Abstract: The invention relates to a compound of formula (I) which may be in base form or in the form of a hydrate or a solvate, for its use as a medicament in the treatment of advanced gastric adenocarcinoma, especially for patients who have failed prior chemotherapy regimens.
Use of cabazitaxel in patients with advanced gastric adenocarcinoma who have failed prior chemotherapy regimens

The present invention relates to the use of cabazitaxel in the treatment of advanced gastric adenocarcinoma, especially for patients who have failed prior chemotherapy regimens.

[Technical problem]

Gastric cancer is a major health problem around the world. About one million new cases of gastric cancer were estimated to have occurred in 2008 (988 000 cases), and it is the second leading cause of cancer death worldwide (738 000 deaths). More than 70% of cases (714 000 cases) occur in developing countries, and the half of the total cases occurs in Eastern Asia, mainly in China. The highest mortality rate is estimated also in Eastern Asia.

Radical surgery offers the only chance of cure for gastric cancer. However, most patients present with unresectable, or metastatic disease at the first diagnosis except in Japan and to a lesser extent in Korea where a screening is performed widely and early detection is often possible. Even after curative surgical resection, however, approximately 60% of patients eventually experience a relapse.

Although a number of systemic palliative chemotherapy regimens have been evaluated extensively in patients with unresectable, recurrent or metastatic gastric cancer, and demonstrated improved survival compared to a best supportive care, there is no globally accepted standard first-line chemotherapy for advanced gastric cancer.

Docetaxel has shown an activity against gastric cancer as a single agent as well as in combination with other agents. In a randomized multinational phase III study (V325), 445 patients with advanced gastric cancer who had not been previously treated were randomized to receive either the combination of docetaxel, cisplatin and 5-fluorouracil (DCF) every 3 weeks or the combination of cisplatin and fluorouracil (CF) every 4 weeks. Time to progression (TTP) and overall survival (OS) were significantly longer with DCF compared to CF; 5.6 vs. 3.7 months (p<0.001), and 9.2 vs. 8.6 months (p=0.02), respectively. Based on the results of this study, US FDA (Food and Drug Administration) approved the DCF regimen for the treatment of advanced gastric cancer including cancer of the gastroesophageal junction in patients who have not received prior chemotherapy for advanced disease. Currently, docetaxel has got the same indication in most Asian countries except mainland China where a local registration trial is ongoing.

In addition to docetaxel, other chemotherapy regimens including 5-fluorouracil (5-FU) or its derivatives, paclitaxel, irinotecan, and platinum derivatives have also demonstrated both palliation and improved survival in randomized studies of patients with advanced disease in the first-line setting. However, generally the median overall survival is less than 1 year in general. The poor
long-term outcomes strongly suggest considerable unmet need for further development of new agents in gastric cancer. Ramucirumab, a monoclonal antibody VEGFR-2 antagonist, has been recently assessed in a phase III trial showing a prolonged overall survival in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma that had progressed after first-line chemotherapy. Nevertheless, the need for new therapies with different mechanisms of action remain urgent in the second and third-line setting as, except ramucirumab, there are no established treatments to date that demonstrate survival benefit compared to the best supportive care in phase III trial, although a number of agents and combination regimens have been investigated as a second-line therapy, including docetaxel, paclitaxel, irinotecan, paclitaxel/cisplatin, irinotecan/cisplatin, and S-1/mitomycin in phase II trials.

Thus the technical problem that the invention intends to solve is that of providing a novel second and/or third line therapeutic option for treating advanced gastric adenocarcinoma, especially for patients who have failed prior chemotherapy regimens.

[Brief description of the invention]
The invention relates to a novel antitumoral pharmaceutical therapeutic use comprising cabazitaxel of formula

The invention also relates to methods of treating patients with advanced gastric adenocarcinoma comprising administering an effective amount of the antitumoral agent cabazitaxel to said patient.

This antitumoral agent may be in the form of anhydrous base, a hydrate or a solvate, intended for treating advanced gastric adenocarcinoma, especially for patients who have failed prior chemotherapy regimens.
In some aspects of the invention, cabazitaxel is administered at a dose (defined for each
administration) of between 15 and 25 mg/m². In some aspects of the invention, cabazitaxel is
administered at a dose (defined for each administration) chosen from 15, 20 and 25 mg/m², for
example at a dose of 15 mg/m². Cabazitaxel may be in the form of an acetone solvate. More
particularly, the acetone solvate of cabazitaxel contains between 5% and 8% and preferably
between 5% and 7% by weight of acetone.

In some aspects of the invention, cabazitaxel may be administered by intravenous infusion at a
dose of between 15 and 25 mg/m², for example at a dose (defined for each administration)
chosen from 15, 20 and 25 mg/m², for example at a dose of 15 mg/m², this administration cycle of
the antitumour agent being repeated at an interval of 3 weeks between each cabazitaxel
administration, which interval may be prolonged by 1 to 2 weeks depending on the tolerance to
the preceding cabazitaxel administration.

In some embodiments, the effective amount of cabazitaxel produces at least one therapeutic
effect improving the survival of the patients selected from the group consisting of:

- Improvement of the objective tumor response rate (ORR), defined as the proportion of
  patients with the best tumor response of confirmed complete response (CR) or partial
  response (PR) according to RECIST 1.1 criteria (Eur J Cancer 2009; 45: 228-47), relative
to the total number of patients in the analysis population.

