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CLINICAL TRIAL PROTOCOL

A Phase II, Open-label, Multicenter Study of PM060184 in Patients with Advanced Colorectal Cancer after Standard Treatment

INVESTIGATIONAL MEDICINAL PRODUCTS: PM060184
Protocol No.: PM60184-B-002-17
EudraCT No.: 2017-000257-39
NCT Code: 03427268

Protocol version 2.0 including substantial amendment #1 dated 27 July 2017

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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Confidentiality statement

STUDY CONTACTS	NAME AND ADDRESS	PHONE, FAX NUMBER, AND E-MAIL ADDRESS
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[1] Abbreviated as PharmaMar or Sponsor in the rest of the protocol.

STUDY CONTACTS	NAME AND ADDRESS	PHONE, FAX NUMBER, AND E-MAIL ADDRESS
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PRINCIPAL INVESTIGATORS

A full list of Investigators will be available as a separate document.

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SYNOPSIS

TITLE	A Phase II, Open-label, Multicenter Study of PM060184 in Patients with Advanced Colorectal Cancer after Standard Treatment.
CODE	PM60184-B-002-17
INVESTIGATORS	A full list of Investigators will be available as a separate document.
TRIAL SITES/ LOCATION	Approximately six sites in the EU, the U.S. and Canada are expected to participate.
STUDY OBJECTIVES	**Primary:** • To evaluate the efficacy of PM060184 in terms of progression-free survival at 12 weeks (PFS3) in patients with advanced colorectal carcinoma (CRC) after standard therapy. **Secondary:** • To evaluate overall survival (OS); progression-free survival (PFS); overall response rate (ORR); and duration of response (DOR). • To characterize the safety profile and feasibility of PM060184 in this population. • To describe peripheral neuropathy (PN) and quality of life (QoL) profiles in this population using patient-reported outcomes (PRO) as measured by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ) for chemotherapy-induced peripheral neuropathy (QLQ-CIPN20) and general QoL (QLQ-C30). • To characterize the pharmacokinetics (PK) of PM060184 in this population. • To characterize the metabolomics of PM060184, i.e., systemic variations in the patient's pre- and post-treatment metabolic profile that allow the identification of potential biomarkers of PK, safety and/or efficacy response to PM060184. • To characterize pharmacogenetics (PGt) of PM060184 in this population by identifying the presence or absence of germline mutations or polymorphisms that may help explain individual variability in the main PK parameters and safety outcomes. • To characterize pharmacogenomics (PGx) of PM060184 in this population by analyzing the potential predictive factors (including BRAF-mutant-like gene expression subtypes) of sensitivity/resistance to PM060184 treatment.
STUDY POPULATION	Patients with relapsed, metastatic/locally advanced CRC with any KRAS-mutation status (wild-type, mutated, or status unknown), progressing after standard treatments (fluoropyrimidine, irinotecan, and oxaliplatin).
STUDY DESIGN	This is a phase II, multicenter, open-label, study of single-agent PM060184 to evaluate efficacy in patients with advanced CRC progressing after standard therapy. Initially, 24 patients who are evaluable for the primary endpoint will be included and a futility analysis will be performed (first

	stage). If at least seven of these patients achieve PFS3, then the study will proceed to a second stage and 36 additional patients will be recruited. If at least 25 of 60 evaluable patients are alive and free of progression at 12 weeks, PM060184 will be considered active and deserving potential development in this setting.
SUBSTUDY DESIGN	An exploratory substudy will address pharmacogenomic and pharmacogenetic objectives. All patients who participate in the PM60184-B-002-17 clinical trial will be eligible for the substudy if they voluntarily sign a separate informed consent. Refusal to participate in the substudy will not affect a patient's participation in the clinical trial.
INCLUSION CRITERIA	1) Voluntarily written informed consent, obtained before the beginning of any study-specific procedures. 2) Age ≥ 18 years. 3) Histologically-cytologically documented adenocarcinoma of colon or rectum that has progressed to the last prior treatment before inclusion. 4) Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. If the only tumor lesion is situated in a previously irradiated area or in an area subjected to other loco-regional therapy, progression in the lesion must be demonstrated radiologically. 5) Previous treatment in any setting with fluoropyrimidine, oxaliplatin and irinotecan in any combination (unless any is contraindicated). a) Adjuvant chemotherapy-based treatments count as prior therapy, as long as relapse had occurred during or within six months of completion of such therapies. b) Cumulative dose of prior oxaliplatin (if any) must be known. c) Prior cetuximab, panitumumab, bevacizumab, aflibercept, and regorafenib are allowed. 6) No more than two prior therapies for metastatic disease. 7) Washout periods for prior therapies (defined in relation to planned start of study treatment [first dose administration]): a) At least three weeks since the last administration of an antineoplastic treatment (chemotherapy, biological, targeted or investigational therapies). b) At least three weeks since radiotherapy involving up to 35% of bone marrow (radiotherapy involving > 35% of bone marrow is not allowed) or two weeks since the end of palliative radiotherapy including single doses. c) At least four weeks since any major surgical procedure, open biopsy, or significant traumatic injury. 8) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. 9) Life expectancy ≥ 3 months. 10) Adequate bone marrow, liver, and kidney function: a) Hemoglobin ≥ 9 g/dL.

	b) Absolute neutrophil count ≥ 1.5×10^9/L. c) Platelet count ≥ 100×10^9/L. d) Serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula). e) Albumin ≥ 2.5 g/dL. f) Total serum bilirubin ≤ 1.5 times the upper limit of normal (ULN), except in case of Gilbert syndrome. g) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5.0 × ULN in the case of liver metastases). 11) Recovery to grade ≤ 1 from any toxicity due to previous therapy (including peripheral sensory/motor neuropathy but excluding alopecia). 12) Left ventricular ejection fraction (LVEF) by echocardiography (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards). 13) Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure during the trial and up to six months after treatment discontinuation, and fertile male patients must agree to refrain from fathering a child or donating sperm during the trial and up to four months after treatment discontinuation.
EXCLUSION CRITERIA	1) Prior exposure to PM060184. 2) Known hypersensitivity to the study drug class or study drug excipient in the formulation. 3) Patients with locally advanced disease amenable to local and/or curative therapy (surgery or radiotherapy) at study entry. 4) Other serious and/or relevant diseases or clinical situations that, in the opinion of the Investigator, are incompatible with the protocol (including any of the following): a) History of another neoplastic disease (except for basal cell carcinoma of the skin, superficial bladder tumors, or properly treated carcinoma in situ of the uterine cervix or melanoma in situ) unless in remission for at least five years and with no recurrence. b) Symptomatic cerebral and/or leptomeningeal metastasis, spinal cord compression or carcinomatous meningitis. c) Neuropathy of any etiology (other than that caused by previous antineoplastic therapy). d) History of cardiac disease, such as myocardial infarction, in the year prior to registration in the clinical trial; symptomatic/uncontrolled angina pectoris; congestive heart failure or uncontrolled cardiac ischemia; any type of uncontrolled arrhythmia, congenital and/or prolonged QT interval or abnormal LVEF, or uncontrolled arterial hypertension (according to the standards of the World Health Organization [WHO]). e) History of significant psychiatric disease.

<table>
<tr><td></td><td>f) Active infection requiring antibiotic, antifungal or antiviral treatment that, in the opinion of the Investigator, could compromise the patient's capacity to tolerate the therapy.
g) Known active liver (hepatitis B or C or cirrhosis) or renal disease.
h) Known human immunodeficiency virus (HIV) infection.
i) Any other concomitant pathology that could jeopardize the patient's safety or commitment to complete the clinical trial.
j) Inability or refusal to comply with the protocol or with the clinical trial procedures.
5) Pregnancy or lactation.</td></tr>
<tr><td>EXPECTED NUMBER OF PATIENTS</td><td>The number of evaluable patients for the first stage (until the futility analysis) is 24, and for the second stage, 36; an expected 60 patients in total.</td></tr>
<tr><td>STUDY DRUG
Formulation</td><td>The drug substance PM060184-CD is a mixture of PM060184 and 2-hydroxypropyl-β-cyclodextrin.
PM060184 drug product (DP) is provided as a sterile lyophilized powder for concentrate for solution for infusion with a strength of 15 mg of the active moiety PM060184.
Before use, PM060184 15-mg vials should be reconstituted with 6 mL of water for injection. The total volume of the reconstituted vial should be diluted with dextrose (5%) up to a total volume of 30 mL to give a PM060184 diluted solution containing 0.5 mg/mL of PM060184. The diluted solution should be protected from exposure to light.
Each 15-mg vial of PM060184 is a single-use vial. The full composition of the reconstituted solution per mL is shown in Table 1.
Table 1. PM060184 vial composition.
<table><tr><th>Component</th><th>Concentration (per mL)</th><th>Function</th></tr><tr><td>PM060184</td><td>2.5 mg/mL</td><td>Active moiety</td></tr><tr><td>2-Hydroxypropyl-β cyclodextrin (DS 4–5)</td><td>200 mg/mL</td><td>Solubilizing agent</td></tr><tr><td>Water for injection</td><td>1 mL</td><td>Solvent</td></tr></table>DS, degree of substitution.</td></tr>
<tr><td>Dose / Route of administration</td><td>9.3 mg/m^2 PM060184 i.v. as a 30-minute infusion via a central or peripheral venous catheter.
Dose can be rounded to the first decimal point.</td></tr>
<tr><td>Treatment Schedule</td><td>PM060184 will be administered on Day 1 and Day 8 q3wk. (Three weeks=one treatment cycle).</td></tr>
</table>

<table>
<tr><td>PROPHYLACTIC MEDICATION</td><td>Primary antiemetic prophylaxis is compulsory before all PM060184 dose administrations. Standard treatment according to the American Society of Clinical Oncology (ASCO) guidelines will be administered:
• 5-HT_3 antagonists (ondansetron 8 mg or equivalent).
• Steroids (dexamethasone 8 mg or equivalent).
Oral or i.v. formulations are allowed according to institutional standards.
If necessary, additional antiemetic therapy can be considered in accordance with ASCO guidelines.</td></tr>
<tr><td>CRITERIA FOR TREATMENT CONTINUATION</td><td>Patients will be treated with additional cycles of PM060184 until disease progression (PD), as long as none of the following occur: unacceptable toxicity, and/or patient refusal, and/or Investigators' decision.
The administration of subsequent cycles (after Cycle 1) should be delayed if criteria for treatment continuation (Table 2) are not met on the corresponding Day 1. If criteria for treatment continuation are not met on Day 8 (i.e., seven days after the first dose administration of a cycle) (Table 2) of any cycle, administration should be omitted instead of delayed.
Table 2. Criteria for treatment continuation.
<table>
<tr><th>Abnormality</th><th>Day 1 [a]</th><th>Day 8</th></tr>
<tr><td>ANC</td><td>≥ 1.5 × 10^9/L</td><td>≥ 1.0 × 10^9/L</td></tr>
<tr><td>Platelets</td><td>≥ 100 × 10^9/L</td><td>≥ 75 × 10^9/L</td></tr>
<tr><td>Hemoglobin [b]</td><td>≥ 9 g/dL</td><td>≥ 9 g/dL</td></tr>
<tr><td>Total bilirubin</td><td colspan="2">≤ 1.5 × ULN (grade 1)</td></tr>
<tr><td>AST/ALT</td><td>Grade ≤ 1 [c]</td><td>Grade ≤ 2</td></tr>
<tr><td>Calculated CrCL (Cockcroft-Gault formula)</td><td>≥ 40 mL/min</td><td>≥ 30 mL/min</td></tr>
<tr><td>Peripheral sensory/motor neuropathy</td><td>Grade ≤ 2</td><td>Grade ≤ 2</td></tr>
<tr><td>Nausea/vomiting, fatigue, anorexia</td><td>Grade ≤ 2</td><td>Grade ≤ 2</td></tr>
<tr><td>Other non-hematological drug-related AEs (except metabolic abnormalities [d])</td><td>Grade ≤ 1</td><td>Grade ≤ 2</td></tr>
</table>
[a] Except Day 1 of Cycle 1.
[b] If hemoglobin levels are not met, the Investigator will have the option of giving the patient a transfusion instead of delaying (on Day 1) or omitting (on Day 8) a dose.
[c] Grade ≤ 2, for patients with liver metastases and with AST and/or ALT levels ≤5.0 x ULN at registration.
[d] Any grade accepted for increased GGT. Up to grade 4 accepted for non-symptomatic metabolic abnormalities (e.g., sodium, magnesium, potassium, calcium).
AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CrCL, creatinine clearance; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.
A maximum delay of 15 days is allowed for the recovery of patients from toxicity. If toxicities have not recovered after this period, the patient should discontinue treatment. Exceptionally, in case of obvious clinical benefit, the patient can remain on</td></tr>
</table>

<table>
<tr><td></td><td>treatment but only after discussion and mutual agreement with the Sponsor, and upon recovery of all parameters according to the aforementioned criteria.
A dose is not delayed if it is administered within the permitted window (further information may be found in the footnote of the Schedule of Assessments and Procedures); delays should be calculated from the planned administration day.</td></tr>
<tr><td>DOSE MODIFICATIONS</td><td>Dose can be reduced on the basis of the worst toxicity (drug-related AE) occurring since the previous dose (e.g., Day 1 or Day 8 of any cycle except for Day 1 of Cycle 1). The PM060184 dose reduction schedule is described in Table 3, and criteria according to toxicity in Table 4 and Table 5.
Table 3. PM060184 dose reduction levels.<table><tr><th>Dose level</th><th>PM060184</th></tr><tr><td>–1</td><td>7.5 mg/m^2</td></tr><tr><td>–2</td><td>6.0 mg/m^2</td></tr></table>Table 4. Criteria for PM060184 dose reduction for hematological toxicity.<table><tr><th>Abnormality</th><th>Nadir value</th><th>PM060184</th></tr><tr><td>ANC</td><td>$< 0.5 \times 10^9$/L with fever (≥ 38.5°C)/ infection, or
$< 0.5 \times 10^9$/L for ≥ 3 days</td><td>Reduce one dose level</td></tr><tr><td>Platelet count</td><td>$< 50 \times 10^9$/L, with significant bleeding, or
$< 25 \times 10^9$/L</td><td>Reduce one dose level</td></tr></table>A second occurrence of the aforementioned toxicities should lead to a further dose reduction (i.e., dose level –2). No more than two dose reductions will be allowed.
ANC, absolute neutrophil count.
Table 5. Criteria for PM060184 dose reduction for non-hematological toxicity.<table><tr><th>Abnormality</th><th>Worst NCI-CTCAE grade</th><th>PM060184</th></tr><tr><td>Peripheral sensory/motor neuropathy</td><td>≥ 3</td><td>Reduce one dose level</td></tr><tr><td>Prolonged peripheral sensory/motor neuropathy [a]</td><td>≥ 2</td><td>Reduce one dose level</td></tr><tr><td>Abdominal pain (if reoccurring after the first administration)</td><td>≥ 3</td><td>Reduce one dose level</td></tr><tr><td>Nausea/vomiting despite adequate antiemetic treatment</td><td>≥ 3</td><td>Reduce one dose level</td></tr><tr><td>Fatigue (if reoccurring or persistent after Cycle 2)</td><td>≥ 3</td><td>Reduce one dose level</td></tr><tr><td>Other treatment-related AEs according to the Investigator’s criteria</td><td>≥ 3</td><td>Reduce one dose level</td></tr></table>A second occurrence of these toxicities should lead to a further dose reduction (i.e., reduction to dose level –2). No more than two dose reductions will be allowed.
[a] Lasting more than two cycles.
AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for the Classification of Adverse Events.</td></tr>
</table>

	No more than two dose reductions per patient will be allowed in the course of this clinical trial. Patients requiring more dose reductions should discontinue treatment, except in the event of obvious clinical benefit, in which case, treatment may continue after discussion and mutual agreement with the Sponsor. No dose escalations will be allowed in this clinical trial.
DRUG-DRUG INTERACTIONS	*In vitro* studies using human liver microsomes have pointed to CYP2C19 and CYP3A4 as the predominant cytochrome (CYP) enzymes responsible for the hepatic metabolism of PM060184. Therefore, concomitant drugs that induce or inhibit any of these cytochromes to a significant extent should be avoided whenever possible.
ALLOWED CONCOMITANT MEDICATIONS	• Therapies for pre-existing and treatment-emergent medical conditions, including pain management. • Blood products and transfusions, as clinically indicated. • Approved therapies for bone metastasis (e.g., bisphosphonates, denosumab). • In case of nausea or vomiting, prophylaxis and/or symptomatic treatment for emesis according to ASCO guidelines. • Erythropoietin use according to ASCO guidelines. • Treatment with granulocyte colony-stimulating factor (G-CSF) in the event of grade 4 neutropenia lasting ≥ 3 days, neutropenic sepsis or febrile neutropenia according to ASCO guidelines. Secondary prophylaxis can be considered if it is in the best interest of the patient. • Megestrol acetate for appetite stimulation. • Anticoagulant therapy for the treatment or secondary prophylaxis of thromboembolic events.
PROHIBITED MEDICATIONS	• Concomitant administration of any other antineoplastic therapy. • Any other investigational agents. • Immunosuppressive therapies other than corticosteroids. • Local therapy such as radiation or surgery if the lesion is the only target lesion, unless agreed in advance with the Sponsor.
EFFICACY EVALUATIONS	Patients will be evaluable for efficacy if they receive at least one complete treatment cycle (or two PM060184 dose administrations over two cycles) and have, at least, one disease assessment at Week 6 and another one at Week 12. In addition, any patient who presents disease progression, symptomatic deterioration due to the disease or clinical progression, dies due to malignant disease, discontinues treatment due to unmanageable toxicity, or dies or discontinues treatment due to a treatment-related AE before evaluation of the response at Week 12 will also be considered evaluable for the primary endpoint and classified as a non-responder. Patients who have no disease assessment at Week 6 but remain on treatment and are assessed at Week 12 (or later, and with no evidence of disease progression) will be considered evaluable for efficacy.

