.

Toutes les informations vous concernant seront rendues anonymes par un système de codage. Certaines informations nominatives (y compris les informations contenues dans votre dossier médical) pourront faire l'objet d'examens supplémentaires en particulier par certaines autorités de santé, ou bien dans le cadre de contrôles qualité, dans des conditions également détaillées dans le formulaire de consentement.

Vous pouvez à tout moment vous adresser à votre médecin afin d'avoir accès à vos données personnelles et notamment aux informations figurant dans votre dossier médical. Vous pouvez également lui demander à tout moment la rectification de vos données ou vous opposer à leur traitement en lui envoyant une demande écrite. Dans ce dernier cas, vous ne pourrez plus participer à la présente étude.

Vos prélèvements sanguins seront identifiés par un code dans le cadre de l'étude. Les données issues de leur analyse resteront strictement confidentielles et seront protégées par les règles du secret médical (sous réserve de l'intervention éventuelle des autorités de santé).

Avec votre accord, votre médecin traitant ou tout autre médecin qui vous suit pourra être informé de votre participation à cette étude.

**Validation des autorités de santé**

Ce protocole a obtenu un avis favorable du comité de protection des personnes (CPP) Ile de France VI le 04/10/2013, a également fait l'objet d'une autorisation par l'Agence Nationale de Sécurité du Médicament (ANSM) le 30/08/2013.

## CONSENTEMENT ECLAIRE DE PARTICIPATION

**Je soussigné (e) Prénom:** **NOM :**

**Adresse :** **CP** |___|___|___|___|___| **Ville :**

Accepte librement et volontairement de participer à la recherche biomédicale intitulée

ETUDE RANDOMISEE DE PHASE II D'UNE CHIMIOTHERAPIE DE PREMIERE LIGNE ASSOCIANT ABI-007 (PACLITAXEL-ALBUMINE) ET GEMCITABINE OU LV5FU2 SIMPLIFIE, CHEZ DES PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

dont le GERCOR est le promoteur et qui m'a été proposée par :

Docteur / Professeur Prénom: NOM :

Téléphone : |__|__| |__|__| |__|__| |__|__| |__|__|

Etant entendu que :

- Le médecin investigateur, qui m'a informé des objectifs, des bénéfices potentiels et des désagréments pouvant résulter de la recherche utilisant ABI007 pour le traitement de mon affection, et qui a répondu à toutes mes questions, m'a précisé que j'étais libre d'accepter ou de refuser de participer à cette recherche,
- Avant de participer à cette recherche j'ai bénéficié d'un examen médical dont les résultats m'ont été communiqués,
- Je pourrais avoir communication par le médecin investigateur au cours ou à l'issue de la recherche des informations qu'il détient concernant ma santé,
- J'ai bien compris dans le formulaire d'information qui m'a été remis que pour pouvoir participer à cette recherche je dois être affilié(e) ou bénéficier d'un régime de sécurité sociale. Je confirme que c'est bien le cas,
- Je suis parfaitement conscient(e) que je peux retirer à tout moment mon consentement à participer à cette recherche quelles que soient mes raisons et sans aucune responsabilité mais je m'engage à en informer le médecin investigateur. Cela ne portera pas atteinte à ma relation avec ce médecin, ni aux soins ultérieurs prodigués.
- Si je le souhaite, à son terme, je serai informé(e) par le médecin investigateur des résultats globaux de cette recherche,
- Mon consentement ne décharge en rien le médecin investigateur et le promoteur de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi,
- Je m'engage à répondre à toutes les questions qui me seront posées à propos de mes antécédents médicaux et à suivre toutes les consignes et instructions qui me seront données par l'Investigateur ou son équipe, dont celles qui sont détaillées dans la Notice d'Information. Par ailleurs, si je présente un symptôme imprévu ou inhabituel anormal en cours d'étude, je m'engage à contacter l'Investigateur dans les délais les plus brefs,
- J'accepte que les données enregistrées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte. J'ai bien noté que le droit d'accès prévu par la loi du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés (art. 39) s'exerce à tout moment auprès du médecin qui me suit dans le cadre de la recherche et qui connaît mon identité. Je pourrai exercer mon droit de rectification et d'opposition auprès de ce même médecin, qui contactera le promoteur de la recherche.

