European Medicines Agency

London, 4 December 2009
Doc. Ref: EMA/CHMP/731026/2009

WITHDRAWAL ASSESSMENT REPORT
FOR
Opaxio

International Non-proprietary Name:
Paclitaxel poliglumex

Procedure No. EMEA/H/C/994

Applicant: CTI Life Sciences, Ltd [1]

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

[1] The Marketing Authorisation Application for Opaxio was initially made by Voisin Consulting S.A.R.L. The applicant was changed to CTI Life Sciences Limited during the procedure.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@ema.europa.eu. http://www.ema.europa.eu
© European Medicines Agency, 2009. Reproduction is authorised provided the source is acknowledged.

TABLE OF CONTENTS

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for paclitaxel poliglumex (CT-2103), in first line chemotherapy of patients with advanced NSCLC and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 2, is **not approvable** since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Patients with advanced or recurrent NSCLC and PS2 represent a significant portion (up to 40%) of the NSCLC population treated in clinical practice. They represent a heterogeneous population, primarily because PS2 may be due to tumour-related symptoms or to concomitant diseases, or both. Compared to PS0-1 patients, PS2 patients are generally considered characterized by lower response rates to chemotherapy, shorter progression free survival and shorter overall survival (historically it rarely exceeds 5 months). Furthermore, PS2 patients are considered at higher risk of severe toxicity, which would counterbalance any potential benefit expected from active cytotoxic therapy.

At present, there is no curative systemic treatment for patients with advanced NSCLC. Platinum-based chemotherapy is considered the standard 1st line treatment for patients with advanced NSCLC and good performance status, as it has been demonstrated to improve survival, albeit modestly, and alleviate disease-related symptoms in this population. However, it is unknown whether these benefits apply to patients with poor performance status. Indeed, historical data over the clinical benefit of chemotherapy in PS2 patients are scanty, because PS2 patients have been generally excluded from clinical trials or, when included, they represented a small percentage (usually far less than 20%) of study populations. Prospective studies for PS 2 patients are lacking, and retrospective information based on sub-group analyses focused on small subgroups of patients with PS2 is the best level of information available from the literature.
Currently, there is no consensus on standard treatment for patients with advanced NSCLC and PS2. The treatment is primarily palliative and options include:

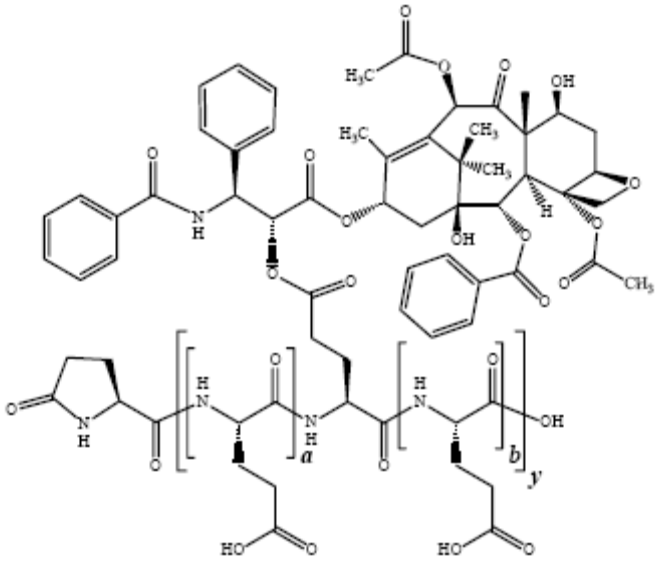
- Supportive care to reduce cancer-related symptoms
- Local radiation to reduce cancer related symptoms and improve QoL
- Chemotherapy, to slow disease progression, prolong survival and improve QoL. Single-agent chemotherapy, non-platinum based combination chemotherapy, and platinum-based combination chemotherapy are considered possible treatment options. Of note, in the recent CALGB 9730 trial evaluating the combination paclitaxel/carboplatin versus single agent paclitaxel in patients with advanced NSCLC, a subgroup analysis focused on the 99 PS2 patients (out of the 561 enrolled) showed increased survival and acceptable tolerability for PS 2 patients treated with doublet agent chemotherapy (paclitaxel/carboplatin) in comparison to single agent chemotherapy (paclitaxel) (Lilenbaum RC et al, 2005).

II.2 About the product

CT-2103 drug substance is the ester conjugate of α- poly (L) - glutamic acid (PGA) and paclitaxel (Figure 1). The conjugated paclitaxel is inactive; however, upon release from the poly-L-glutamic acid backbone via metabolic processes, it yields the bioactive paclitaxel molecule. According to the Applicant, paclitaxel is released after uptake and proteolytic/hydrolytic degradation of the conjugate in tumour tissue.
CT-2103 was developed in order to improve the safety profile of paclitaxel. Polymeric conjugation, thus improving the dissolvability, eliminates the need of Cremophor EL from the pharmaceutical preparation of paclitaxel, and thereby potentially avoids the acute toxicities generally ascribed to Cremophor EL including cardiac side effects, hypersensitivity reactions, arthralgias and myalgias. Indeed, potentially CT-2103 could allow for shorter time infusions than paclitaxel (10-30 minutes versus 3 hours) without routine pre-

medication for hypersensitivity reactions. Also, according to the Applicant, the polymeric formulation was expected to improve the pharmacokinetics profile of paclitaxel, by decreasing the volume of distribution and prolonging the distribution and elimination phases. By slow release of active paclitaxel from the polymer carrier (presumably secondary to metabolism by lysosomal proteases), it ideally leads to a reduced active drug exposure of normal tissues (with the exception of spleen and liver). Enhanced permeability and retention (EPR) effect in tumour tissue for CT-2103 was also hypothesized, which is supposed to improve the antitumour activity of the compound compared with paclitaxel.
However, it should be recognized that to date, although demonstrated in preclinical studies, the EPR effect claimed for other conjugated polymeric forms of cytotoxic compounds has never been reported to translate in an improved efficacy and safety profile of such drugs in clinical practice.

Figure 1 CT-2103 (paclitaxel poliglumex)



Paclitaxel poliglumex belongs to the taxane class of chemotherapeutic agents. It binds to β-tubulin, promotes the assembly of tubulin into microtubules, stabilizes the microtubules, prevents their disassembly, and eventually causes cell death. The taxane paclitaxel (Taxol) is currently indicated, in combination with cisplatin, for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

Formal scientific advice was given by CHMP (June 2006), a Pre-Scientific Advice pre-meeting teleconference took place in December 2005. Scientific recommendations were given by Danish Medicines Agency (DMA January 2005 and July 2005), Swedish Medical Products Agency (MPA January 2005 and July 2005), Dutch Medicine Evaluation Board (MEB February 2005).

The clinical development plan that establishes the basis for this submission of CT-2103 for 1st line treatment of patients with NSCLC and PS 2 is based on the pivotal phase III PGT-304 study, evaluating CT-2103 as single-agent versus gemcitabine or vinorelbine in 477 chemo-naïve patients with advanced or recurrent NSCLC and PS 2. Other phase II-III studies (CTI-1069, PGT-302, PGT-303 and PGT-305) have been submitted as supportive. The Applicant states that the studies have been executed in compliance with Good Clinical Practices and according to all relevant international, national, and local regulations.
A description of the clinical studies included in the CT-2103 development program is given in Table 1.

Table 1 Description of Clinical Efficacy and Safety studies with CT-2103

Study	Design	Treatment	N. patients	Diagnosis	Primary objective
PGT-103	Phase I	CT-2103 plus RT	11	1st line NSCLC PS 0-2	MTD, safety
PGT-105	Phase I	CT-2103	27 enrolled 25 treated	1st - 3rd line NSCLC PS 0-2	MTD, DLT
PGT-107	Phase I-B	CT-2103	7	Advanced solid tumors PS 0-1	Effect on coagulation cascade
PGT-202	Phase II	CT-2103/carboplatin	74 enrolled 73 treated	1st line NSCLC PS 0-2	Tumor response, time to disease progression, pharmacokinetics
CTI-1069	Phase II	CT-2103	33 enrolled 30 treated	1st line NSCLC PS 2 or age ≥ 70	OS, Tumor response,
PGT-302	Phase III	CT-2103 *vs* docetaxel	849	2nd line NSCLC, PS 0- 2	OS
PGT-303	Phase III	CT-2103/carboplatin *vs* paclitaxel/carboplatin	400	1st line NSCLC, PS 2	OS
PGT-304	Pivotal Phase III	CT-2103 *vs* gemcitabine or vinorelbine	477	1st line NSCLC, PS 2	OS
PGT-305	Phase III	CT-2103 *vs* paclitaxel	200	1st line NSCLC PS 2 women	OS

NSCLC: Non Small Cell Lung Cancer; PS: ECOG Performance Status; MTD: Maximum Tolerated Dose; DLT: Dose-Limiting toxicity; OS: Overall Survival; RT: Radiotherapy.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The product at issue is a powder for concentrate for solution for infusion containing paclitaxel covalently bound to polyglutamic acid. The molecular weight of the paclitaxel poliglumex polymer ranges between 20,000-50,000 Daltons. Approximately one paclitaxel molecule is bound to every tenth amino acid of the polypeptide. The product is supplied as a sterile, lyophilised powder for solution for infusion consisting of approximately 269 mg of CT-2103 DS containing 94 mg paclitaxel, conjugated to PGA, in a 20 ml clear, glass vial (Type I) with a butyl rubber stopper (Flurotec/B2-coated) and an aluminium seal with a polypropylene flip-off cap. Before use, it should be reconstituted with 10 ml of sterile water for injections and subsequently diluted using either dextrose for injection, sodium chloride for injection, or lactated Ringer's solution before being administered to the patient in a 10-30 minute infusion.

Drug Substance

Paclitaxel poliglumex is a new chemical entity. Paclitaxel is the bioactive moiety released after uptake and proteolytic/hydrolytic degradation of the conjugate in tumour tissue.

Paclitaxel is currently described in the Ph.Eur. and the USP. The substance is a white to off-white solid with an amorphous form, soluble in methanol and DMF. The drug substance is not soluble in water. However at higher pH, in ionized form it dissolves.

- Manufacture

A flow diagram is present of the manufacturing process, starting with the production of the starting materials. Sufficient information has been provided on the upstream synthesis of the starting materials. Additional information is asked for with regard to the herbal origin and upstream semi-synthesis.

Appropriate specifications have been adopted for all other materials used and the PGA intermediate.

- Quality Control

In the drug substance specification requirements have been adopted for appearance, identification, conjugated paclitaxel, diconjugated paclitaxel, related conjugated and non-conjugated substances, residual reagents, residual solvents, water content, residue on ignition, heavy metals, molecular weight and polydispersity, completeness of solution, microbial purity and endotoxins. The specification seems adequate in view of manufacturing process, batch analysis data, the Ph.Eur. monograph for the paclitaxel moiety and relevant guidelines. However, some limits set should be either tightened or further qualified and a point regarding the purity of the substance remains at this moment.

- Stability

Long term stability studies are performed at a storage temperature of −20º ± 2ºC and 6 months accelerated studies at a temperature of 5º ± 2ºC in the proposed packaging). At this moment long term results are available and the accelerated studies performed on the stability batches are finished. Parameters tested were appearance, conjugated paclitaxel (assay), related substances including conjugated substances and non-conjugated substances, apparent molecular weight and polydispersity, and water content. The claimed re-test period can be granted.

Drug Product

- Pharmaceutical Development

The excipients are used for acceptable dissolution of the drug substance.
Reconstitution with 10 ml sterile water for injections yields a solution containing 9 mg/ml paclitaxel, in conjugated form with 5 mg/ml poloxamer 188, 20 mg/ml disodium phosphate and 16 mg/ml sodium dihydrogen phosphate. The excipients are usual (also in the amounts used) for parenteral preparations. The product is compatible with the infusion sets and intravenous (iv) bags used for its administration. The formulation contains no preservatives and it is intended for single use. All clinical batches included in the pivotal clinical studies and in the primary stability studies contained the identical composition and were manufactured using manufacturing processes equivalent to that proposed for commercial manufacturing and used during validation.

- Manufacture

The production process includes dissolution of the drug product components, sterile filtration followed by aseptic filling, lyophilisation and stoppering. Due to the heat sensitive nature of the drug product, terminal heat sterilisation is not feasible and the formulation is sterile-filtered to ensure sterility. The sterile-filtered bulk drug product solution is filled into vials in a Grade A (ISO 5) filling suite and subsequently aseptically lyophilised, stoppered and sealed. No overage is included in the vials. The process has been described in sufficient detail. Three validation batches were manufactured at full scale and the lyophilization and holding time have been validated.
The batch release data for the relevant batches demonstrate that pivotal phase 3 batches, primary stability batches and validation batches are comparable with equivalent quality.

- Quality Control

In the drug product specification requirements have been adopted for a.o. appearance, identification, related substances, assay, molecular weight and polydispersity, water content, reconstitution time, uniformity of dosage units, osmolality, pH, sterility and endotoxins, particulate matter. Some limits proposed for impurities are not sufficiently qualified yet and some limits need to be re-evaluated when more batches are produced. A major quality issue is formulated with regard to the calculation and qualification of the conjugated impurity levels.

- Stability

The shelf life claim seems to be acceptable in view of the stability data, but it cannot be granted yet, as the levels of conjugated impurities are not calculated properly and the limits for impurities are not qualified sufficiently.
The additional storage condition ‘Keep the vial in the outer carton in order to protect from light’ is needed in view of the light sensitivity of the product. The six months accelerated stability studies at 25º ± 2ºC/60 ± 5% relative humidity (RH) of the primary stability lots are completed; no significant changes were noted.

When reconstituted and diluted to concentrations ranging from 0.8 to 4 mg/ml, the product is stable when stored refrigerated (2° to 8°C) or at ambient conditions.

III.2 Non clinical aspects

Pharmacology

CT-2103 contains paclitaxel (PTX) conjugated to a poly-L-glutamic acid (PGA) backbone. Paclitaxel is known to disrupt the normal arrangement of the microtubule network in cells that is required for correct mitosis. The pharmacological studies of CT-2103 were specifically aimed at elucidating its Primary Pharmacodynamics *in vitro* and *in vivo* on several tumour models and it's Safety Pharmacology.

CT-2103 did not stabilize tubulin polymerization suggesting that paclitaxel must be cleaved from the CT-2103 PGA backbone before promoting microtubule stabilization.

CT-2103 can yield free paclitaxel by two processes. The first is the slow non-enzymatic hydrolysis of the ester bond between the PTX and PGA backbone. The second process is via endocytosis and intracellular proteolysis, presumably through the action of lysosomal proteases. Indirect immunofluorescence studies in CT-2103-treated murine monocyte/macrophage-like and human lung adenocarcinoma (adenoca.) cell cultures using an anti-CT-2103 monoclonal antibody suggest that these cells are capable of endocytosis of CT-2103 molecules. Using the anti-CT-2103 monoclonal antibody, immunohistochemical analysis of tumour and healthy tissues from CT-2103-treated murine and human tumour models confirmed this result. CT-2103 was taken up by tissue-associated macrophages in the reticuloendothelial system (liver, spleen and lung) and in tumour tissue.

In vitro studies to measure the toxic effect of CT-2103 against tumour cells have not been performed.

In vivo data show that CT-2103 is therapeutically active against a variety of carcinoma, also in conditions with substantial tumour load. In some models not only tumour growth delay was observed, but also cure was seen. Usually repeated treatments with CT-2103 are therapeutically more effective than a single treatment. CT-2103 is in most tested models therapeutically more effective than paclitaxel/cremophor, but in most cases when administered at much higher doses compared to paclitaxel/cremophor. No superiority of antitumour activity was demonstrated in lung carcinoma models for CT-2103 compared to paclitaxel/cremophor. Also intramuscular tumours were sensitive to iv injected CT-2103.

CT-2103 is therapeutically effective in both mdr + and mdr- tumours, whereas paclitaxel/cremophor is effective against mdr- tumours but not effective against mdr+ tumours.

Following *in vivo* combination studies of CT-2103 with carboplatin, doxorubicin, irinotecan and gemcitabine in Oca-1, a syngeneic mouse ovarian tumour demonstrated a synergistic antitumour effect of CT-2103 in combination with carboplatin, when CT-2103 was administered prior to carboplatin. Similarly, CT-2103 produced a supra-additive antitumour effect when co-administered with gemcitabine, doxorubicin, or irinotecan in a schedule-independent manner. The least effective combination was with gemcitabine.

Furthermore CT-2103 enhanced the response of both single and fractionated radiation therapy in different tumour models. With the exception of one study, the enhancement factor ranged from 1.3 to > 4, with most values above 2.65. In addition, unlike standard paclitaxel, CT-2103 did not sensitize the jejunum, skin, or hair follicles to the effect of radiation. Thus, its effect appeared to be tumour-specific.

Secondary pharmacodynamics of CT-2103 was not investigated. Pharmacodynamic effects of the active moiety paclitaxel are well known, however, no information was provided as to whether the PGA backbone might have relevant biological activities.

Safety pharmacology did not reveal substantial effect of CT-2103 on the cardiovascular and respiratory systems. Safety Pharmacology studies demonstrate that CT-2103 does not induce ECG alterations up to the highest tested dose (600 mg/m^2) in dogs. At this dose, a transient decrease in heart rate and blood pressure was observed. Evidence of dose and time dependent neuroxicity was seen after repeated administration in rats and dogs. In rats CT-2103 induced behavioural and (delayed) histopathological neurotoxic effects, while in dogs mostly histopathological effects were seen. The observed histopathological effects in both species consisted of nerve fibre degeneration of peripheral and central nervous system. No recovery and even aggravation of nerve fibre degeneration was seen after the recovery period with the exception of the 26-week dog study in which the severity and incidence of lesions appeared somewhat reduced after the 12-week recovery period.

Pharmacokinetics
The pharmacokinetics of CT-2103 and unconjugated paclitaxel have in general been well studied. The plasma pharmacokinetic of CT-2103 was assessed after single and repeated intravenous dose in the mouse, rat, rabbit and dog.