	Patients who refuse further treatment before Week 12 due to reasons other than related AEs not considered unmanageable toxicity will be replaced. A futility analysis will be performed once the first 24 evaluable patients complete the Week 12 (± 5 days) tumor assessment; progress; die due to PD; or discontinue treatment due to unmanageable toxicity (whichever occurs first). If seven patients or more achieve PFS3, then 36 additional patients will be recruited (second stage). Tumor assessment will be measured using RECIST v.1.1.
SAFETY EVALUATIONS	Patients will be evaluable for safety if they receive at least one (complete or incomplete) dose of PM060184. Safety will be evaluated by clinical examinations, analysis of vital signs, clinical assessment of AEs, changes in the analytical parameters (hematological and biochemical), and any other analyses that may be considered necessary. All treatment-related AEs must be followed-up—even if the administration of PM060184 has finalized—until the AE or its sequelae have resolved or stabilized at an acceptable level (grade ≤ 2). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4), and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).
PATIENT-REPORTED-OUTCOMES	EORTC QLQ-CIPN20 and QLQ-C30 will be used to collect information on patients' self-reported QoL and neurotoxicity, targeting symptoms, functional limitations, and patient concerns specifically associated with treatment-induced PN, and potential activity impairment. Patients will be asked to complete both QLQs at baseline, on Day 8 of each cycle, at the end-of-treatment visit. Patients will be asked to complete the QLQ-CIPN20 (only) during the follow-up period (about every three months until start of subsequent antitumor therapy). If a patient discontinues treatment due to grade ≥ 3 PN, however, the QLQ-CIPN20 should be completed more frequently during the follow-up period (every month after EOT) until recovery to grade ≤ 2 (or until start of subsequent antitumor therapy).
PHARMACO-KINETICS	The plasma PK of PM060184 will be evaluated in Cycle 1 and Cycle 2 during both stages of the study. In the first stage, PK will be evaluated on Days 1 and 2 of Cycle 1 and Cycle 2 with a sampling schedule of ten samples; in the second stage, PK will be evaluated on Day 1 of Cycle 1 and Cycle 2 only with eight samples (Table 6).

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Table 6. Pharmacokinetic sampling schedule for PM060184.

Sample number	Day	Relative times	Sampling times for PM060184	Sampling window
#1	1	0 min	Before start of administration	-
#2	1	30 min	Just before EOI	- 2 min
#3	1	45 min	15 min after EOI	± 2 min
#4	1	1 h	30 min after EOI	± 5 min
#5	1	1.5 h	1 h after EOI	± 10 min
#6	1	2.5 h	2 h after EOI	± 10 min
#7	1	4.5 h	4 h after EOI	± 10 min
#8	1	6.5 h	6 h after EOI	± 10 min
#9 [a]	1 [a]	12.5 h	12 h after EOI	± 1 h
#10 [a]	2 [a]	24.5 h	24 h after EOI	± 4 h

[a] Samples #9 and #10 are required only in patients included in the first stage of the study.
EOI, end of infusion; h, hour; min, minute.

</td></tr>
<tr><td>METABOLOMIC BIOMARKERS</td><td>The metabolomics of PM060184 will be characterized by evaluating systemic variations in pre- and post-treatment metabolic profile to identify potential biomarkers of PK, safety and/or efficacy response to PM060184.
Patients will have blood samples collected before drug administration on Day 1 and Day 8 of Cycle 1, and also on Day 8 of Cycle 2, to evaluate the pretreatment profile of endogenous metabolite levels and changes after PM060184 treatment.</td></tr>
<tr><td>PHARMACO-GENETICS</td><td>To explore PGt factors that may help to explain individual variability in main PK parameters, as well as susceptibility to develop treatment-related AEs, the presence or absence of germline mutations or polymorphisms that may be involved in the metabolism and/or transport of PM060184 will be analyzed in leukocyte DNA extracted from blood collected preferably before PM060184 treatment start from those patients who have also consented to the substudy.</td></tr>
<tr><td>PHARMACO-GENOMICS</td><td>The analysis of potential predictive factors to PM060184 treatment will be analyzed in paraffin-embedded tumor tissue samples from patients participating in the substudy. These factors will include, among others, tubulin isotypes and other factors related to the mechanism of action of PM060184 and to the tumor microenvironment (such as angiogenic factors, and markers of lymphocyte subpopulations and tumor associated macrophages), and their expression will be analyzed at the protein level and/or mRNA level by immunohistochemistry or quantitative PCR, respectively; their polymorphisms and mutations might also be analyzed, if relevant.
BRAF-mutant-like gene expression subtypes (and potentially full genome expression) will be determined to show potential correlation with response or outcome after treatment with</td></tr>
</table>

	PM060184. At final study analysis—and if feasible according to overall efficacy and to the number of patients with available biopsy—the subgroup characteristics will be statistically analyzed for correlation with the study efficacy parameters: PFS, ORR, DOR, and OS.
STATISTICAL METHODS	**Sample size:** Patients will be treated with PM060184 to test the null hypothesis (H0) that 30% or less patients are alive and free of progression at 12 weeks (PFS3) according to RECIST v.1.1 ($p \leq 0.30$) versus the alternative hypothesis (H1) that 50% or more patients are alive and free of progression at twelve weeks according to the aforementioned criteria ($p \geq 0.50$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.1; hence, statistical power is 90%. Sixty evaluable patients are necessary to test the hypothesis. A futility analysis using O'Brien-Fleming boundaries is planned when 24 patients can be evaluated (first stage). If there are seven or more patients achieving PFS3 in the first stage then the trial will proceed to a second stage and a total of 60 patients will be recruited. If at least 25 of 60 evaluable patients are alive and free of progression at 12 weeks then the null hypothesis can be rejected and PM060184 considered active and deserving potential development in this setting. **Primary endpoint:** • PFS3, defined as the percentage of patients remaining alive and progression-free at Week 12 (Month 3) after the first treatment dose. **Secondary endpoints:** • Overall survival (OS), defined as the time from the first day of treatment to the date of death or last contact. • Progression-free survival (PFS), defined as the time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation. • Overall response rate (ORR), defined as the percentage of patients with either complete response (CR) or partial response (PR) according to RECIST v.1.1. • Duration of response (DOR), defined as the time between the date when response criteria (PR or CR, the first to be reached) are fulfilled and the first date when PD, recurrence or death is objectively documented. • Treatment safety, including AEs, SAEs and laboratory abnormalities graded according to NCI-CTCAE v.4. Dose reductions or delays due to treatment-related AEs, and reasons for treatment discontinuations will also be analyzed. • PN and QoL profiles as reported by patients using the EORTC QLQ-CIPN20 and QLQ-C30. • PK parameters will be evaluated in plasma by population PK

	modeling and/or non-compartmental analysis. • Metabolomics of PM060184, i.e., intra- and interpatient systemic variations in the patient's pre- and post-treatment metabolic profile. • PGt of PM060184 will be evaluated to identify the presence or absence of germline mutations or polymorphisms that may help explain individual variability in the main PK parameters and safety outcomes. • PGx of PM060184 will be evaluated to determine predictive/prognostic markers of response and/or resistance to PM060184. **Methods of analysis:** Frequency tables will be prepared for categorical variables and summary tables, including median, mean, standard deviation, minimum, and maximum values for each variable, will be used for continuous variables. Exploratory comparisons will be performed at a 0.05 level. The exact binomial estimator and its 95% confidence interval (CI) will be used for the primary endpoint (PFS3) and categorical variables (i.e., ORR). Time-to-event variables (DOR, PFS, OS) and their fixed time estimates will be analyzed according to the Kaplan-Meier method. Safety analyses will consider AEs, SAEs, analytical results, deaths and the reasons for study discontinuations. All AEs and SAEs will be graded according to the NCI-CTCAE v.4, and will be coded using MedDRA. PRO analysis will be performed on summary measures and longitudinal modelling of patients' QLQ responses. Other analyses will include: number of prior treatment lines, prior oxaliplatin exposure, KRAS status, BRAF-like expression, and other prognostic/predictive factors.
PLANNED TRIAL PERIODS	Patients will be evaluated at scheduled visits in the following study periods: • **Screening:** from signature of informed consent to registration (confirmation of eligibility) or screen failure. • **Pretreatment:** from registration to first dose of study treatment. • **Treatment:** from first administration of study treatment to end of treatment (EOT). EOT is standardly defined as 30 days (± 15 days) after the day of last administration of study treatment, unless the patient starts a new antitumor therapy or dies within 30 days of the last dose, in which case the date of administration of this new antitumor therapy or the date of death will be considered the EOT date. Patients will receive study drug while considered to be in their best interest or until study termination. Specifically, treatment will continue until: • Disease progression. • Unacceptable toxicity (including any toxicity leading to the need for a third dose reduction or severe hypersensitivity

	reactions, except in the case of obvious clinical benefit, in which event the patient could be allowed to remain on treatment once agreed with the Sponsor). • Patient refusal to receive further study treatment and/or non-compliance with study requirements. • Intercurrent serious illness. • Pregnancy. • Investigator's decision. • Protocol deviation with an effect on the risk/benefit ratio of the clinical trial. • PM060184 treatment delay > 15 days from the due date (except in case of clear clinical benefit and with the Sponsor's approval). **Note:** this maximum delay of 15 days already includes the window of ± 2 days allowed for Day 1 administration. • Clinical cutoff. Patients who have not progressed at these time points could be treated in a compassionate use program (according to country regulations). • **Follow-up:** after EOT, patients will be followed for both safety and efficacy. 1) **Safety:** every four weeks until resolution or stabilization of drug-related AEs (if any). 2) **Efficacy**: about every three months until death, refusal to continue participating in the study, or study termination (clinical cutoff), whichever occurs first. Subsequent off-study therapies should be provided until death, refusal, and/or clinical cutoff (whichever occurs first). **Note:** patients without disease progression who discontinue treatment due to a drug-related AE must be followed both for the AE and for efficacy. **PFS and survival follow-up timelines for the whole population:** If the study ends after the futility analysis at 24 evaluable patients (first stage): • Patients who are still on study will be followed up to 12 weeks after the first PM060184 administration of the last patient evaluable for the futility analysis. If the futility analysis results in continuation of recruitment (second stage): • All patients will be followed up to 12 months after the first PM060184 administration of the last evaluable patient treated in the study, regardless of the stage at which the patients have been included.
REPLACEMENT OF PATIENTS	Patients must be replaced if they are considered not evaluable for the primary endpoint (PFS3), i.e., if they are withdrawn from the study due to significant clinical deterioration of unknown reason, hypersensitivity reactions, unrelated AEs without any tumor assessments after the start of study treatment, if they receive less than one complete treatment cycle (at least two PM060184 dose administrations over two cycles unless treatment discontinuation was due to unmanageable toxicity), or do not have the disease assessment at Week 12 (except in the case of treatment

	discontinuation/death due to a treatment-related AE, symptomatic deterioration due to the disease, clinical progression, PD or death due to malignant disease).
PLANNED TRIAL CALENDAR	The total duration of the study will be approximately 36 months. **Planned start date (first patient first visit):** 4Q2017. **Planned enrollment period:** approximately 24 months. **Planned study termination (clinical cutoff):** 12 months after the first PM060184 administration of the last evaluable patient treated in the study.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessments and procedures	Days prior to registration	Treatment					Follow -up [2]
		Cycle 1		Further cycles		EOT [1]	
		Day 1 *	Day 8	Day 22=Day 1	Day 8		
Written IC	•	-	-	-	-	-	-
Demographic data	–28	-	-	-	-	-	-
Medical history [3]	–28	-	-	-	-	-	-
Cancer history [4]	–28	-	-	-	-	-	-
Physical examination	–10	•	-	•	-	• [5]	-
ECOG PS	–10	•	-	•	-	• [5]	-
Vital signs	–10	•	•	•	•	• [5]	-
Hematology [6]	–10	•	•	•	•	• [5]	-
Biochemistry-A [6]	–10	•	•	•	•	• [5]	-
Biochemistry-B	–10	•	-	•	-	• [5]	-
Pregnancy [7]	–7	-	-	• [7]	-	• [7]	-
ECG	–28	Repeat if clinically indicated					-
LVEF	–28	Repeat if clinically indicated				•	-
PM060184 administration	-	•	•	•	•	-	-
Pharmacokinetics [8]	-	Cycle 1 and Cycle 2 [8]				-	-
Metabolomics [9]	-	•	•	-	-	-	-
Pharmacogenetics [10]	-	• [10]				-	-
Pharmacogenomics [11]	Archived sample	[11]				-	-
Tumor assessment [12]	–28	-	-	[12]		-	[12]
Concomitant therapies	–14	← Throughout the on-treatment period →					[2]
Adverse events [13]	•	← Throughout the on-treatment period →					[2]
PRO QLQs [14]	–10	-	•	-	•	•	• [14]

Registration=confirmation of eligibility and inclusion; Day 1=day of first cycle administration (with infusion start); Day 8=seven days after the first dose administration of a cycle (± 2 days); Day 22 = Day 1 (± 2 days) of the following cycle.

* Permitted windows for assessments before Day 1 of Cycle 1:
If physical examination, ECOG PS, vital signs, hematology/biochemistry were assessed >10 days before Day 1 of Cycle 1, the tests must be repeated within 2 days before the first study drug administration.
If pregnancy test was done >7 days before Day 1 of Cycle 1, the test must be repeated within 2 days before the first study drug administration.
If tumor assessments were done >28 days before Day 1 of Cycle 1, the tests must be repeated within 2 days before the first study drug administration.
A patient should only be treated if eligibility criteria are still met according to assessments performed closest to treatment start.

Permitted windows for assessments after Day 1 of Cycle 1:
- 2 days for physical examination and ECOG PS (on Day 1) and for vital signs (on Days 1 and 8), always before study drug administration.
+ 7 days for tumor assessments (except in Week 12 when there is a maximum 5-day window).
± 2 days for Day 1 study drug administration (from Cycle 2 onwards).
± 2 days for Day 8 study drug administration.
– 2 days for laboratory tests. To confirm criteria for treatment continuation, laboratory assessments must be performed within 2 days prior to drug administration.

If a drug administration is delayed beyond the permitted protocol window, assessments planned for the original administration day must be repeated on the day the dose is finally administered.