- Improvement of Progression free survival (PFS), defined as the time interval between the
date of the first study treatment and the date of radiological tumor progression defined by
RECIST 1.1 criteria or death due to any cause;

- Improvement of Overall survival (OS), defined as the time interval between the date of the
first study treatment and the date of death due to any cause.

The present invention also relates to a pharmaceutical composition that treats patients with
advanced gastric adenocarcinoma, especially patients who have failed prior chemotherapy
regimens, comprising a clinically proven safe and effective amount of cabazitaxel.

[Description of the invention]
Definitions
- Effective amount, as used herein, means an amount of a pharmaceutical compound, such
  as cabazitaxel, that produces an effect on the cancer to be treated.
- Clinically proven, as used herein, means clinical efficacy results that are sufficient to meet
  FDA approval standards.
- Patient, as used herein, includes both human and animals. In one embodiment, a patient
  is a human.

This compound and a preparative method thereof is described in WO 96/30355, EP 0817779 B1 and US 5847170, which are hereby incorporated herein by reference. Cabazitaxel may be administered in base form (cf. above formula), or in the form of a hydrate. It may also be a solvate, i.e. a molecular complex characterized by the incorporation of the crystallization solvent into the crystal of the molecule of the active principle (see in this respect page 1276 of J. Pharm. Sci. 1975, 64(8), 1269-1288). In particular, it may be an acetone solvate, and, more particularly, may be the solvate described in WO 2005/028462. It may be an acetone solvate of cabazitaxel containing between 5% and 8% and preferably between 5% and 7% by weight of acetone (% means content of acetone/content of acetone+cabazitaxel x 100). An average value of the acetone content is 7%, which approximately represents the acetone stoichiometry, which is 6.5% for a solvate containing one molecule of acetone.

The procedure described below allows the preparation of an acetone solvate of cabazitaxel: 940 ml of purified water are added at 20±5°C (room temperature) to a solution of 207 g of 4a-acetoxy-2a-benzoyloxy-5p,20-epoxy-13-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13a-yl (2R,3S)-3-te/i-butoxycarbonylamino-2-hydroxy -3-phenylpropionate at about 92% by weight in about 2 litres of acetone, followed by seeding with a suspension of 2 g of 4a-acetoxy-2a-
benzoyl0xy-5\textsubscript{P},20-epoxy-i\textsubscript{-}ha\textsubscript{d}roxy-7\textsubscript{p},10(3-dimethoxy-9-oxo-11-taxon-13a-y\textsubscript{l} (2R,3S)-3 -\textit{t}rt-butoxycarbonylamino-2-hydroxy-3-phenylpropionate isolated from acetone/water in a mixture of 20 ml of water and 20 ml of acetone. The resulting mixture is stirred for about 10 to 22 hours, and 1.5 litres of purified water are added over 4 to 5 hours. This mixture is stirred for 60 to 90 minutes, and the suspension is then filtered under reduced pressure. The cake is washed on the filter with a solution prepared from 450 ml of acetone and 550 ml of purified water, and then oven-dried at 55°C under reduced pressure (0.7 kPa) for 4 hours. 197 g of 4\textsubscript{a}-acetoxy-2\textsubscript{a}-benzo\textsubscript{y}loxy-5\textsubscript{p},20-epoxy-i\textsubscript{-}\textit{h}a\textsubscript{d}roxy-7\textsubscript{p},10β-dimethoxy-9-oxo-11-taxon-13a-y\textsubscript{l} (2R,3S)-3 -\textit{t}rt-butoxycarbonylamino-2-hydroxy-3-phenylpropionate acetone containing 0.1% water and 7.2% acetone (theoretical amount: 6.5% for a stoichiometric solvate) are obtained.

Cabazitaxel may be administered parenterally, such as via intravenous administration. A galenical form of cabazitaxel suitable for administration by intravenous infusion is that in which the cabazitaxel is dissolved in water in the presence of excipients chosen from surfactants, cosolvents, glucose or sodium chloride, etc. For example, a galenical form of cabazitaxel may be prepared by diluting a premix solution of cabazitaxel contained in a sterile vial (80 mg of cabazitaxel + 2 ml of solvent + Polysorbate 80) with a sterile vial containing a solution of 6 ml of water and ethanol (13% by weight of 95% ethanol) in order to obtain 8 ml of a solution ready to be rediluted in a perfusion bag. The concentration of cabazitaxel in this ready-to-redilute solution is about 10 mg/ml. The perfusion is then prepared by injecting the appropriate amount of this ready-to-redilute solution into the perfusion bag containing water and glucose (about 5%) or sodium chloride (about 0.9%).

One aspect of the invention is a compound of formula

![Chemical structure](https://example.com/structure.png)

which may be in base form or in the form of a hydrate or a solvate,
for its use as a medicament in the 2nd line or 3rd line treatment of patients with advanced gastric adenocarcinoma, especially patients who have failed prior chemotherapy regimens.

Advanced gastric adenocarcinoma is for example an unresectable or metastatic gastric adenocarcinoma including adenocarcinoma of gastroesophageal junction.

According to the invention, cabazitaxel may be in the form of an acetone solvate. The acetonate solvate may contain between 5% and 8% and preferably between 5% and 7% by weight of acetone.

Accordingly, one aspect of the invention is a method of treating advanced gastric adenocarcinoma, especially for patients who have failed prior chemotherapy regimens, comprising administering to a patient in need thereof an effective amount of cabazitaxel.

Cabazitaxel may be administered at a dose (defined for each administration) of between 15 and 25 mg/m². In some aspects of the invention, cabazitaxel is administered at a dose (defined for each administration) chosen from 15, 20 and 25 mg/m², for example at a dose of 15 mg/m².