**EN SIGNANT CE DOCUMENT J'ACCEPTE DE PARTICIPER A CETTE ETUDE CLINIQUE DANS LES CONDITIONS DECRITES CI-DESSUS. J'AI EU UNE REPONSE A TOUTES MES QUESTIONS ET J'ATTESTE AVOIR RECU UN EXEMPLAIRE ORIGINAL DE CE DOCUMENT.**

**PATIENT** Date : |__|__|-|__|__|-|__|__|__|__|

NOM : …….. Signature :

Date : |__|__|-|__|__|-|__|__|__|__|

Signature :

**INVESTIGATEUR**

NOM :…….

**LETTRE D'INFORMATION ET CONSENTEMENT ECLAIRE POUR DES RECHERCHES SUR DES MATERIELS BIOLOGIQUES**

**La recherche sur les matériels biologiques n'inclut que des patients volontaires sans compromettre leur possibilité de participer à l'essai clinique proposé.**

**ETUDE AFUGEM:**

ETUDE RANDOMISEE DE PHASE II D'UNE CHIMIOTHERAPIE DE PREMIERE LIGNE ASSOCIANT ABI-007 (PACLITAXEL-ALBUMINE) ET GEMCITABINE OU LV5FU2 SIMPLIFIE, CHEZ DES PATIENTS ATTEINTS D'UN CANCER DU PANCREAS METASTATIQUE

Vous avez accepté de participer à l'étude AFUGEM conduite par le GERCOR (promoteur de l'étude) dans laquelle vous allez être traité(e) pour un cancer du pancréas métastatique par l'une des deux associations suivantes :

- ABI-007 associé à gemcitabine

  ou
- ABI-007 associé à LV5FU2

Vous êtes également invité(e) à prendre part à une recherche complémentaire portant sur des matériels biologiques.

Vous pouvez prendre tout le temps nécessaire pour lire ces informations. N'hésitez pas à solliciter votre médecin si vous souhaitez obtenir des informations complémentaires.

**Participation volontaire**

Votre participation au projet de recherche complémentaire sur les matériels biologiques est entièrement volontaire et vous aurez suffisamment de temps pour décider si vous voulez y participer ou non.

Vous êtes libre de décider à tout moment que vous ne souhaitez plus participer au projet de recherche sur les matériels biologiques sans donner aucune raison. Votre retrait de ce projet n'affectera aucunement votre participation à l'étude clinique AFUGEM, ni vos relations avec votre médecin ou le personnel hospitalier. En cas de retrait de votre part, vos données ne seront pas (ou plus) utilisées. Seules les données collectées jusqu'à ce moment seront conservées pour la recherche et l'analyse. Tous les matériels non utilisés seront retournés à votre médecin, si nécessaire. A tout moment de l'étude, vous pourrez demander la destruction de votre matériel.

Si vous êtes d'accord votre médecin traitant sera également informé de votre participation à cette étude et de ce que cela implique.

**Objectif**

L'étude de certaines caractéristiques biologiques et moléculaires de votre tumeur ainsi que l'évaluation de votre réaction aux médicaments étudiés est d'un intérêt scientifique majeur pour déterminer un traitement personnalisé pour les patients atteints d'un cancer du pancréas métastatique à l'avenir.

L'étude de biomarqueurs a pour but d'essayer de déterminer des facteurs biologiques et moléculaires capables de prédire la tolérance et l'efficacité d'une chimiothérapie comportant ABI-007 et également de la gemcitabine ou du LV5FU2, et d'étudier des facteurs qui pourraient influencer l'évolution naturelle de votre maladie.

**Quels types d'examens ou de procédures cette étude biologique va-t-elle comporter ?**

Un échantillon de votre tumeur pourra être utilisé. Ces prélèvements ont été effectués à titre systématique au moment du diagnostic de votre maladie pour déterminer l'histologie de la tumeur (les caractéristiques des cellules tumorales).
Il n'y aura pas de visite particulière pour cette étude des biomarqueurs.
Les analyses seront faites dans des centres spécialisés. Ces échantillons biologiques et les données seront traités avec la même confidentialité que pour le reste des données recueillies.