1. EOT assessments should take place approximately 30 days (± 15 days) after the last drug administration or before starting new therapy. Loss to follow-up, or failure to attend the EOT visit due to a deteriorated clinical condition or due to personal reasons such as returning to their previous hospital, will not be considered protocol deviations.
2. Patients discontinuing treatment due to a drug-related AE should be followed for safety every four weeks until recovery or stabilization. Regardless of the reason for treatment discontinuation, all patients will be followed for efficacy about every three months until death, refusal to continue participating in the study, or study termination (clinical cutoff), whichever occurs first. Subsequent antitumor therapies should be provided until death, refusal, and/or clinical cutoff (whichever occurs first). For the purpose of collecting information on patient's survival, a documented telephone call, email or medical chart review is acceptable; follow-up for survival will be completed for all patients only if the study continues to the second stage. **Note: patients without disease progression who discontinue treatment due to a drug-related AE must be followed both for the AE and for efficacy (see 12. below).**
3. Medical history includes relevant conditions and syndromes that started before registration and are not ongoing (no signs or symptoms) at time of registration or are controlled and do not require evaluation for severity or causality. Also includes any event qualifying as serious occurring prior to registration.
4. Cancer history includes primary diagnosis, response history, date of last confirmed PD, and all prior treatment (including cumulative dose of prior oxaliplatin, if any).
5. The listed assessments are required if no recent data are available (i.e. within the previous 10 days) or if the last data available show a grade ≥ 2 treatment-related alteration whenever the medical condition of the patient allows.
6. If any clinically-relevant, treatment-related grade ≥ 3 AE occurs, the abnormality should be reassessed at least every 2–3 days until recovery to at least grade 2. In the event of febrile neutropenia, grade 4 neutropenia and/or grade 4 thrombocytopenia, reassessment should be performed **daily** until recovery to at least grade 3 (or until fever resolution, if applicable) and then every 2–3 days thereafter until recovery to at least grade 2.
7. Assessment of β-hCG only if the patient is a WOCBP. During the on-treatment period, testing should be every cycle within 2 days before study drug administration (or, at least, every month).
8. The plasma PK of PM060184 will be evaluated in Cycle 1 and Cycle 2 during both stages of the study. Ten plasma PK samples are required from patients included in the first stage: just before start of administration, just before EOI, and then 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, and 12.5 h (Day 1) and 24.5 h (Day 2) after EOI in Cycle 1 and Cycle 2. Only eight plasma samples are required from patients included in the second stage: the samples scheduled at 12.5 h and 24.5 h after EOI in Cycle 1 and Cycle 2 are not required.
9. One blood sample should be collected prior to each drug administration on Day 1 and Day 8 of Cycle 1, and also on Day 8 of Cycle 2.
10. If the patient consents to the substudy, an additional blood sample for PGt analysis should be collected at any time during the trial but ideally at the same time as the pretreatment PK sample (sample #1) of Cycle 1.
11. If the patient consents to the substudy, the availability of tumor tissue samples used for the initial diagnosis of the disease, or obtained at relapse, should be confirmed and should be prepared and shipped during the trial following the instructions detailed in a separate laboratory manual.
12. To be performed every six weeks (+ 7 days, except for Week 12 when a window of ± 5 days applies). **The Week-12 disease evaluation is the primary endpoint of the study and should be performed in all non-PD patients (including those who discontinued treatment without progression).** The same radiological method should be used throughout the study for each individual patient. Anonymized copies of images showing a response (CR or PR) must be submitted to the Sponsor. Tumor assessment should be performed about every three months during follow-up in patients who discontinue treatment without disease progression. **Note: patients without disease progression who discontinue treatment due to a drug-related AE must be followed both for the AE AND for efficacy (see 2. above).**
13. Baseline conditions, signs and symptoms and ongoing toxicities at registration should be reported as screening AEs. Clinical assessment of the patient's signs and symptoms (if any and including nurses' assessment and patient-reported issues) should continue on an ongoing basis throughout the study and be reported at least every cycle as AEs graded according to NCI-CTCAE v.4. SAEs will be collected from the time of IC signature (reported in paper if a patient is not yet registered). During screening and pretreatment periods, AEs are considered baseline and non-treatment emergent. If a condition previously reported in Medical History changes during treatment, the event should be reported as an AE.
14. Patients will be asked to complete both QLQs at baseline, on Day 8 of each cycle, at the end-of-treatment visit. Patients will be asked to complete the QLQ-CIPN20 (only) during the follow-up period (every three months until start of subsequent antitumor therapy). If a patient discontinues treatment due to grade ≥ 3 PN, however, the QLQ-CIPN20 should be completed more frequently during the follow-up period (every month after EOT) until recovery to grade ≤ 2 (or until start of subsequent antitumor therapy).

Assessment details

Biochemistry-A: ALP, AST, ALT, total bilirubin (and direct bilirubin if total is >1.5 x ULN), GGT, creatinine/CrCL (Cockcroft-Gault formula), glucose, LDH, and serum electrolytes (Na^+, K^+, Total calcium).

Biochemistry-B: Total proteins and albumin.

ECG: including rhythm definition and PR interval; heart rate; QT interval (raw); QRS complex duration, as well as

any ECG anomaly or variation (change in grade) with respect to baseline.

Hematology: Complete blood count, differential WBC (neutrophils, lymphocytes), hemoglobin, and platelets.

Left ventricular ejection fraction: assessed by ECHO or MUGA scan.

Physical examination: Including weight, height (when needed for BSA calculation) and clinical assessment. BSA and dosing should be recalculated in the event of weight variation of ±10%.

Tumor assessment: Clinical and radiological disease assessment using RECIST v.1.1. Helical i.v. and oral contrast-enhanced CT-scan (if appropriate) for chest, abdomen and pelvis and other areas of suspected diseases. If i.v. contrast is contraindicated for the CT-scan, chest evaluation should be performed using non-contrasted CT and abdomen/pelvis evaluation using gadolinium-enhanced MRI. Tumor markers alone or chest radiography alone are not sufficient to assess tumor burden.

Vital signs: Heart rate, arterial blood pressure, and temperature

Abbreviations

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CIPN, chemotherapy-induced peripheral neuropathy; CR, complete response; CrCL, calculated creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; EOT, end of treatment; GGT, gamma-glutamyltransferase; IC, Informed Consent; i.v., intravenous; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PGt, pharmacogenetics; PK, pharmacokinetics; PN, peripheral neuropathy; PR, partial response; PRO, patient reported outcomes; PS, performance status; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; ULN, upper limit of normal; WBC, white blood cells; WOCBP, woman of childbearing potential.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-HT$_3$	Serotonin
5-FU	5-fluorouracil
ABP	Arterial Blood Pressure
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BSC	Best Supportive Care
CI	Confidence Interval
CIPN	Chemotherapy-induced Peripheral Neuropathy
CL	Clearance
CR	Complete Response
CRC	Colorectal Cancer
CrCL	Creatinine Clearance
CT	Computed Tomography
d	Day
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DP	Drug Product
DOR	Duration of Response
DS	Drug Substance; Degree of Substitution
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of Treatment
FP	Fluoropyrimidine
G-CSF	Granulocyte Colony-stimulating Factor
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI$_{50}$	Growth Inhibition at 50%
GMT	Greenwich Meridian Time
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HSD	Honestly Significant Difference
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Investigational Ethics Committee
IF	Immunofixation
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
i.v.	Intravenous(ly)

LC-MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
MTI	Microtubule Inhibitor
MUGA	Multiple-gated Acquisition Scan
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small Cell Lung Cancer
OPLS	Orthogonal Partial Least-squares to Latent Structures
ORR	Overall Response Rate
OS	Overall Survival
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-free Survival
PFS3	Progression-free Survival at 12 weeks (three months)
PGt	Pharmacogenetics
PGx	Pharmacogenomics
PhV	Pharmacovigilance
PIF	Peak Inspiratory Flow
PK	Pharmacokinetics
PN	Peripheral Neuropathy
PR	Partial Response
PRO	Patient Reported Outcomes
PS	Performance Status
PSN	Peripheral Sensory Neuropathy
QoL	Quality of Life
QLQ	Quality of Life Questionnaire
q28d	Every 28 Days
q3wk	Every Three Weeks
q4wk	Every Four Weeks
RD	Recommended Dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Respiratory Rate
Rt-m/z	Retention Time and Mass-to-charge Ratio Pairs
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SD	Stable Disease
ULN	Upper Limit of Normal
UPLC	Ultra Performance Liquid Chromatography
U.S.	United States of America
V_2	Peripheral Volume
V_{ss}	Volume of Distribution at Steady State
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells
WHO	World Health Organization

WMA	World Medical Association
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1 DISEASE BACKGROUND

Worldwide, colorectal cancer (CRC) is the third most common cancer (1,360,602 new cases in 2012), accounting for 10% of all cancers (not including non-melanoma skin cancer) and an estimated 693,933 deaths (8.5% of the total number of cancer deaths; the fourth most common cause of cancer deaths) (1). Almost 55% of new cases occur in more developed regions. In Europe, there were 447,000 new CRC cases and 215,000 deaths (12% of all cancer deaths) in 2012 (2). The National Cancer Institute (NCI) estimates 134,490 new CRC cases and 49,190 deaths (8% of all cancer deaths) in the U.S. in 2016 (3).

The median age at diagnosis is 68 years, and 90% of cases are diagnosed in those over 50 years of age. The lifetime risk for CRC is 6% in average-risk persons living in the U.S. The CRC-related 5-year survival rate is 65%. Approximately 20–25% of patients present with metastases (metastatic CRC [mCRC]) at initial diagnosis and almost 50% of the remainder will subsequently develop metastases, contributing to the high mortality rates reported for CRC. The overall prognosis of patients with mCRC is poor, with five-year survival in the 5–8% range. However, recent chemotherapeutic regimens combined with targeted agents have significantly improved their two-year survival.

For patients with non-curable mCRC, combination chemotherapy including oxaliplatin-based and irinotecan-based regimens remains standard for first-line and second-line therapies. For patients with wild-type KRAS tumors, cetuximab (an epidermal growth factor receptor inhibitor) is a common option for third-line therapy, improving median survival from 4.8 to 9.5 months when compared with supportive care alone (4). When 5-fluorouracil (5-FU) was the only active agent, overall survival (OS) was approximately one year. There are now eight different classes of drugs with significant antitumor activity in mCRC and patients routinely live longer than two years:

- Fluoropyrimidines (FP) (including 5-FU, which is usually given with leucovorin, capecitabine, S-1, and tegafur plus uracil).
- Irinotecan.
- Oxaliplatin.
- Cetuximab and panitumumab, two monoclonal antibodies directed against the epidermal growth factor receptor (EGFR).
- Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF).
- Aflibercept, a recombinant fusion protein consisting of VEGF binding portions from the human VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G1.
- Regorafenib, an orally active inhibitor of angiogenic tyrosine kinases (including the VEGF receptors 1 to 3), as well as other membrane and intracellular kinases.
- Trifluridine-tipiracil (TAS-102), an oral cytotoxic agent that consists of the nucleoside analog trifluridine and tipiracil, which inhibits trifluridine metabolism and has antiangiogenic properties.

A median OS of 18.2 months in first-line mCRC patients is now reported with combinations of cytotoxic and biological therapies (5). Because OS may be prolonged by second- and subsequent-line therapies, exposure to all available treatment options at some stage (rather than in a particular order) may be more important so choosing an

appropriate treatment approach remains complex with several open questions and the need for new drugs as the underlying biology becomes better known and understood (6).

The best way to combine and sequence these agents is not yet established, and the goals of chemotherapy in this setting differ according to clinical scenario: for non-resectable disease in patients without symptoms, induction of a tumor response is not as important as is delaying tumor progression as long as possible. Systemic 5FU-based chemotherapy produces meaningful improvements in median survival and progression-free survival (PFS) compared with best supportive care (BSC) alone. These benefits are most pronounced with regimens containing irinotecan or oxaliplatin in combination with FU, which represent the mainstay of advanced and metastatic CRC chemotherapy. Consequently, when patients with advanced or metastatic CRC have received prior FP, irinotecan and oxaliplatin -based regimens (in addition to any ad hoc therapy targeting EGFR, and/or VEGF, according to tumor characteristics), new agents within clinical trials are warranted.

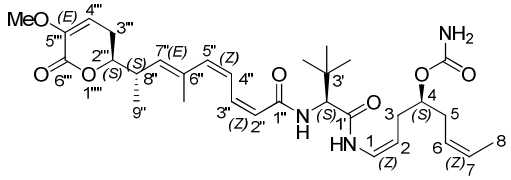
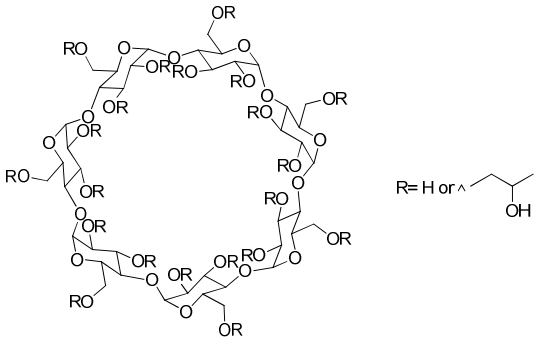
1.2 INFORMATION ON STUDY DRUG

The drug substance (DS) PM060184-CD is a mixture of PM060184 and 2-hydroxypropyl- β-cyclodextrin:

Chemical Name (IUPAC)	(1Z,4S,6Z)-1-((3S)-8-((2S)-5-methoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-6-methylnona-2,4,6-trienoyl]-3-methyl-L-valyl)amino)octa-1,6-dien-4-yl carbamate
	2-Hydroxypropyl-β-cyclodextrin (DS 4 – 5)
Other name	PM060184
	HPβCD

The structural and molecular formulas of PM060184 are shown in Figure 1.

Figure 1. Chemical structure of PM060184.

Structural Formula	PM060184	
	HPβCD	
Molecular Formula	PM060184	$C_{31}H_{45}N_3O_7$
	HPβCD	$(C_6H_9O_5)_7(C_3H_7O)_n$ n=4-5
Molecular Weight	PM060184	571.7049
	HPβCD	About 1400
Proportion (w/w)	PM060184	1
	HPβCD	10

1.2.1 Non-clinical Data

Pharmacodynamics

PM060184 depolymerizes tubulin fibers and causes disorganization and fragmentation of the microtubule network, inducing multipolar mitosis, prometaphase arrest as well as an induction of caspase-dependent apoptosis and/or the appearance of cells in a multinucleated interphase-like state.

PM060184 demonstrated a potent *in vitro* cytotoxic activity (average growth inhibition at 50% [GI_{50}] of 718 pM) in a broad panel of solid human carcinoma cell lines, the strongest activity seen against BT-474 (breast), HT-29 (colon), RXF-393 (renal) and Igrov-1 (ovarian) cell lines. In animals bearing xenografted human-derived tumors, PM060184 displayed a dose-related, strong antitumor activity (minimal T/C ranging from 34.0 to –39.3%), especially against MAXF 401 (breast), HCT-116 (colon), HGC-27 (gastric), H460 (NSCLC), 22Rv1 (prostate), Caki-1 or MRI-H-121 (renal) and A2780 or OVXF 899 (ovarian).

In male rats, no significant gross behavioral or physiological changes were induced by the administration of PM060184 at 8 mg/kg. Also, in male rats administered at 8 mg/kg, decreases in inspiration time and enhanced pause, as well as increases in peak inspiratory flow (PIF), respiratory rate (RR) and in minute volume were recorded at 1 h post-dose; these changes were followed (at 2.5 or 3.5 h post-dose) by increases in expiration time and decreases in RR and in minute volume. In dogs, heart rate (HR) and lead II electrocardiogram (ECG) derived variables monitoring revealed reductions in HR and increases in RR in males at 30 min after a single PM060184 administration (0.8 mg/kg). In a separate study (3 weekly consecutive doses), following the first administration, PM060184 induced decreases in HR and increases in RR and QT intervals, the largest variations found at 1 hour post-dose; also, QTc increases (both genders) were seen at 6 h, still present at 24 h in the highly dosed groups. No alterations in any parameter were seen on Day 15, after the third consecutive weekly administration.

Pharmacokinetics and Metabolism

The terminal elimination half-lives, following intravenous administration of PM060184 in nonclinical species (mice, rats, dogs, rabbits, monkeys and mini-pig) were short and ranged from 1.5 to 8.1 h, indicating a relatively high plasma clearance. Similar volume of distribution at steady state was found between genders which was much higher than the plasma volume for all animal species tested suggesting extensive extravascular distribution. The *in vitro* plasma protein binding of PM060184 was high in all species tested, ranging from 97.8 to 99.1 %; in humans, 98.7 % of PM060184 was bound to plasma proteins.