Analysis. The analysis of CT-2103 and unconjugated paclitaxel meet quality criteria. In many cases plasma concentrations of unconjugated paclitaxel could only be determined for a short period after dosing, due to the low concentration of unconjugated paclitaxel in plasma. The spontaneous release of unconjugated paclitaxel from CT-2103 has been investigated and solved by storing plasma samples on wet ice (during a few hours).

Absorption. The free paclitaxel concentration approximately follows the profile of the conjugated taxanes, but at a much lower level. The bi-exponential profile of the plasma pharmacokinetics of conjugated taxanes is profound. There is a fast initial decline of conjugated and unconjugated paclitaxel in plasma, followed by a phase in which there is almost no decrease in plasma concentration for days. During the first phase the drug is mainly restricted to plasma, showing a very limited distribution to tissues (with Vd approximating the total body water), in keeping with the polymeric structure of CT-2103. In the second phase, the polymer is slowly and progressively taken up by tissues. The plasma concentration of this second phase is usually higher after repeated dose than after single dose. C_{max} and AUC of both rat and dog increased approximately proportionately with the administered doses, although at the highest dose appeared greater than dose proportional in both species. No significant gender difference was seen in both species.

Distribution. After a single dose of CT-2103 radioactivity showed a prolonged retention in many tissues. Even after weeks considerable amounts of radioactivity are recovered in tissues (e.g. 21% of dose is found in dog liver 28 days after dosing). This indicates that after repeated dosing accumulation of CT-2103 or its metabolites in tissues is anticipated, even if the dosing interval is several weeks. No tissue distribution studies were performed after repeated administration. Thus accumulation in tissues was not investigated. Highest levels of accumulation are expected in liver and other tissues of the reticuloendothelial system (spleen, bone marrow, mesenteric lymph nodes). Nevertheless, accumulation in other tissues will also occur as elimination is very slow, although tissue distribution to other tissues is lower.
Differences were observed between males and females regarding the pharmacokinetic parameters in a range of tissues, with females showing a higher exposure in many tissues.

Paclitaxel. Poliglumex is transported to a limited amount across the placenta of pregnant rats. High concentrations of radioactivity were found in the ovaries and amnion of pregnant rats, but not in the whole fetus and in fetal blood. Placenta concentrations of radioactivity were lower than maternal plasma concentrations up to 8 hours but increased to levels above the maternal plasma concentration throughout the period of evaluation (48hr).
Large differences are observed between the distribution of CT-2103 to that of paclitaxel in Cremophor. Plasma AUC of paclitaxel is very low after dosing with CT-2103 compared with dosing with paclitaxel. However, in case of dosing with CT-2103, AUC values for total taxanes (including CT-2103), extractable taxanes (paclitaxel and its metabolites) and paclitaxel are higher in tumour tissue, but also in liver and spleen, and possibly also in other tissues. Thus, in case of dosing with CT-2103, systemic exposure to unconjugated paclitaxel is much lower, whereas tissue exposure is higher compared to dosing with paclitaxel in Cremophor. This should be considered when assessing the toxicity of CT-2103.
Plasma protein binding of CT-2103 has not been investigated.

Metabolism. The metabolism of CT-2103 involves the breakdown of the poly-(L)glutamic acid backbone and the biotransformation of the bioactive fragment molecule paclitaxel. Breakdown of the poly-(L)glutamic acid backbone is mediated by intracellular lysosomal proteases such as cathepsin B (carboxydipeptidase), but also cathepsin X (carboxymonopeptidase) and other endo- and exopeptidases. This enzymatic degradation occurs intracellulary. The role of cathepsin B as the primary enzyme responsible of CT-2103 biotransformation was confirmed *in vivo* in cathepsin B knock-out mice. The breakdown released paclitaxel as the primary biotransformation product, and to a minor extent other compounds such as mono- and diglutamyl paclitaxel (with either an –OH or $–NH_2$ terminus). However, the role of these enzymes for release of paclitaxel is unclear.

After cleavage of conjugated paclitaxel by cathepsins or other endopeptidases it is assumed that eventually free paclitaxel is formed, which in turn is assumed to be metabolised according to the recognized paclitaxel molecules through the hepatic CYP enzyme system. While assumption may be considered to be likely, differences in the metabolism of paclitaxel may occur due to location where free paclitaxel is formed, i.e. in intracellular lysosomes, in case of dosing with CT-2103.
In vivo studies show that limited amounts of metabolites are circulating in plasma when CT-2103 is administered to the animals. The excreta of animals, instead, mainly contain metabolites suggesting that CT-2103 is metabolized.
Metabolic profile in bile and urine in rats and dogs indicate that the polyglutamate backbone is subject to proteolysis and that mono- and di-glutamyl paclitaxel molecules, in addition to free paclitaxel, are present in excreta in relatively high concentrations. There is also evidence in the excreta that paclitaxel released from polyglutamate backbone undergoes subsequent metabolism to form the recognized paclitaxel metabolites: monohydroxy-paclitaxel, 10-deacetyl paclitaxel, 7-epi-paclitaxel, 7-epi-10-deacetyl paclitaxel, and Baccatin III. Hydrolysis of the benzene ring from paclitaxel yielded benzoic acid and its derivatives, hydroxybenzoic acid and benzoic acid conjugates (hippuric acid and benzoic acid glucuronide). The further biotransformation of paclitaxel is highly predictable to occur through hepatic CYP 450 enzyme system.

Excretion. Excretion of CT-2103 and/or its metabolites occurs mainly through bile and faeces. In line with the distribution data which showed a very slow decline in levels of radioactivity in many tissues, the amount of radioactivity that is retained in the tissues is considerable.
Limited excretion into milk of lactating females was seen. The AUC (0-120hr) of total radioactivity into milk represented only 4 % of the exposure in plasma in the same collection period.

Drug interactions. Interactions via protein binding are not expected.
In vitro and *in vivo* studies on drug interactions indicate that interaction of CT-2103 with a number of CYP enzymes is possible. Interaction with CYP2A6 is especially likely, and a warning for co-administration with drugs that are metabolized by CYP2A6 is included in the SPC.
Other likely interactions are those with drugs metabolized by CYP2C8 and CYP3A4, as CT-2103 is also metabolized by these enzymes.
No alteration of plasma protein binding of phenytoin, warfarin, naproxen or valproic acid was seen in the presence of 2-500 μg/ml of drug suggesting that CT-2103 has poor affinity for human plasma proteins.

Toxicology
The toxicity of CT-2103 was assessed following intravenous dosing in a number of studies including: single dose, repeat dose, and reproductive and developmental toxicity. In addition, genotoxicity and other toxicity studies (i.e., local tolerance, hypersensitivity-sensitization, immunogenicity, and hemolysis) were conducted. Single dose toxicity studies were conducted in mice, rats and dogs. Repeated dose toxicity studies were performed in rats and dogs with a dosing schedule similar to the proposed clinical administration schedule and route.

In the single dose toxicity studies, bone marrow suppression and lymphoid atrophy/necrosis in the blood forming organs, hepatocellular degeneration/necrosis, and mitosis/necrosis in the gastrointestinal tract were observed in all three species tested. Marked to severe degeneration/necrosis of the testes, and oligo/aspermia was seen in rodents. These changes were seen at doses prior to changes in clinical signs of toxicity and death. In the mice also tail lesions were seen which could indicate limited local tolerance. In general, excluding the greater sensitivity of the reproductive tracts of males in rodents, no marked differences were observed in the sensitivity of males and females.
Two different lots of CT-2103 were compared for their toxic effect in a single dose rat study. No marked differences in toxicity between the lots.

The repeated dose toxicity studies in both rats and dogs demonstrated effects in target organs similar to those observed in the single dose studies. In addition, repeated dosing resulted in male reproductive effects in the dog similar to those seen after single doses in rats and nerve fibre degeneration in the spinal cord and peripheral nerves was observed in both the rat and dog. No consistent differences were seen in target organ sensitivity of either gender. Complete or substantial recovery after cessation of dosing was most commonly seen for effects in the reticuloendothelial/hematopoietic tissues, gastrointestinal tract, and liver. Changes in the testes/epididymis and nerve fibre degeneration only infrequently showed improvement at the end of the

recovery period. Because of the delay in appearance of nerve fibre degeneration, this finding was commonly more severe at the end of recovery than at the end of treatment. Regarding the effects on adipose tissue seen in dogs further evaluation is requested by the applicant.

CT-2103 does not induce mutations in the Ames test, but CT-2103 was found to be clastogenic both *in vitro* and *in vivo*. The carcinogenic potential of CT-2103 has not been studied, which is agreed based on the life-expectancy of the indicated population and the unequivocal genotoxic effects. Based on the genotoxic potential of CT-2103, the compound can be presumed to be a carcinogen.

CT-2103 produced adverse effects on both male and female fertility in the rat as well as embryo-foetal development in the rat and rabbit. In the male fertility study, testicular toxicity was the most sensitive endpoint; consistent with the findings in the single and repeat dose toxicity studies. Testicular atrophy and oligo/aspermia in the epididymis were seen with daily dosing at doses as low as 2 mg/m^2 CT-2103 (0.8 mg/m^2 paclitaxel equivalents). The testicular effects resulted in a failure to produce litters at 32 mg/m^2 (12.2 mg/m^2 paclitaxel equivalents). In the female rat, administration of CT-2103 produced disruption of the normal estrus cycle, decreased corpora lutea and implantations, increased resorptions, a decreased fertility index, and a decreased number of live foetuses/litter only at 32 mg/m^2 (12.2 mg/m^2 paclitaxel equivalents), a dose associated with substantial maternal toxicity (mortality, signs of deterioration, multi-organ toxicity). Foetal effects resulting from CT-2103 administration to dams during embryo-foetal development exhibited some separation from maternal toxicity in the rabbit, but in the rat, foetal effects were observed only at doses associated with maternal toxicity. In rats embryo-foetal toxicity consisted of increased late foetal deaths, decreased foetal body weights, increased incidence of dwarfs, of foetuses with ventricular septal defects and of skeletal anomalies (of ribs and sternebrae), variations and decreased ossification. In rabbits maternal toxicity was observed from the lowest dose on (1.25 mg/m^2 CT-2103), while clear embryo/fetotoxicity (increased post-implantation loss, decreased foetal weight) and teratogenicity, consisting of e.g. cranioschisis, cleft face and several other (single and multiple) malformations, was seen at 20 mg/m^2 CT-2103. Increased incidence of slight foetal anomalies (small gallbladder) was seen at 5 mg/m^2 CT-2103. Furthermore, one foetus with a muscular foetal septum defect was seen at the lowest tested dose vs. 0 in the control group.
Considering the nature of the compound, it is acceptable that no data were provided on prenatal/postnatal development, and juvenile toxicity studies are not needed for the proposed indication.

CT-2103 causes local irritation. The microscopic findings of degeneration/necrosis, increased mitotic figures can be explained by the pharmacological action of CT-2103. Of note, local effects of injection have been seen in the mice single dose study.

A dose-dependent prolongation of PT and APTT and inhibition of platelet aggregation was seen in whole human blood *in vitro* at concentration ranging from 0.2 to 2 mg/ml. A further study demonstrated that CT-2103 is a weak, competitive inhibitor of Thrombin and Factor Xa (K_i 37 and 38 μM respectively), concentrations slightly higher than C_{max} measured in patients at the proposed clinical dose of 175 mg/m^2. Factors IXa, XIa and XIIa were not inhibited. These effects are likely due to the polyanionic structure of CT-2103, in which it resembles the heparin molecule. At a clinical dose of 175 mg/m^2, a 1.9 x prolongation of PT values and a 6.8 x prolongation of aPTT values can occur in *ex vivo* normal human plasma during the first 24-48 hrs post infusion.

CT-2103 did not induce active systemic anaphylaxis or reactive antibody formation in the guinea pig sensitization model. Neither poly-L-glutamic acid nor CT-2103 elicited a detectable specific antibody response in the rabbit immunogenicity model.

The applicant is asked to provide proper justifications for all impurities or adjust the specified limits.

For the environmental risk assessment, a refinement of Fpen was used, underpinned with data and the PECsurfacewater was below the action limit. The Applicant did not calculate the PEC surfacewater in accordance with the current guideline by taking into account the treatment schedule. In principle the guideline should be followed, however for this application the calculation of the applicant is accepted because the patient would not survive daily administration of the maximum daily dose. Therefore no Phase II risk assessment is needed. An experimental logKow is missing and needs to be performed.

III.3 Clinical aspects

Pharmacokinetics

CT-2103 is a soluble polymer conjugate of paclitaxel to poly-glutamic acid through an ester linkage. The conjugated paclitaxel is inactive, however, cleavage of this linkage slowly releases paclitaxel into the bloodstream and tissues. By this conjugation paclitaxel is made water soluble so that Cremophor EL solvent-based solution is not needed and may overcome many of the problems associated with cremophor containing paclitaxel formulations.

Taking into account the statement of the applicant that the quantity of paclitaxel contained in CT-2103 is not equivalent to paclitaxel, it is unacceptable to give dose recommendations for CT-2103 in terms of paclitaxel equivalents.

Pharmacokinetics properties of CT-2103 were studied in eight Phase 1 / 2 trials in patients with advanced cancers treated with CT-2103 as a single agent or in combination with cisplatin or carboplatin. Both single and multiple dose studies were performed. The pharmacokinetics of both the conjugated and unconjugated paclitaxel were determined.
The recommended dose of CT-2103 is 175 mg/m^2 administered as short intravenous infusion over 10 - 30 minutes every three weeks.

Analysis. Plasma concentrations of conjugated and unconjugated paclitaxel in plasma were determined by liquid chromatography - tandem mass spectrometry (LC/MS/MS). The applicant is requested to submit the validation report of the analytical method and to discuss the overestimation of plasma paclitaxel concentrations in three of the phase 1 studies due to incorrect sample preparation.

Bioavailability. CT-2103 is administered intravenously, therefore, no bioavailability studies have been conducted with the product.
Following a 10 to 30 min intravenous infusion, plasma concentrations of the conjugated paclitaxel declined bi-phasically. The initial phase lasts up to approximately 48-72 hr post administration, and then the terminal phase begins. Unconjugated paclitaxel plasma concentration declined over time in a biexponential fashion in parallel to the decline of conjugated paclitaxel. This suggests that the disposition of free paclitaxel is formation rate–limited its distribution and elimination depends on the release of paclitaxel from the polymeric backbone. The plasma concentrations of unconjugated paclitaxel were approximately 1% of the concentration of conjugated paclitaxel. In 4 patients with NSCLC administered the 175 mg/m^2 dose of CT-2103, mean C_{max} and AUC values were 90 µg/ml and 1162 µg/ml.hr for conjugated paclitaxel and 0.5 µg/ml and 6.6 µg/ml.hr for unconjugated paclitaxel, respectively.

Distribution. The distribution volume Vss ~4 L/m^2 suggests that CT-2103 is initially restricted to plasma compartment. At the terminal phase, the volume of distribution increased, Vz was ~40 L/ m^2, indicating a slow uptake in tissues. The blood –to–plasma distribution should be determined for CT-2103 and unconjugated paclitaxel.
Due to the high molecular weight of CT-2103 protein binding could not be determined. Protein displacement studies indicated that the potential of CT-2103 to affect the protein binding of other drugs seems low.

Metabolism. Preclinical studies indicated that paclitaxel is not released from the conjugate in the blood but the conjugate should be taken up by cells first. Subsequently paclitaxel is released by Cathepsin B, a lysosomal cysteine protease present in reticuloendothelial cells.
In clinical studies, the applicant has not studied any other compounds than CT-2103 and unconjugated paclitaxel assuming that paclitaxel generated by CT-2103 follows a similar metabolic pathway of Taxol. It is agreed that when unconjugated paclitaxel has become systemic available, it can be assumed that paclitaxel generated by CT-2103 follows a similar metabolism pathway as paclitaxel/Taxol. On the other hand, the altered pharmacokinetics and distribution of paclitaxel due to the slow release of paclitaxel from the conjugate inside tissues may affect the metabolism and excretion of paclitaxel. Therefore, differences in

overall metabolic fate of paclitaxel released from CT-2103 compared to cremophor containing paclitaxel formulations can not be excluded and the metabolic fate of paclitaxel should be examined.
Excretion/Elimination. Across all studies, the systemic plasma clearance of conjugated paclitaxel is low and ranges from 117 to 170 mL/hr/m^2 in the dose range from 175 to 270 mg/m^2 . The terminal elimination half-life of conjugated paclitaxel is long. At the 175 mg/m^2, the elimination half-life was 262 hr. The mean terminal half-life of unconjugated paclitaxel was 34 hr.
Approximately 10 % of the administered dose is excreted in the urine of which unconjugated paclitaxel accounted for approximately 3% of the administered dose. Most of the drug was excreted in the urine within the first 48 hours. Urinary excretion of conjugated and unconjugated was comparable when CT-2103 was administered as single agent or in combination with cisplatin or carboplatin.
The applicant did not conduct a mass balance study because pre-clinical data in rat and dog indicated that a substantial portion of the dose binds extensively to tissues, in dogs approximately 30% of the applied dose was retained in the body after 28 days, resulting in a very slow terminal elimination. If such a substantial part of CT-2103 is accumulated in tissues in man, this may raise concerns regarding safety compared to conventional paclitaxel formulations. A mass balance study during the first cycle of CT-2103 administration could provide information on the body accumulation of CT-2103 and should be considered.

Dose and time dependency. Systemic exposure to conjugated and unconjugated paclitaxel increased with the dose without a marked deviation from dose-linearity in the dose range 89-270 mg/m^2. Although at doses ≥200 mg/m^2, levels greater than the LLOQ may be still measurable 3 weeks after administration, there was no significant accumulation of conjugated and unconjugated paclitaxel after repeated dosing of CT-2103 once every three weeks.