**Qu'adviendra-t-il de ces échantillons biologiques ?**

Les fragments tumoraux seront conservés au département d'anatomopathologie de L'Institut Mutualiste Montsouris (14 boulevard Jourdan 75014 Paris) sous la responsabilité du Docteur Pierre Validire.
Les recherches réalisées sur ces échantillons biologiques seront fonction des avancées de la science. Tout nouveau projet de recherche réalisé avec ces matériels biologiques commencera après avoir été préalablement approuvé par un Comité de Protection des Personnes en accord avec toutes les lois en vigueur.

Si vous refusez cette recherche, cela n'aura pas de conséquence sur votre traitement, ni sur votre prise en charge.

Si vous donnez votre consentement pour cette recherche, cela implique également que vous acceptiez la conservation de ces matériels biologiques pour une durée pouvant aller jusqu'à 20 ans. Les fragments tumoraux issus de la réalisation des biopsies seront manipulés et conservés en accord avec toutes les lois en vigueur.

On ne peut exclure que les résultats obtenus par l'utilisation de matériels biologiques puissent conduire à l'obtention de droits exclusifs reposant sur des découvertes liées à la recherche. Vous ne recevrez aucune contrepartie financière. Au cas où le promoteur de l'étude bénéficierait d'un financement, il serait réinvesti dans la recherche contre le cancer dans le seul but d'en améliorer la connaissance ou le traitement.

**Bénéfices attendus**

Il est peu probable que les résultats des recherches sur les matériels biologiques soient disponibles dans un avenir proche. En effet, la recherche peut être longue et les prélèvements et les données doivent être recueillis auprès de nombreux patients durant plusieurs années avant que les résultats ne soient connus.

Des informations nouvelles pourront éventuellement être obtenues auprès du médecin qui vous a traité(e) dans le cadre de l'essai. N'hésitez pas à questionner votre médecin à ce sujet.

**Protection des données**

Ces échantillons biologiques et ces données seront traités avec la même confidentialité que pour le reste des données recueillies lors de l'essai clinique.

Toutes les données vous concernant (personnelles, cliniques, et les données provenant des recherches sur les matériels biologiques) seront traitées en accord avec la «Directive sur la protection des individus concernant le traitement des données personnelles » et les lois nationales en vigueur.

Il est très important que les informations collectées soient précises et, par conséquent, elles seront comparées de temps à autre à celles contenues dans votre dossier médical. Des personnes dûment autorisées (le Promoteur ou ses représentants, les représentants des autorités sanitaires nationales) peuvent avoir accès à votre dossier médical. A l'exception de l'accès par ces personnes toutes les informations seront strictement confidentielles.

L'essai clinique auquel vous participez et l'étude biologique que nous vous proposons ont été approuvés par le Comité de Protection des Personnes (CPP) Ile de France VI, le 04/10/2013 et par l'Agence Nationale de Sécurité du Médicament (ANSM) le 30/08/2013.

*Personnes à contacter*- En cas de problème ou de question votre médecin est à votre disposition et peut être contacté comme suit :

| |
|---|
| Nom du médecin |
| Hôpital |
| Téléphone |

Un exemplaire de ce document vous revient de droit après que vous et votre médecin l'aurez signé.

GERCOR

**RECHERCHE SUR DES MATERIELS BIOLOGIQUES**

CONSENTEMENT ECLAIRE

J'ai reçu et ai bien compris les informations relatives à la recherche complémentaire sur les matériels biologiques réalisée dans le cadre de l'étude AFUGEM. J'ai eu suffisamment de temps pour réfléchir à ma participation.

J'ai reçu un exemplaire de la lettre d'information pour le patient.

Tous mes droits m'ont été clairement expliqués.