In vitro metabolism studies in subcellular fractions demonstrated that PM060184 undergoes extensive microsomal-mediated, NADPH-dependent metabolism in animal species, including man. The *in vitro* half-lives of intact PM060184 ranged from 15.5 (CD-1 male mouse) to 1.6 (*Cynomolgus* male monkey) min; in human, the half-life was calculated as 1.86 min. Preliminary metabolite identification suggests hydroxylation, oxidation (either mono- or di-) and N-dealkylation as the major pathways for PM060184 metabolism. PM060184 displayed high stability in plasma of all species studies, human included.

Based on *in vitro* evaluations, PM060184 has a limited potential for cytochrome CYP450 either inhibition or induction.

Toxicokinetic evaluations conducted in support of toxicology studies in rats and dogs demonstrated similar results, regardless of the administration schedule (single or repeated dose). Dose-proportionality and no accumulation of PM060184 plasma concentrations were seen in rats and dogs following up to three consecutive weekly administrations. Consistency between drug exposures (*ca*. 2-fold higher) and maximum tolerated dose (MTD) (*ca*. 2-fold lower) values was shown in female rats.

PM060184 exhibits consistent inter-species pharmacokinetic (PK) parameters with a good *in vitro-in vivo* correlation. Therefore, from a pharmacokinetic viewpoint, the evidence so far does not raise any concerns to proceed with the evaluation of this agent in cancer patients.

Toxicology

PM060184 has been tested in rats and dogs via the intravenous (i.v.) route either as single- or repeat-dose i.v. administration. The most toxicologically relevant findings in animals (either in rats and/or dogs) were seen in:

- the hematopoietic system, characterized by a moderate to severe reticulopenia, leukopenia, and thrombocytopenia, atrophy of the thymus, decrease in bone marrow cellularity (mainly in rats), and extramedullary hematopoiesis in the liver and spleen;
- the gastrointestinal system (mainly in dogs); and,
- the testes (azoospermia with severe testicular atrophy) in rats and dogs, at all dose levels tested.

Most of the alterations were resolved by the end of the observation period, with exception of the testicular lesions, as expected due to the limited observation period.

During repeat-dose toxicity studies, unscheduled mortality was observed in one female rat at 3.5 mg/kg (21 mg/m^2, on Day 9) and two dogs (after the first drug administration at 0.6 and 0.8 m/kg [12 and 16 mg/m^2]). In all cases moderate to marked immunosuppression (moderate to severe reticulopenia and thrombocytopenia), necrosis, hemorrhages in several organs (cervical lymph nodes, and/or spleen, liver, gastro-intestinal tract, adrenals, thymus, and bone marrow) and thrombosis were considered the factors most likely contributory to the deaths of these animals.

Clinical chemistry evaluation in rats and dogs revealed changes in liver and kidney related parameters. These changes were of limited magnitude and not dose-related, without inter-parameter consistency (e.g., a three-fold increase in alkaline phosphatase and alanine aminotransferase, with 75 % decrease in aspartate aminotransferase) and lack of concurrent findings on the histopathology examination.

Injection site injury was sporadically noted in dogs and rats; thus, the irritating potential of PM060184 cannot be ruled out. The *in vitro* genotoxicity evaluation indicated mutagenic properties attributable to PM060184. No phototoxic potential for PM060184 is predicted from the in vitro experiment performed.

The MTDs calculated in two animal species either as single or repeated bolus administration are summarized in **Table 1**.

Table 1. Maximum tolerated dose calculated for PM060184 in different animal species.

Species (Strain)	Gender	MTD mg/kg (mg/m^2)	
		Single-Dose	Repeat-Dose
Rat (Sprague-Dawley)	M	8.0 (48)	5.0 (30)
	F	4.0 (24)	2.0 (12)
Dog (Beagle)	M	0.8 (16)	0.4 (8)
	F	0.8 (16)	0.4 (8)

F, female; M, male; MTD, maximum tolerated dose.

According to the current data (MTD normalized by body surface area, mg/m^2), the dog is slightly more sensitive than the rat to PM060184 following single administration; in the repeated dose studies, closer figures are seen in rats and dogs: MTD was determined as 30 and 12 mg/m^2 (5 and 2 mg/kg) for male and female rats, respectively, and 8 mg/m^2 (0.4 mg/kg) in dogs. Therefore, starting doses in patients are similarly predicted either by taking 1/10th of the lowest rat-derived MTD (1.2 mg/m^2) or 1/6th of the dog-derived MTD (1.3 mg/m^2).

In conclusion, the toxicology properties of PM060184 make the compound suitable for further evaluation in cancer patients. The major toxicities observed in animals (rats and dogs) are expected for chemotherapeutic agents, and can be adequately monitored by hematological, biochemical, and cardiac assessments during clinical development.

1.2.2 Clinical Data

Up to the cutoff date of the 30 September 2016, 113 patients had been treated and evaluated with PM060184 as single agent in the clinical development program at PharmaMar (**Table 2**). The phase I program includes two single-agent clinical trials and one combination clinical trial (assessing different schedules of administration in patients with solid tumors refractory to standard therapy or for which no standard therapy exists). Currently, one phase II clinical trial is evaluating the efficacy of PM060184 in advanced, hormone receptor positive, HER2 negative, breast carcinoma.

Table 2. Summary of the clinical program of PM060184.

Study	Schedule	Included patients [a]	Evaluated patients [b]	Status
Phase I trials				
PM60184-A-001-10	PM060184 10-min and 3-h infusions **d1,8,15 q4wk**	47	44	Completed
PM60184-A-002a-10	PM060184 10-min infusion **d1,8 q3wk**	38	38	Completed
PM60184-A-002b-10	PM060184 10-min infusion **d1–3,15–17 q4wk**	22	22	Ongoing
PM60184-A-003-14	Gemcitabine 30-min infusion/ PM060184 10-min infusion **d1,8 q3wk**	23	21	Ongoing
Phase II trials				
PM60184-B-001-15	PM060184 5- and 1-min infusions **d1,8 q3wk.** The 1-min i.v. administration was validated.	12 [c]	9	Ongoing
Total		**142**	**134**	

Cutoff date: 30 September 2016.
[a] Patients registered in PharmaMar clinical database at cutoff, including patients not finally treated.
[b] Patients treated and with available data in PharmaMar clinical database at cutoff.
[c] Three patients were included but data were not available in the PharmaMar clinical database at cutoff.
d, day; min, minute; q3wk, every three weeks; q4wk, every four weeks.

To date, two phase I clinical trials have treated 104 solid tumor patients with different PM060184 schedules administered as single agent and as a 10-minute (min) i.v. administration: Days 1, 8 and 15 every four weeks (q4wk), Days 1 and 8 every three weeks (q3wk), and Days 1 to 3 and 15 to 17 every 28 days (q28d). The recommended dose (RD) has been established at 9.3 mg/m^2 for the Days 1 and 8 q3wk schedule. Most toxicities reported to date were mild to moderate, with peripheral motor/sensory neuropathy as the most frequent dose-limiting-toxicity (DLT), occurring in 6% of patients at doses above the RD.

As expected from a microtubule-binding agent, peripheral sensory neuropathy (PSN) was the principal dose-limiting toxicity. Fatigue, nausea/vomiting were also expected toxicities (but not dose-limiting). Hematological and biochemical abnormalities (regardless of relationship) did not represent a major safety concern.

Preliminary evidence of antitumor activity has been observed, four partial responses (PR) were reported in patients with cervix carcinoma, non-small cell lung cancer (NSCLC), breast and ovarian cancers, and 21 disease stabilizations (SDs) ≥ 3 months in several tumor types. Thirteen evaluable CRC patients were treated and six (46%) had SD lasting three months or longer. Their median number of prior lines of chemotherapy for advanced or metastatic disease was three (range, 2–5) and median PFS was 4.7 months (range, 3.7–12.8 months).

Pharmacokinetics

Preliminary analysis of the integrated data available from clinical trials to date (three phase I and one phase II) has shown that the PK of PM060184 is characterized by:

- A wide distribution to peripheral tissues (195 L).
- Low inter-patient variability in CL and peripheral volume (V_2).
- A moderate to high total clearance (CL) (62.55 L/h).
- Distribution and elimination linearity at the dose levels explored.
- Negligible renal elimination.
- A clear effect between body surface area (BSA) and CL, weight and V_2.

1.3 STUDY RATIONALE

Systemic 5-FU-based chemotherapy produces meaningful improvements in median survival and PFS compared with BSC alone (7). These benefits are most pronounced with regimens containing irinotecan or oxaliplatin in combination with 5-FU, which represent the mainstay of advanced and metastatic CRC chemotherapy.

Consequently, when patients with advanced or metastatic CRC have received prior FP, irinotecan and oxaliplatin-based regimens (in addition to any ad hoc therapy targeting EGFR, and/or VEGF, according to tumor characteristics), clinical trials with investigational medicinal products (IMPs) are warranted.

PM060184 is a novel microtubule inhibitor (MTI), with a different, specific binding site on the β-tubulin, that is distinct from the vinca domain used by vinca alkaloids, as well as the taxane domain and binding site. PM060184 induces microtubule depolymerization (8) and caspase-dependent, as well as non-classical apoptosis pathways (9). PM060184 has shown *in vitro* and *in vivo* antitumor activity at nanomolar concentrations in CRC (10). Thirteen evaluable CRC patients were treated with single-

agent PM060184 to date and six (46%) had SD lasting three months or longer with a median PFS of 4.7 months (range, 3.7–12.8 months).

This trial will evaluate the efficacy of PM060184 in terms of progression-free survival at 12 weeks (PFS3) in advanced or metastatic CRC patients progressing after standard treatments (fluoropyrimidine, irinotecan, and oxaliplatin).

Patients in this trial will receive PM060184 as a 30-minute i.v. infusion on Days 1 and 8 q3wk. The dose selected (9.3 mg/m^2) is the recommended dose for phase II studies that was determined for this same schedule, with PM060184 given as a 10-minute i.v. infusion, in study PM60184-A-002a-10 (see Section 1.2.2).

Metabolomic (Biomarkers) Study Rationale

Metabolomics (metabonomics/metabolomics), i.e., the determination of endogenous low-molecular-weight molecules or metabolites in a body fluid and their changes as a consequence of stimuli such as medical interventions, is currently being used to evaluate the efficacy and safety of medical interventions in cancer (11), thus allowing for the discovery of predictive biomarkers of drug response (12).

The metabolic profile of the patients before and after treatment with PM060184 will be compared to search for systematic variations that may serve as biomarkers of PK, safety and/or efficacy response to treatment with PM060184. Particular attention will be given to specific metabolic patterns observed in patients who develop peripheral neuropathy associated with PM060184. For this purpose, a blood sample will be collected prior to treatment administration on Day 1 and Day 8 of Cycle 1, and also on Day 8 of Cycle 2.

Pharmacogenomic/Pharmacogenetic Substudy Rationale

The rationale of the exploratory and optional substudy includes the evaluation of potential markers of sensitivity to PM060184 treatment with microtubule-interacting agents in a population of advanced CRC patients. These molecular markers would help in the future selection of patients who might preferentially benefit from PM060184 therapy, thus contributing to improved health care through a more individualized medicine.

There is growing evidence that the effects of tubulin-targeting drugs in endothelial cells are much more subtle than originally thought. In fact, some tubulin-binding drugs have been known to have antivascular (antiangiogenesis or vascular-disrupting) activities that can target abnormal tumor vessels (13, 14). PM060184 inhibits tubulin polymerization inducing alterations of the microtubule mass and dynamics, as well as the appearance of multipolar spindles. These effects will induce cell cycle arrest at G2/M. Cells will finally die by apoptosis or remain blocked in a multinucleated state. Thus, since PM060184 induces cytotoxicity by inhibiting tubulin polymerization, it is possible that alterations in β-tubulin isotype content and/or MAPs may alter sensitivity to this agent.

BRAF-mutant colon cancers have a characteristic gene expression signature that is also found in some tumors lacking this mutation: BRAF-like KRAS mutants and double wild-type patients have similarly poor prognosis. This suggests a common biology between these tumors and adds prognostic and biologic information that is not captured by the mutation classification alone (15).

These BRAF-like tumors represent 20% of colon cancers and have been shown to display far greater sensitivity to the microtubule poison, vinorelbine, and will also be explored by the genomic assays in the pharmacogenomic (PGx) substudy (16).

PM060184 is a very potent microtubule inhibitor; thus the sensitivity of this subset of patients, should sample size allow it, will be explored more specifically for potential differences.

Finally, a pharmacogenetic (PGt) analysis will explore factors that may help explain individual variability in the main PK parameters and safety outcomes, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA.

2. OVERALL STUDY DESIGN

This is a phase II, multicenter, open-label, study of single-agent PM060184 to evaluate efficacy in patients with advanced CRC progressing after standard therapy.

Initially, 24 patients who are evaluable for the primary endpoint will be included and a futility analysis will be performed (first stage). If at least seven of these patients achieve PFS3, then the study will proceed to a second stage and 36 additional patients will be recruited.

An exploratory substudy will address pharmacogenomic and pharmacogenetic objectives. All patients who participate in the PM60184-B-002-17 clinical trial will be eligible for the substudy if they voluntarily sign a separate informed consent (IC). Refusal to participate in the substudy will not affect a patient's participation in the clinical trial.

3. STUDY OBJECTIVES

Primary:

- To evaluate the efficacy of PM060184 in terms of progression-free survival at 12 weeks (PFS3) in patients with advanced CRC after standard therapy.

Secondary:

- To evaluate OS; PFS; overall response rate (ORR); and duration of response (DOR).
- To characterize the safety profile and feasibility of PM060184 in this population.
- To describe PN and quality of life (QoL) profiles in this population using patient-reported outcomes (PRO) as measured by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ) for chemotherapy-induced peripheral neuropathy (QLQ-CIPN20) and general QoL (QLQ-C30).
- To characterize the PK of PM060184 in this population.
- To characterize the metabolomics of PM060184, i.e. PM060184, i.e., systemic variations in the patient's pre- and post-treatment metabolic profile that allow the identification of potential biomarkers of PK, safety and/or efficacy response to PM060184.
- To characterize PGt of PM060184 in this population by identifying the presence or absence of germline mutations or polymorphisms that may help explain individual variability in the main PK parameters and safety outcomes.
- To characterize PGx of PM060184 in this population by analyzing the potential predictive factors (including BRAF-mutant-like gene expression subtypes) of sensitivity/resistance to PM060184 treatment.

4. SELECTION OF PATIENTS

Patients with relapsed, metastatic/locally advanced CRC with any KRAS-mutation status (wild-type, mutated, or status unknown), progressing after standard treatments (fluoropyrimidine, irinotecan, and oxaliplatin).

4.1 INCLUSION CRITERIA

1) Voluntarily written informed consent, obtained before the beginning of any study-specific procedures.
2) Age ≥ 18 years.
3) Histologically-cytologically documented adenocarcinoma of colon or rectum that has progressed to the last prior treatment before inclusion.
4) Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 (17). If the only tumor lesion is situated in a previously irradiated area or in an area subjected to other loco-regional therapy, progression in the lesion must be demonstrated radiologically.
5) Previous treatment in any setting with fluoropyrimidine, oxaliplatin and irinotecan in any combination (unless any is contraindicated).
   a) Adjuvant chemotherapy-based treatments count as prior therapy, as long as relapse had occurred during or within six months of completion of such therapies.
   b) Cumulative dose of prior oxaliplatin (if any) must be known.
   c) Prior cetuximab, panitumumab, bevacizumab, aflibercept, and regorafenib are allowed.
6) No more than two prior therapies for metastatic disease.
7) Washout periods for prior therapies (defined in relation to planned start of study treatment [first dose administration]):
   a) At least three weeks since the last administration of an antineoplastic treatment (chemotherapy, biological, targeted or investigational therapies).
   b) At least three weeks since radiotherapy involving up to 35% of bone marrow (radiotherapy involving > 35% of bone marrow is not allowed) or two weeks since the end of palliative radiotherapy including single doses (18).
   c) At least four weeks since any major surgical procedure, open biopsy, or significant traumatic injury.
8) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (**Appendix 1**).
9) Life expectancy ≥ 3 months.
10) Adequate bone marrow, liver, and kidney function:
   a) Hemoglobin ≥ 9 g/dL.
   b) Absolute neutrophil count (ANC) ≥ 1.5×10^9/L.
   c) Platelet count ≥ 100×10^9/L.
   d) Serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula, **Appendix 2**).
   e) Albumin ≥ 2.5 g/dL.
   f) Total serum bilirubin ≤ 1.5 times the upper limit of normal (ULN), except in case of Gilbert syndrome.

g) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5.0 × ULN in the case of liver metastases).