Special populations. No controlled studies have been presented which investigate the effects of impaired organ function, age, gender or race. Based on the PK studies, there is no significant difference in pharmacokinetics of conjugated and unconjugated paclitaxel between females and males. The indicated population is likely to include elderly patients, patients with renal or hepatic impairment subjects. Elderly were included in the PK studies. Patients with bilirubin and creatinine levels up to twice the upper limit of normal were included in the clinical studies. The applicant is requested to evaluate the effect of age, race, creatinine clearance and bilirubin levels on the pharmacokinetics (AUC/dose or clearance) of conjugated and unconjugated paclitaxel.
Based on data with cremophor containing paclitaxel formulations, hepatic metabolism and excretion of paclitaxel and metabolites in the bile are the main elimination routes and patients with hepatic impairment have an increased risk for toxicity. Therefore, a study in patients with hepatic impairment should be conducted in order to propose appropriate dose modifications. Until such a study has been performed, the absence of this information should be included in the SPC and patients with severe hepatic impairment should not be treated with CT-2103.

Interactions. *In vitro* CYP inhibition studies using microsomes were conducted with CT-2103. CT-2103 is capable to inhibit many CYP enzymes but CYP2A6 (IC50 = 0.5 µg/ml), CYP2C8 (IC50 = 26 µg/ml) and CYP1A2 (IC50 = 30 µg/ml most prominently. The C_{max} value of CT-2103 at the 175 mg/m^2 dose was 90 µg/ml and the mean average plasma concentration of CT-2103 was 3.3 µg/ml. The applicant should discuss in more detail why based on the *in vitro* inhibition data important drug-drug-interactions are not expected to occur *in vivo.* Moreover CYP inhibition has been shown to occur in rat and dog *in vivo* studies.
No formal drug interaction studies have been performed with CT-2103 but in 3 studies CT-2103 has been co-administered with cisplatin or with carboplatin. There was a tendency of lower unconjugated paclitaxel exposure in the combination studies of CT-2103 with platinum agents compared to administration of CT-2103 alone (study PGT105), but this may have been due to very low paclitaxel plasma exposures in one study. Pharmacokinetics of carboplatin seemed not to be affected by co-administration with CT-2103.
In study CTI 1055, in 6 patients who were on warfarin therapy during treatment with the combination of CT-2103/cisplatin, R-and S-warfarin concentrations at steady-state were assessed. No increase in R- and S-warfarin concentrations was observed after CT-2103 administration. Thus there is no indication that CT-2103 inhibits the metabolism of R- and S-warfarin.
Paclitaxel is metabolised by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering CT-2103 concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, imidazole antifungals) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

CT-2103 is indicated for mono-therapy. CT-2103 should not be used in combination with other anticancer drugs without investigation of potential drug interactions.
Comparison with standard paclitaxel. No direct comparison between pharmacokinetics of paclitaxel released form CT-2103 and conventional, cremophor containing paclitaxel formulation has been performed. Comparison is based on literature data for Taxol. The pharmacokinetic profile of paclitaxel released from CT-2103 was clearly different from that of paclitaxel given as Taxol. Eventhough CT-2103 was administered as a 10 min infusion compared to 3h infusion for conventional paclitaxel, C_{max} was 10-fold lower after CT-2103 administration. The elimination half-life of paclitaxel when CT-2103 is given was about 20-40h and about 5-20h greater than when given as Taxol.The applicant claims that the AUC of paclitaxel upon CT-2103 175 mg/m^2 is similar to that of the same dose of conventional paclitaxel, however, based on the submitted data mean paclitaxel AUC values following CT-2103 administration seemed to be 20 to 60% decreased compared to paclitaxel AUC following equidoses of Taxol.
A mass balance study with CT-2103 was not conducted because pre-clinical data in rat and dog indicated that a substantial portion of the dose binds extensively to tissues, resulting in a very slow terminal elimination. If a substantial part of CT-2103 is accumulated in tissues, this may explain the apparent lower paclitaxel AUC following CT-2103 administration. The apparent lower paclitaxel exposure and potential tissue accumulation may raise concerns regarding efficacy and safety compared to conventional paclitaxel formulations. In study PGT303 where CT-2103 with carboplatin was compared with conventional paclitaxel with carboplatin, the onset of neuropathy with CT-2103 was delayed compared to paclitaxel but the frequency of grade 3 and 4 neuropathy was higher in the CT-2103 arm. The applicant hypothesised that the slower onset was due to accumulation of CT-2103 in tissue. No difference in overall survival between CT-2103 and conventional paclitaxel was observed in study PGT303 although the response rate was lower for CT-2103. Thus, it can not be excluded that differences in the pharmacokinetics of paclitaxel following CT-2103 vs. conventional paclitaxel may have consequences for clinical efficacy and safety.

In conclusion, by the conjugation to poly-glutamic acid, paclitaxel is made water soluble so that Cremophor EL solvent-based solution is not needed. Cremophor interacts with the pharmacology of paclitaxel. The conjugation also affects the pharmacokinetics of paclitaxel and, therefore, differences between conventional cremophor containing paclitaxel and CT-2103 are anticipated. However, biodistribution, excretion and metabolism of conjugated and unconjugated paclitaxel following CT-2103 administration have not been investigated in detail. The absence of a direct comparison between pharmacokinetics of paclitaxel released from CT-2103 and conventional, cremophor containing paclitaxel formulation and the incomplete data on excretion and metabolism of unconjugated and conjugated paclitaxel, hinders the full evaluation of the pharmacokinetics following CT-2103 administration.
As there appear to be differences in efficacy and safety between CT2103 and paclitaxel containing paclitaxel, potential tissue accumulation of CT-2103 and consequences for paclitaxel exposure should be further investigated. A mass balance study should be conducted. During the first cycle of CT-2103, the body retention, metabolic fate and excretion of CT-2103 could be examined and for unconjugated paclitaxel should also be performed. Furthermore, pharmacokinetics and pharmacodynamics of paclitaxel upon CT-2103 administration should be compared directly in a single, preferably cross-over, study with standard paclitaxel administration. In addition to this major deficiency some other concerns regarding evaluation of special populations, more information is required for patients with hepatic impairment.

Pharmacodynamics
Paclitaxel binds to β-tubulin, promotes the assembly of tubulin into microtubules, stabilizes the microtubules, prevents their disassembly, and eventually causes cell death. Paclitaxel has a broad spectrum of antitumoural activity e.g. breast, ovarian, NSCLC cancer and AIDS-KS. As paclitaxel is the active component of CT-2103, the applicant considers the pharmacodynamics of paclitaxel release from CT-2103 to be fundamentally the same as conventional paclitaxel formulations.
Given the physicochemical characteristics of CT-2103 and the major differences between CT-2103 and paclitaxel in pharmacokinetics, pharmacodynamics of CT-2103 has been extensively studied preclinically. In clinical settings, pharmacokinetic-pharmacodynamic relationship and haematological toxicity was evaluated in the phase 1 studies. Dose response for neuropathy has been addressed in the safety section of the clinical overview.
The potential relationship with haematological toxicity are mainly based on data from study PGT105, as this study included the most patients and different doses of CT-2103 were applied, because of the limited data available, pharmacokinetics was usually determined in a subset of patients. Neutropenia seemed to

correlate with the duration of paclitaxel concentrations above 0.05 μM and also with the exposure of both conjugated and unconjugated paclitaxel. At CT-2103 doses > 175 mg/m^2, the absolute neutrophil count (ANC)% was reduced more pronounced. No information on neutropenia upon repeated dosing was presented.
In the pivotal study PGT304, it was observed that at the 235 mg/m^2 dose, several deaths were related to infection and neutropenia or occurred at the time of the expected neutrophil nadir. This resulted in dose reduction to 175 mg/m^2 of CT-2103. Also in study PGT303, there was significantly more neutropenia in the CT-2103 (210 mg/m^2)/carboplatin arm compared to the Taxol (225 mg/m^2)/carboplatin arm. It appears that CT-2103 causes more neutropenia than conventional paclitaxel. As the plasma levels of paclitaxel may be above the threshold of 0.05 μM for a longer period of time compared to conventional Taxol, more neutropenia may occur with CT-2103. The PK-PD relationship for paclitaxel following CT-2103 and conventional paclitaxel should be compared in more detail.
No correlation was observed between drug exposure and thrombocytopenia.
A PK-PD correlation, which is not found for conventional paclitaxel formulations but is found for CT-2103, is the effect on coagulation. In patients treated with CT-2103, both as single agent and in combination with platinum agents, a transient increase in coagulation parameters PT, aPTT, PTT and thrombin time was observed, just after the administration of CT-2103. Values returned to baseline between 48-96 hours from CT-2103 administration. Patients may be at higher risk for bleeding during this time period. This may be of particular importance for patients who are receiving anticoagulant therapy such as warfarin and may be at increased risk for bleeding. While serious haemorrhage was observed in two patients on warfarin therapy in study PGT202, no increased incidence of serious haemorrhage was noted in any of the phase 3 studies. CT-2103 may be a non-competitive inhibitor of Factor Xa and thrombin. A warning for patients who are receiving anticoagulant therapy such as warfarin and who may be at increased risk for bleeding should be added to the SPC section 4.4.

Clinical efficacy
The Applicant seeks marketing authorization for CT-2103 at 175 mg/m^2 in 1st line monotherapy of patients with advanced NSCLC and ECOG PS 2.
Overall, the clinical development program of CT-2103 in NSCLC was based on 4 Phase III (PGT-302, PGT-303, PGT-304, PGT-305, all included in the so called STELLAR program) and two Phase II studies (PGT-202 and CTI-1069) (Table 2). The PGT-304 study is presented as pivotal, since only this trial supplies data over CT-2103 in a phase III randomised fashion with the dosage, the administration regimen and the target population as proposed in the MAA.
Of note, study PGT-305 (comparing CT-2103 versus conventional paclitaxel in the target population and at the dose proposed in the present MAA) was terminated early due to excessive rate of on-study deaths in the CT-2103 arm. Therefore, the protocol specified enrolment numbers were not met and the results were available only for safety.

Table 2 Clinical development program of CT-2103 in NSCLC.

					Number of patients		
Study	Phase	Line-therapy	PS	CT-2103 Dosages	CT-2103	Comparator	
PGT-304	III	1st	2	235 mg/m^2 1d q21d or 175 mg/m^2 1d q21d	191 (at dose 175 mg/m^2) + 96 (at dose 235 mg/m^2)	190	
PGT-303	III	1st	2	210 mg/m^2 1d q21d plus carboplatin AUC 6	199	201	
PGT-302	III	2nd	0-2	210 mg/m^2 1d q21d or 175 mg/m^2 1d q21d	25 (at dose 175 mg/m^2) + 402 (at dose 210 mg/m^2)	422	
CTI-1069	II	1st	2 or ≥ 70 ys	235 mg/m^2 1d q21d or 175 mg/m^2 1d q21d	28 (at dose 175 mg/m^2) + 2 (at dose 235 mg/m^2)	0	
PGT-202	II	1st	0-2	210 mg/m^2 1d q21d plus carboplatin AUC 6	73	0	
PGT-305	III	1st	2	175 mg/m^2 1d q21d	99 (Efficacy N/A)	101 (Efficacy N/A)	
Total					1115	914	
Available for efficacy					**920**	**813**	

Efficacy N/A: Efficacy data not available, results evaluated only for safety.

Dose-response studies

No formal dose-response studies of single-agent CT-2103 have been performed in patients with recurrent or advanced NSCLC and ECOG Performance Status 2. The proposed CT-2103 dosing-regimen of 175 mg/m^2 i.v. every 21 days was selected on the basis of the results of phase I dose-finding trials conducted in patients with various solid malignancies (study CTI-1052a; PGT-101; CTI-1055; CTI-1072), the phase I PGT-105 study conducted in PS 0-2 patients with NSCLC and on the basis of several phase II (study CTI-1069) and III studies (study PGT-302, PGT-303, PGT-304) amended for drug toxicity . In phase I dose escalation trials, conducted in patients with advanced solid tumours, the Maximum Tolerated Dose (MTD) of CT-2103 as a single agent administered every 21 days was 233 mg/m^2 (with DLT of grade 4 neutropenia) in CTI-1052a study, and 235 mg/m^2 in study PGT-101.

In combination regimens, the MTD of CT-2103 was 210 mg/m^2 (with DLT of neuropathy) in combination with cisplatin (study CTI-1055) or 225 mg/m^2 (with DLTs of neutropenia and thrombocytopenia) in combination with carboplatin (study CTI-1072).

Alternative dosing schedules, with other than 21 day treatment cycles were also investigated but the experience is limited (study CTI-1052b and PGT-102). However, these studies did not show a clear improvement in activity or safety of CT-2103 administered with a weekly or a 2 weekly-schedule compared with the proposed 3-weekly schedule.

Considering that a formal dose and schedule-defining procedure in NSCLC patients with PS 2 is lacking, the efficacy of CT-1203 at 175 mg/m^2 q3w as 1st line treatment, as employed in PGT-304 study, should be evaluated carefully in order to assure that the 175 mg/m^2 dose administered (amended from 235 mg/m^2 due to toxicity) results in acceptable activity as was claimed by the Applicant.

Main clinical studies

Study PGT-304

PGT-304 is a pivotal multi-center, multi-national, randomized, open-label, phase III trial comparing the efficacy and safety of CTI-2103 to that of gemcitabine or vinorelbine in chemotherapy-naïve patients with recurrent of advanced NSCLC and ECOG PS2. A total of 477 patients were randomized, 191 at the CT-2103 dose of 175 mg/m^2 (administered via 10-30 min i.v. infusion in 21 day-cycles) and 190 patients in the gemcitabine/vinorelbine arm (gemcitabine: 1000 mg/m^2 via 30 min i.v. infusion on day 1,8,15 every 28 day-cycles; vinorelbine: 30 mg/m^2 via 6-10 min i.v. infusion on day 1,8,15, every 21 day-cycles).

Other 96 patients (enrolled before amendment 3 was approved due to observation of a high rate of on-study deaths at time of the expected haematological nadirs) were treated at the CT-2103 dose of 235 mg/m^2.

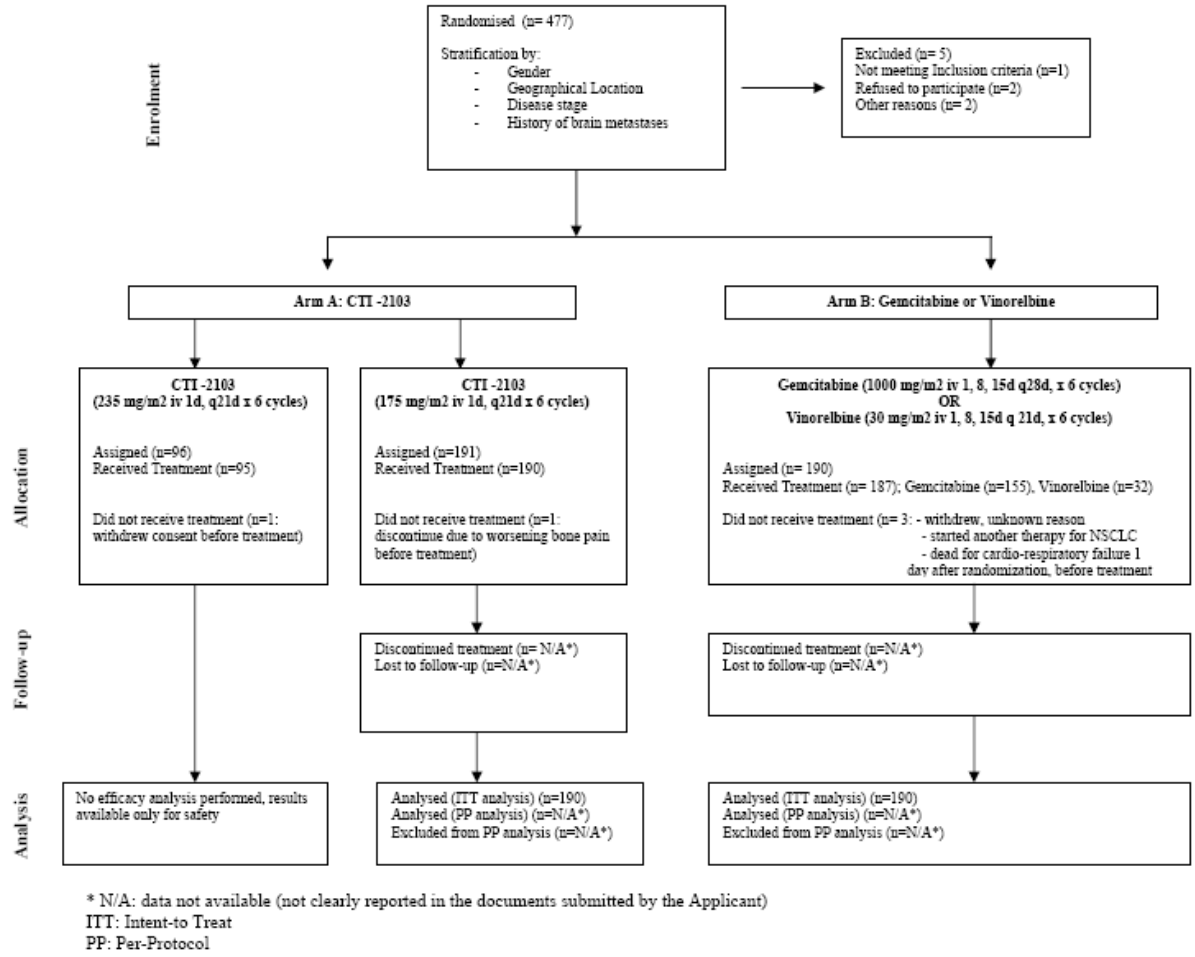
These patients were not evaluated for efficacy, but they were included in the safety analysis. Treatments were administered for up to 6 cycles. The PGT-304 study protocol allowed for up to 2 CT-2103 dose reductions (from 175 to 135 to 90 mg/m^2) for hematologic and non-hematologic toxicities. Dose adjustment guidelines for gemcitabine and vinorelbine were applied in compliance with the Gemzar and Navelbine package inserts, respectively.