Cabazitaxel may be administered repeatedly according to a protocol that depends on the patient to be treated (age, weight, treatment history, etc.), which can be determined by a skilled physician. In one aspect of the invention, cabazitaxel is administered by perfusion to the patient according to an intermittent program with a time interval between each administration of 3 weeks, which may be prolonged by 1 to 2 weeks depending on the tolerance to the preceding administration. Examples of doses for cabazitaxel are given in the "Example" section. The currently recommended dose is 15 mg/m² of cabazitaxel administered as a one-hour infusion.

Another aspect of the invention is a pharmaceutical composition that treats patients with advanced gastric adenocarcinoma, especially patients who have failed prior chemotherapy regimens, comprising a clinically proven safe and effective amount of cabazitaxel as disclosed here above.

Another aspect of the invention is a method of increasing the survival of a patient with advanced gastric adenocarcinoma, especially patients who have failed prior chemotherapy regimens, comprising administering a clinically proven effective amount of cabazitaxel as disclosed here above to the patient.
Example

STUDY TITLE
A Phase 2, Multicenter Study of Cabazitaxel Single Agent Administered as a 1-Hour Intravenous Infusion Every 3 Weeks to Evaluate the Safety, Tolerability and Anti-tumor activity in Patients with Advanced Gastric Adenocarcinoma Who Have Failed Prior Chemotherapy Regimens

INVESTIGATOR/TRIAL LOCATION
Korea

STUDY OBJECTIVE(S)
Primary Objective
- To evaluate the anti-tumor activity of cabazitaxel by assessing objective tumor response rate (ORR) at the recommended dose (RD) when administered as a single agent every 3 weeks in patients with advanced gastric adenocarcinoma who have failed prior chemotherapy regimens

Secondary Objective(s)
- To determine the RD of cabazitaxel when administered as a single agent every 3 weeks
- To evaluate safety of cabazitaxel when administered as a single agent every 3 weeks
- To estimate the overall survival (OS) and progression free survival (PFS)
- To assess the pharmacokinetics (PK) profile of cabazitaxel

STUDY DESIGN
This is a single-arm phase 2 study.
The study consists of two parts; part 1 and part 2.

Part 1:
A "3+3" dose escalation design will be employed to determine the maximum tolerated dose (MTD) of cabazitaxel by assessing the dose-limiting toxicity (DLT) of cabazitaxel when administered as a single agent every 3 weeks. Sequential cohorts of 3 to 6 patients will be treated.
As shown in Table A, there will be 3 dose levels and the starting dose of cabazitaxel will be 20 mg/m2 (Level 1). The lowest and highest doses tested for cabazitaxel in the study will be 15 mg/m2 and 25 mg/m2, respectively.
Table A - Cabazitaxel Dose Escalation Schedule

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose of Cabazitaxel (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
</tbody>
</table>

For safety reasons, the maximum body surface area (BSA) for the actual dose calculation of cabazitaxel will be 2.1 m².

No intra-patient dose escalation will be permitted.

The dose escalation decision rules are defined in Table B. Dose escalation will be based on DLT observed during Cycle 1, with decisions made by the Steering Committee (SC).

Table B - Cabazitaxel Dose Escalation Decision Rules

<table>
<thead>
<tr>
<th>Number of patients with DLT at Level 1 during Cycle 1</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 of first 3 patients</td>
<td>Open Level 2 and enter 3 patients.</td>
</tr>
<tr>
<td>1 of first 3 patients</td>
<td>Enter 3 additional patients at the same dose level. If 0 of the 3 additional patients experience DLT in Cycle 1, then open Level 2 and enter 3 patients. If ≥1 of the 3 additional patients experience DLT, open Level -1*.</td>
</tr>
<tr>
<td>≥2 of first 3 patients</td>
<td>Open Level -1*.</td>
</tr>
</tbody>
</table>

*: if there are ≥2 of 6 patients experience DLT during Cycle 1 at Level -1, decision for next steps will be made by the SC.

Enrollment to the next dose level should not proceed before at least 3 patients treated at the current dose level have received at least 1 cycle of study treatment (3 weeks) and safety has been evaluated for the criteria defining a DLT.

Patients who are not evaluable for DLT during Cycle 1 and/or withdrawn during Cycle 1 for any reason other than a DLT will be replaced.

Definition of Dose-limiting toxicity (DLT):
To qualify for DLT, the adverse event (AE) or laboratory abnormality should be study drug-related as assessed by the investigator.