11) Recovery to grade ≤ 1 from any toxicity due to previous therapy (including peripheral sensory/motor neuropathy but excluding alopecia).
12) Left ventricular ejection fraction (LVEF) by echocardiography (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards).
13) Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure during the trial and up to six months after treatment discontinuation, and fertile male patients must agree to refrain from fathering a child or donating sperm during the trial and up to four months after treatment discontinuation.*

* Valid methods to determine the childbearing potential, adequate contraception and requirements for WOCBP partners are described in **Appendix 3**.

4.2 EXCLUSION CRITERIA

1) Prior exposure to PM060184.
2) Known hypersensitivity to the study drug class or study drug excipient in the formulation.
3) Patients with locally advanced disease amenable to local and/or curative therapy (surgery or radiotherapy) at study entry.
4) Other serious and/or relevant diseases or clinical situations that, in the opinion of the Investigator, are incompatible with the protocol (including any of the following):
   a) History of another neoplastic disease (except for basal cell carcinoma of the skin, superficial bladder tumors, or properly treated carcinoma in situ of the uterine cervix or melanoma in situ) unless in remission for at least five years and with no recurrence.
   b) Symptomatic cerebral and/or leptomeningeal metastasis, spinal cord compression or carcinomatous meningitis.
   c) Neuropathy of any etiology (other than that caused by previous antineoplastic therapy).
   d) History of cardiac disease, such as myocardial infarction, in the year prior to registration in the clinical trial; symptomatic/uncontrolled angina pectoris; congestive heart failure or uncontrolled cardiac ischemia; any type of uncontrolled arrhythmia, congenital and/or prolonged QT interval or abnormal LVEF, or uncontrolled arterial hypertension (according to the standards of the World Health Organization [WHO]).
   e) History of significant psychiatric disease.
   f) Active infection requiring antibiotic, antifungal or antiviral treatment that, in the opinion of the Investigator, could compromise the patient's capacity to tolerate the therapy.
   g) Known active liver (hepatitis B or C or cirrhosis) or renal disease.
   h) Known human immunodeficiency virus (HIV) infection.
   i) Any other concomitant pathology that could jeopardize the patient's safety or commitment to complete the clinical trial.

j) Inability or refusal to comply with the protocol or with the clinical trial procedures.

5) Pregnancy or lactation.

5. TREATMENT

5.1 STUDY DRUG FORMULATION AND SUPPLY

The drug substance PM060184-CD is a mixture of PM060184 and 2-hydroxypropyl-β-cyclodextrin.

PM060184 drug product (DP) is provided as a sterile lyophilized powder for concentrate for solution for infusion with a strength of 15 mg of the active moiety PM060184.

Before use, PM060184 15-mg vials should be reconstituted with 6 mL of water for injection. The total volume of the reconstituted vial should be diluted with dextrose (5%) up to a total volume of 30 mL to give a PM060184 diluted solution containing 0.5 mg/mL of PM060184. The diluted solution should be protected from exposure to light.

Each 15-mg vial of PM060184 is a single-use vial. The full composition of the reconstituted solution per mL is shown in **Table 3**.

Table 3. PM060184 vial composition.

Component	Concentration (per mL)	Function
PM060184	2.5 mg/mL	Active moiety
2-Hydroxypropyl-β cyclodextrin (DS 4–5)	200 mg/mL	Solubilizing agent
Water for injection	1 mL	Solvent

DS, degree of substitution.

For instructions regarding drug inventory, handling, reconstitution, dilution, storage and disposal, please refer to the Preparation Guide for infusion for PM060184 and the PM060184 Investigator's Brochure (IB), both provided as separate documents. Medication preparation records will be kept by the site.

5.2 ADMINISTRATION OF STUDY MEDICATION

PM060184 at a dose of 9.3 mg/m^2 (dose can be rounded to the first decimal point) will be administered as a 30-minute i.v. infusion via a central or peripheral venous catheter, on Day 1 and Day 8 q3wk (three weeks=one treatment cycle).

5.3 CRITERIA FOR TREATMENT CONTINUATION

Patients will be treated with additional cycles of PM060184 until disease progression (PD), as long as none of the following occur: unacceptable toxicity, and/or patient refusal to receive further study treatment, and/or Investigators' decision.

The administration of subsequent cycles (after Cycle 1) should be delayed if criteria for treatment continuation (**Table 4**) are not met on the corresponding Day 1. If criteria for treatment continuation are not met on Day 8 (i.e. seven days after the first dose administration of a cycle) of any cycle, administration should be omitted instead of delayed.

Table 4. Criteria for treatment continuation.

Abnormality	Day 1 [a]	Day 8
ANC	≥ 1.5 × 10^9/L	≥ 1.0 × 10^9/L
Platelets	≥ 100 × 10^9/L	≥ 75 × 10^9/L
Hemoglobin [b]	≥ 9 g/dL	≥ 9 g/dL
Total bilirubin	≤ 1.5 × ULN (grade 1)	
AST/ALT	Grade ≤ 1 [c]	Grade ≤ 2
Calculated CrCL (Cockcroft-Gault formula)	≥ 40 mL/min	≥ 30 mL/min
Peripheral sensory/motor neuropathy	Grade ≤ 2	Grade ≤ 2
Nausea/vomiting, fatigue, anorexia	Grade ≤ 2	Grade ≤ 2
Other non-hematological drug-related AEs (except metabolic abnormalities [d])	Grade ≤ 1	Grade ≤ 2

[a] Except Day 1 of Cycle 1.
[b] If hemoglobin levels are not met, the Investigator will have the option of giving the patient a transfusion instead of delaying (on Day 1) or omitting (on Day 8) a dose.
[c] Grade ≤ 2, for patients with liver metastases and with AST and/or ALT levels ≤5.0 x ULN at registration.
[d] Any grade accepted for increased GGT. Up to grade 4 accepted for non-symptomatic metabolic abnormalities (e.g., sodium, magnesium, potassium, calcium).
AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CrCL, creatinine clearance; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

A maximum delay of 15 days is allowed for the recovery of patients from toxicity. If toxicities have not recovered after this period, the patient should discontinue treatment. Exceptionally, in case of obvious clinical benefit, the patient can remain on treatment but only after discussion and mutual agreement with the Sponsor, and upon recovery of all parameters according to the aforementioned criteria.

5.4 DOSE REDUCTION

Dose can be reduced on the basis of the worst toxicity (drug-related adverse event [AE]) occurring since the previous dose (e.g., Day 1 or Day 8 of any cycle except for Day 1 of Cycle 1). The PM060184 dose reduction schedule is described in **Table 5**, and criteria according to toxicity in **Table 6** and **Table 7**.

Table 5. PM060184 dose reduction levels.

Dose level	PM060184
–1	7.5 mg/m^2
–2	6.0 mg/m^2

Table 6. Criteria for PM060184 dose reduction for hematological toxicity.

Abnormality	Nadir value	PM060184
ANC	$< 0.5 \times 10^9$/L with fever (≥ 38.5°C)/infection, or $< 0.5 \times 10^9$/L for ≥ 3 days	Reduce one dose level
Platelet count	$< 50 \times 10^9$/L, with significant bleeding, or $< 25 \times 10^9$/L	Reduce one dose level

A second occurrence of the aforementioned toxicities should lead to a further dose reduction (i.e., dose level –2). No more than two dose reductions will be allowed.
ANC, absolute neutrophil count.

Table 7. Criteria for PM060184 dose reduction for non-hematological toxicity.

Abnormality	Worst NCI-CTCAE grade	PM060184
Peripheral sensory/motor neuropathy	≥ 3	Reduce one dose level
Prolonged peripheral sensory/motor neuropathy [a]	≥ 2	Reduce one dose level
Abdominal pain (if reoccurring after the first administration)	≥ 3	Reduce one dose level
Nausea/vomiting despite adequate antiemetic treatment	≥ 3	Reduce one dose level
Fatigue (if reoccurring or persistent after Cycle 2)	≥ 3	Reduce one dose level
Other treatment-related AEs according to the Investigator's criteria	≥ 3	Reduce one dose level

A second occurrence of these toxicities should lead to a further dose reduction (i.e., reduction to dose level –2). No more than two dose reductions will be allowed.
[a] Lasting more than two cycles.
AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for the Classification of Adverse Events.

No more than two dose reductions per patient will be allowed in the course of this clinical trial. Patients requiring more dose reductions should discontinue treatment, except in the event of obvious clinical benefit, in which case, treatment may continue after discussion and mutual agreement with the Sponsor.

No dose escalations will be allowed in this clinical trial.

5.5 CONCOMITANT MEDICATION

All medication at study registration, received within the 14 days prior to first drug administration and during the on-treatment period must be documented in the electronic case report forms (e-CRF). The details to be entered for each type of treatment will depend on factors such as relationship to, for example, AEs, underlying disease and symptoms, and will be defined in the study's e-CRF completion guidelines.

5.5.1 Prophylactic Medication

Primary antiemetic prophylaxis is compulsory before all PM060184 dose administrations. Standard treatment according to the American Society of Clinical Oncology (ASCO) guidelines will be administered:

- 5-HT_3 antagonists (ondansetron 8 mg or equivalent).
- Steroids (dexamethasone 8 mg or equivalent).

Oral or i.v. formulations are allowed according to institutional standards.

If necessary, additional antiemetic therapy can be considered in accordance with ASCO guidelines.

5.5.2 Allowed Medications/Therapies

- Therapies for pre-existing and treatment-emergent medical conditions, including pain management.
- Blood products and transfusions, as clinically indicated.
- Approved therapies for bone metastasis (e.g., bisphosphonates, denosumab).
- In case of nausea or vomiting, prophylaxis and/or symptomatic treatment for emesis according to ASCO guidelines.
- Erythropoietin use according to ASCO guidelines.
- Treatment with granulocyte colony-stimulating factor (G-CSF) in the event of grade 4 neutropenia lasting ≥ 3 days, neutropenic sepsis or febrile neutropenia according to ASCO guidelines. Secondary prophylaxis can be considered if it is in the best interest of the patient.
- Megestrol acetate for appetite stimulation.
- Anticoagulant therapy for the treatment or secondary prophylaxis of thromboembolic events.

5.5.3 Prohibited Medications/Therapies

- Concomitant administration of any other antineoplastic therapy.
- Any other investigational agents.
- Immunosuppressive therapies other than corticosteroids.
- Local therapy such as radiation or surgery if the lesion is the only target lesion, unless agreed in advance with the Sponsor.

5.5.4 Drug-drug Interactions

In vitro studies using human liver microsomes have pointed to CYP2C19 and CYP3A4 as the predominant cytochrome enzymes responsible for the hepatic metabolism of PM060184. Therefore, concomitant drugs that induce or inhibit any of these cytochromes to a significant extent should be avoided whenever possible (**Appendix 4**).

5.6 DRUG ACCOUNTABILITY

Each study site will keep records to allow a comparison of quantities of drug received and used at each site. The Investigators at each study site will be the person ultimately responsible for drug accountability at the site.

All unused drug supplied by the Sponsor will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor. If the Sponsor agrees, unused drug supplies may be returned to the drug repository.

5.7 TREATMENT COMPLIANCE

The Investigator is responsible for supervising compliance with the instructions described in this study protocol.

6. PLAN OF THE STUDY

6.1 DURATION OF THE STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 36 months.

- **Planned start date (first patient first visit):** 4Q2017.
- **Planned enrollment period:** approximately 20 months.
- **Planned study termination date:** 12 months after the first PM060184 administration of the last evaluable patient treated in the study.

6.2 DURATION OF THE STUDY (PER PATIENT)

Patients will be evaluated at scheduled visits in the following study periods:

- **Screening:** from signature of informed consent to registration (confirmation of eligibility) or screen failure.
- **Pretreatment:** from registration to first dose of study treatment.
- **Treatment:** from the first administration of the study treatment to end of treatment (EOT). EOT is standardly defined as 30 days (± 15 days) after the day of last administration of study treatment, unless the patient starts a new antitumor therapy or dies within 30 days of the last dose, in which case the date of administration of this new antitumor therapy or the date of death will be considered the EOT date.
- **Follow-up:** after EOT, patients will be followed for both safety and efficacy.
  1) **Safety:** every four weeks until resolution or stabilization of drug-related AEs (if any).
  2) **Efficacy:** about every three months until death, refusal to continue participating in the study, or study termination (clinical cutoff), whichever occurs first.

  Subsequent off-study antitumor therapies should be provided until death, refusal and/or clinical cutoff (whichever occurs first).

  Note: patients without disease progression who discontinue treatment due to a drug-related AE must be followed both for the AE and for efficacy.

Patients will be considered to be **on-study** from the signature of the informed consent form (ICF) to the end of the follow-up period (or screening failure). Investigators can appraise potential study candidates in a pre-screening period but only perform study-specific screening assessments after the patient formally consents. Patients will be considered to be **on-treatment** from the date of first dose until EOT.

Patients may withdraw their consent at any time; if consent to study participation is withdrawn, no further study activities will be conducted on them (Section 6.3.3). If consent only to receive the study treatment is withdrawn, treatment will be stopped and other study procedures performed as normal (see 7.5 and 7.6 below).

6.3 DISCONTINUATIONS

6.3.1 Treatment Discontinuation

Treatment discontinuation occurs when an enrolled patient ceases to receive the study medication, regardless of the circumstances. By convention, the date of end of treatment will be 30 days (± 15 days) after the date of the last administration of study drug, unless the patient starts a new antitumor therapy or dies within those 30 days, in which case the

date of administration of this new therapy or the date of death will be considered the date of end of treatment.

The primary reason for any discontinuation will be recorded on the patient's e-CRF.

If a patient discontinues treatment, every effort should be made to complete the scheduled assessments.

6.3.2 Reasons For Treatment Discontinuation

Patients will receive study treatment while it is considered to be in their best interest or until study termination. Specifically, treatment will continue until:

- Disease progression.
- Unacceptable toxicity (including any toxicity leading to the need for a third dose reduction or severe hypersensitivity reactions, except in the case of obvious clinical benefit, in which event the patient could be allowed to remain on treatment once agreed with the Sponsor).
- Patient refusal to receive further study treatment and/or non-compliance with study requirements.
- Intercurrent serious illness.
- Pregnancy.
- Investigator's decision.
- Protocol deviation with an effect on the risk/benefit ratio of the clinical trial.
- PM060184 treatment delay > 15 days from the due date (except in case of clear clinical benefit and with the Sponsor's approval).
- Clinical cutoff. Patients who have not progressed at these time points could be treated in a compassionate use program (according to country regulations).

Patients who are withdrawn for any reasons must not be re-treated in the context of this study at any time. For follow-up activities, please refer to Section 7.6.

6.3.3 Study Discontinuation

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason. Patients have the right to withdraw consent at any time; if this is the case, no further study procedures should be performed. The date and reason for study discontinuation will be clearly documented on the patient's e-CRF.

6.3.4 Replacement of Patients

Patients must be replaced if they are considered not evaluable for efficacy for the primary endpoint (PFS3), i.e., if they are withdrawn from the study due to significant clinical deterioration of unknown reason, hypersensitivity reactions, unrelated AEs without any tumor assessments after the start of study treatment, if they receive less than one complete treatment cycle (at least two PM060184 dose administrations over two cycles unless treatment discontinuation was due to unmanageable toxicity), or do not have the disease assessment at Week 12 (except in the case of treatment discontinuation/death due to a treatment-related AE, symptomatic deterioration due to the disease, clinical progression, PD or death due to malignant disease).

6.4 PROTOCOL DEVIATIONS

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and the Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, Investigator's responsibilities, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient's evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as incorrect dosing of the IMP due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to compliance with GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting Serious Adverse Events, etc.

As a general rule, NO deviations that may have an effect on the evaluation of the risk/benefit ratio of the study treatment will be authorized. All protocol deviations detected during the study will be appropriately documented, and those considered particularly relevant (i.e., those related to ethical issues, fulfillment of GCP guidelines and with an effect on the evaluation of the risk/benefit ratio) will be notified to the pertinent IEC/IRB and, if applicable, to the Competent Authorities as established by local regulations.

Failure to attend the EOT visit exclusively due to a deteriorated clinical condition will not be considered a protocol deviation.

Any protocol deviation will also be discussed with the Investigator during monitoring visits.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 ELIGIBILITY ASSESSMENTS

The patient will be allocated a patient number in the e-CRF after signing the ICF and screening for eligibility begins. This patient number should be used on all future documentation and correspondence referring to this patient. During the screening period, the Investigator will assess the patient's eligibility for inclusion in the study by conducting the assessments summarized below.