Methodology (study PGT-304)
Study PGT-304 was originally designed as a superiority trial but, before termination and unblinding of the data, the protocol was amended to include a non-inferiority analysis with a fixed-margin method (and delta 1.1) as secondary analysis of the primary endpoint of efficacy. Overall Survival (OS) was the primary endpoint of the study. Secondary endpoints were time to progression (TTP), disease control, response rate, lung cancer symptoms evaluation (assessed with the FACT-LCS score) and safety.
After seeing the results of the study, the Applicant proposed a switch of the primary analysis from superiority to non-inferiority and also a shift of the non-inferiority margin from 1.1 to 1.2. Scientific Advice was issued by EMEA CHMP on these points on 2 June 2006. Based on specific arguments for switching from superiority to non-inferiority, this was considered in principle acceptable, but the CHMP underlined that the consideration over the switching to non-inferiority did "not involve any judgement on the choice of comparator regimens, nor of the non-inferiority margin". The design of the study is shown in Figure 2.

The active-control design of PGT-304 study is considered justified because, although currently there is no consensus over the standard therapy for patients with advanced NSCLC and poor performance status, there is increasing published evidence over the potential clinical benefit of chemotherapy in this subset of the population and recent international guidelines have addressed this issue (ELCWG guideline, 2007 www.elcwp.org/New/En/index.html; Pfister et al, 2004; Jett JR et al, 2007, NCCN guideline, www.nccn.org). Moreover, difficulties in conducting placebo-control trials in this population have been identified in recent clinical studies. These difficulties encompass the willingness of NSCLC patients to receive active treatment even in presence of a potential little benefit (Gridelli et al, 2004: Slevin ML et al, 1990; Silvestri G, et al, 1998).

However, regarding the switching of the primary efficacy analysis from superiority to non-inferiority, as decided by the Applicant, there are major concerns regarding the choice of the comparator (gemcitabine or vinorelbine), essentially due to the scanty historical data over the efficacy of gemcitabine or vinorelbine versus best supportive care (BSC) in patients with NSCLC and PS2. To date, the clinical benefit of vinorelbine and gemcitabine versus BSC in NSCLC has been addressed in only two trials: the ELVIS study and the study published by Anderson (ELVIS study group, 1999; Anderson H et al, 2000). Importantly, the study published by Anderson failed to show an improvement in survival for gemcitabine versus BSC. Moreover, besides that both trials were not specifically designed for PS 2 patients, only a small number of patients with poor PS were enrolled: only 37 of the 161 patients enrolled in ELVIS study had PS2. Also, the use of the Karnofsky scale to assess the performance status in the study published by Anderson led to considerable discrepancy in the proportion of patients identified to have PS2 (108 versus 215 patients) in two different recently published review articles. Furthermore, both studies (published by Anderson and ELVIS study) differed from the PGT-304 trial in terms of population enrolled (elderly PS 0-2 patients in ELVIS trial and patients with Karnofsky PS $\geq$ 60 in the study published by Anderson), dose and schedule of study drug administered, and methods to assess performance status (ECOG vs Karnofsky).

Figure 2 Design of study PGT-304



* N/A: data not available (not clearly reported in the documents submitted by the Applicant)
ITT: Intent-to Treat
PP: Per-Protocol

Baseline characteristics (PGT-304 study)

A total of 477 patients were randomized into the study: 287 in the CT-2103 group (96 patients at the dose of 235 mg/m^2 –before Protocol Amendment 3 was approved-, and 191 patients at the dose of 175 mg/m^2), and 190 in the gemcitabine/vinorelbine arm.

Patients were stratified based on gender (male, female); geographical location (United States of America, Western Europe and Canada, Rest of the World); disease stage (IV, other); history of brain metastases (yes, no).

The PGT-304 study population is comparable to the typical population of patients with advanced NSCLC for several aspects: the great majority of patients were males (72%), Caucasian (90%), with a median age of 62 years (range, 35-90 yr), histopatologic diagnosis of squamous cell (49%) or adenocarcinoma (35%), stage IV disease at original diagnosis (68%) and a smoking history (82%). Around 67% of the population studied had no weight loss ≥ 5% within 6 months before study entry. Baseline characteristics are shown in Table 3. However, an important difference with the 'general' population with NSCLC is that patients with PS2 who require systemic therapy in clinical practice would include those with significant hepatic or renal co-morbidities, with neuropathy, with unstable medical conditions, and with non pre-treated brain metastases. These patients were not enrolled in PGT-304 study. These findings raise concerns on the extrapolation of the results to the total PS2 patient population with NSCLC requiring systemic therapy in clinical practice, as can be anticipated upon in view of the currently proposed indication ("1st line monotherapy of patients with advanced NSCLC and ECOG PS 2 ").

No obvious imbalances between the CT-2103 and the control arms were observed in some demographic and baseline characteristics as evaluated. Minor differences in demographic and baseline characteristics between treatment arms were observed in terms of percentage of patients with squamous cell histology and

time from diagnosis to randomization, whereas statistically significant differences are observed between the two study treatments regarding geographic regions, raising concerns over the appropriateness of the stratification method. The issue is relevant, considering that in the subgroup analysis over OS within geographical regions, the HR observed varied by region, with a HR of 0.70 (95% CI 0.34, 1.43) in the US region, versus a HR of 1.29 (95% CI 0.65, 2.57) observed in Western Europe and Canada.
Of note, in the list of concomitant medications (likely during study treatment) it appears that more patients in the gemcitabine/vinorelbine arm were taking analgesics (36% vs 45%, and in particular opioid preparations), antiemetics (7% vs 17%), antihistaminergic compounds (6% vs 9%), antithrombotic/anticoagulants (12% vs 20%), cardioactive medications (beta-blockers, digitalis and other antiarrhythmics, diuretica, vasodilatants) and agents for gastrointestinal disorders. However, no data have been provided by the Applicant in the Day 120 response document over the number, severity and distribution of co-morbidities in the PGT-304 study population as well as over the use of medications at time of enrolment. These data are considered particularly relevant in the heterogeneous poor performance status population, because patients may be classified as PS2 because of significant tumour-related symptoms or because of other co-morbidities. These two components may contribute in a very variable fashion to the definition of poor PS. As a consequence, while the administration of systemic chemotherapy might be relevant in reducing symptoms due to cancer (thus improving the clinical benefit), it might have a negligible effect or being potentially harmful in patients with severe co-morbidities from other causes.

Table 3 Demographic and baseline characteristics by treatment arms in study PGT-304.

	CT-2103 (175 mg/m^2) (N=191)	Gemcitabine or Vinorelbine (N=190)	CT-2103 (235 mg/m^2) (N=96)
Gender			
Male	142 (74.3%)	134 (70.5%)	66 (68.8%)
Female	49 (25.7%)	56 (29.5%)	30 (31.3%)
Race Category			
Caucasian	170 (89.0%)	170 (89.5%)	89 (92.7%)
Black	3 (1.6%)	9 (4.7%)	2 (2.1%)
Asian	2 (1.0%)	1 (0.5%)	0 (0%)
Hispanic	13 (6.8%)	7 (3.7%)	1 (1.0%)
Other	3 (1.6%)	3 (1.6%)	4 (4.2%)
Age at Randomization			
n	191	190	96
Mean (std)	61.4 (9.85)	62.8 (10.29)	63.8 (10.39)
Median (range)	61.0 (36-86)	64.0 (30-90)	65.0 (35-87)
Geographic Location Code			
US	16 (8.4%)	24 (12.6%)	16 (16.7%)
W. EU and Canada	16 (8.4%)	25 (13.2%)	20 (20.8%)
ROW	159 (83.2%)	141 (74.2%)	60 (62.5%)
Stage at Randomization			
IIIa	1 (<1%)	2 (1%)	2 (2%)
IIIb	60 (31%)	59 (31%)	28 (29%)
IV	130 (68%)	129 (68%)	66 (69%)
History of Brain Metastases			
Yes	6 (3%)	6 (3%)	5 (5%)
No	185 (97%)	184 (97%)	91 (95%)

Efficacy Results (study PGT-304)

Primary Objective: Overall Survival (OS)
The analysis was based on 294 observed events, 141 in the CT-2103 and 153 in the gemcitabine/vinorelbine arm.
In the ITT population there was no significant difference in OS between treatment arms (HR=0.95, 95% CI 0.76-1.2, p=0.686). The median OS was 220 days (95% CI: 198-263) in the CT-2103 arm and 198 days (95% CI: 173-220) in the comparator arm, with an estimated 1- year OS rate of 26% in both groups. The estimated 2-year survival rate was higher in the CT-2103 arm (15%) compared to the control arm (10%)

Table 4; Figure 3).
According to the Cox model, indicators of disease status and specific co-morbidities were predictors of survival across the models. The results were consistent with or without treatment included in the model.

Figure 3 Kaplan-Meier Plot of OS (ITT Population) in study PGT-304

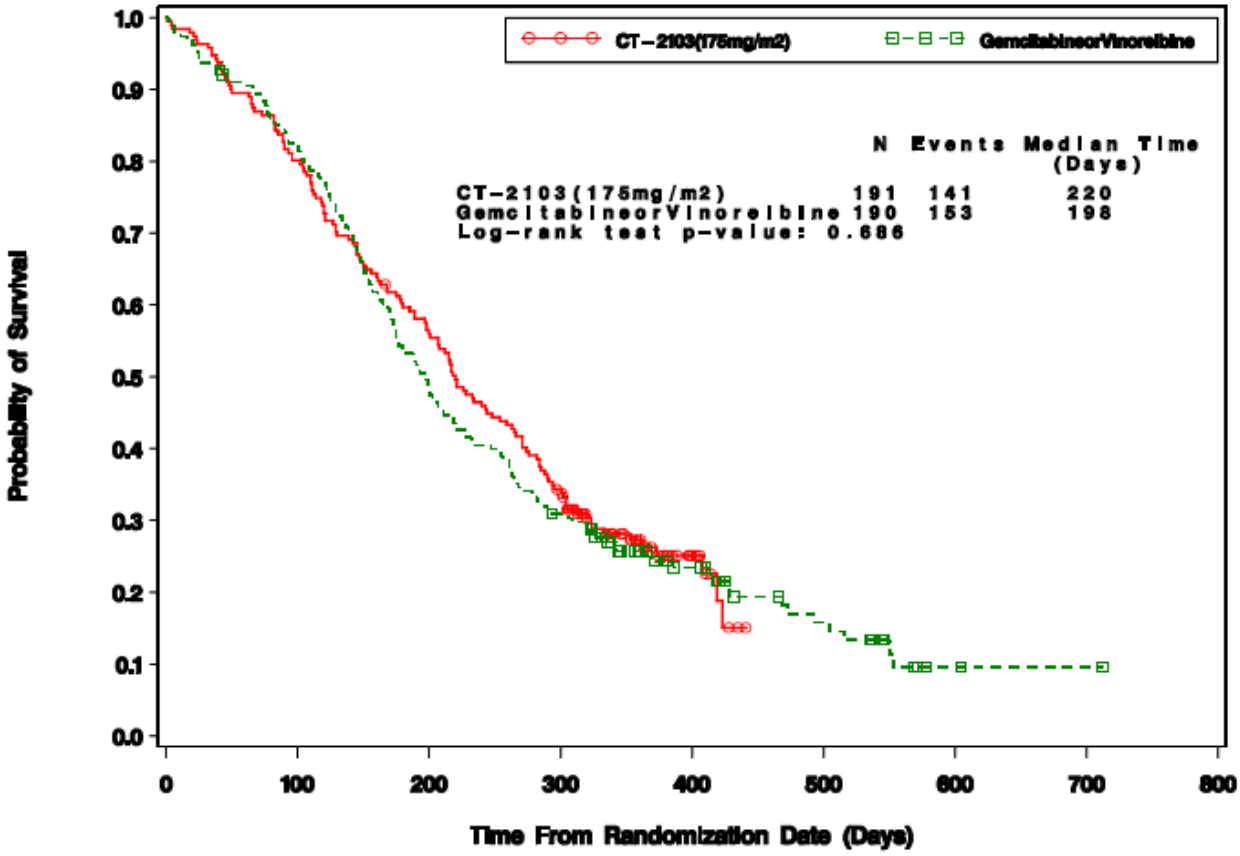


Table 4 Summary of Primary and Secondary Endpoint Results in study PGT-304

Endpoint	CT-2103 (n =191)	Gemcitabine or Vinorelbine (n =190)	p – Value (Log-rank)
Primary			
Median Overall Survival, days (95% C.I.)	220 (198, 263)	198 (173, 220)	0.686
Hazard ratio	0.95 (0.76, 1.20)		
Secondary			
Disease control (95% CI)	52% (45%, 59%)	59% (52%, 67%)	0.149
Tumor Response (95% CI) (CR+PR)	11% (6%, 16%)	15% (10%, 21%)	0.210
TTP (days)	87	107	0.480
Hazard ratio	1.08 (0.87, 1.33)		

C.I. = confidence interval, CR = complete response, PR = partial response, TTP = time to progression

Non-inferiority analysis

The Statistical Analysis Plan (SAP) of study PGT-304, stated that a non-inferiority analysis would have been performed using a fixed-margin non-inferiority test with a delta of 1.1, meaning that non-inferiority would have been accepted if CT-2103 did not increase the hazard of death by more than 10% compared to the control.

Nevertheless, the pivotal study results yielded a HR of 0.95 with 95% CI: 0.76-1.20, thus non-inferiority was not met according to the analysis specified in the SAP; non-inferiority would have been demonstrated only if the entire 95% CI for the HR would have been below 1.1.

After seeing the results the Applicant proposed a switch of the primary efficacy analysis from superiority to non-inferiority, and a shift of the non-inferiority margin from 1.1 to 1.2.

As reported above, during SA issued on 1 June 2006 on these issues, the CHMP stated that the switch to non-inferiority proposed by the Applicant could in principle be justified, but it was underlined that the advice did not involve any judgment on the choice of the comparators. In addition, the CHMP could not decide whether the shift of delta to 1.2 would have been acceptable, due to insufficient data provided by the Applicant over the safety profile of the drug.

The CHMP considers the switch to non-inferiority not justified because of serious concerns relating to the appropriateness of the comparator to support a non-inferiority claim. Indeed, as already outlined in the section "Methodology of PGT-304 study", the only two small studies assessing the clinical benefit of gemcitabine or vinorelbine versus best supportive care (BSC) were not specifically designed for PS2 patients, enrolled a very limited amount of PS2 patients and significantly differ from the PGT-304 in terms of study population, dose and schedule of study drug administered, and methods to assess performance status (ECOG vs Karnofsky). Moreover, the only study published to date evaluating gemcitabine vs BSC failed to show superiority of gemcitabine over BSC in terms of OS; this is relevant, considering that the majority of patients (155/187, 84%) enrolled in the control arm of study PGT-304 were treated with gemcitabine. Moreover, the lack of assay sensitivity of PGT-304 study and the absence of results obtained in per-protocol analysis, further demonstrates the inappropriateness of the proposed switch (refer to CPMP/EWP/482/99).

Moreover, in view of the CHMP the shift of delta from 1.1 to 1.2 is also insufficiently justified, since this shift would imply acceptance of a difference in OS of 42 days (instead of 17-24 days) between the two study arms. This difference is by principle not negligible in view of the low life expectancy of the poor performance status population with NSCLC, and could be considered acceptable, according also to the scientific advice, only in view of a clear superiority of the CT-2103 over comparator in terms of quality of life and safety profile, superiority that has not been demonstrated yet by CT-2103 in any of all the phase III studies performed in patients with NSCLC and PS2.

In addition to the non-inferiority analysis specified by the SAP, the Applicant claimed non-inferiority using the fraction retention method (with δ=0.5) and activity of CT-2103 over placebo using an indirect comparison to placebo method (as proposed by Gaffney). Besides that the two analyses were not specified in the SAP, and, as outlined also by the CHMP during SA, the fraction retention method is usually not recommended, and particularly in this case due to the scanty historical data demonstrating activity of the comparator over BSC, both analyses are not considered acceptable because they were based on historical data consisting of one small study evaluating the effect of vinorelbine versus BSC (ELVIS trial), whereas in PGT-304 study the great majority of patients enrolled in the comparator arm were treated with gemcitabine (83%). In addition, as already reported above, in ELVIS trial only 24% (37/161) of patients had ECOG PS2, all patients enrolled were >70 years, and dose and schedule of vinorelbine administered significantly differed from the ones used in PGT-304 study.

Secondary endpoints: TTP, Response Rate, Disease Control, Duration of tumour response, cancer related symptoms score (FACT-LCS) (study PGT-304)

From the analysis of the secondary endpoints evaluated in the ITT population of PGT-304 study no statistically significantly difference was found between the CT-2103 and the gemcitabine/vinorelbine arm in terms of:

-Time to progression (TTP) (mean TTP 87 days [95% CI: 81-122] *vs* 107 days [95% CI: 87-112], respectively; HR=1.08, p=0.480),

-Response Rate (PR+CR), according to RECIST CRITERIA (11% *vs* 15%, respectively; p=0.210),

-Disease Control, defined as the percentage of patients alive without documented disease progression for at least 12 weeks (52% *vs* 59%, respectively; p=0.149),

-Duration of tumour response, defined as the time between the date of the first assessment of PR or CR and the date of assessment of Disease Progression [PD]), (median 96 days *vs* 107 days, respectively, p=0.472)
-FACT-LCS score (Cancer related symptoms score).

Also, the analysis of the secondary endpoints of the study is biased by the absence of an external, blinded and independent review committee for the evaluation of progression events, by the significant difference in cycle length between different treatments (q3w for vinorelbine treatment and CT-2103 versus q4w for gemcitabine treatment). This must be considered to have affected timing of the radiological and clinical assessments. Also the lack of planned follow-up intervals to control for TTP variability in the study protocol, and the open-label design of the study may have introduced discrepancies and bias that could have influenced the results. Indeed, no sensitivity analyses have been performed by the applicant in order to explore the potential effects of assessment and investigator bias, that could have supported the robustness and the reliability of the results.

Ancillary analyses (study PGT-304)

Sensitivity analyses

A sensitivity analysis was conducted by the Applicant consisting in simulations for study PGT-304. A random sample of 40 patients (10% of patients enrolled into the study) was removed and the primary endpoint was evaluated. This simulation was repeated 1000 times without significant discrepancies in results. On this basis, the Applicant states that the results are robust. An analogous analysis was conducted also for the supportive studies (PGT-303, PGT-302) with similar results. However the analysis, as outlined also by scientific advice issued on 1 June 2006, does not address the more important issue of assay sensitivity, i.e. whether the study is capable of showing differences, if they exist.