The DLT will be defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE v.4.03) as any of the following events during
Cycle 1:
• Hematological toxicities defined as:
  Grade 4 neutropenia >7 days duration
  Grade 3 or 4 neutropenia complicated by documented infection
  Grade 3 or 4 neutropenia with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than an hour with life threatening consequences (grade 4 febrile neutropenia)
  Grade 3 or 4 neutropenia with a single temperature of >38.3°C or a sustained temperature of >38°C for more than an hour without life threatening consequences (grade 3 febrile neutropenia)
may be considered DLT if neutropenia does not improve to ≤grade 3 within 7 days and results in treatment delay or dose reduction despite adequate treatment including the appropriate use of granulocyte-colony stimulating factor (G-CSF)
  Grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by serious bleeding
  • Non-hematological toxicities defined as:
  Grade 4 non-hematological toxicities
  Grade 3 non-hematological toxicities EXCEPT the followings that are manageable with appropriate treatment, unless the investigator and sponsor agree that such inclusion is necessary (e.g. if these events were excessive in frequency or duration, or required excessive use of supportive therapy):
  Grade 3 fever without documented infection and without concomitant grade 3 or 4 neutropenia
  Grade 3 anorexia, nausea, or vomiting
  Grade 3 diarrhea in the absence of maximal effective therapy
  Grade 3 fatigue
  Grade 3 peripheral neuropathy that recovers to grade 1 or baseline prior to next treatment cycle
  • Delay of Cycle 2 by more than two weeks due to delayed recovery of toxicities
In part 1, G-CSF may be administered prophylactically after Cycle 1 or therapeutically at any time during the study if the patient demonstrates evidence of neutropenia and/or its clinical consequence. The use of G-CSF will be at the investigator discretion, and needs to be recorded in the e-CRF.
In part 2, G-CSF may be administered prophylactically or therapeutically at any time during the study.
Study treatment must be delayed for any patient who experiences a DLT, but may resume after the toxicity has resolved to ≤grade 1 or baseline at the same or lower dose. Study treatment may be delayed by a maximum of 2 weeks to permit resolution of toxicity.
Definition of Maximum Tolerated Dose (MTD):
The MTD will be defined as the highest dose level up to 25 mg/m2 at which less than 33% of all evaluable patients experience DLT during Cycle 1. It will be defined based on at least 6 patients.
Definition of Recommended Dose (RD):
The RD of cabazitaxel for part 2 will be the dose level as the same as or below the MTD but not above 25 mg/m². It will be decided by the SC considering MTD, overall safety (during and after Cycle 1) and PK profiles. It will be also defined based on at least 6 patients.

**Part 2:**
After the RD is defined, the subsequent patient will then accrue to part 2. Patients at the RD in part 1 will be included in part 2, provided that these patients have a measurable lesion.
All eligible patients will be treated with cabazitaxel single agent every 3 weeks until disease progression, unacceptable toxicity, or another discontinuation criterion is met, whichever comes first.
Each patient's on-study duration consists of Screening period, Registration, Treatment period, End of treatment and Post-treatment follow-up period.

**STUDY POPULATION**
Main selection criteria:
Inclusion Criteria:
- Histologically or cytologically confirmed unresectable or metastatic gastric adenocarcinoma including adenocarcinoma of gastroesophageal junction, which have failed 2 prior chemotherapy regimens. (For countries where a standard of care has not been established for the 2nd line treatment for advanced gastric cancer, those who failed 1 or 2 prior chemotherapy regimens can be included)
  
  Prior chemotherapy should include at least one of the following: 5-FU or derivatives, taxanes, platinum, or irinotecan.
  
  Prior (neo)adjuvant chemotherapy with relapse within 6 months after the end of treatment will be considered retrospectively as the 1st prior palliative chemotherapy.
- Signed informed consent
  
  Patients need to sign a separate consent form for part 1 and part 2, respectively.

Exclusion Criteria
Related to methodology:
- Patients who have received >2 prior systemic chemotherapy regimens for advanced gastric cancer.
- For patients entering part 2, those without at least one measurable lesion at baseline according to RECIST 1.1 criteria
- ECOG performance status >1
- Age <18 years or >85 years
- Life expectancy <2 months
- Inadequate organ and bone marrow function as evidenced by:

**SUBSTITUTE SHEET (RULE 26)**
Hemoglobin <9.0 g/dL
Absolute neutrophil count (ANC) <1500/mm3
Platelet count <100 000/mm3
Total bilirubin >1.5 x Upper limit of normal (ULN)
AST and/or ALT ≥2.5 x ULN if no evidence of liver metastases or AST and/or ALT >5.0 x ULN with liver metastases
Serum creatinine >1.5 x ULN. If creatinine 1.0-1.5 x ULN, estimated glomerular filtration rate (eGFR) should be calculated according to CKD-EPI formula. Patients with eGFR <60 mL/min/1.73 m2 will be excluded.

- Prior surgery, chemotherapy, targeted agents, investigational agents, or other anti-cancer therapy within 4 weeks prior to enrollment in the study (6 weeks for mitomycin-containing regimens)
- Prior radiation therapy within 6 weeks prior to enrollment (except palliative radiation for a local pain control)
- Previous treatment with cabazitaxel
- Hematopoietic growth factors including G-CSF or blood transfusion administered within 2 weeks prior to enrollment in the study
- Known brain or leptomeningeal involvement of cancer
- Patients with known acquired immunodeficiency syndrome (AIDS) related illness or known HIV infection requiring antiretroviral treatment.
- Patients with active varicella zoster infection, or known hepatitis B or C infection.
- Active secondary cancer including prior malignancy from which the patient has been disease-free for ≤5 years. However, adequately treated superficial skin cancer other than melanoma or in situ cervix cancer more than 4 weeks prior to enrollment will not be considered cause for exclusion
- Other concurrent serious illness or medical condition, including active infection requiring systemic antibiotic/anti-fungal medication
- Failure to recover to NCI CTCAE v.4.03 ≤grade 1 from all clinically significant toxic effects of previous anti-cancer therapy except alopecia and grade 2 peripheral neuropathy
- Concurrent treatment in another clinical trial or with any other anti-cancer therapy including chemotherapy, targeted therapy, radiation therapy, or plans to receive these treatments during the study
- Unwillingness or inability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
- Any severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the patient's safety, inhibit protocol participation, or interfere with interpretation of study results, and in
the judgment of the investigator would make the patient inappropriate for entry into this study

- For women of childbearing potential: pregnancy, breast feeding, lack of a negative pregnancy test within 7 days prior to registration, or lack of agreement on protection by a highly effective contraceptive method of birth control during period from the time the patient gives informed consent until 3 months after last study drug administration.