Table 8. Screening period assessments.

	ASSESSMENT	TIME
1.Written informed consent	The informed consent process involves an explanation and discussion with the patient including time for questions and answers and culminates in signing and dating the consent form if the patient agrees. Document registration in the patient's medical chart as well. Substudy participation is optional and requires a separate signed consent.	Before any study-specific procedures.
2.Medical and cancer history/ clinical examination	**Demographic data** (race/ethnicity [if permitted], age, sex). **Medical history:** Includes relevant conditions and syndromes that started before registration and are not ongoing (no signs or symptoms) at time of registration or are controlled and do not require evaluation for severity or causality. Also includes any event qualifying as serious occurring prior to registration. **Cancer history:** Primary diagnosis, response history, date of last confirmed PD, and all prior treatment (including cumulative dose of prior oxaliplatin, if any).	Within 28 days prior to registration.
	Physical examination: Including weight, height (for BSA calculation). **Vital signs:** HR, ABP, and temperature. **ECOG** performance status (**Appendix 1**).	Within 10 days prior to registration.
	Concomitant therapies: All Medications taken by the patient (including any not prescribed by the Investigator) should be documented with indication.	Within 14 days prior to registration.
3.Laboratory tests	**Hematology:** Complete blood count, differential WBC (neutrophils, lymphocytes), hemoglobin, and platelets. **Biochemistry-A**: ALP, AST, ALT, total bilirubin (and direct bilirubin if total is >1.5 x ULN), GGT, creatinine/CrCL (Cockcroft-Gault formula, **Appendix 2**), glucose, LDH, and serum electrolytes (Na^+, K^+, Total calcium). **Biochemistry-B:** Total proteins and albumin.	Within 10 days prior to registration.
4.Pregnancy test	Assessment of β-hCG only if the patient is a WOCBP (**Appendix 3**).	Within 7 days prior to registration.
5.Cardiac assessment	**ECG**: Including rhythm definition and PR interval; heart rate; QT interval (raw); QRS complex duration.. **LVEF:** ECHO or MUGA scan.	Within 28 days prior to registration.
6.Disease assessments	**Clinical/radiological tumor assessment:** Helical i.v. and oral contrast-enhanced CT-scan (if appropriate) for chest, abdomen and pelvis and other areas of suspected diseases. If i.v. contrast is contraindicated for the CT-scan, chest evaluation should be performed using non-contrasted CT and abdomen/pelvis evaluation using gadolinium-enhanced MRI. Tumor markers alone or chest radiography alone are not sufficient to assess tumor burden.	Within 28 days prior to registration.
7.Adverse events	Only information on SAEs that occurred after signature of the informed consent is required before treatment start. Grading should be as per the NCI-CTCAE v.4.	Within 14 days prior to registration.
	PRO QLQs: Patients will be asked to complete the EORTC QLQ-CIPN20 and QLQ-C30.	Within 10 days prior to registration.

Registration=confirmation of eligibility and inclusion.

	ASSESSMENT	TIME

Permitted windows for assessments before Day 1 of Cycle 1:
If physical examination, ECOG PS, vital signs, hematology/biochemistry were assessed >10 days before Day 1 of Cycle 1, the tests must be repeated within 2 days before the first study drug administration.
If pregnancy test was done >7 days before Day 1 of Cycle 1, the test must be repeated within 2 days before the first study drug administration.
If tumor assessments were done >28 days before Day 1 of Cycle 1, the tests must be repeated within 2 days before the first study drug administration.
A patient should only be treated if eligibility criteria are still met according to assessments performed closest to treatment start.

ABP, arterial blood pressure; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CrCL, calculated creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GGT, gamma-glutamyltransferase; HR, heart rate; IC, Informed Consent; IF, immunofixation; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PRO, patient reported outcomes; PS, performance status; QLQ, quality of life questionnaire; SAE, serious adverse event; ULN, upper limit of normal; WBC, white blood cells; WOCBP, woman of childbearing potential..

7.2 PATIENT REGISTRATION

Eligibility will be checked before registration confirmed by the Sponsor. The patient will be a screening failure if not all inclusion criteria are met, if any exclusion criterion is met, or if the Sponsor does not approve registration. Regardless of circumstances, Investigators will not be allowed to treat any patient before appropriate receipt of the Sponsor's agreement to proceed with registration. A patient should only be treated if eligibility criteria are still met according to assessments performed closest to first drug administration.

A patient who has been treated without the Sponsor's agreement may not be considered evaluable for the primary endpoint of the study and may need to be replaced (although can continue in treatment provided this does not pose a risk to the patient until discontinuation for any other reason).

For patients included in the study (all registered patients) but never treated, only baseline and off-study visit modules of the e-CRF should be completed but serious adverse events (SAEs) occurring during screening need to be reported (using paper SAE forms).

For screen failures (patients who started screening but were not finally registered), only the screening form of the e-CRF should be completed but SAEs occurring during screening need to be reported (using paper SAE forms).

7.3 RANDOMIZATION

Not applicable.

7.4 EVALUATIONS DURING TREATMENT

The assessments to be done while the patient is on treatment are shown in **Table 9**.

Table 9. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	**Physical examination:** Including weight and clinical assessment. BSA and dosing should be recalculated in the event of weight variation of ±10% from baseline. **ECOG** performance status (Appendix 1).	Day 1 of Cycle 2 and subsequent cycles (always prior to drug administration). Also repeat on Day 1 of Cycle 1 (prior to drug administration) if more than 10 days have passed since the screening assessment.
	Vital signs: HR, ABP, and temperature.	Day 1 of Cycle 2 and subsequent cycles (always prior to drug administration). Also repeat on Day 1 of Cycle 1 (prior to drug administration) if more than 10 days have passed since the screening assessment.
2. Laboratory tests	**Hematology:** Complete blood count, differential WBC (neutrophils, lymphocytes), hemoglobin, and platelets. **Biochemistry-A**: ALP, AST, ALT, total bilirubin (and direct bilirubin if total is >1.5 x ULN), GGT, creatinine/CrCL (Cockcroft-Gault formula, Appendix 2), glucose, LDH, and serum electrolytes (Na^+, K^+, Total calcium).	Day 1 of Cycle 2 and subsequent cycles (always prior to drug administration). Also repeat on Day 1 of Cycle 1 (prior to drug administration) if more than 10 days have passed since the screening assessment. If any clinically-relevant, treatment-related grade ≥ 3 AE occurs, the abnormality should be reassessed at least every 2–3 days until recovery to at least grade 2. In the event of febrile neutropenia, grade 4 neutropenia and/or grade 4 thrombocytopenia, reassessment should be performed **daily** until recovery to at least grade 3 (or until fever resolution, if applicable) and then every 2–3 days thereafter until recovery to at least grade 2
	Biochemistry-B: Total proteins and albumin.	Day 1 of Cycle 2 and subsequent cycles (always prior to drug administration). Also repeat on Day 1 of Cycle 1 (prior to drug administration) if more than 10 days have passed since the screening assessment.
3. Pregnancy test	Assessment of β-hCG only if the patient is a WOCBP (Appendix 3).	Repeat every cycle or (at least) every month while on-treatment.
4. Cardiac assessment	**ECG**: Including rhythm definition and PR interval; heart rate; QT interval (raw); QRS complex duration, as well as any ECG anomaly or variation (change in grade) with respect to baseline.	Repeat if clinically indicated.
	LVEF: ECHO or MUGA scan	
5. Pharmaco-kinetics	Ten plasma PK samples are required from patients included in the first stage of the study: just before start of administration, just before EOI, and then 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, and 12.5 h (Day 1) and 24.5 h (Day 2) after EOI. Only eight plasma PK samples are required from patients included in the second stage of the study: the samples scheduled at 12.5 h and 24.5 h after EOI are not required.	Days 1 and 2 of Cycle 1 and Cycle 2 in all patients included in the first stage. Day 1 of Cycle 1 and Cycle 2 in all patients included in the second stage. See Table 10.
6. Metabolomics	Three blood samples should be collected	One prior to each dose administration on Day 1 and Day 8 of Cycle 1, and also on Day 8 of Cycle 2.

	ASSESSMENT	TIME
7. Pharmaco-genomics	For those patients who consent to participate in the substudy, archived paraffin-embedded tumor tissue samples should be available.	The availability of tumor tissue samples used for the initial diagnosis of the disease, or obtained at relapse, should be confirmed and should be prepared and shipped during the trial following the instructions detailed in a separate laboratory manual.
8. Pharmaco-genetics	If the patient consents to the substudy, an additional blood sample for PGt analysis should be collected.	At any time during the trial but ideally at the same time as the pretreatment PK sample (sample #1) in Cycle 1.
9. Disease assessments	**Clinical/radiological tumor assessment:** Using RECIST v.1.1. Helical i.v. and oral contrast-enhanced CT-scan (if appropriate) for chest, abdomen and pelvis and other areas of suspected diseases. If i.v. contrast is contraindicated for the CT-scan, chest evaluation should be performed using non-contrasted CT and abdomen/pelvis evaluation using gadolinium-enhanced MRI. The same radiological method should be used throughout the study for each individual patient. Anonymized copies of images showing a response (CR or PR) must be submitted to the Sponsor. Tumor markers alone or chest radiography alone are not sufficient to assess tumor burden.	To be performed every six weeks (+ 7 days, except for Week 12 when a window of ± 5 days applies).
10. Concomitant medications	All concomitant therapies taken by the patient (including any not prescribed by the Investigator) should be documented with indication.	Throughout the on-treatment period.
11. Adverse events	Grading should be as per the NCI-CTCAE v.4.	Throughout the on-treatment period.
	PRO QLQs: Patients will be asked to complete the EORTC QLQ-CIPN20 and QLQ-C30.	On Day 8 (day of second dose administration) of every treatment cycle.

Registration=confirmation of eligibility and inclusion; A patient should only be treated if eligibility criteria are still met according to assessments performed closest to first drug administration. Day 1=day of first cycle administration (with infusion start); Day 8=seven days after the first dose administration of a cycle (± 2 days); Day 22 = Day 1 (± 2 days) of the following cycle.

Permitted windows for assessments before Day 1 of Cycle 1:
If physical examination, ECOG PS, vital signs, hematology/biochemistry were assessed >10 days before Day 1 of Cycle 1, the tests must be repeated within 2 days before the first study drug administration.
If pregnancy test was done >7 days before Day 1 of Cycle 1, the test must be repeated within 2 days before the first study drug administration.
If tumor assessments were done >28 days before Day 1 of Cycle 1, the tests must be repeated within 2 days before the first study drug administration.
A patient should only be treated if eligibility criteria are still met according to assessments performed closest to treatment start.

Permitted windows for assessments after Day 1 of Cycle 1:
- 2 days for clinical assessments (physical examination, ECOG PS, vital signs), always before study drug administration.
+ 7 days for tumor assessments (except in week 12 when there is a maximum 5-day window).
± 2 days for Day 1 study drug administration (from Cycle 2 onwards).
± 2 days for Day 8 study drug administration.
– 2 days for laboratory tests. To confirm criteria for treatment continuation, laboratory assessments must be performed within 2 days prior to drug administration.
If a drug administration is delayed beyond the permitted protocol window, assessments planned for the original administration day must be repeated on the day the dose is finally administered.

ABP, arterial blood pressure; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; β-hCG, beta subunit of human chorionic gonadotropin; BSA, body surface area; CrCL, calculated creatinine clearance; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; EORTC, European Organisation for Research and Treatment of Cancer; EOT, end of treatment; GGT, gamma-glutamyltransferase; HR, heart rate; IC, Informed Consent; i.v., intravenous; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PGt, pharmacogenetics; PK, pharmacokinetics; PR,

	ASSESSMENT	TIME

partial response; PRO, patient reported outcomes; PS, performance status; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; ULN, upper limit of normal; WBC, white blood cells; WOCBP, woman of childbearing potential.

7.5 EVALUATIONS AT END OF TREATMENT

The EOT visit should take place approximately 30 days (± 15 days) of the last study drug administration, unless the patient starts any subsequent antitumor therapy, in which case the EOT visit should be performed immediately before the start of the new therapy (ideally the day before or the same day). If a patient dies within 30 days from the last dose, the date of death will be considered EOT.

The assessments listed below are required if no recent data are available (i.e. within the previous 10 days) or if the last data available show a grade ≥ 2 treatment-related alteration, whenever the medical condition of the patient allows.

- Assessment of disease-related symptoms.
- Complete physical examination (including weight).
- ECOG PS.
- Vital signs (heart rate, blood pressure, body temperature).
- Concomitant therapies.
- Hematology.
- Biochemistry-A.
- Biochemistry-B.
- Pregnancy test (if patient is a WOCBP).
- LVEF.
- PRO QLQs (EORTC QLQ-CIPN20 and QLQ-C30)
- Adverse events.

For individual patients (and if clinically indicated according to Investigator's criteria), it might also include the following:

- ECG.
- Other tests as appropriate.

Adverse events must be reported during 30 days after the last study drug administration. All SAEs occurring within 30 days of the last study drug administration will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 8.5.2).

The Sponsor will evaluate all safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

Loss to follow-up, or failure to attend the EOT visit due to a deteriorated clinical condition or due to personal reasons such as returning to their previous hospital, will not be considered protocol deviations.

7.6 FOLLOW-UP AFTER THE END OF TREATMENT VISIT

After EOT, patients will be followed every four weeks until resolution or stabilization of toxicities (if any). During follow-up, the QLQ-CIPN20 should be completed every

three months until the start of a new antitumor therapy; unless the patient discontinued treatment due to grade ≥ 3 PN, in which case, repeat the assessment monthly until recovery to grade ≤ 2 (or until start of subsequent antitumor therapy).

The primary endpoint of the study is PFS3, defined as the percentage of patients remaining alive and progression-free at Week 12. Therefore, the Week-12 disease evaluation should be performed in all non-PD patients. Tumor assessment should be performed about every three months during follow-up in patients who discontinue treatment without disease progression.

Regardless of the reason for treatment discontinuation, all patients will be followed about every three months until death, refusal to continue participating in the study, or study termination (clinical cutoff), whichever occurs first. Subsequent antitumor therapies should be provided until death, refusal, and/or clinical cutoff (whichever occurs first).

Patients without disease progression who discontinue treatment due to a drug-related AE must be followed both for the AE and for efficacy.

Progression-free Survival and Survival Follow-up Timelines for the Whole Population:

If the study ends after the futility analysis at 24 evaluable patients (first stage):

- Patients who are still on study will be followed up to 12 weeks after the first PM060184 administration of the last patient evaluable for the futility analysis.

If the futility analysis results in continuation of recruitment (second stage):

- All patients will be followed up to 12 months after the first PM060184 administration of the last evaluable patient treated in the study, regardless of the stage at which the patients have been included.

For the purpose of collecting information on patient's survival, a documented telephone call, email or medical chart review is acceptable; follow-up for survival will be completed for all patients only if the study continues to the second stage.

7.7 STUDY TERMINATION (CLINICAL CUTOFF)

The planned study termination date (clinical cutoff) will be: 12 months after the first PM060184 administration of the last evaluable patient treated in the study.

7.8 PHARMACOKINETICS

The plasma PK of PM060184 will be evaluated in Cycle 1 and Cycle 2 during both stages of the study. In the first stage, PK will be evaluated on Days 1 and 2 of Cycle 1 and Cycle 2 with a sampling schedule of ten samples; in the second stage, PK will be evaluated on Day 1 of Cycle 1 and Cycle 2 only with eight samples (**Table 10**). Concentration data will be pooled with that from other clinical studies with PM060184 as a single agent and PK parameters will be calculated by means of population PK analysis and/or non-compartmental methods.

Table 10. Pharmacokinetic sampling schedule for PM060184.

Sample number	Day	Relative times	Sampling times for PM060184	Sampling window
#1	1	0 min	Before start of administration	-
#2	1	30 min	Just before EOI	- 2 min
#3	1	45 min	15 min after EOI	± 2 min
#4	1	1 h	30 min after EOI	± 5 min
#5	1	1.5 h	1 h after EOI	± 10 min
#6	1	2.5 h	2 h after EOI	± 10 min
#7	1	4.5 h	4 h after EOI	± 10 min
#8	1	6.5 h	6 h after EOI	± 10 min
#9 [a]	1 [a]	12.5 h	12 h after EOI	± 1 h
#10 [a]	2 [a]	24.5 h	24 h after EOI	± 4 h

[a] Samples #9 and #10 are required only in patients included in the first stage of the study.
EOI, end of infusion; h, hour; min, minute.