Post-hoc analyses

Subgroup analyses were performed by the Applicant according to the SAP for the randomization strata (gender, geographic location, disease stage, history of brain metastases) and predefined baseline prognostic factors. No statistically significant difference in term of OS was found between the two arms for each of the factor analyzed, with the exception of patients with brain metastases where OS was significantly longer in CT-2103 arm. A trend versus improved OS was also found in the CT-2103 arm in women overall and in the subgroup with age <55 years. However, the very limited number of patients used in the analyses precludes any meaningful conclusion.

Clinical studies in special populations

CT-2103 has not been studied in children (< 18 years) or in pregnant or lactating women.
Moreover to date, the effect of hepatic or renal impairment on CT-2103 pharmacokinetics, disposition and safety has not been studied in patients. Indeed, patients with hepatic impairment have been excluded by trials performed with CT-2103, considering that paclitaxel is metabolized by the CYP system and largely excreted by the biliary pathway, and that high plasma levels and increased myelosuppression have been seen in patients with hepatic impairment treated with paclitaxel.

Analysis performed across trials (pooled analyses AND meta-analysis)

A meta-analysis of non-inferiority using as delta 1.1 was performed by the Applicant according to the Peto method and employing the totality of data obtained in the phase III STELLAR program (PGT-302, PGT-303, PGT-304), in order to assess the overall treatment effect of CT-2103. The analysis yielded an estimate of the overall hazard ratio of CT-2103: Control for all 3 studies (PGT-302, PGT-303, PGT-304) of 0.98 (0.88,1.09) thus fitting the criteria of non-inferiority according to delta 1.1.
However, according also to the scientific advice, the meta-analysis performed is not according to "CPMP Points to consider on applications with 1.Meta-analysis; 2. One pivotal trial" (CPMP/EWP/2330/99) and therefore it cannot be used for a marketing claim. Moreover, the remarkable heterogeneity of the studies used (in terms of study population and CT-2103 dose) makes the result highly questionable.

Supportive studies

The Applicant has submitted other 2 phase III studies (PGT-302 and PGT-303) and two phase II (CTI-1069, PGT-202) trials that can be considered supportive at best, because they differ from the marketing claim in terms of study population, dose administered line of therapy. Indeed, the evidence coming from the two phase II studies (PGT-202 and CTI-1069) is limited, because in both trials only 12 patients had

PS2, and in PGT-202 study CT-2103 was administered in combination with carboplatin (AUC6) and at dose of 210 mg/m^2.

Study PGT-305 should be mentioned also. PGT-305 study was a multicenter, open-label, phase III study to compare efficacy and safety of CT-2103 (175 mg/m^2 on day 1, every 21-day cycles) versus paclitaxel (175 mg/m^2 on day 1, every 21-day cycles) when administered as 1st line chemotherapy to female patients with advanced NSCLC and PS2. Although 600 women were planned to be enrolled, the study was stopped early after the randomization of 200 women (99 in the CT-2103 arm and 101 in the paclitaxel arm), based on a difference in on-study deaths between arms (17 deaths in the CT-2103 arm and 2 deaths in the paclitaxel arm). After final data collection, the ratio was 18 to 8 (due in part to the late reporting of some on-study deaths in the paclitaxel arm), a difference not statistically significant anymore. However, the rate of non-study deaths in CT-2103 arm was still numerically higher than the control arm, and, importantly, the rate was significantly higher compared with the rate of on-study deaths reported in the CT-2103 arm of PGT-304 study. All patients were discontinued from study treatment on the same date, therefore, most patients did not receive the protocol defined treatment. For these reasons, interpretation of the efficacy analyses was considered not possible by the Applicant. Results were presented only for safety.

Study PGT-302

Study PGT-302 was a randomized open-label study performed in 2nd line therapy of patients with NSCLC and PS 0-2 in order to evaluate efficacy of single-agent CT-2103 administered at 210 mg/m^2 dose every 21 days versus docetaxel 75 mg/m^2 every 21 days. The study was designed as a superiority trial. Of the 849 PS 0-2 patients recruited, the last 25 PS 2 patients (enrolled after the study was amended due to safety concerns) were treated with an initial CT-2103 dose of 175 mg/m^2. Median OS (primary endpoint) was 206 days in both study arms (HR= 1.09; p=0.257); 1- and 2-year estimated survival rates were similar between treatment groups.

Although the SAP did not pre-specify a non-inferiority analysis, the same analyses that were done for studies PGT-303 and PGT304 to show non-inferiority have been performed for PGT-302 by the Applicant, but importantly, the switch to non-inferiority has not been justified by the Applicant.

Non-inferiority was not met according to the fixed-margin method, using a non-inferiority margin of 1.1; indeed, the PGT-302 study results yielded a HR of 1.09 (95% CI: 0.94, 1.27).

Non-inferiority of CT-2103 to comparator (docetaxel) was not met using the fraction-retention method (Rothmann procedure) (p-value= 0.157 and 0.13 in two analyses).

The activity of CT-2103 over placebo using PGT-302 data was evaluated by the Applicant. In the results estimation of activity of CT-2103 over placebo analysis (using the method of Gaffney) the HR (CT-1203: placebo)= 0.61 (95% CI: 0.38, 0.98) was claimed to be supporting the activity of CT-2103 in the target population. However, the appropriateness of the historical data used is highly questionable because they consisted in one study comparing two different dosing regimen of docetaxel (100 and 75 mg/m^2) versus BSC but only 25% of patients enrolled (49/204) had PS2.

From the analysis of the secondary endpoints of PGT-302 study, median TTP was longer in the docetaxel arm (78 days, 95% CI: 63-84) than in the CT-2103 arm (60 days, 95% CI: 50-77), but the difference was not statistically significant (p=0.075), whereas men in the docetaxel arm had a significantly longer median TTP than in the CT-2103 arm (78 vs 51 days, respectively, HR=1.2, p=0.025). Tumour Response Rate (CR + PR) was significantly lower in CT-2103 arm compared with the comparator (8% vs 13%, respectively, p=0.039). Disease control and evaluation of cancer related symptoms (by FACT-LCS score) did not show any significant superiority of CT-2103 over placebo. (Table 5)

Table 5 Summary of Primary and Secondary Endpoint Results for study PGT302

	CT-2103 N=427	Docetaxel N=427	P – Value (Log-rank)
Primary Endpoint			
Median Overall Survival, days (95% CI)	206 (182, 235)	206 (179, 239)	0.257
Hazard ratio	1.09 (0.94, 1.27)		
Secondary Endpoint			
Disease control (95% CI)	40% (35%, 44%)	45% (40%, 50%)	0.096
Tumor Response (95% CI) (CR+PR)	8% (6%, 12%)	13% (10%, 17%)	0.039
TTP (days)	60 (50, 77)	78 (63, 84)	0.075
Hazard ratio	1.13 (0.99, 1.30)		

C.I. = confidence interval, CR = complete response, PR = partial response, TTP = time to progression

Study PGT-303

Study PGT-303 was a randomized open-label study conducted in 1st line therapy of patients with advanced NSCLC and PS 2 in order to compare efficacy and safety of CT-2103 administered at 210 mg/m^2 dose in combination with carboplatin (at AUC 6) every 21 days, versus the combination paclitaxel/carboplatin. Of note, PGT-303 trial presented similar design, identical primary and secondary endpoints, inclusion and exclusion criteria, and was conducted in similar geographic regions were study PGT-304 was performed. Similarly to PGT-304 study, PGT-303 was designed as a superiority trial but the SAP was amended before data were unblinded to include a non-inferiority analysis (with fixed margin of 1.1) as secondary analysis of the primary endpoint of the study. After seeing the results the Applicant proposed a switch of the primary analysis from superiority to non-inferiority, and a shift of the fixed non-inferiority margin from 1.1 to 1.2.

Nevertheless, PGT-303 study failed to show survival superiority of the CT-2103/carboplatin arm over the comparator: median OS was 237 days versus 239 days, respectively (HR=0.97, log rank p=0.769; 95% CI: 0.78-1.21). The estimated 1 year overall survival rate was the same in both arms (31%).

In the non-inferiority analysis, non-inferiority was not met according to the fixed-margin method, using the pre-specified delta of 1.1 (HR=0.97; 95% CI: 0.78-1.21). According to the Applicant, non-inferiority of CT-2103/carboplatin to comparator was established using the fraction retention method (with δ=0.5); moreover, activity of CT-2103/carboplatin over placebo was claimed by the Applicant using the indirect comparison method described by Gaffney. However, the latter two analyses were not specified in the SAP; moreover, the appropriateness of the historical data used in the two methods is questionable, primarily due to scanty historical data.

From the analysis of the secondary endpoints of PGT-303 study: TTP, Disease control and Duration of tumour response were not statistically significantly different between treatment arms, whereas Tumour Response Rate (CR+PR) was significantly lower in the CT-2103/carboplatin (20%) compared to paclitaxel/carboplatin (37%) (p=0.0012). Overall, no significant differences were found between treatment groups in the evaluation of cancer related symptoms (FACT-LCS score). (Table 6)

Table 6 Summary of Primary and Secondary Endpoint Results for study PGT-303

	CT-2103 + carboplatin (n =199)	Paclitaxel + carboplatin (n =201)	p – Value (Log-rank)
Primary endpoint			
Median Overall Survival, days (95% CI)	237 (205, 271)	239 (206, 287)	0.769
Hazard ratio	0.97 (0.78, 1.21)		
Secondary			
Disease control (95% CI)	64% (57%, 70%)	69% (62%, 75%)	0.342
Tumor Response (95% CI) (CR+PR)	20% (15%, 27%)	37% (30%, 44%)	<0.001
TTP (days)	118 (100, 129)	139 (118, 156)	0.210
Hazard ratio (95% CI)	1.14 (0.93,1.40)		

C.I. = confidence interval, CR = complete response, PR = partial response, TTP = time to progression

Clinical safety

A total of 1701 patients who received at least one dose of CT-2103 in 17 clinical phase I, II and III studies and in different type of tumours have been analyzed, including data from 1153 patients enrolled in 7 clinical studies performed in NSCLC (Table 7).
Safety analyses are focused on the data available for the target population, represented by 1st-line, advanced NSCLC patients with PS2, and treated with the target dose (175 mg/m^2). Such data come essentially by the safety analysis of the pivotal PGT-304 study. The safety analysis of study PGT-305 was kept in careful consideration too, in particular the analysis of on-study deaths that led to early termination of the study. The safety of CT-2103 administered in combination regimen in the PGT-303 study was also reported.

Table 7 Overall Extent of Exposure to Study Drug

		Extent of exposure to study drug			Exposure to CT-2103 by dose		
		N. Patients			N. Patients		
Study Type	N. Studies	Dosage(s)	CT-2103	Comparator	≤175 mg/m^2	176 to 210 mg/m^2	>210 mg/m^2
Clinical Pharmacology/ Pharmacokinetic Studies	7	<175 to 270 mg/m^2	196	-	18 (3 +cisplat 3 +carbo)	95 (24 +cisplat 10 +carbo)	83 (16 +cisplat 9 +carbo)
Phase I/II Studies in Ovarian Cancer	5	175 to 235 mg/m^2	293	3	242 (65 +carbo)	20 (20 +carbo)	31
Phase I/II NSCLC[a]	3	175 to 270 mg/m^2	130	-	34	82 (73 +carbo)	14
PGT-302[b]	1	175 to 210 mg/m^2	422	416	25	397	-
PGT-303[c]	1	210 mg/m^2	199	201	-	199 (+carbo)	-
PGT-304[d]	1	175 mg/m^2 235 mg/m^2	190 95	187	190	-	95
PGT-305[e]	1	175 mg/m2	98	97	98	-	-
Other Clinical Studies[f]	4	20 to 80 mg/m^2	76	-	65 (39 +RT)	11	-
Total	23		1699	904	672	804	223

[a] This includes studies PGT-105, PGT-202, and CTI-1069.
[b] Study PGT-302 (phase III): CT-2103 versus docetaxel in 2nd line therapy in patients with NSCLC and PS0-2.
[c] Study PGT-303 (phase III): CT-2103/carboplatin versus paclitaxel/carboplatin in 1st line therapy in patients with NSCLC and PS2.
[d] Study PGT-304 (phase III): CT-2103 versus gemcitabine or vinorelbine in 1st line therapy in patients with NSCLC and PS2.
[e] Study PGT-305 (phase III): CT-2103 (175 mg/m^2) versus paclitaxel (175 mg/m^2) in 1st line chemotherapy in women with advanced NSCLC and PS2. The study was early terminated due to safety concerns.
[f] This includes studies PGT-103 and PGT-104 evaluating CT-2103 in combination with radiotherapy and studies PGT-102 and CTI-1052b evaluating weekly administration of CT-2103.

Patient exposure
In study PGT-304, 190 patients received 175 mg/m^2 of CT-2103, and 187 patients received either gemcitabine or vinorelbine. Other 95 patients enrolled before Protocol Amendment 3 was approved received CT-2103 at 235 mg/m^2; the amendment was done in view of the increased incidence of deaths in patients treated at 235 mg/m^2 dose, co-incident with the expected time of the white blood cell and neutrophil nadirs. The median number of cycles administered was 4 for CT-2103 at 175 mg/m^2 and 3.5 for the gemcitabine/vinorelbine arm. More patients received 6 cycles of treatment in the CT-2103 arm than in the comparator arm (38% vs. 23%, p = 0.002). The mean cumulative dose administered was 681.1 mg/m^2 for CT-2103, 10327 mg/m^2 for gemcitabine and 200 mg/m^2 for vinorelbine. Median dose intensities by cycle were generally stable relative to the planned dose in both the CT-2103 treatment and the comparator arms. (Table 7)

Adverse events (AEs)
Adverse events were coded using MedDRA 5.1 and graded using the National Cancer Institute Common Toxicity Criteria (version 2).
In study PGT-304 the frequency of adverse events (AEs) regardless of relationship was similar between treatment arms (93% in the CT-2103 arm versus 96% in the comparator arm) (Table 8). More treatment related AEs and more grade 3 or 4 AEs occurred in the comparator arm (67% and 63%, respectively) compared with CT-2103 arm (55% and 52%, respectively). However, the percentage of patients with serious AEs and with AEs leading to withdrawal was not statistically significant between treatment arms (p= 0.057 and p=0.213, respectively).

Table 8 Summary of Treatment Emergent AEs in study PGT-304

	CT-2103 (N=190)	Gemcitabine or Vinorelbine (N=187)	P-Value*
Subjects with AEs	176 (93%)	179 (96%)	0.272
Subjects with Treatment-Related AEs	104 (55%)	126 (67%)	0.015
Subjects with Grade 3 or 4 AEs	98 (52%)	117 (63%)	0.037
Subjects with Grade 3or 4 and Related	30 (16%)	42 (22%)	0.116
Subjects with Serious AEs	49 (26%)	66 (35%)	0.057
Subjects with Serious Related AEs	9 (5%)	9 (5%)	1.000
Subjects with AEs Leading to Withdrawal	100 (53%)	111 (59%)	0.213
Subjects with Related AEs Leading to Withdrawal	10 (5%)	12 (6%)	0.666

* P-value based on Fisher's exact test.

Consistent with the expected pharmacology of the drug and the population treated, the most commonly reported (>10%) AEs of all severities regardless of relationship in the CT-2103 arm in PGT-304 study were primary tumour-related (malignant neoplasm progression [52%], dyspnoea [22%]), gastrointestinal (nausea [19%], vomiting [8%], constipation [7%]), neurological (peripheral neuropathy [16%]) and haematological (anaemia [14%], neutropenia [6%]). Fatigue (16%), infections (16%), anorexia (14%), asthenia (11%), and chest pain (11%) were also reported. (Table 9)
The comparator arm had a significantly higher frequency of anaemia (36% vs 14%), neutropenia (14% vs 6%), nausea (29% vs 19%), vomiting (17% vs 8%), constipation (14% vs 7%), fatigue (25% vs 16%), pyrexia (17% vs 9%), and peripheral oedema (12% vs 4%).
In contrast, peripheral neuropathy occurred at a significantly higher frequency in the CT-2103 arm (16% vs 2%).

Table 9 Number (%) of Patients with AEs of all Intensities Reported in ≥ 10% of Patients in Either Arm in study PGT-304

System Organ Class/ Preferred Term	CT-2103 (175 mg/m^2) (N=190)	Gemcitabine or Vinorelbine (N=187)	P-Value*
Patients with any AE	176 (93%)	179 (96%)	0.272
Infect & Infest	30 (16%)	24 (13%)	0.463
Neoplasms	99 (52%)	104 (56%)	0.536
Malignant neoplasm progression	98 (52%)	101 (54%)	0.680
Blood & Lymphatic	51 (27%)	99 (53%)	< 0.001
Anaemia NOS	27 (14%)	68 (36%)	< 0.001
Neutropenia	11 (6%)	27 (14%)	0.006
Leukopenia NOS	14 (7%)	20 (11%)	0.285
Metab. & Nutrition	38 (20%)	56 (30%)	0.032
Anorexia	27 (14%)	27 (14%)	1.000
Psychiatric	24 (13%)	25 (13%)	0.879
Nervous System	66 (35%)	36 (19%)	< 0.001
Peripheral sensory neuropathy	30 (16%)	3 (2%)	< 0.001
Cardiac	13 (7%)	28 (15%)	0.013
Vascular	22 (12%)	26 (14%)	0.539
Resp.,Thoracic &Med.	78 (41%)	97 (52%)	0.039
Dyspnoea NOS	41 (22%)	56 (30%)	0.077
Cough	18 (9%)	29 (16%)	0.087
GI	56 (29%)	82 (44%)	0.004
Nausea	37 (19%)	54 (29%)	0.041
Vomiting NOS	16 (8%)	32 (17%)	0.013
Constipation	13 (7%)	26 (14%)	0.028
Skin & Subcut.	14 (7%)	38 (20%)	< 0.001
Musc.skel. & connect.	35 (18%)	42 (22%)	0.372
Gen. & Admin.	79 (42%)	103 (55%)	0.010
Fatigue	31 (16%)	46 (25%)	0.055
Pyrexia	17 (9%)	32 (17%)	0.021
Asthenia	20 (11%)	29 (16%)	0.169
Chest pain	21 (11%)	26 (14%)	0.438
Oedema peripheral	7 (4%)	22 (12%)	0.003
Invest.	27 (14%)	47 (25%)	0.009
Weight decreased	14 (7%)	23 (12%)	0.121

* P-value based on Fisher's exact test.