- Patient status as investigator, sub-investigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the protocol

Related to the current knowledge of Cabazitaxel:

- History of severe hypersensitivity reaction ≥ grade 3 to drugs formulated with polysorbate 80 such as docetaxel
- Concurrent or planned treatment with strong inhibitors or inducers of CYP3A. A one-week washout period is required prior to the first dose of study treatment for patients already on these drugs.

Total expected number of patients:

Up to 45 patients will be treated in the study: 9-18 patients evaluable for DLT in part 1, and approximately 33 eligible patients in part 2 including at most 6 patients treated at the RD in part 1, provided that these patients have a measurable lesion.

For part 2, at least 10 patients treated with 1 prior chemotherapy regimen, and at least 10 patients with taxane failure will be included.

STUDY TREATMENT(s)

Cabazitaxel (XRP6258)

Investigational Product(s)

Formulation

Cabazitaxel is supplied as a sterile, non-pyrogenic, non-aqueous, yellow to brownish yellow concentrate for solution for infusion at 60 mg/1.5 ml and packaged in a 15 mL clear type I glass vial stoppered with a rubber closure. The closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. The solution contains polysorbate 80 as the excipient.

The cabazitaxel concentrate for solution for infusion will be diluted before use as described in the clinical study protocol.

The solvent for cabazitaxel is supplied as a 13% w/w ethanol solution in water for injection. This solvent is supplied in a 15 mL single dose clear type I glass vial stoppered with a rubber closure.
The rubber closure is crimped to the vial with a gold-color aluminum cap covered with a clear plastic flip-off cap.

The preparation of the cabazitaxel infusion solution for administration requires preparation of a premix solution at 60 mg/6 mL (nominal concentration). This must be done with a 13% w/w ethanol solution in water for injection supplied with cabazitaxel concentrate for solution for infusion.

Each cabazitaxel vial and each solvent vial are overfilled to ensure that 60 mg dose can be extracted after the preparation of the premix. Each vial of cabazitaxel must be diluted with the ENTIRE content of the solvent vial.

Route(s) of administration:
Cabazitaxel will be administered intravenously.

Dose regimen:

Part 1:
On day 1 of each cycle, patients will receive cabazitaxel, administered by IV infusion over 1 hour, at the dose specified for each dose level. Required IV premedication will include: antihistamine (dexamfetamine 5 mg, diphenhydramine 25 mg, or equivalent antihistamines); corticosteroids (dexamethasone 8 mg or equivalent steroids); H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist). These premedications will be administered by IV infusion, at least 30 minutes before each dose of cabazitaxel. Anti-emetic prophylaxis (oral or intravenous) can be administered whenever necessary.

For those patients who have had a DLT, further treatment may be continued at the same or lower. Safety data will continue to be collected from these patients.

Part 2:
Patients will receive cabazitaxel on day 1 of each cycle in the same manner as that in part 1.

Cycle lengths in both part 1 and part 2 are 3 weeks. New cycles should not begin until ANC ≥1500/mm3, platelet count ≥75000/mm3, serum creatinine ≤1.5 x ULN, liver function tests are within the range indicated in exclusion criteria, and non-hematological toxicities (except alopecia, local reactions, and other toxicities that are uncomfortable but do not cause serious morbidity to patients) have recovered to grade ≤1 or baseline. Dose modification should be done for any significant toxicity (see Table C: cabazitaxel dose reduction schedule). A maximum of 2 weeks treatment delay is allowed between treatment cycles. Patients should discontinue study treatment if treatment delay is more than 2 weeks.

Table C - Cabazitaxel Dose Reduction Schedule

<table>
<thead>
<tr>
<th>Projected Initial Dose</th>
<th>Does Reduction 1</th>
<th>Dose Reduction 2</th>
</tr>
</thead>
</table>

SUBSTITUTE SHEET (RULE 26)
PRIMARİY AND SECONDARY ENDPOINTS

Primary Endpoint:
- ORR, defined as the proportion of patients in part 2 with the best tumor response of confirmed complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria, relative to the total number of patients in the analysis population.

Secondary Endpoints:
- MTD and RD determination in part 1 by assessing DLT of cabazitaxel when administered as a single agent during Cycle 1
- Safety profile of cabazitaxel including AEs/SAEs and clinical laboratory parameters
- OS, defined as the time interval from the date of the first study treatment to the date of death due to any cause
- PFS, defined as the time interval from the date of the first study treatment to the date of radiological tumor progression or death due to any cause
- PK profile of cabazitaxel and parameters of maximal plasma concentration (Cmax), area under the concentration-time curve (AUC), AliClast, terminal half-life (t1/2), plasma clearance (CL) and the volume of distribution at steady state (Vss)

ASSESSMENT SCHEDULE

Safety Data:
Vital signs, medical and surgical history, physical examination, ECOG PS, and laboratory tests (including complete blood counts, biochemistry, and urinalysis) will be obtained prior to drug administration and at designated intervals throughout the study. Treatment-emergent adverse events (TEAEs) will be collected during the study and up to 30 days after the last dose of study medication. AEs will be graded according to the NCI CTCAE v.4.03. Ophthalmologic examination will be performed during the screening (this should not delay the start of the study treatment), and at the end of treatment only if a follow-up exam is needed.