J'accepte la conservation, puis la recherche sur ces matériels biologiques. Je participe de mon plein gré et j'ai la possibilité de retirer mon consentement à tout moment sans donner d'explication. Cela n'affectera pas ma participation à l'essai clinique, ni mes relations avec mon médecin ou le personnel hospitalier. Les données me concernant seront strictement confidentielles.

J'accepte que toute recherche future sur le cancer puisse être réalisée sur ces matériels biologiques.

J'accepte que les données qui me concernent et qui auront été consignées lors de cette étude soient traitées informatiquement pour ou par le promoteur. J'ai bien noté que le droit d'accès prévu par la loi « Informatique et Liberté » (article 40 et suivants) s'exerce à tout moment auprès du médecin de l'étude. Je pourrai exercer mon droit de rectification des données personnelles en contactant ce médecin.

En cas de collaboration du promoteur avec un tiers, j'accepte que mes matériels biologiques soient utilisés par :

- une autre institution/organisme universitaire,
- une compagnie pharmaceutique.

Mon consentement ne décharge en rien les organisateurs de la recherche de leur responsabilité et je conserve tous mes droits garantis par la loi.

Nom du patient :_____

Signature du patient : _____ Date: _____

Nom de l'investigateur :_____

Titre/statut: _____

Signature de l'investigateur:_____ Date: _____

**Ce document est à réaliser en 3 exemplaires dont le premier doit être gardé 15 ans par l'investigateur, un autre remis à la personne donnant son consentement et le troisième transmis au promoteur.**

## 17.2. COPY OF THE INSURANCE CERTIFICATE

ACE European Group Ltd
Le Colisée
8, avenue de l'Arche
92419 COURBEVOIE CEDEX

33 (0)1 55 91 45 45 *tél*
33 (0)1 47 88 45 10 *fax*
www.acegroup.com/fr

ace europe

ATTESTATION D'ASSURANCE

RESPONSABILITE CIVILE
PROMOTEUR DE RECHERCHES BIOMEDICALES

Nous soussignés, **ACE European Group Limited**, Immeuble le Colisée - 8, avenue de l'Arche - 92419 Courbevoie Cedex attestons que la Société :

**GERCOR**
151, rue du Faubourg St Antoine
75011 Paris
France

agissant en tant que Promoteur,

est assurée au titre du contrat Responsabilité Civile référencé **FRCAN12107**, prenant effet le **01 juillet 2013**, et conforme aux dispositions légales et réglementaires françaises sur les recherches biomédicales notamment aux dispositions du décret n° 2006-477 du 26 avril 2006 pris en application de la loi n° 2004-806 du 9 août 2004.

Titre anglais

**Randomized Phase II Study of Weekly ABI-007 plus Gemcitabine or Simplified LV5FU2 as First-line Therapy in Patients with Metastatic Pancreatic Cancer**

Titre français

**Etude randomisée de phase II d'une chimiothérapie de première ligne associant ABI-007 (PACLITAXEL-ALBUMINE) et GEMCITABINE ou LV5FU2 simplifié, chez des patients atteints d'un cancer du pancréas métastatique.**

| | |
|---|---|
| Référence de l'étude | : **AFUGEM D12-2** |
| Date de début de l'étude | : 01 juillet 2013 |
| Date de fin d'étude | : 01 juillet 2018 |
| Phase | : II |
| Nombre de patients | : 114 |

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ACE European Group Ltd
Le Colisée
8, avenue de l'Arche
92419 COURBEVOIE CEDEX

33 (0)1 55 91 45 45 *tél*
33 (0)1 47 88 45 10 *fax*
www.acegroup.com/fr

Conformément à l'article L 1121-10 du Code de la Santé Publique, le contrat ci-dessus référencé garantit la responsabilité civile du promoteur ainsi que celle de tout intervenant à cette recherche biomédicale.