The most commonly reported Grade 3 and Grade 4 AEs in the CT-2103 arm were respiratory and toracic events (18%, particularly dyspnoea [13%]), blood and lymphatic disorders (8%, especially anaemia (3%), neutropenia and leukopenia (2% each)), nervous system AEs (8%, i.e. dizziness (1%), peripheral neuropathy (4%)), infections (5%), psychiatric disorders (4%, i.e. disorientation, allucination and confusional state), fatigue (10%), asthenia (7%), chest pain (5%). Of note, grade 3/4 of nausea and vomiting were not reported. No grade 4 neuropathy was observed. Grade 4 AEs were limited: febrile neutropenia was observed in 2 patients (1%), one patient experienced a grade 4 anaphylactic reaction, 2 patients (1%) experienced grade 4 respiratory events and 3 patients (1.6%) had grade 4 cardiac AEs.

Grade 3/4 adverse events that occurred at a significantly higher frequency in the comparator arm compared with CT-2103 arm were anaemia (9% vs 3%) and neutropenia (8% vs. 2%). Grade 3 events of neuropathy occurred only in the CT-2103 arm (4%).

Review of the commonly observed adverse events in the completed phase III NSCLC trials (PGT-302, PGT-303, PGT-304) demonstrates CT-2103 dose-dependent neuropathy and myelosuppression with a clinically significant decrease in overall incidence and severity at the lower dose of 175 mg/m^2 (Table 10). Compared with other taxane treatments (paclitaxel/carboplatin,docetaxel), in patients treated with CT-2103 there was a significantly decreased incidence of alopecia, that was demonstrated even at doses higher than 175 mg/m^2, as well as a lower rate of hypersensitivity reactions (HSR). However, the real clinical relevance of such HSR is not clear, considering that, although pre-medication was not required in patients receiving CT-2103, it was allowed by study protocol, and a percentage of patients varying from 18 to 40% between different studies received routine pre-medication.

Table 10 Number (%) of Most Common AEs in Phase III Studies in NSCLC with CT-2103

System Organ Class	PGT 304		PGT303		PGT302	
	CT-2103 (175 mg/m^2) N=190	Gemcitabin/ vinorelbine N=187	CT-2103+ Carboplatin N=199	Paclitaxel+ Carboplatin N=198	CT-2103 N=422	Docetaxel N=416
Nervous system	66 (35%)	36 (19%)	119 (60%)	128 (65%)	257 (61%)	187 (45%)
Blood and Lymph	51 (27%)	99 (53%)	130 (65%)	87 (44%)	161 (38%)	254 (61%)

Serious adverse events (SAEs)

In PGT-304 study, serious adverse events occurred less frequently in the CT-2103 treatment arm, although the difference was not statistically significant (26% vs 35%; p=0.057; Table 11). The events primarily responsible for the difference were malignant neoplasm progression (10% in the CT-2103 arm vs 19% in the comparator arm), anaemia (0% vs 4%, respectively), cardiac (5% vs 8%, respectively, mostly cardiopulmonary failure) and respiratory events (8% vs 14%, respectively). Psychiatric and nervous systems AEs were SAEs that occurred predominantly in the CT-2103 arm.

Table 11 Number (%) of Patients with Serious Treatment Emergent AEs that Occurred in at least 2 Patients in study PGT-304

System Organ Class/ Preferred Term	CT-2103 N=190	gem/vin N=187	P-Value*
Dehydration	2 (1%)	3 (2%)	0.683
Hyperglycaemia NOS		3 (2%)	NE
Psychiatric	3 (2%)		NE
Disorientation	2 (1%)		NE
Hallucination NOS	2 (1%)		NE
Nervous System	7 (4%)	5 (3%)	0.771
Cerebrovascular accident	2 (1%)	1 (<1%)	1.000
Peripheral motor neuropathy	4 (2%)		NE
Peripheral sensory neuropathy	4 (2%)		NE
Cardiac	9 (5%)	15 (8%)	0.211
Cardiopulmonary failure	1 (<1%)	6 (3%)	0.066
Atrial fibrillation		2 (1%)	NE
Cardiac failure NOS	1 (<1%)	1 (<1%)	1.000
Cardio-respiratory arrest	1 (<1%)	1 (<1%)	1.000
Myocardial infarction	1 (<1%)	1 (<1%)	1.000
Myocardial ischaemia	1 (<1%)	1 (<1%)	1.000
Cardiac tamponade	2 (1%)		NE
Vascular	6 (3%)	3 (2%)	0.503
Deep vein thrombosis	2 (1%)	2 (1%)	1.000
Thromboembolism	2 (1%)		NE
Resp.,Thoracic &Med.	15 (8%)	26 (14%)	0.069
Respiratory failure		9 (5%)	NE
Dyspnoea NOS	7 (4%)	7 (4%)	1.000
Hypoxia	2 (1%)	3 (2%)	0.683
Pulmonary embolism	1 (<1%)	3 (2%)	0.369
Pleural effusion	1 (<1%)	2 (1%)	0.621
Pulmonary haemorrhage		2 (1%)	NE
Cough	1 (<1%)	1 (<1%)	1.000
Haemoptysis	2 (1%)	1 (<1%)	1.000
Pneumothorax NOS	1 (<1%)	1 (<1%)	1.000
GI	1 (<1%)	4 (2%)	0.213
Musc.skel. & connect.	3 (2%)	2 (1%)	1.000
Muscle weakness NOS	1 (<1%)	1 (<1%)	1.000
Renal & Urinary		2 (1%)	NE
Gen. & Admin.	3 (2%)	3 (2%)	1.000
Chest pain	1 (<1%)	1 (<1%)	1.000
Pyrexia	1 (<1%)	1 (<1%)	1.000

* P-value based on Fisher's exact test. NE = Not Estimable.

System Organ Class/ Preferred Term	CT-2103 N=190	gem/vin N=187	P-Value*
Patients with any Serious AE	49 (26%)	66 (35%)	0.057
Infect & Infest	11 (6%)	13 (7%)	0.678
Pneumonia NOS	5 (3%)	7 (4%)	0.572
Lobar pneumonia NOS		2 (1%)	NE
Lower respiratory tract infection NOS	2 (1%)		NE
Neoplasms	19 (10%)	37 (20%)	0.009
Malignant neoplasm progression	19 (10%)	36 (19%)	0.013
Blood & Lymphatic	1 (<1%)	11 (6%)	0.003
Anaemia NOS		8 (4%)	NE
Neutropenia		2 (1%)	NE
Metab. & Nutrition	3 (2%)	8 (4%)	0.138

Moreover, in patients enrolled in PGT-304 study and treated with CT-2103 at dose 235 mg/m^2, an higher incidence of serious AEs was observed (49% vs 26%), in particular in terms of infections (13% vs 6%),

myelosuppression (9% vs <1%), metabolism and nutrition (9% vs 2 %), nervous system (9% vs 4%), cardiac (11 vs 5%), respiratory (19% vs 8%) and gastrointestinal events (9% vs <1%).

Review of the SAE data in the other completed phase III NSCLC trials suggested that SAEs directly attributed to progression of NSCLC were the most frequently observed in all 3 studies. The incidence of these events was similar between treatment arms in PGT-303 and PGT-302 but was lower in the CT-2103 (175 mg/m^2) arm of PGT-304. The frequency of CT-2103 SAEs more likely to be treatment-related, specifically myelosuppression and peripheral neuropathy, was lower in the PGT304 (175 mg/m^2) than in PGT303 and PGT304 in which the dose of CT-2103 was 210 mg/m^2; according to the Applicant, this should indicate that lowering the dose of CT-2103 by 235 mg/m^2 to 175 mg/m^2 resulted in an overall lower incidence of serious toxicities.

Deaths

In the PGT-304 study, there were fewer deaths within 30 days after the last dose of study drug in the CT-2103 compared to the comparator arm (10% [19/190] vs 17% [31/187], respectively). The primary cause of death, as attributed by investigators, was disease progression (CT-2103: 37% [7/19]; comparator: 55% [17/31]). Cardiovascular diseases, including cerebrovascular events, were the second leading cause of death (CT-2103: 47%, [9/19]; comparator: 32% [10/31]). No deaths occurring within 30 days after the last dose of study drug were considered by the investigators as possibly related to study medication.

Of note, in study PGT-304, the initial starting dose of 235 mg/m^2 was amended to 175 mg/m^2 after enrolment of 95 patients, due to the observed increased incidence of on-study deaths related to severe infection or occurring at a time concurrent to the expected neutrophil nadir. The incidence of on-study death was significantly higher in the group of patients treated with CT-2103 235 mg/m^2 compared with patients treated with CT-2103 175 mg/m^2 (21% [20/95)] vs 10% [19/190], respectively).

Table 12 Summary of Deaths ≤ 30 Days from Last Treatment In Completed Phase III NSCLC Trials

Study	CT-2103	Comparator
PGT304 (CT-2103 - 175 mg/m^2)	19 (10%)	31 (17%)
PGT304 (CT-2103 - 235 mg/m^2)	20 (21%)	NA
PGT303	23 (12%)	24 (12%)
PGT302	49 (12%)	65 (16%)
Total	111 (12%)	120 (15%)

On-study deaths in PGT-305 study

PGT305 study was terminated early due to a statistically significant increased number of on-study deaths in the CT-2103 arm (ratio CT-2103: paclitaxel: 17: 2 at the time of study closure). However, after the final data were collected the difference was not statistically significant anymore (ratio 18: 8, respectively), and according to the Applicant this was due at least in part to late reporting of deaths in the control arm. However, a numerical difference between treatment was still present and, importantly, the rate of on study deaths reported in the CT-2103 arm of PGT-305 study (18%, 18/98) was significantly higher than the rate observed in the CT-2103 arm of the PGT-304 study (10%, 19/190).

The evaluation of the potential etiology of such deaths is made difficult by the fact that the specific AE terms used to describe clinical events leading to death were broad and somewhat not specific; moreover in some patients narratives were incomplete and causes of death unknown. However, no clear adverse event pattern was associated with those deaths: there was no clustering of the deaths by geographical location, age, and occurrence of neutropenia, as well as there was no temporal association from the time of the last dose with a range of 2 days to 28 days. Moreover, Charlson Comorbidity Assessment did not suggest a difference in comorbidity burden between the two arms of the study.

In contrast, in the CT-2103 group, a clinically significant weight loss at baseline (>5% body weight) was observed in patients with early cycle death. However, this association was not observed in the paclitaxel arm. In the Day 120 response document, the Applicant provided results of a pooled analysis of risk factors in trials PGT-303 and PGT-304, and compares this pooled analysis with the result of a similar risk factor analysis in trial PGT-305. The Applicant concludes that risk factors predict overall survival consistently

both in the pooled analysis of trials PGT-303 and PGT-304; however, such analysis is not considered justified and results not convincing.
In the view of the CHMP, in absence of an exhaustive explanation, the high rate of on-study deaths reported in PGT-305 study should suggest caution in the use of CT-2103 in the target population at the dose claimed for registration.

Laboratory findings
In PGT-304 study, mean values of hemoglobin, white blood cell count (WBC), neutrophils and platelets generally were all stable from baseline through cycle 6 and at follow up for both CT-2103 (at 175 mg/m^2) and comparator. The analysis of data by assessment of percent of patients experiencing toxicity grade (NCI-CTC v. 2) shifts from baseline during treatment and at the end of treatment suggested that both treatments might have a mild to moderate myelosuppressive effect that was transient and generally improved by the end of treatment. However, the shifts tended to occur to a greater degree in the comparator arm. Indeed, there were more grade 4 abnormalities in the comparator arm but overall the rates were low in both treatment groups. Reduction in haemoglobin levels was observed in 65% of patients (114/186) in the CT-2103 arm and 87% of patients (89/109) in the comparator arm: in the majority of cases they consisted of grade 1-2 shifts (97% of shifts in both arms). Decrease in neutrophil count was observed in 30% of patients in the CT-2103 and 52% of patients in the comparator arm, with grade 3/4 shifts in the 3% and 6% of patients respectively.
Platelet count decreased in 17% of patients in the CT-2103 compared with 47% in the comparator arm. Grade 3/4 shifts in platelet count were seen in < 1% of patients in both arms.
Of note, data regarding the timing (days) within cycles of nadir values for hemoglobin, neutrophils, and platelets as well as the timing of recovering of neutrophil and/or platelet counts in the majority of cycles have not been provided by the Applicant due to the very limited number of patients who experienced clinically significant nadir values.

In PGT-304 and in general in the other studies performed with CT-2103 in NSCLC, no clinically concerning changes in electrolytes and/or creatinine were identified. Increases in transaminases during treatment that improved by the end of therapy were observed.

Of note, considering that no effect of CT-2103 on QTc prolongation has been observed in preclinical studies and that the analogous paclitaxel has not been reported to affect QTc, the potential effect of CT-2103 on QTc has not been evaluated in clinical studies. Routine risk management plan should follow this issue.

Safety in special populations
Renal and/or Hepatic Impairment: To date, the effect of hepatic or renal impairment on CT-2103 pharmacokinetics, disposition and safety has not been studied in patients, therefore it is not known whether dose adjustment is appropriate. The Applicant proposed a contraindication for patients with severe hepatic impairment that is endorsed. The statement included in the SPC for caution in the use of CT-2103 in patients with hepatic or renal impairment is agreed.
Pregnancy, Lactation and Fertility: There are no adequate data about the use of CT-2103 in pregnant women and it is not known whether CT-2103 is excreted in human breast milk. However, studies in animals have shown reproductive toxicity and transfer of CT-2103 into milk. A fertility study has not been performed, but genotoxic effects and testicular atrophy were observed with CT-2103 in preclinical studies. Male patients treated with CT-2103 are advised not to father a child during and up to 6 months after treatment. The Applicant should clarify if male patients should seek advice on conservation of sperm prior to treatment due to a potentially irreversible anti-fertility effect of CT-2103.
Elderly: The safety analysis of the 161 patients ≥ 65 years old enrolled in PGT-304 study (75 patients in the CT-2103 (175 mg/m^2) arm and 86 patients in the comparator arm) revealed a trend towards increased toxicity in both treatment arms as well as in the CT-2103 arm in terms of myelosuppression (neutropenia, anaemia, thrombocytopenia, and febrile neutropenia), infections (both overall and severe), gastrointestinal events, fatigue, anorexia, psychiatric events (20% vs 13%), peripheral neuropathy (23% vs 16%), respiratory events (49% vs 41%), dyspnea (28% vs 22%), cough (15% vs 9%) and skin (16% vs 7%) and hemorrhage events (primarily due to higher rate of hemoptysis [15% vs 9%]).
The results were consistent with results obtained in PGT-302 (75 patients) and PGT-303 study (163 patients), where higher doses of CT-2103 used led to a trend versus increased incidence of infections,

myelosuppression (especially neutropenia, both all grades and 3-4 grades), metabolism and nutrition, cardiac, gastrointestinal and skin events, and haemorrhage.
However, according to the Applicant, no clinically concerning difference in cycles of treatment received, adverse events resulting in discontinuation or dose delays was observed between elderly patients and non elderly patients treated with CT-2103 in PGT-304 study. There was a trend towards a decrease in dose intensity in cycles 5 and 6 in elderly patients although the small number of elderly patients receiving 5 or 6 cycles limits interpretation.

Immunological events
In PGT-304 study, hypersensitivity reactions (HSR) were uncommon in both treatment arms. They occurred in 2% of patients in the CT-2103 arm and in 4% of patients in the comparator arm. One grade 3 reaction and 1 anaphylactic reaction occurred in the CT-2103 arm. No grade 3 or 4 reactions occurred in the comparator arm. HSR resulted in withdrawal in 2 patients in the CT-2103 arm.
Overall, the incidence of CT-2103 hypersensitivity reactions (hypersensitivity NOS and drug hypersensitivity) in all patients who have received CT-2103 across all studies is 4% (1% grade 3, <1% grade 4). However, the evaluation of the real incidence of such events was biased because, although pre-medication was not required for patients who received CT-2103, it was allowed by study protocol and was administered in 18-40% of patients in the different studies.

Safety related to drug-drug interactions and other interactions
No formal drug interaction studies have been performed with CT-2103. Results of investigations for the ability of CT-2103 to inhibit the major Cytochrome P450 (CYP) enzymes in human liver microsomes *in vitro* indicated the potential for inhibition of a broad spectrum of enzymes, overlapping, in part, with those catalyzing the metabolism of paclitaxel, including CYP2C8 and CYP3A4. The relevance of these *in vitro* biochemical findings for CYP450 inhibition by CT-2103 to its clinical use is unclear. However, considering also that paclitaxel is metabolized by CYP 450 isoenzymes CYP2C8 and CYP3A4, a warning should be included in the SPC for caution in administering CT-2103 concomitantly with compounds known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil,warfarin) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4. Moreover, in absence of definitive data regarding the potential interaction between CT-2103 and warfarin and warfarin-like compounds, a warning for careful monitoring of patients in concomitant therapy with anticoagulants and CT-2103 should be included in the SPC.
In addition, considering that experience with paclitaxel and other formulations of paclitaxel indicated an increased toxicity associated with combinations of paclitaxel with other cytotoxic compounds (i.e., cyclophosphamide, antracyclines, cisplatin) and the finding that toxicity of each combination was dependent on the order of drug administration, in absence of data over efficacy and safety of CT-2103 in combination regimens, the use of CT-2103 should be eventually limited to single-agent therapy and a warning over cautions for using CT-2103 in combination with other cytotoxic anticancer drugs should be included in the SPC.