Efficacy Data:
Antitumor activity will be assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and any other areas if clinically indicated. These exams will be performed at baseline (screening), every 6 weeks, whenever disease progression is suspected, or until disease progression, using the same method for each assessment. Patients
who discontinue study treatment prior to disease progression will continue to have tumor assessments every 6 weeks until disease progression or the start of new anti-cancer therapy.

Pharmacokinetic Data:
Cabazitaxel PK: blood samples (during Cycle 1 and right before the study drug infusion on C2D1) will be collected from all patients enrolled in part 1 and 12 Chinese patients enrolled in part 2 by the standard PK sampling.

STATISTICAL CONSIDERATIONS
Sample size determination:
The part 1 of the study is to determine the MTD of cabazitaxel by assessing the DLT observed during Cycle 1, and determine the RD for part 2. The number of evaluable patients in the part 1 ranges from 9 to 18.
The part 2 of the study is to estimate the ORR at the RD in the study population. The sample size is calculated using one sample Chi-square method with Yates’ correction for continuity. The null hypothesis is that response rate equals to 5% and alternative hypothesis is that response rate equals to 20%. A total of 33 treated patients will ensure a power of no less than 80% at a true response rate equals 20% with one-sided alpha level of 0.025. If ≥ 5 responses are observed among the 33 patients, the null hypothesis will be rejected in favor of the alternative hypothesis.

Of 33 patients in part 2, at most 6 patients treated at the RD in part 1 will also be included, provided that they have a measurable lesion. Therefore up to 45 patients will be treated in total for this study.

Analysis Population:
DLT evaluable population: This population includes all registered patients in part 1 who received a full dose of study drug and completed evaluation for DLT in Cycle 1 or received a partial dose of study drug and developed DLT during Cycle 1. Analyses related to DLT evaluation will be conducted based on the DLT evaluable population.

Modified intention-to-treat (mITT) population: This population consists of all treated patients in part 2. This population is the primary population for all efficacy analysis in part 2.

ORR evaluable population: This population is a subset of mITT population. It consists of all patients in part 2 who have received at least two cycles of study treatment, have a baseline tumor assessment, and at least one post-baseline tumor assessment no earlier than 5 weeks (35 days) after the first study treatment. In addition, patients who have progressed as per RECIST 1.1 before the first planned post-baseline tumor assessment will be defined as early progression and will also be considered as evaluable for ORR.

Safety population: This population includes all patients who receive at least one dose (including a partial dose) of study drug. This population will be used in all safety summaries. Safety analysis will be performed in part 1 and 2, respectively.
Analysis of primary endpoint:
ORR will be calculated as the proportion of patients in part 2 with the best response of confirmed CR or PR relative to the total number of patients in the mITT population. The response rate will be checked using Chi-square test with Yates' correction. The 95% confidence interval of the response rates will be provided using normal approximation.
The data cut-off date for ORR will be the date when every patient from part 2 gets the first confirmed post-baseline tumor assessment or discontinues study treatment, whichever comes first.

Analysis of secondary endpoints
In part 1, MTD and RD will be determined by DLT assessment during Cycle 1. Due to the small sample size, the analysis will be descriptive only.
The cut-off date for part 1 will be the date when RD is determined.
The safety profile of cabazitaxel including AEs/SAEs and laboratory parameters will be summarized by frequency in patients and by worst grades. Worst grades per patient and per cycle will be tabulated for selected adverse events and laboratory measurements using NCI CTCAE v.4.03.
Overall survival will be summarized using Kaplan-Meier survival statistics. Graphical displays of the Kaplan-Meier curves will be provided separately. If death is not observed during the study, data on OS will be censored at the last date when the patient is known to be alive or at the end of study (EOS), whichever comes first,
PFS will be summarized using Kaplan-Meier survival statistics. Graphical displays of the Kaplan-Meier curves will be provided separately. If death or progression is not observed, data on PFS will be censored at the date of the last available tumor assessment without evidence of progression or at EOS, whichever comes first.
Pharmacokinetics parameters will be summarized with descriptive statistics.

DURATION OF STUDY PERIOD (per patient)
The study consists of:
- Screening period: From the day of signed informed consent to Registration. It should be no longer than 14 days.
- Registration: When eligibility of patient is confirmed based on inclusion/exclusion criteria after all baseline examinations are completed during the screening period.
- Treatment period: The study drug starts within 3 days of registration. The treatment cycle is 3 weeks and may be delayed up to 2 weeks in case of unresolved toxicity. The day of study drug administration will be the Day 1 of the given cycle. All patients will continue to receive treatment until disease progression, unacceptable toxicity, or another discontinuation criterion is met.
- End of treatment (EOT): When a patient discontinues study treatment for any reason (except death or lost to follow-up), the EOT evaluation should be performed within 30 days after the last dose of study treatment. If a decision of discontinuation is made beyond 30 days after the last dose of treatment due to a treatment delay, the EOT evaluation should be made within 7 days after such decision is made.

- Post-treatment follow-up period: After EOT, patients will be contacted either in person or by phone every 2 months to check the survival status and the use of new anti-cancer therapy until death or EOS, whichever comes first.

Patients who discontinue study treatment prior to disease progression will continue to have tumor assessments every 6 weeks until disease progression or start of new anti-cancer therapy. Patients still receiving treatment beyond the data cut-off date can continue treatment until disease progression, unacceptable toxicity, or another discontinuation criterion is met. Study drug administration, all SAEs regardless of relationship to study drug, and AEs considered related to study drug, and the reason for discontinuation will be collected during this period. The end of study for all patients will be at 3 months after all patients enrolled in part 1 and part 2 achieve EOT.