Fait à Courbevoie, le 25 juin 2013

Ace European Group Limited
Le Colisée
8, Avenue de l'Arche
92419 Courbevoie Cedex

## 17.3. ECOG PERFORMANCE STATUS CLASSIFICATION

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease activities without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work or office work |
| 2 | Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self care. Totally confined to bed or chair |
| 5 | Dead |

## 17.4. SUMMARY OF PRODUCT CHARACTERISTICS

The current SmPC of Abraxane® can be found on the European Medicines Agency website on:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000778/human_med_000620.jsp&mid=WC0b01ac058001d124

## 17.5. EORTC QLQ C-30 QUESTIONNAIRE (FRENCH VERSION 3)

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.
*Merci de préciser:*

Vos initiales: | | |
Date de naissance (jour/mois/année): | | | | | | | | |
La date d`aujourd`hui (jour/mois/année): | | | | | | | | |

| | | **Pas du tout** | **Un peu** | **Assez** | **Beaucoup** |
|---|---|---|---|---|---|
| 1. | Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provision chargé ou une valise? | 1 | 2 | 3 | 4 |
| 2. | Avez-vous des difficultés à faire une longue promenade? | 1 | 2 | 3 | 4 |
| 3. | Avez-vous des difficultés à faire un petit tour dehors? | 1 | 2 | 3 | 4 |
| 4. | Etes-vous obligé(e) de rester au lit ou dans un fauteuil pendant la journée ? | 1 | 2 | 3 | 4 |
| 5. | Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes? | 1 | 2 | 3 | 4 |

Au cours de la semaine passée:

| | | **Pas du tout** | **Un peu** | **Assez** | **Beaucoup** |
|---|---|---|---|---|---|
| 6. | Avez-vous été gêné(e) pour faire votre travail ou vos activités de tous les jours? | 1 | 2 | 3 | 4 |
| 7. | Avez-vous été gêné(e)dans vos activités de loisirs? | 1 | 2 | 3 | 4 |
| 8. | Avez-vous eu le souffle court? | 1 | 2 | 3 | 4 |
| 9. | Avez-vous ressenti de la douleur? | 1 | 2 | 3 | 4 |
| 10. | Avez-vous eu besoin de repos? | 1 | 2 | 3 | 4 |
| 11. | Avez-vous eu des difficultés pour dormir? | 1 | 2 | 3 | 4 |
| 12. | Vous êtes-vous senti(e)faible? | 1 | 2 | 3 | 4 |
| 13. | Avez-vous manqué d'appétit? | 1 | 2 | 3 | 4 |

Passez à la page suivante S.V.P.

Au cours de la semaine passée**:**

| | | Pas du tout | Un peu | Assez | Beaucoup |
|---|---|---|---|---|---|
| 14. | Avez-vous eu des nausées (mal au cœur)? | 1 | 2 | 3 | 4 |
| 15. | Avez-vous vomi? | 1 | 2 | 3 | 4 |
| 16. | Avez-vous été constipé(e)? | 1 | 2 | 3 | 4 |
| 17. | Avez-vous eu de la diarrhée? | 1 | 2 | 3 | 4 |
| 18. | Etiez-vous fatigué(e)? | 1 | 2 | 3 | 4 |
| 19. | Des douleurs ont-elles perturbé vos activités quotidiennes? | 1 | 2 | 3 | 4 |
| 20. | Avez-vous eu des difficultés à vous concentrer sur certaines choses, par exemple, pour lire le journal ou regarder la télévision? | 1 | 2 | 3 | 4 |
| 21. | Vous êtes-vous senti(e)tendu(e)? | 1 | 2 | 3 | 4 |
| 22. | Vous êtes-vous fait du souci? | 1 | 2 | 3 | 4 |
| 23. | Vous êtes-vous senti(e) irritable? | 1 | 2 | 3 | 4 |
| 24. | Vous êtes-vous senti(e)déprimé(e)? | 1 | 2 | 3 | 4 |
| 25. | Avez-vous eu des difficultés pour vous souvenir de certaines choses? | 1 | 2 | 3 | 4 |
| 26. | Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans votre vie familiale? | 1 | 2 | 3 | 4 |
| 27. | Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma...)? | 1 | 2 | 3 | 4 |
| 28. | Votre état physique ou votre traitement médical Vous ont-ils causé des problèmes financiers? | 1 | 2 | 3 | 4 |

**Pour les questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation**

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Très mauvais | | | | | | Excellent |

30. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Très mauvais | | | | | | Excellent |