Discontinuation due to AES
Overall, in PGT-304 study there was no significant difference in adverse events leading to discontinuation between the two treatment arms, 52% (99/190) in the CT-2103 vs 58% (109/187) in the comparator arm. The most frequent reason for discontinuation of study drug was disease progression accounting for 42% of patients in both arms. Other AEs that resulted in discontinuation of study drug in the CT-2103 and the comparator arm included cardiac events (3% and 5%, respectively), respiratory disorders (5% and 11%, respectively), nervous system disorders (3% and 2%, respectively) metabolism and nutrition disorders (2% and 7%, respectively), infections (2% in both arms). Events leading to withdrawal in psychiatric disorders (1%) and immune system disorders (1%) were only seen in the CT-2103 arm, whereas events leading to withdrawal in blood and lymphatic disorders (2%) and gastrointestinal disorders (2%) were seen only in the comparator arm. Overall, events leading to withdrawal in immune and nervous systems as well as due to psychiatric and vascular disorders were more frequent in the CT-2103 compared with the comparator arm.
In PGT-304 study, the incidence of AEs that lead to study drug dose reduction was higher in the comparator arm (13%, 25/187) than in the CT-2103 arm (4%, 8/190). In general, neurological events (mostly neuropathy, 2%) where the most frequent AEs leading to dose reduction in the CT-2103 arm, whereas haematological events (thrombocytopenia, neutropenia, anaemia) most frequently resulted in dose reduction in the comparator arm (9% in the comparator versus <1% in the CT-2103 group).

Of note, in PGT-304 study, in patients treated with CT-2103 at 235 mg/m^2 (before amendment of study protocol), adverse events leading to withdrawal were more frequent than at the 175 mg/m^2 dose level (65% vs 52%). Similarly to the 175 mg/m^2 group, at 235 mg/m^2 dose the most frequent reason for discontinuation of study drug was malignant neoplasm progression, but significantly higher discontinuations due to infections (8% vs 2%), nervous system (14% vs 3%) and respiratory events (11% vs 5%) were observed.

Use of Supportive Medications

In PGT-304 study the use of erythropoietin, G-CSF and related growth factors, and the frequency of red blood cell transfusion was greater in the comparator arm than in the CT-2103 arm. In general, the trends for the use of supportive medications were consistent across phase III studies in which CT-2103 was administered and consistent with a dose-related myelotoxicity of CT-2103 (Table 13). Of note, in study PGT-305 the extent of the myelosuppression, transfusion and growth factor support required might be greater than that observed, because, due to the early termination of the study, many patients did not receive a full course of treatment and some only received one cycle.

Table 13 Supportive care use in study arms of phase III studies conducted in NSCLC with CT-2103

	PGT-304		PGT-305		PGT-303		PGT-302	
	CT-2103 (175 mg/m2)	Gem/Vinor	CT-2103 (175 mg/m2)	Paclitaxel	CT-2103/carb (210 mg/m2)	Paclit/carb	CT-2103 (175/210 mg/m2)	Docetaxel
RBCT	4%	13%	3%	5%	13%	8%	7%	12%
EGF	3%	8%	4%	3%	14%	14%	11%	14%
MGF	2%	6%	3%	3%	17%	14%	6%	18%

Safety of CT-2103 in study PGT-303

In PGT-303 study, the combination CT-2103 (210mg/m^2)/carboplatin was significantly less tolerated compared with the paclitaxel (225 mg/m^2)/carboplatin: patients in the CT-2103 arm reported higher incidence of grade 3/4 AEs (73% vs 63%, p=0.032), serious AEs (49% vs 40%), AEs leading to withdrawal (51% vs 40%) and to dose reductions (25% vs 17%). Frequency of grade 3/4 haematological events was significantly higher in the CT-2103 arm both overall (46% vs 27%, p<0.001) and in terms of neutropenia (p=0.01), anaemia (p=0.02) and thrombocytopenia (p<0.001). A statistically significant higher frequency of grade 3/4 AEs in the Nervous System SOC was seen in the CT-2103 arm, driven by higher rates of severe grade 3/4 peripheral neuropathy (17% vs 10%, p=0.07). Importantly, the rate of discontinuation for myelosuppression and nervous system events was higher in the CT-2103/carboplatin arm compared with paclitaxel/carboplatin (9% and 14% versus 4% and 7%, respectively). Moreover, a significantly higher percentage of patients in the comparator arm completed study protocol (p=0.041). The incidence of hypersensitivity reactions was reduced in the CT-2103 arm (2%) compared with the comparator (4%), but the evaluation is biased by the fact that, although pre-medication was not required by study protocol for patients treated with CT/carboplatin, around 30-40 % of patients in the CT-2103 received such pre-medication. The use of supportive care medication was comparable in the two study arms, with a slightly increased frequency in the CT-2103 arm of blood cell transfusions and myeloid growth factor administration.

Safety of CT-2103 versus paclitaxel in PGT-305 study

Study PGT-305 is the only phase III study conducted in NSCLC patients (women) with PS2, evaluating single agent CT-2103 (175 mg/m^2) versus single agent paclitaxel (225 mg/m^2). However, the study was terminated early (after enrolment of 200 patients) due to a high number of on-study deaths in the CT-2103 arm (see section *On-study deaths in PGT-305 study*). As a consequence, many patients did not receive a full course of treatment and some received only one cycle of therapy, thus making any conclusion over the comparison between the safety profile of single agent CT-2103 versus paclitaxel hazardous. Overall, the median number of cycle administered was 3 in both study arms; the percentage of patients who received 6 cycles of therapy was higher in the paclitaxel (22%) compared with the CT-2103 arm (12%). Data regarding the median dose intensity in the two study arms are missing. Frequency and type of adverse events were generally similar between treatment arms, with the exception of a significantly higher incidence of neuropathy (33% vs 19%), arthralgia (15% vs 3%), myalgia (10% vs 1%) and alopecia (53% vs 9%) in the paclitaxel arm, and a significantly higher incidence of grade 3-4 (44% vs 34%) and serious

adverse events (36% vs 23%) in the CT-2103 arm, driven by an increased rate of cardiovascular events. Adverse events leading to withdrawal were similar between treatment arms, whereas the percentage of patients with dose reduction per cycle of therapy administered was higher in the CT-2103 arm. No significant difference in incidence and severity of myelosuppression and use of rescue medications was observed between the two treatment arms. Neuropathy was reported in 19% of patients in the CT-2103 arm and 33% in the paclitaxel arm, whereas grade 3 neuropathy was 4% and 2%, respectively. Hypersensitivity reactions occurred in 3% of patients in the CT-2103 arm and 7% in the paclitaxel arm, but 22% of patients in the CT-2103 arm received pre-medication and other 8% were in treatment with corticosteroids or antihistamines for other clinical reasons. The increase in transaminases (in particular AST) occurred more frequently in the CT-2103 arm and persisted to a greater degree at the end of treatment.
However, the inappropriateness of the comparison between the safety profile of CT-2103 and paclitaxel as observed in PGT-305 study is further demonstrated by the significantly lower incidence of neuropathy, myelosuppression and other adverse events reported in the two arms of study PGT-305 compared with the rate observed in study PGT-304 (where similar CT-2103 dose (175 mg/m^2) and same target population were employed) and in historical trials performed with paclitaxel in NSCLC, respectively.

Pharmacovigilance system

The applicant has submitted an updated description of the pharmacovigilance system in which some of the concerns raised by the CHMP have been addressed. However, the description of the pharmacovigilance system has not been signed by the QPPV and the applicant and a formal pharmacovigilance statement has not been included in the description of the pharmacovigilance system. Information still has to be provided on the frequency of the internal audits of the pharmacovigilance system. The information provided in the Response Document should be integrated into the section on quality management in the next revision of the description of the pharmacovigilance system. In addition, this revised version has several deficiencies that were not in the old version and that should be rectified in the next update of the description of the pharmacovigilance system: The description of the pharmacovigilance system should be prefaced by a version and date. Section 1.8.1.6 “Documented Procedures” does not clearly state that there are SOPs for the pharmacovigilance activities “monitoring and signal detection”, “handling of USRs and other safety variations” and “meeting commitments to competent authorities in relation to a marketing authorisation”, and a copy of the EudraVigilance registration of the QPPV should be provided. These issues should be solved before a positive opinion can be granted.

Risk Management Plan

Non-clinical and clinical safety specifications
Identified pre-clinical safety specifications include peripheral neuropathy, bone marrow suppression with neutropenia, thrombocytopenia, and, anorexia, vomiting, diarrhea, body weight decrease, anaemia, and Aspartate AminoTransferase (AST) and Alanine AminoTransferase (ALT) elevation. Reproductive toxicity was observed in males and females and severe embryo-fetal developmental toxicity was also observed.
Clinical safety specifications consist of the risk of neuropathy, hypersensitivity reactions, myelosuppression, infection, elevated AST and ALT, atrial fibrillation, geriatric use, and thrombin inhibition. As requested by the CHMP, atrial fibrillation has been added as an important identified risk. All cardiac disorders included in section 4.8 of the SPC under the SOC “Cardiac disorders” should be included as an identified risk in the RMP. This can be done under a general term “Cardiac disorders” with further specification of the cardiac disorders of interest. Safety data from clinical study PGT-305 was not included in the RMP. Study PGT-305 was early terminated due to an imbalance of on-study deaths (deaths within 30 days after the last study drug administration). Due to its early termination, many patients did not receive the full protocol directed course of treatment. It was felt by the applicant that this limits the interpretation of the safety data when compared to completed studies. Data on important toxicities such as neuropathy and myelosuppression might appear less severe than they would have if all patients received the full protocol directed therapy. It was this assessment that led the applicant to not include the safety data for PGT-305 alongside the data from completed studies. The reasoning of the applicant was followed and considered acceptable.
Bleeding was included as a potential risk and since CT-2103 is metabolised by Cytochrome P450 there is a potential risk that CT-2103 may affect the metabolism of other agents, such as warfarin or warfarin like compounds that are also metabolized by this system. As requested the MAA has included the potential for

interaction at the CYP P450 level in the appropriate section of the RMP. However, the applicant has not discussed pharmacovigilance activities to further study this potential risk.
Pregnant and lactating women, patients with an absolute neutrophil count <1500/µl and patients with ≥grade 2 neuropathy were excluded from the clinical trials and are contra-indicated in the proposed SPC. Paediatric patients were excluded as well and use in paediatric patients is not recommended. The MAA will do their best to obtain all relevant information on adverse events reported with the use of CT-2103 in the paediatric populations and should specifically address this in future PSURs. There is limited experience with elderly. Since more than 50% of the patients with NSCLC is >65 years of age, the MAA has included a description of the safety profile in the elderly in the updated RMP and has added a statement to section 4.2 of the SPC stating that higher frequencies of certain adverse events were seen in the elderly. This information should also be included in section 4.8 of the SPC. Hepatic and renally impaired patients were excluded from the clinical trials as well. The applicant has added severe hepatic impairment as a contra-indication to section 4.3 of the SPC and information concerning use of CT-2103 in hepatic impaired patients will be discussed in future PSURs. However, use of CT-2103 in the hepatic impaired patients should still be added as missing information to the RMP. In addition to the discussed population not studied, the MAA has added a statement to the RMP that most patients receiving CT-2103 were Caucasians and that there is no information if there is any variation in the safety profile based on ethnicity or race. Inclusion of this statement in the RMP is not deemed sufficient. Additional information on potential implications of the limited experience of CT-2103 in non-Caucasians and if deemed necessary additional activities to further evaluate the safety of CT-2103 in non-Caucasians should be proposed.
The MAA should take care of the potential off-label use since there is the possibility that in several malignancies, although the present MAA is only for single-agent CT-2103, CT-2103 will be used in combination with other cytotoxic compounds (antracyclines, platinum compounds) and considering the experience with other paclitaxel formulations where combination and sequence of administration might significantly affect toxicities.

Pharmacovigilance plan and risk minimization activities
The applicant proposes routine pharmacovigilance practices for all identified risks. To further study the potential for bleeding with the use of CT-2103 the MAA proposes to monitor adverse events associated with bleeding, investigate the timing of bleeding in relation to the last dose of CT-2103 and provide specific update in the PSUR.

Routine risk minimisation activities are deemed sufficient to cover the identified and potential risks.

IV. ORPHAN MEDICINAL PRODUCTS
V.

N/A

VI. BENEFIT RISK ASSESSMENT

Introduction
At present, there is no curative systemic treatment for patients with advanced NSCLC. Platinum-based chemotherapy is considered the standard 1st line treatment for patients with advanced NSCLC and good performance status, as it has been demonstrated to improve survival, albeit modestly, and alleviate disease-related symptoms in this population. However, it is unknown whether these benefits apply to patients with poor performance status. Patients with advanced or recurrent NSCLC and PS2 represent a significant portion (up to 40%) of the NSCLC population treated in clinical practice. Historical data over the clinical benefit of chemotherapy in PS2 patients are scarce, because PS2 patients have been generally excluded from clinical trials or, when included, they represented a small percentage (usually far less than 20%) of study populations. Prospective studies for PS 2 patients are lacking, and retrospective information based on sub-group analyses focused on small subgroups of patients with PS2 is the best level of information available from the literature.
Currently, there is no consensus on the standard treatment for patients with advanced NSCLC and PS2. The treatment is primarily palliative and options include best supportive care (BSC) and local radiation (to

reduce cancer related symptoms and improve quality of life), and chemotherapy (to slow disease progression, prolong survival and improve quality of life). Single-agent chemotherapy with a drug shown to be effective compared with BSC, non-platinum based combination chemotherapy and platinum-based combination chemotherapy have been recently proposed by European and American guidelines (ASCO guidelines 2004; NCCN guideline 2008; ACCP guideline 2007; ELCWP guidelines 2007). Of note, in the recent CALGB 9730 trial evaluating the combination paclitaxel/carboplatin versus single agent paclitaxel in patients with advanced NSCLC, a subgroup analysis focused on the 99 PS2 patients (out of the 561 enrolled) showed increased survival and acceptable tolerability for PS 2 patients treated with doublet agent chemotherapy (paclitaxel/carboplatin) in comparison to single agent chemotherapy (paclitaxel).

CT-2103 (paclitaxel poliglumex) was developed in order to improve the safety profile of the taxane paclitaxel, due to the elimination of Cremophor EL from the pharmaceutical preparation. Also, the polymeric formulation was expected to improve the pharmacokinetics profile of paclitaxel, by decreasing the volume of distribution and prolonging the distribution and elimination phases. Enhanced permeability and retention (EPR) effect in tumour tissue for CT-2103 was also hypothesized, which is supposed to improve the antitumour activity of the compound compared with paclitaxel. However, to date, although demonstrated in preclinical studies, the EPR effect claimed for other conjugated polymeric forms of cytotoxic compounds has never been reported to translate in an improved efficacy and safety profile of such drugs in clinical practice.

In the present MAA registration is requested for CT-2103 for 1st line monotherapy of patients with advanced NSCLC and ECOG PS of 2, at 175 mg/m^2. Indeed in the Day 120 response document the Applicant clarified that the claimed indication for CT-2103 is monotherapy and not combination therapy.

VI.1 Demonstrated Benefits and uncertainties

The present submission for MAA is mainly based on the pivotal PGT-304 study, which is a multicenter randomized phase III study conducted with CT-2103 single agent, at the dose of 175 mg/m^2 proposed for registration, versus gemcitabine or vinorelbine, in chemo-naïve patients with advanced or recurrent NSCLC and ECOG PS2. Other studies are supportive at best (PGT-303, PGT-304, PGT-202) because they were conducted in combination regimens and/or at CT-2103 doses and/or in target populations that differ from the proposed indication. A particular mention needs to be made for study PGT-305, a phase III randomized trial conducted with CT-2103 versus conventional paclitaxel using the dosage, the administration regimen and the (female) target population as proposed in the MAA: the trial was early terminated due to an (unexplained) excessive rate of on-study deaths in the CT-2103 arm.

Relevant limitations in the studied population are that in all the phase III studies performed with CT-2103 in NSCLC, patients with significant hepatic or renal impairment, unstable medical conditions, neuropathy, and with non-pretreated brain metastases were excluded. Moreover, only around 20% of patients enrolled had age >70 years. This would significantly limit the population treated in clinical practice since the poor performance status population is highly heterogeneous and co-morbidities are expected.

Pivotal PGT-304 study was originally designed as a superiority trial but, before termination and unblinding of the data, the protocol was amended to include a non-inferiority analysis (with a fixed-margin method) as secondary analysis of the primary endpoint of efficacy. Overall Survival (OS) was the primary endpoint. Secondary endpoints were time to progression (TTP), disease control, response rate, lung cancer symptoms evaluation (assessed with the FACT-LCS score) and safety.
The results of PGT-304 study failed to show superiority of the CT-2103 arm over the comparator (gemcitabine or vinorelbine) in terms of OS (median OS was 220 days [198-263] in the CT-2103 arm, and 198 days [173-220] in the comparator arm; HR: 0.95, 95% CI: 0.76-1.20). Moreover, non-inferiority was not met according to the fixed-margin method using the pre-specified non-inferiority margin (delta) of 1.1 (p=0.23). In view of these negative results and of analogous outcomes observed in the other studies of the so-called STELLAR program (i.e., PGT303 and PGT-302, in addition to PGT-304, see below), the Applicant proposed a switch of the primary efficacy analysis from superiority to non-inferiority for PGT-304 and the other studies performed in the STELLAR program, and a shift of the non-inferiority margin from 1.1 to 1.2. Non-inferiority is the basis of this MAA.