**Results**

**Patient population**
- Sixteen patients (8 males, 8 females) were included in the study (Table 1)
- Median age was 50.0 years and 14/16 patients (87.5%) were <65 years of age.
- The primary tumor site was the stomach in all patients; all patients had metastatic disease (Table 2).
- Thirteen patients (81.3%) had prior curative or palliative gastrectomy and 1 patient (6.3%) received prior radiotherapy. Prior adjuvant chemotherapy had been given in 7 patients (43.8%) and the median number of prior palliative chemotherapy regimens was 2 (range 1-2). Eleven patients (68.8%) had prior taxane exposure.

**Dose escalation**
- At DL1, no DLTs occurred in any of the first 3 patients.
- At DL2, 4 patients were enrolled (due to 1 patient discontinuing prematurely). Only 1 DLT (Grade 4 febrile neutropenia) was observed. However, all 4 patients experienced febrile neutropenia.
Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Planned dose level of cabazitaxel</th>
<th>Total (N=16)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>15 mg/m2 (n=6)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>57.5 (50–67)</td>
<td>50.0 (28–67)</td>
</tr>
<tr>
<td>Age group, years, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>4 (66.7)</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>65–74</td>
<td>6 (100)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>≥75</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (100)</td>
<td>8 (50.0)</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>8 (50.0)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>6 (100)</td>
<td>16 (100)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status

- Therefore, 3 more patients were enrolled at DL1 to further explore safety at the lower dose. Two DLTs (Grade 4 neutropenia >7 days' duration) occurred in 2 of 3 patients.
- In response, DL-1 was opened, with no DLTs observed in 6 DLT-evaluable patients; therefore, DL-1 (15 mg/m2) was confirmed as the MTD.

Study treatment exposure

- The median numbers of cycles administered were 5 (1-6) at DL1, 1.5 (1-6) at DL2 and 3 (2-6) at DL-1.
- The most common reason for discontinuation was progressive disease (93.8%). One patient (6.3%) discontinued treatment due to an AE not related to the study drug.

Safety

- All 16 patients experienced at least 1 AE regardless of causality, of which 13 (81.3%) had ≥1 Grade 3/4 AE (Table 3). The most frequent all-grade AEs (>35% of all patients) were neutropenia (n = 11, 68.8%), decreased appetite (n = 8, 50.0%), anemia, febrile neutropenia and nausea (all n = 6, 37.5%). The most frequent Grade 3/4 AEs (>10% of patients) were neutropenia (n = 10, 62.5%) and febrile neutropenia (n = 6, 37.5%); 5 of 6 patients who developed febrile neutropenia had received previous taxane therapy.
- Grade ≥3 non-hematologic AEs were infrequent at all DLs.
- All-grade hematologic abnormalities included anemia (n = 16, 100%), neutropenia (n = 14, 87.5%), leukopenia (n = 13, 81.2%) and thrombocytopenia (n = 6, 37.5%). Grade 3/4 hematologic abnormalities included leukopenia and neutropenia (both n = 10, 62.5%). No Grade 3/4 anemia or
thrombocytopenia was reported.

• Ten patients (62.5%) experienced 15 SAEs regardless of causality. The only SAE that occurred in >1 patient was febrile neutropenia (n = 6, 37.5%; all Grade 3/4 and related to study treatment).
• Dose reduction due to AEs occurred in 6 patients (37.5%): Grade 3 febrile neutropenia (n = 2) and Grade 4 neutropenia (n = 2) at DL1 and Grade 3 or 4 febrile neutropenia (n = 2) at DL2.

Table 2. Baseline disease characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Planned dose level of cabazitaxel</th>
<th>Total (N=16)</th>
</tr>
</thead>
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<td></td>
<td>15 mg/m2 (n=6)</td>
<td>20 mg/m2 (n=6)</td>
</tr>
<tr>
<td>Gastric tumor histopathology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>5 (83.3)</td>
<td>0</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1 (16.7)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>0</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Cancer stage at study entry, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV (metastatic)</td>
<td>6 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Number of organs involved at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>2</td>
<td>2 (33.3)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>3</td>
<td>2 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;3</td>
<td>0</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Organs involved at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>0</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Liver</td>
<td>5 (83.3)</td>
<td>0</td>
</tr>
<tr>
<td>Lungs</td>
<td>2 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1 (16.7)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Pleura</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Prior gastrectomy, n (%)</td>
<td>5 (83.3)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Prior radiotherapy, n (%)</td>
<td>1 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy, n (%)</td>
<td>3 (50.0)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Number of prior palliative chemotherapy regimens, median (range)</td>
<td>2.0 (1-2)</td>
<td>2.0 (2-2)</td>
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</table>
Table 3. Most frequent all-grade and Grade ≥ 3 AEs (≥25% of total patients, all grades)

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>Cabazitaxel dose level</th>
<th>Total (N=16)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>15 mg/m2 (n=6)</td>
<td>20 mg/m2 (n=6)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Any AE</td>
<td>3 (50.0)</td>
<td>6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

AE, adverse event

Efficacy

* One patient (6.3%) at DL-1 had partial response (PR) as the best overall response; this patient had not received prior taxane therapy.
* Eight patients (50%) (5 patients at DL1, 1 patient at DL2 and 2 patients at DL-1) had stable disease as the best overall response, including 1 patient at DL1 with unconfirmed PR who had received prior taxane therapy.
* One patient (6.3%) discontinued study treatment due to an AE and had no post-baseline tumor assessment.