The accurate recording of actual sampling times is more important than strict adherence to the scheduled times.

Blood samples for PK analysis will be obtained through a peripheral vein located in the contralateral side to that of drug administration, whenever possible. In any case, the sampling vein has to be different to that in which drugs are administered. Even the last sample **must never be collected from the catheter used for drug administration**.

A separate manual describes in more detail the required procedures. Please read it carefully before PK sampling. In short, after collection, each sample will be centrifuged and the resulting plasma layer transferred into a new tube for the determination of PM060184 concentration. The plasma-containing tubes will be stored frozen until their shipment to the Central Laboratory for further delivery to the Laboratory for PK Samples (see Study Contacts). All the material for PK procedures will be provided by the Central Laboratory.

Once all samples from a patient have been collected, they should be shipped for analysis to the Central Laboratory as soon as possible, ideally on the next shipping day. If the same site has samples from several patients, the samples can be sent in the same shipment. However, **the time span between the collection time of the last PK sample from a patient and the shipment of all the samples from that patient to the Central Laboratory should not exceed one week**.

7.9 METABOLOMICS

Metabolomics (the determination of endogenous low-molecular-weight molecules or metabolites in a body fluid and their changes as a consequence of stimuli such as medical interventions), is currently being used to evaluate the efficacy and safety of medical interventions in cancer (11), thus allowing for the discovery of predictive biomarkers of drug response (12).

The metabolomics of PM060184 will be characterized by evaluating systemic variations in pre- and post-treatment metabolic profile to identify potential biomarkers of PK, safety and/or efficacy response to PM060184.

Three blood samples are required for this analysis. Patients will have one blood sample collected before each drug administration on Day 1 and Day 8 of Cycle 1, and also on Day 8 of Cycle 2, to evaluate the pretreatment profile of endogenous metabolite levels and changes after PM060184 treatment.

Blood must be collected without anticoagulant and with a separating gel, allowed to clot, and centrifuged. Serum will be collected and stored. The samples should be frozen at –80°C within 24 h. If not possible, they can be frozen at –20°C, but only for a maximum period of two weeks before shipping in dry ice to the central laboratory.

The required procedures for the collection, processing and storage of the sample for metabolomics are described in more detail in the laboratory manual. Please read it carefully before sample extraction.

7.10 PHARMACOGENETICS

To explore PGt factors that may help to explain individual variability in main PK parameters, as well as susceptibility to develop treatment-related AEs, the presence or absence of germline mutations or polymorphisms that may be involved in the metabolism and/or transport of PM060184 will be analyzed in leukocyte DNA extracted from blood collected at any time during the trial but ideally at the same time as the pretreatment PK sample (sample #1) in Cycle 1 from those patients who have also consented to the substudy.

The collection and management of this additional sample are quite different from those for PK assessment. Please carefully follow the instructions detailed in a separate manual. The assessment of polymorphisms is not affected by treatment; hence, the Sponsor may require the collection of additional samples later on, if the first assessment has not been performed accurately.

Only patients who voluntarily sign the IC for the PGx/PGt substudy will participate in the PGt evaluation. Refusal to participate in the PGx/PGt substudy will not affect patient participation in the clinical study PM60184-B-002-17.

7.11 PHARMACOGENOMICS

Provision of samples for PGx analyses will be optional and performed upon patient consent by signing the substudy ICF. For those patients who consent to participate in the substudy, the availability of tumor tissue samples used for the initial diagnosis of the disease, or obtained at relapse, should be confirmed and should be prepared and shipped during the trial following the instructions detailed in a separate laboratory manual.

The objective of the PGx substudy is to evaluate the role of potential markers of sensitivity to treatment with microtubule-interacting agents in a population of advanced CRC patients treated with PM060184. These molecular markers would help in the future selection of patients who might preferentially benefit from PM060184 therapy, thus contributing to improved health care through a more individualized medicine.

Analyses will be performed at the Central Laboratory for PGx samples (see Study Contacts). The analytical methods required for this molecular characterization analysis

are described in a separate document detailing the procedures to be followed for sample collection, labeling, and shipment.

The following analyses will be performed on paraffin-embedded tumor tissue samples from patients participating in the substudy if there is evidence of clinical benefit:

- Quantification of protein and/or mRNA expression levels of tubulin isotypes and other factors related to the mechanism of action of PM060184 and to the tumor microenvironment by immunohistochemistry (IHC) or quantitative polymerase chain reaction (PCR) in tumor tissue microarrays constructed from the patients' samples.
- Analysis of polymorphisms and mutations of the above-mentioned selected genes, if relevant, by reverse transcription polymerase chain reaction (RT-PCR) and/or DNA sequencing.
- Analysis of BRAF-mutant-like gene expression subtypes (and potentially full genome expression).

If possible, expression levels of the different markers will be correlated with the study efficacy parameters.

8. STUDY EVALUATIONS

8.1 EFFICACY

Patients will be evaluable for efficacy if they receive at least one complete treatment cycle (or two PM060184 dose administrations over two cycles) and have, at least, one disease assessment at Week 6 and another one at Week 12.

In addition, any patient who presents disease progression, symptomatic deterioration due to the disease or clinical progression, dies due to malignant disease, discontinues treatment due to unmanageable toxicity, or dies or discontinues treatment due to a treatment-related AE before evaluation of the response at Week 12 will also be considered evaluable for the primary endpoint and classified as a non-responder.

Patients who have no disease assessment at Week 6 but remain on treatment and are assessed at Week 12 (or later, and with no evidence of disease progression) will be considered evaluable for efficacy.

Patients who refuse further treatment before Week 12 due to reasons other than related AEs not considered unmanageable toxicity will be replaced.

A futility analysis will be performed once the first 24 evaluable patients complete the Week 12 (± 5 days) tumor assessment; progress; die due to PD; or discontinue treatment due to unmanageable toxicity (whichever occurs first). If seven patients or more achieve PFS3, then 36 additional patients will be recruited (second stage).

Tumor assessment will be measured using RECIST v.1.1 (17).

8.2 SAFETY

Patients will be evaluable for safety if they receive at least one (complete or incomplete) dose of PM060184.

Safety will be evaluated by clinical examinations, analysis of vital signs, clinical assessment of AEs, changes in the analytical parameters (hematological and biochemical), and any other analyses that may be considered necessary.

All treatment-related AEs must be followed-up—even if the administration of PM060184 has finalized—until the AE or its sequelae have resolved or stabilized at an acceptable level to the Investigator and the Sponsor. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4), and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.3 PATIENT REPORTED OUTCOMES

EORTC QLQ-CIPN20 and QLQ-C30 will be used to collect information on patients' self-reported QoL and neurotoxicity, targeting symptoms, functional limitations, and patient concerns specifically associated with treatment-induced PN, and potential activity impairment.

Patients will be asked to complete both QLQs at baseline, on Day 8 of each cycle, at the end-of-treatment visit.

Patients will be asked to complete the QLQ-CIPN20 (only) during the follow-up period (about every three months until start of subsequent antitumor therapy). If a patient discontinues treatment due to grade $\geq$ 3 PN, however, the QLQ-CIPN20 should be completed more frequently during the follow-up period (every month after EOT) until recovery to grade $\leq$ 2 (or until start of subsequent antitumor therapy).

8.4 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, (e.g., an abnormal laboratory finding), or a disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Illnesses with onset during the study or exacerbations of pre-existing illnesses, including but not limited to clinically significant changes in physical examination findings and abnormal objective test findings (e.g., X-ray, ECG) should be recorded. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- The test result is associated with clinically significant symptoms, and/or
- The test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or
- The test result leads to any of the outcomes included in the definition of a SAE (see definition below), and/or
- The test result is considered to be clinically relevant by the Investigator.

For the purposes of this protocol, disease progression, worsening of the underlying disease or appearance of new tumor lesions, or any sign or symptom clearly related with this circumstance is NOT required to be reported as an AE.

8.4.1 Serious Adverse Event (SAE)

A SAE is any adverse experience occurring at any dose that:

- Results in death (is fatal),
- Is life-threatening,
- Requires or prolongs inpatient hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect,
- Is medically significant, or
- Is any suspected transmission of an infectious agent via a medicinal product.

Medical and scientific judgment should be exercised in deciding medically significant events; this criterion should be applied to AEs that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

8.4.2 Death

Death as such is the outcome of a SAE and should not be used as the SAE term itself, whenever possible. The cause of death should be recorded as the SAE term instead. When available, the autopsy report will be provided by the Sponsor.

8.4.3 Life-threatening Event

Any event in which the patient was at risk of death at the time of the event is considered life-threatening; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.4.4 Hospitalization or Prolongation of Hospitalization

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE unless exempted from SAE reporting. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet the criteria for SAE reporting are:

a. Reasons described in the protocol (e.g., IMP administration, protocol-required intervention/investigations, etc.). However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.

b. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an AE.

c. Pre-planned hospitalizations: any pre-planned hospitalization, surgery or procedure must be documented in the source documentation. Only if the pre-planned hospitalization, surgery or procedure needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

Other situations that MUST NOT be considered as hospitalizations are the following:

d. An emergency visit due to an accident where the patient is treated and discharged.

e. When the patient is held 24 hours for observation and finally is not admitted.

f. Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc.).

8.4.5 Unlisted/Unexpected Adverse Event

An AE, the nature or severity of which is not consistent with the applicable reference safety information.

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the IB for PM060184.

8.4.6 Adverse Reactions

All untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition covers also medication errors and uses outside what is foreseen in the protocol, including overdose, lack of efficacy, misuse and abuse of the product.

8.4.7 Adverse Events Related to the Study Drug

An AE is considered related to a study drug/IMP if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 8.4.9).

The Investigator will assess the causal relationship of the IMP(s) to the AE.

The Sponsor may also consider related to the study drug(s)/IMP(s) those events for which the Investigator assesses the causal relationship with the IMP(s) as "Uk (unknown)" when it cannot rule out a role of the IMP(s) in the event.

8.4.8 Expedited Reporting

The Sponsor is responsible for the appropriate expedited reporting to the Competent Authorities, Investigators, and IECs/IRBs according to the current legislation, unless otherwise required and documented by the IECs/IRBs.

8.4.9 Assessment of Causal Relationship to the Study Drug

The Investigator must provide an assessment of the causal relationship of each clinical trial IMP(s) to each SAE according to the following scale:

Y There is a reasonable possibility that the IMP(s) caused the SAE.

N There is no reasonable possibility that the IMP(s) caused the SAE and other causes are more probable.

Uk. (Unknown). Only to be used in special situations where the Investigator has insufficient information (i.e., the patient was not seen at his/her center) if none of the above can be used.

8.5 ADVERSE EVENTS REPORTING PROCEDURES

8.5.1 Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy, whichever occurs first. All AEs suspected to be related to the study drug/IMP must be followed-up after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs, including misuse, overdose, abuse and medication error, must be recorded in English using medical terminology in the source document and the e-CRF. Whenever

possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v.4 and assign a relationship to each study drug(s)/IMP(s); and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the e-CRF.

Abnormal laboratory tests occurring during the study must only be recorded in the AE section of the e-CRF if the disorder:

- is associated with clinically significant symptoms, and/or;
- represents a reason for change in study dosing or for discontinuation from the study treatment, significant additional concomitant drug treatment or other therapy, and/or;
- leads to any of the outcomes included in the definition of a SAE.
- it is considered clinically relevant by the Investigator.

Otherwise, laboratory results should be reported in the corresponding section of the e-CRF (e.g., biochemistry, hematology).

8.5.2 Reporting Serious Adverse Events

The Sponsor will collect SAEs from the time of signing of the ICF until 30 days after administration of the last dose of study drug/IMP or until the start of a new antitumor therapy, whichever occurs first (or until screening failure, if applicable). Beyond this period of time, only those SAEs suspected to be related to the IMP will be collected. Nonetheless, the Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All SAEs (as defined above) occurred after patient registration regardless of relationship to the study drug(s)/IMP(s) must be reported immediately, and always within 24 hours to the Pharma Mar S.A. Pharmacovigilance Department, electronically by completing the applicable e-CRF section.

SAEs occurring during the screening phase, SAEs that may occur off-study, or in case the electronic system fails or is not available, will be reported within 24 hours to the Pharmacovigilance Department using the paper SAE form by fax (+34 91 846 6004), e-mail (phv@pharmamar.com) or telephone (+34 91 823 4633).

Out of office hours [Greenwich Meridian Time (GMT)], assistance on SAE reporting can be obtained by calling the Pharmacovigilance Department at +34 681 263 592. SAEs initially reported by alternative methods (not electronically), must be followed by a completed electronic SAE reporting on e-CRF from the investigational staff within one working day.

All SAEs suspected to be related to the IMP(s) must be followed until the event or its sequelae resolves or stabilizes at an acceptable level by the Investigator.

8.5.3 Reporting Pregnancy Cases Occurred within the Clinical Trial

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the IMP(s) at any time during pregnancy, via either maternal or paternal exposure, is suspected.

Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or within six months in female patients and within four months in male patients after the last study drug administration, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP(s) is suspected.
- Possible exposure of a pregnant woman (this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMPs).
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Sponsor Pharmacovigilance immediately by facsimile using the Pregnancy Report form. In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her informed consent to provide the information by using the applicable form provided by the Sponsor who will also advise the Investigator in these situations.

The Investigator will follow the pregnancy until its outcome, and must notify PharmaMar Pharmacovigilance of the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to PharmaMar Pharmacovigilance by facsimile within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug(s)/IMP(s) should also be reported to PharmaMar Pharmacovigilance by facsimile within 24 hours of the Investigators' knowledge of the event.

8.5.4 Adverse Events Monitoring

Safety review will be performed by the Sponsor once SAE forms have been received electronically or by fax and the e-CRFs have been electronically completed by the Investigator.

Periodic safety review of clinical data will be performed; however, no formal Data Safety Monitoring Board has been appointed for this trial. AEs will be monitored by the Investigators and by the Sponsor study team. The personnel in charge of this process are listed in the Study Contacts section of this protocol. In general, the clinical oncologist medical monitor together with the PharmaMar Pharmacovigilance Department will review the safety data of this trial on an ongoing basis.

SAEs will be collected, assessed and reported as per the applicable Regulations by the Pharmacovigilance Department. Periodic safety reviews of SAE reports are to be conducted by the Pharmacovigilance Department every 3–6 months, depending on recruitment.

Non-serious AEs will be verified during monitoring visits by the monitor, who will discuss them with the Investigators, if applicable.

At every monitoring visit the consistency between the e-CRF/SAE data reported to the Pharmacovigilance Department and the patient's source data will be reviewed. When a discrepancy is found, data in the e-CRF and the SAE form/information will be amended/updated and reported to the Pharmacovigilance department (when applicable), according to source data.

9. STATISTICAL METHODS

9.1 PRIMARY ENDPOINT

Progression-free survival rate at 12 weeks (PFS3), defined as the rate estimate of the percentage of patients who are alive and progression-free at 12 weeks (~3 months) after the first treatment administration.

9.2 SECONDARY ENDPOINTS

- Overall Survival (OS), defined as the time from the first day of treatment to the date of death or last contact.
- Progression-free Survival (PFS), defined as the time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation.
- Overall Response Rate (ORR), defined as the percentage of patients with objective response (OR), either complete response (CR) or partial response (PR) according to the RECIST v.1.1.
- Duration of Response (DOR), defined as the time between the date when response criteria (PR or CR, the first to be reached) are fulfilled and the first date when PD, recurrence or death is objectively documented.
- Treatment safety, including AEs, SAEs, and laboratory abnormalities graded according to NCI-CTCAE v.4. Dose reductions or delays required due to treatment-related AEs, and reasons for treatment discontinuations will also be analyzed.
- Profiles of peripheral neuropathy and quality of life as reported by patients using the EORTC QLQ-CIPN20 and QLQ-C30.
- Pharmacokinetics (PK) parameters will be evaluated in plasma by population PK modeling and/or standard non-compartmental analysis.
- Metabolomics of PM060184, i.e., intra- and inter-patient systemic variations in the patient’s pretreatment metabolic profile.
- Pharmacogenetics (PGt) of PM060184 will be evaluated to identify the presence or absence of germline mutations or polymorphisms that may help explain individual variability in the main PK parameters and safety outcomes.