Scientific advice from the CHMP was issued on 1 June 2006 on these issues: the CHMP stated that the switch to non-inferiority as proposed by the Applicant could in principle be justified, but it was emphasized that the advice did not involve any judgment on the choice of the comparators and on the choice of the non-inferiority margin. In addition, due to insufficient data provided by the Applicant at the time of the SA, the CHMP could not decide whether the shift of delta to 1.2 would have been acceptable.
Regarding the switch of the primary analysis to non-inferiority proposed by the Applicant, the major concerns raised over the choice of the comparators are still not solved. Particularly in relation to study PGT-304 the data from the medical literature on the efficacy of gemcitabine or vinorelbine (as comparator in PGT-304) in patients with NSCLC and PS2 are scanty. To date, the clinical benefit of vinorelbine and gemcitabine versus BSC in NSCLC has been addressed in only two trials: the ELVIS study (comparing vinorelbine vs BSC) and in one study published by Anderson (evaluating gemcitabine vs BSC) (ELVIS study group, 1999; Anderson H et al, 2000). The study published by Anderson failed to show an improvement in survival for gemcitabine versus BSC. This is relevant, considering that the majority (155/187, 83%) of patients enrolled in the comparator arm of PGT-304 study were treated with gemcitabine. Moreover, besides that both trials were not specifically designed for PS 2 patients, only a small number of patients with poor PS were enrolled: only 37 of the 161 patients enrolled in ELVIS study had PS2. Also, the use of the Karnofsky scale to assess the performance status in the study published by Anderson led to considerable discrepancy in the proportion of patients identified to have PS2 (108 versus 215 patients) in two different recently published review articles. Furthermore, both studies (published by Anderson and ELVIS study) differed from the PGT-304 trial in terms of dose and schedule of study drug administered. These concerns, together with the lack of study assay sensitivity, further supports the inappropriateness of switching the superiority design towards non-inferiority (CPMP/EWP/482/99).
The shift of delta from 1.1 to 1.2 is also considered insufficiently justified. Indeed, besides the fact that the change has been proposed after results of the study showed that the margin of 1.1 was not met, the shift of delta to 1.2 would imply the acceptability of a difference in OS of 42 days (instead of 17-24 days) between the two study arms. This difference is by principle not negligible in view of the low life expectancy of the poor performance status population with NSCLC, and could be considered acceptable, according also to the scientific advice, only in view of a clear superiority of the CT-2103 over comparators in terms of quality of life and safety profile. However, such superiority has not been demonstrated yet by CT-2103 in any of the phase III studies performed. No further convincing justifications have been provided by the Applicant over these issues in the Day 120 response document.

In addition, the Applicant claimed non-inferiority according to the fraction retention method (with delta=0.5) and activity of CT-2103 versus placebo using an analysis of indirect comparison over placebo (as proposed by Gaffney). Besides that the two analyses were not specified in the SAP of PGT-304, and, as outlined also by the scientific advice, the fraction retention method is usually not-recommended, both analyses are not considered acceptable because they were based on historical data consisting of the ELVIS trial (evaluating the effect of vinorelbine versus BSC), whereas in PGT-304 study the great majority of patients enrolled in the comparator arm were treated with gemcitabine (83%). In addition, as already mentioned above, ELVIS trial included only 37 PS2 patients out of 161 enrolled, and significantly differed from PGT-304 in terms of study population and dose-regimen administered.
From the analysis of the secondary endpoints evaluated in the ITT population of PGT-304 study no supportive evidence for clinical benefit of CT-2103 in the target population was observed, as no statistically significantly difference was found between the CT-2103 and the gemcitabine/vinorelbine arm in terms of TTP, Response Rate (PR+CR), Disease Control, Duration of tumour response and cancer related symptoms (FACT-LCS). However, the analysis of the secondary endpoints is biased by the absence of an external, blinded and independent review committee for the evaluation of progression events, by the significant difference in cycle length between different treatments (which would have affected timing of the radiological and clinical assessments), by the lack of planned follow-up intervals to control for TTP variability in the study protocol, and finally, by the open-label design of the study.

In addition both PGT-303 and PGT-302 did not show any supportive evidence of a clinically meaningful benefit of CT-2103, neither as single agent (PGT-302), nor in combination regimen (PGT-303) in NSCLC. Indeed, no advantage of CT-2103 arm over comparators was achieved based on any of the predefined study endpoints. Both studies PGT-303 and PGT-302 failed to show survival superiority of CT-2103 over the comparators. But then, non-inferiority was not met according to the fixed-margin method (fixed margin of

1.1). Moreover, in both studies Tumour Response Rate (CR+PR, secondary endpoint) was significantly higher in the comparator arms (paclitaxel/carboplatin, docetaxel) compared with the CT-2103 arm.

Finally, the Applicant performed a meta-analysis on non-inferiority using all data obtained in the completed phase III studies of the STELLAR program (PGT-302, PGT-303, PGT-304). Criteria of non-inferiority using a delta 1.1 were applied and met. However, the meta-analysis is considered not acceptable for a marketing claim because it is not in agreement with the CHMP guidelines *(CPMP/EWP/2330/99)*. Moreover, the remarkable heterogeneity of the studies used (in terms of study population and CT-2103 dosage) and the absence of sensitivity analyses demonstrating consistency and robustness of the findings, makes the result highly questionable and therefore not even acceptable as supportive evidence.

VI.2 Demonstrated Risks and uncertainties

Taken into account the statement of the applicant that the quantity of paclitaxel contained in CT-2103 is not equivalent to paclitaxel it is unacceptable to give dose recommendations for CT-2103 in terms of paclitaxel equivalents. In order to prevent potential confusion (which already happened) the applicant is requested to

- delete any wrong statements on paclitaxel content in CT-2103, or paclitaxel equivalents of CT-2103
- to give clear information on the dosing of CT-2103 in the monotherapy trials 304 and 305
- to give dosing information for CT-2103 in the SPC (and delete dosing information in terms of paclitaxel).

Plasma pharmacokinetics of CT-2103 and unconjugated paclitaxel are different from cremophor containing paclitaxel formulations and there are indications that PD of CT-2103 is also different, which can not be fully explained at this moment. Clarification of the uncertainties in PK of unconjugated and conjugated paclitaxel can help to understand the clinically observed (differences in) efficacy and safety data.
There are uncertainties in how much and where paclitaxel is released from CT-2103, in distribution/tissue accumulation of unconjugated and conjugated paclitaxel, elimination, excretion and systemic exposure of unconjugated paclitaxel. The claim that paclitaxel systemic exposure of CT-2103 and Taxol is similar actually precludes a substantial retention in tissues of unconjugated and conjugated paclitaxel following CT-2103 administration. The low volume of distribution of CT-2103 and the high AUC values suggest that CT-2103 is largely confined to the blood compartment during the first 4 days. The systemic exposure of unconjugated paclitaxel was determined mainly during this period. This may suggest that paclitaxel is largely released in the blood compartment rather than after uptake in the tissues. A mass balance study during the first cycle including the measurement of metabolites should be performed to clarify to above uncertainties.
Because the PK of paclitaxel following CT-2103 and cremophor containing paclitaxel have not been compared directly and the measured data indicate that the systemic paclitaxel concentration may be lower compared to Taxol, a direct pharmacokinetic comparison between CT-2103 and Taxol is highly recommended to establish the differences in paclitaxel pharmacokinetics, which may explain differences observed for neuropathy and neutropenia.

Overall, the safety profile of CT-2103 was consistent across studies and was typical for a cytotoxic compound belonging to the taxane class: hematologic toxicities and neurotoxicity were prominent and dose limiting, whereas gastrointestinal toxicities were limited. As expected due to the absence of Cremophor EL in the CT-2103 formulation, hypersensitivity reactions were limited and the drug could be administered over a short infusion time (10-30 minutes compared with 3 hours of paclitaxel).
An increased incidence and severity of AEs with CT-2103 increased dose has been suggested.
In study PGT-304, myelosuppression was less frequent in the CT-2103 arm (27%) versus the comparator arm (53%) ($p<0.05$). No patient experienced dose reduction or withdrawal due to myelosuppresion in the CT-2103 arm, whereas data over time to nadir values and time to recovery have not been analysed by the Applicant due to the very limited number of patients who experienced clinically significant nadir. Of note, in PGT-304 study, the use of erythropoietin, G-CSF and related growth factors as well as the frequency of blood cell transfusion was statistically significantly greater in the comparator than the CT-2103 arm (3%, 2% and 4% vs 8%, 6%, 13%, respectively). In general, a CT-2103 dose-related myelotoxicity has been reported. Indeed, in PGT-304 study the initial dose of 235 mg/m^2 was amended to 175 mg/m^2 due to an increase in on-study deaths that occurred within the time-window of the expected haematological nadir.

This finding has been confirmed in the other studies employing higher doses of CT-2103, where the incidence of myelosuppression significantly increased and was associated with a consistently increased use of rescue medications.

In general, the incidence of severe grade 3-4 neuropathy was significantly higher in the CT-2103 compared with the comparator arms in all studies included in STELLAR phase III program (4% vs 0% in PGT-304, 17% vs 10% in PGT-303, 19% vs 3% in PGT-302). Moreover, the incidence and severity of CT-2103 associated neuropathy appeared to be dose dependent and to increase in incidence by cycle, whereas no data have been provided by the Applicant over the durability of this important adverse event. General incidence of neuropathy (all grade) in CT-2103 arm (30%) of PGT-304 study appears to be lower than the incidence reported with conventional paclitaxel, but it should be noted that no historical data are available over the safety profile of conventional paclitaxel in the PS2 patient population. Moreover, assessment of neuropathy in all the studies of the STELLAR program could have been subjected to investigators' bias, thus potentially reducing the real impact of neuropathy in the patient population receiving CT-2103.
The Applicant proposes measures to reduce the incidence of severe neuropathy consisting primarily in dose reduction for neuropathy symptoms encountered at earlier doses (i.e., in case of development of grade 1 neuropathy) and dose delay or discontinuation unless neuropathy returns to grade $\leq$ 1: however, considering the high rate of patients experiencing neuropathy during treatment with CT-2103 (30%), the CHMP wonder whether the early dose reduction or dose delay as proposed will affect the efficacy of the drug.

Gastrointestinal events (in particular nausea, vomiting and constipation) were reported in around one third (29%) of CT-2103 treated patients in study PGT-304 (comparator: 44%) and were considered manageable: of note, grade 3-4 of nausea or vomiting were not reported.

Hypersensitivity reactions were reported with an incidence of 4% (1% grade 3, <1% grade 4) evaluated in all patients treated with CT-2103 across all studies. However, the clinical relevance is not clear, considering that a percentage of patients varying from 18 to 40% between different studies received routine pre-medication. The potential of these events should be further assessed within the risk-management plan.

An increased risk of bleeding in the first 48-72 hours after CT-2103 administration was hypothesized in patients taking anticoagulants (such as warfarin or warfarin-like compounds) but no increased incidence of bleeding in that time was observed in patients using warfarin therapy in the phase III STELLAR studies. However, considering the low number of patients on anticoagulant therapy during CT-2103 treatment that have been evaluated, a warning for careful monitoring of patients treated with anticoagulant therapy concomitant to CT-2103 should be included in the SPC and the issue should be implemented in the Risk Management Plan.

Alopecia was reported in 15% (9% grade 1, 4% grade 2) of patients receiving CT-2103 overall, and around 6% (range 2-9%) at CT-2103 175 mg/m^2 dose.
In general, no clinically concerning changes in common laboratory parameters, such as electrolytes and/or renal function tests were identified; however, increase in transaminases (AST and ALT) of mild severity during CT-2103 treatment that improved by the end of therapy was observed.

To date, the effect of hepatic or renal impairment on CT-2103 pharmacokinetics, disposition and safety has not been studied in patients, therefore, it is not known whether dose adjustment is indicated.

Of note, the obvious comparison between the safety profile of single-agent CT-2103 and single-agent paclitaxel in the target population is not possible, because the only phase III study evaluating CT-2103 (175 mg/m^2, dose proposed for marketing claim) versus paclitaxel (225 mg/m^2) in 1st line therapy of women with advanced NSCLC and PS2 (study PGT-305) was terminated early due to a high number of on-study deaths in the CT-2103 arm (18/98, 18%), a rate that was numerically higher compared with the comparator arm (paclitaxel) of PGT-305 study (8/97, 9%), and that was also higher than the CT-2103 arm of the PGT-304 study (19/190, 10%). Importantly, this high rate of on-study deaths observed in the CT-2103 arm is still unexplained. As a consequence of the early termination of the trial, many patients enrolled in PGT-305 study did not receive a full course of treatment and some received only one cycle. Adverse events in study PGT-305 were generally similar between treatment arms, with the exception of a significantly higher

incidence of neuropathy (33% vs 19%), arthralgia (15% vs 3%), myalgia (10% vs 1%) and alopecia (53% vs 9%) in the paclitaxel arm, and a significantly higher incidence of grade 3-4 and serious adverse events in the CT-2103 arm, driven by an increased rate of cardiovascular events. However, the inappropriateness of the comparison between the safety profile of CT-2103 and paclitaxel as observed in PGT-305 study is also demonstrated by the significantly lower incidence of neuropathy, myelosuppression and other adverse events reported in the two arms of study PGT-305 compared with the rate observed in study PGT-304 (where similar CT-2103 dose (175 mg/m^2) and same target population were used) and in historical trials performed with paclitaxel in NSCLC, respectively.
Moreover, a comparison between the safety profile of single-agent CT-2103 as observed in PGT-304 study and single-agent paclitaxel as reported in historical studies performed in NSCLC patients with PS2 is not feasible too, due to the scanty historical data published about the safety of paclitaxel in the target population (1st line therapy of patients with advanced NSCLC and PS2) and the significant heterogeneity of such studies in terms of dose of paclitaxel administered, inclusion and exclusion criteria and methods employed for toxicity evaluation.

In summary, the safety profile of CT-2103 appeared to be consistent across studies. Haematological and neurological toxicities were the most commonly reported, of which the severity appears to be related to CT-2103 cumulative dose. Treatment emergent AEs were mostly of mildly to moderately severity and were reported to be manageable in the target population. However, the high rate of on-study deaths observed in the CT-2103 arm of PGT-305 study remains unexplained, thus raising concerns about the safety profile of the drug at the dose proposed in the target population.

VI.3 Balance

Overall, the benefit/risk ratio is considered negative. The claimed benefits of CT-2103 as monotherapy in advanced stage NSCLC and ECOG PS2 is based on the pivotal PGT-304 study: the trial failed to show superiority of CT-2103 over comparator (gemcitabine and vinorelbine); non-inferiority was also not met in a secondary analysis using a pre-specified fixed margin. Also the secondary endpoints (TTP, RR, disease control rate, duration of tumour response and lung cancer symptom control) showed no statistically significant differences. Moreover, the early termination of study PGT-305 due to the high rate of on-study deaths in the CT-2103 arm cannot be ignored, considering that the population enrolled and the CT-2103 dosing regimen administered in PGT-305 study are that of the proposed indication. The efficacy results do not lead to convincing evidence in favour of CT-2103. Of note, according to CHMP guideline, licensing based on one pivotal study requires demonstration of efficacy at levels beyond standard criteria for statistical significance (CPMP/EWP/2330/99).
Moreover, the switching of the primary efficacy analysis from superiority to non-inferiority as proposed by the Applicant for study PGT-304 is still considered not appropriate: the appropriateness of the comparator (gemcitabine and vinorelbine) has not been sufficiently justified by the Applicant, therefore the major objections raised on this issue are still not solved. Essentially there is a lack of historical data clearly establishing the clinical benefit of the comparator over best supportive care in the target population. Indeed, as outlined by EMEA guidelines, “a comparator chosen for a demonstration of superiority may not be acceptable for a conclusion of non-inferiority. In order for it to be acceptable, data from good quality controlled superiority trials showing consistent evidence that the comparator is an effective treatment and establishing the size of its effect relative to no treatment, are needed” (CPMP/EWP/482/99). Such data have not been provided by the Applicant.
From a regulatory perspective “non-inferiority results are acceptable only if a non-inferiority margin can be defined based on historical study results for the reference regimen. If an estimation of the difference between the reference and placebo in the intended patient population, obtained via a systematic review of the literature, is not possible, the sensitivity of a non-inferiority study using this comparator may be questioned and only superiority of the test product to a comparator (active or placebo) would be acceptable... It would not be good practice to define an arbitrary achievable delta and use that to claim non-inferiority” (CPMP/EWP/2158/99). On this basis, and considering also that CT-2103 failed to show a clear superiority over comparators in terms of control of cancer related symptoms and safety profile, the proposed shift of the non-inferiority margin from 1.1 to 1.2 is not justified too, also because it has been chosen after having seen the results. In addition, it should be recognized that, the choice of a new non-inferiority margin of 1.2 would not necessary imply demonstration of non-inferiority of CT-2103, considering that the upper limit of the 95% confidence interval obtained in the study PGT-304 (HR 0.95;

95% CI 0.76-1.20) would just correspond to the margin, thus making the consistency of the results weak. Indeed, according to CHMP guidelines, "when the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the 95% confidence bound is well below the non-inferiority margin" (CPMP/EWP/205/95/Rev.3/Corr.2).

For CT-2103 the benefit is unclear, because in PGT-304 study the absence of an acknowledged benefit of the comparator over BSC in the target population makes any comparison inappropriate and hazardous.
In addition, no formal evaluation of quality of life has been performed, and the evaluation of cancer related symptoms, that may also be biased by the open label-design of the study, did not show any superiority of CT-2103 over the comparators.
Finally, the apparently improved safety profile of the drug, characterized by lower rate of hypersensitivity reactions compared with other taxanes, and decreased myelosuppression and gastrointestinal events versus the comparators (gemcitabine/vinorelbine) in PGT-304 study, is counterbalanced by a significantly increased incidence of grade 3-4 neuropathy in all the phase III studies. Of note, a direct comparison between the safety profile of CT-2103 and the analogous paclitaxel is not feasible, since the only study (PGT-305) evaluating the efficacy and safety of single agent CT-2103 (175 mg/m^2) versus single agent paclitaxel (225 mg/m^2) in the target population was terminated early due to a high rate of on-study deaths in the CT-2103 arm. Indeed, in the absence of a clear explanation, the high rate of on-study deaths reported with CT-2103 in study PGT-305 should be interpreted as a warning for caution in the use of CT-2103 in the target population and at the dose proposed in the claimed indication.

VI.4 Conclusions

Overall, the benefit/risk ratio of CT-2103 in first line treatment of patients with advanced NSCLC and ECOG PS 2 is considered negative. Efficacy has not been demonstrated. The toxicity profile does not provide a clear benefit over alternative compounds. Moreover, the major concerns raised over the appropriateness of the comparator used in study PGT-304 make a non-inferiority claim not acceptable.