SUBSTITUTE SHEET (RULE 26)
Mean plasma concentration-time profiles of cabazitaxel at each DL are shown in Figure 1.

Consistent with previous Phase I studies, the overall PK profile of cabazitaxel was characterized by a long terminal elimination half-life (73.05 h), a high clearance (33.6 L/h/m²) and a large volume of distribution (approximately 2420 L/m²) at the 15-25 mg/m² dose range.

Dose proportionality was assessed at all DLs; for a 1.67-fold increase in dose from 15 to 25 mg/m², the corresponding estimated ratios of Cmax, AUClast and AUC were 2.06, 2.08 and 2.03, respectively (Table 4, Figure 2). Although confidence intervals were wide for the estimated ratios, mainly due to higher variability at the lowest dose (15 mg/m²), lack of deviation from dose proportionality was confirmed between 20 and 25 mg/m².

No dose effect was observed. Across the 20-25 mg/m² doses, the overall terminal half-life was 92.7 h and clearance was 31.6 L/h/m².

Table 4. Dose proportionality assessment for cabazitaxel on Cycle 1 after a single infusion of cabazitaxel (estimates with 90% CI for r-fold increases)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose ratio</th>
<th>Estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>(r) = 1.67</td>
<td>2.06</td>
<td>(1.01–4.19)</td>
</tr>
<tr>
<td>Beta Estimate</td>
<td>1.41</td>
<td>(0.02–2.80)</td>
<td></td>
</tr>
<tr>
<td>AUClast</td>
<td>(r) = 1.67</td>
<td>2.08</td>
<td>(1.21–3.61)</td>
</tr>
<tr>
<td>Beta Estimate</td>
<td>1.44</td>
<td>(0.37–2.51)</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>(r) = 1.67</td>
<td>2.03</td>
<td>(1.17–3.52)</td>
</tr>
<tr>
<td>Beta Estimate</td>
<td>1.38</td>
<td>(0.30–2.46)</td>
<td></td>
</tr>
</tbody>
</table>

Cmax = 3.67 x dose1.41 ; AUClast = 6.28 x dose1.44 ; AUC = 9.53 x dose1.38; AUC, area under the concentration-time curve; Cmax, maximum plasma concentration.

Discussion and conclusions

The MTD of cabazitaxel in Asian patients with advanced gastric cancer was 15 mg/m².

Consistent with previous studies, the most significant toxicity of cabazitaxel was neutropenia and its related complications. There were no unexpected findings in the safety profile,

The frequent occurrence of neutropenic complications with cabazitaxel in this study may be attributed in part to the heavily pretreated nature of the patients and the accumulated bone marrow toxicity resulting from prior taxane therapy. The majority of patients received 2 prior...
chemotherapies, and 5 of 6 patients who developed febrile neutropenia had received prior taxane therapy.

- Two PRs were observed, one confirmed in a patient at 15 mg/m2 without prior taxane therapy, and one unconfirmed in a patient at 20 mg/m2 with prior taxane therapy.
- The PK parameters of cabazitaxel in this Asian population are similar to those observed in Phase I studies in Caucasian populations, hence ethnic differences are less likely to explain the difference in MTD.
CLAIMS

What is claimed is:

1. Compound of formula which may be in base form or in the form of a hydrate or a solvate, for its use as a medicament in the 2nd line or 3rd line treatment of patients with advanced gastric adenocarcinoma.

2. Compound according to claim 1, where the treated patients have failed prior chemotherapy regimens.

3. Compound according to any one of claims 1 or 2, in the form of an acetone solvate.

4. Compound according to Claim 3, in which the acetone solvate contains between 5% and 8% and preferably between 5% and 7% by weight of acetone.

5. Compound according to any one of claims 1 to 4, administered at a dose of between 15 and 25 mg/m².

6. Compound according to claim 5, administered at a dose of 15 mg/m².

7. Compound according to any one of claims 1 to 6, comprising repeating the administration of such compound as a new cycle every 3 weeks.
8. Compound according to any one of claims 1 to 7, which when administered to a group of patients gives an increased objective tumor response rate.

9. A pharmaceutical composition comprising a compound as defined in claims 1 to 8.

10. A method of increasing the survival of a patient with advanced gastric adenocarcinoma, comprising administering a clinically proven effective amount of a compound as defined in any one of claims 1 to 8 to the patient.
Figure 1
Mean cabazitaxel plasma concentration–time profiles following infusion of 15, 20 and 25 mg/m² doses (semi-logarithmic scale)
LOQ, limit of quantification
Figure 2
Individual and mean (± SD) cabazitaxel AUClast following cabazitaxel infusion
AUC, area under the concentration-time curve; SD, standard deviation
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/337 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"F" document member of the same patent family

Date of the actual completion of the international search: 16 March 2015

Date of mailing of the international search report: 25/03/2015

Name and mailing address of the ISA/Autorized officer:

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Lemarchand, Aude
<table>
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<td>We 2012/113897 Al (AVENTIS PHARMA SA [FR]; BISSERY MARI E-CHRISTINE [FR]; DÉDIÉ JEAN-FRANÇOIS) 30 August 2012 (2012-08-30) claims 1-5, 7, 10, 23 page 11; table 1</td>
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<th>Relevant to claim No.</th>
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