- Pharmacogenomics (PGx) of PM060184 will be evaluated to determine predictive/prognostic markers of response and/or resistance to PM060184 (including BRAF-mutant-like gene expression subtypes).

9.3 SAMPLE SIZE

Patients will be treated with PM060184 to test the null hypothesis (H0) that 30% or less patients are alive and free of progression at twelve weeks (PFS3) according to RECIST v.1.1 ($p \leq 0.30$) versus the alternative hypothesis (H1) that 50% or more patients are alive and free of progression at 12 weeks according to the aforementioned criteria ($p \geq 0.50$). The variance of the standardized test is based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.1; hence, statistical power is 90%.

Sixty evaluable patients are necessary to test the hypothesis. A futility analysis using O'Brien-Fleming boundaries is planned when 24 patients can be evaluated (first stage). If there are seven or more patients achieving PFS3 in the first stage then the trial will proceed to a second stage and a total of 60 patients will be recruited.

If at least 25 of 60 evaluable patients are alive and free of progression at 12 weeks then the null hypothesis can be rejected and PM060184 considered active and deserving potential development in this setting.

9.4 STATISTICAL ANALYSIS

Frequency tables will be prepared for categorical variables and summary tables, including median, mean, standard deviation, minimum, and maximum values for each variable, will be used for continuous variables. Exploratory comparisons will be performed at a 0.05 level. Other analyses will include: number of prior treatment lines, prior oxaliplatin exposure, KRAS status, BRAF-like expression, and other prognostic/predictive factors.

9.5 EFFICACY ANALYSIS

The exact binomial estimator and its 95% confidence interval (CI) will be used for the primary endpoint (PFS3) and categorical variables (i.e., ORR). Time-to-event variables (DOR, PFS and OS) and their fixed time estimates will be analyzed according to the Kaplan-Meier method. For categorical variables, comparisons will be carried out by a Fisher exact test and a multivariate analysis by logistic regression. For time-to-event variables, comparisons will be carried out by a log-rank test and by a Cox regression analysis. No formal conclusions will be expected on these grounds.

9.6 SAFETY ANALYSIS

Safety analyses will consider AEs and SAEs, according to their relationship with study treatment, as well as analytical results, deaths and the reasons for treatment discontinuations, delays and/or dose reductions. All AEs and SAEs will be graded according to NCI-CTCAE v.4., and they will be coded using the MedDRA.

9.7 PATIENT REPORTED OUTCOMES

PRO analysis will be performed on summary measures and longitudinal modelling of patients' QLQ responses. QoL and PN will be evaluated by changes in the EORTC QLQ-CIPN20 and QLQ-C30 scores over time and tested for statistical significance by means of repeat-measure analyses of variance. The scores will be compared at the pre-specified time points using a T-test for related samples to establish differences, if any,

between pairs of assessments. A p-value of < 0.05 is considered statistically significant for the exploratory comparisons.

9.8 PHARMACOKINETICS ANALYSIS

Pharmacokinetic data will be listed in the population PK-report for all patients with available concentrations of PM060184. Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g. improper handling of PK samples, incomplete administration of the study agent, missing time or dosing information). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. All patients and samples excluded from the analysis will be retained in the data set, but they will be flagged out and the criteria for the exclusion documented.

Population PK analysis of plasma concentration-time data of PM060184 will be performed using non-linear mixed-effects modeling. Data may be combined with those of a selection of phase I and II studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Pharmacokinetic analysis will be the responsibility of the Sponsor and will be performed in accordance with the current guidelines on population pharmacokinetics analyses. Clearance and volume of distribution will be the primary parameters of interest for the population PK analysis. Additional PK parameters will be calculated, if deemed appropriate.

Non-compartmental PK analysis may also be used instead of or in addition to population PK analysis.

Plasma samples will be analyzed to determine concentrations of PM060184 using a validated, specific, and sensory liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the Sponsor.

9.9 METABOLOMICS (BIOMARKERS) ANALYSIS

Patients' pretreatment metabolic profile will be evaluated to search for systematic variations that may serve as biomarkers of PK, safety and/or efficacy response to treatment with PM060184. Systematic variations in the metabolic profile will be compared among patients with differences in any of these responses. Particular attention will be given to specific metabolic patterns observed in patients who develop PN associated with PM060184.

Metabolite extraction will be accomplished by fractionating the serum sample (19). Briefly, an ultra performance liquid chromatography (UPLC)-single quadrupole-MS amino acid analysis system will be combined with two separate UPLC-time-of-flight-MS based platforms analyzing methanol and chloroform/methanol serum extracts.

Data will be processed using the TargetLynx application manager for MassLynx 4.1 software (Waters Corp., Milford, USA). A set of predefined retention time and mass-to-charge ratio pairs (Rt-m/z), corresponding to metabolites included in the analysis will be fed into the program. Normalization factors will be calculated for each metabolite (20).

The metabolomics data analysis will include univariate and multivariate data analysis, with pathway mapping tools and visualization capacities to facilitate result interpretation.

Principal component analysis (PCA; non-supervised) and orthogonal partial least-squares to latent structures (OPLS; supervised) multivariate methods will be used to reduce the dimensionality of the complex data set to enable easy visualization of any metabolic clustering in samples from patients sharing a common outcome.

Among univariate data analysis, a Shapiro-Wilk test (to test the normality of data), a Student's t-test and a Wilcoxon signed-rank test, an analysis of variance (ANOVA) and a Tukey's HSD (Honestly Significant Difference) *post hoc* test will be used.

9.10 PHARMACOGENETICS ANALYSIS

In order to explore factors that may help explain individual variability in the main PK parameters and safety outcomes, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from a blood sample obtained preferably before treatment start (along with PK sample #1 and the first metabolomics sample of Cycle 1). The influence of known polymorphisms on main PK parameters or safety outcomes will be assessed by a Student's test or a Mann-Whitney's U test as appropriate.

9.11 PHARMACOGENOMICS ANALYSIS

The analysis of potential predictive factors to PM060184 treatment will be analyzed in paraffin-embedded tumor tissue samples from patients participating in the substudy. These factors will include, among others, tubulin isotypes and other factors related to the mechanism of action of PM060184 and to the tumor microenvironment (such as angiogenic factors, and markers of lymphocyte subpopulations and tumor associated macrophages), and their expression will be analyzed at the protein level and/or mRNA level by IHC or quantitative PCR, respectively; their polymorphisms and mutations might also be analyzed, if relevant.

BRAF-mutant-like gene expression subtypes (and potentially full genome expression) will be determined to show potential correlation with response or outcome after treatment with PM060184.

At final study analysis—and if feasible according to overall efficacy and to the number of patients with available biopsy—the subgroup characteristics will be statistically analyzed for correlation with the study efficacy parameters: PFS, ORR, DOR, and OS.

These analyses will include the use of molecular biology techniques to identify and validate PGx markers from pretreatment tumor samples. The basal expression levels of these markers will be correlated with the patient's outcome data. In addition, the experimental data will be analyzed with respect to duration of response and time to disease progression.

Analysis of RNA/protein expression, polymorphisms and mutations will be performed blind, and clinical data compiled only after all analyses are completed. A Fisher's exact test/logistic regression for categorical variables and log rank test/Cox regression for time to event variables will be used to test whether a specific profile is associated with clinical outcome after treatment with PM060184. The prognosis value of markers will be explored for objective clinical response, PFS and OS. In each case, if

applicable, a multivariate model will be developed by stepwise selection. All tests of statistical significance will be two-sided, and significance will be set at 0.05.

10. ADMINISTRATIVE SECTION

10.1 ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki (**Appendix 5**) and will be consistent with GCP guidelines and pertinent regulatory requirements.

The study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective task(s).

The study will be conducted in compliance with the protocol. The protocol, any amendments and the patient informed consent will receive IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigators, and a copy of this decision will be provided to the Sponsor before the beginning of the study.

The Investigator and/or the Sponsor is/are responsible for keeping the IEC/IRB informed of any significant new information about the study drug.

All protocol amendments will be agreed upon by the Sponsor and the Investigator.

Administrative changes of the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted.

10.2 MONITORING, AUDITING AND INSPECTING

The study will be monitored by regular site visits and telephone calls to the Investigator by the clinical trial monitor designated by the Sponsor.

During site visits, the trial monitor should revise original patient records, drug accountability records and document retention (study file). Additionally, the trial monitor should observe study procedures and will discuss any problems with the Investigator.

Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given direct access (as per International Conference on Harmonization [ICH] Topic E6 Guideline for Good Clinical Practice, Sections 4.9.7 and 6.10) to source documents (i.e., hospital or private charts, original laboratory records, appointment books, etc.) of the patient which support data entered in the CRFs, as defined in the ICH Topic E6 Guideline for Good Clinical Practice, Sections 1.51 and 1.52.

Systems and procedures will be implemented to ensure the quality of every aspect of the trial.

During the course of the trial, the Sponsor's Clinical Quality Assurance department or designee may conduct an onsite audit (ICH Topic E6 Guideline for GCP, Section 1.6).

Participation in this trial implies acceptance of potential inspection by national or foreign Competent Authorities.

10.3 PATIENT INFORMED CONSENT

The rights, safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

The informed consent process will include all elements required by ICH, GCP and applicable regulatory requirements.

Prior to registration in the trial, the Investigator or a person designated by the Investigator, must provide the patient with one copy of the ICF. This copy must provide written full information about the clinical trial, in a language that is non-technical and easily understood. The Investigator should allow the necessary time for the patient or his/her legally acceptable representative to inquire about the details of the clinical trial; then, the ICF must be freely signed and personally dated by the patient and by the person who conducted the informed consent discussion before the beginning of the study. The patient should receive a copy of the signed ICF and any other written information provided to study patients prior to participation in the trial. Participation in the substudy requires separate consent.

During a patient's participation in the trial, any updates to the consent forms and any updates to the written information will be provided to him/her.

If there is a need to obtain new consent from the patients, the Investigator or a person designated by the Investigator should inform the patients of any new information relevant to the patients' willingness to continue participation in the study, before obtaining the written consent.

10.4 CONFIDENTIALITY/IDENTIFICATION OF PATIENTS

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial.

It is the Investigator's responsibility that sufficient information on the identity of the patients be retained.

The trial monitor, the Sponsor's auditor, the IECs/IRBs, and the Competent Authorities should have direct access to all requested trial-related records, and agree to keep the identity of study patients confidential.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Explicit consent for the processing of personal data will be obtained from the participating patient before data collection, if applicable, and this consent should also address the transfer of the data to other entities and countries.

The Sponsor shall comply with the Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

10.5 ELECTRONIC CASE REPORT FORMS

Electronic case report forms (e-CRFs) will be used to record all data for each patient. It is the responsibility of the Investigator to ensure that e-CRFs are timely, properly and completely filled in, in English. E-CRFs must be completed for all patients who have given their informed consent and have been enrolled into the study.

A patient's source documentation is the patient's records (included but not limited to physician/hospital notes, nurses notes, IMP preparation records including reconstitution and dilution, IMP administration records, QLQs, etc.) and as such, they should be maintained at the study site.

Data collected in the e-CRF will be entered into the Sponsor's databases, which comply with the Spanish Act implementing the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

Baseline and off-study visit should be completed for patients registered but never treated.

10.6 INSURANCE

The Sponsor will provide insurance or indemnity in accordance with applicable regulatory requirements.

10.7 RETENTION OF RECORDS

The Investigator/Institution should maintain trial documents according to Section 8 of the ICH Topic E6 Guideline for Good Clinical Practice and as required by applicable regulatory requirements.

Essential documents should be retained as per the aforementioned ICH guideline or for a longer period of time, if required by the applicable regulations.

10.8 USE OF INFORMATION AND PUBLICATIONS

Before the Investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning the study drug or products, the Sponsor must be provided with at least 60 days to revise and approve the proposed publication or disclosure to ensure that confidential and proprietary data are protected.

If the Sponsor determines that patentable patient matter is disclosed in the proposed publication or disclosure, the publication or disclosure will be withheld for a period of time considered convenient. If the study is part of a multicenter study, the first publication of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the Investigators and the institutions from all appropriate sites that are contributing data, analysis and comments. However, if such a multicenter publication is not submitted within 12 months after conclusion, abandonment or termination of the study at all sites, the present study may be published individually in accordance with the procedure established above.

The order of the coauthors will reflect the relative contribution of each one to study development and analysis. In general, the first author will be the Investigator who recruits the highest number of patients with information finally available for data analysis. Relevant personnel from the Sponsor who have fully participated in the study must be considered for co-authorship of the publication.

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12. APPENDICES

Appendix 1. ECOG PERFORMANCE STATUS ASSESSMENT SCALE

Grade	ECOG PS*
0	Fully active, able to carry on all pre-disease performance 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, 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

*As published in Am. J. Clin. Oncol *5:649-655, 1982*: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group.*

Appendix 2. COCKCROFT-GAULT FORMULA

For Calculated Creatinine Clearance

$$\text{CrCL (mL/min)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{Creatinine}_{\text{serum}}(\text{mg/dL})} \times 0.85 \text{ if female}$$

Cockcroft D.W., Gault M.H. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976;16:31–41 (DOI:10.1159/000180580)

Appendix 3. CONTRACEPTION AND PREGNANCY TESTING

This document is based on the Heads of Medicines Agencies' Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials, published by the Clinical Trial Facilitation Group (CTFG) on 15 September 2014 and available at http://www.hma.eu/ctfg.html (accessed 1 September 2016)

A woman is considered of childbearing potential (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Immediately after detecting a case of suspected pregnancy in a patient, the decision on her continued participation in the clinical trial will be jointly taken by the patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate discontinuation any investigational medicinal product (IMP).

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Fertile male patients included in this study should refrain from fathering a child or donating sperm during the study and for four months following the last IMP dose. If they have WOCBP partners the male subject should use condom during treatment and for four months following the last IMP dose.

Highly effective birth control methods are:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
    a. oral
    b. intravaginal
    c. transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
    a. oral
    b. injectable
    c. implantable [2]
3. Intrauterine device (IUD) [2]
4. Intrauterine hormone-releasing system (IUS) [2]
5. Bilateral tubal occlusion [2]
6. Vasectomized partner [2,3]
7. Sexual abstinence [4]
8. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see below).

[2] Contraception methods that are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in this trial. It cannot be excluded that the IMP may reduce exposure to substrates of CYP3A through enzyme induction; the efficacy of hormonal contraceptives may be reduced if co-administered with the IMP.

Appendix 4. CYP1, CYP2 AND CYP3 INHIBITORS, INDUCERS AND SUBSTRATES

Table 1. Classification of In Vivo Inhibitors of CYP Enzymes (1)

CYP enzymes	Strong Inhibitors (2) ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors (3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors (4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein, (5), disulfiram, Echinacea, (5) famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6			Clopidogrel, ticlopidine prasugrel
CYP2C8	Gemfibrozil(6)		Fluvoxamine, ketoconazole, trimethoprim
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	Fluconazole, (7) Fluvoxamine, (8) ticlopidine (9)	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives (10)
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, (11) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, (11) imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, (5) goldenseal, (5) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, (5) escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
2. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
3. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
4. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.

5. Herbal product.
6. Gemfibrozil also inhibits OATP1B1.
7. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
8. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
9. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
10. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
12. Withdrawn from the United States market because of safety reasons.

Table 2. Classification of In Vivo Inducers of CYP Enzymes(1)

CYP enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers (2)	Moricizine, omeprazole, phenobarbital,
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort (3,4)
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, (5) carbamazepine, phenytoin, rifampin, St. John's wort (3)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,(**4)** pioglitazone, prednisone, rufinamide
CYP2D6	None known	None known	None known

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link:
2. For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.
3. The effect of St. John's wort varies widely and is preparation-dependent.
4. Herbal product.
5. Not a marketed drug.

Table 3. Examples (1) of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP enzymes	Sensitive substrates (2)	Substrates with narrow therapeutic range (3)
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 (4)	Bupropion, efavirenz	
CYP2C8	Repaglinide (5)	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A (6)	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, (7) cisapride, (7) cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(7)
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

1. Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
2. **Sensitive CYP substrates** refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.
3. CYP **substrates with narrow therapeutic range** refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
4. The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.
5. Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.
6. Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
7. Withdrawn from the United States market because of safety reasons.

Appendix 5. DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for

them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are

accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.