European Medicines Agency
Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT
FOR

Orathecin (Rubitecan)
Applicant: EuroGen Pharmaceuticals Ltd

Procedure No. EMEA/H/C/608

Day 172 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.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

EuroGen Pharmaceuticals Ltd sought a marketing authorisation for Orathecin (rubitecan) for the treatment of patients with locally advanced (non-resectable) or metastatic adenocarcinoma of the pancreas who failed at least one prior chemotherapy.
Following review of the application submitted, the CHMP considered that the data presented were not sufficient to demonstrate a clinical benefit for patients treated with rubitecan.

The company informed the EMEA, on 19 January 2006, that it could not address at this stage the issues raised by the CHMP and has decided to withdraw its application (*see questions and answers document<link>*).

2 SCIENTIFIC DISCUSSION

Based on the review of the data submitted and the applicant's response to the CHMP list of questions, the CHMP considered, when the application was withdrawn, that the efficacy of Oratecin (rubitecan) in advanced or metastatic pancreatic cancer had not been demonstrated. Both pivotal studies analysis were negative in terms of overall survival. A difference in survival (or significant benefits in terms of quality of life) would have been necessary to demonstrate the efficacy of rubitecan as second line treatment in advanced pancreatic cancer (due to the course of the disease and the absence of available treatment improving survival). Secondary endpoints also did not provide clear evidence of efficacy of rubitecan in the applied indication. Moreover two quality major issues remained: one concerned impurity limits in the finished product shelf life specification and the other one concerned the absence of stability data for the finished product stored in commercial packaging.

The aim of this report is to provide the status of the CHMP assessment at the time of the withdrawal of Orathecin. The assessment was not finalised at this stage, and some of the issues raised were still under discussion. As a consequence the CHMP could not draw definite conclusions on the benefit/risk balance of the product.

2.1. Problem statement

Pancreatic cancer remains a major health concern, with a 5-year survival of less than 5%. Early diagnosis is rare, the initial diagnosis of a pancreatic carcinoma may be difficult, very radical surgery is rarely curative, and the lack of effective systemic therapy constitutes the major reasons for this very poor prognosis. Radiotherapy with or without concomitant 5-FU chemotherapy is frequently used in unresectable disease and pre- or post surgery to improve survival. In many countries gemcitabine has become the most commonly used first line therapy for patients with advanced pancreatic adenocarcinoma, based on a modest survival benefit compared with 5-FU, combined with clinically meaningful benefits in terms of quality of life. However the median survival for patients with metastatic disease remains less than 6 months.

2.2 About the product

Rubitecan is the pure 20(*S*) enantiomer of 9-nitrocamptothecin (9-NC). Both rubitecan and its major metabolite, 9-aminocamptothecin (9-AC), were described as direct *in vitro* inhibitors of the cellular enzyme topoisomerase I (topo I). As any other camptothecins CPTs, two forms of rubitecan and 9-AC exist in equilibrium in solution: the active lactone form and the inactive carboxylate form. Rubitecan and 9-AC were shown to exert their antitumour activity by interfering with the action of topo I in replicating cells. Topo I is a nuclear enzyme that modulates the topological state of chromatin DNA by introducing transient DNA breaks. CPT derivatives stabilise the covalently linked complexes of DNA-topo I (cleavable complexes), which leads to irreversible DNA strand breaks and degradation. The posology proposed was 1.5 mg/m^2/day, administered orally, on a five-days-on, two-days-off schedule, with at least three litres of fluid per day to reduce the risk of developing cystitis.

2.4 Quality aspects

Active substance

Rubitecan is a topoisiomerase I inhibitor derived from the plant alkaloid campothecin. It is a yellowish powder, which is practically insoluble in water and ethanol. It contains one chiral centre, but it synthesised solely as the *S*-enantiomer and as a well-characterised single polymorphic form. The manufacture and specification of the active substance were evaluated without giving rise to major objections. However, insufficient data were provided regarding the starting material (e.g. impurity profile). Considering the pharmaceutical form selected, attention focussed on the particle size of the active, which is likely to be important to the rate and possibly the extent of absorption. Satisfactory data were provided to support the stability of rubitecan.

Medicinal product

Orathecin is formulated as hard capsules containing either 0.5 mg or 1.25 mg of rubitecan. The primary packaging consists of PVC/Aclar/aluminium blisters.

The pharmaceutical development was satisfactorily described. It focused mainly on enhancing the dissolution rate of the active and its homogeneity in the finished product. Satisfactory data were provided regarding rubitecan milling technique/resulting particle size distribution, the impact of particle size distribution on the dissolution rate, and the development of the blending process. It was shown that that the milling did not affect the crystal form of rubitecan. The excipients selected are commonly used for this kind of formulation. However, the TSE-risk associated with the gelatine was not sufficiently addressed.

The manufacturing process allows to obtain reproducible finished product batches. Both strengths are manufactured from a common blend and the capsules are filled proportionate to the respective dose. Acceptable in-process controls were defined and satisfactory process validation data were presented.

Acceptable release specification, allowing to control that the finished product is manufactured in a consistent/reproducible way, were presented. However, the descriptions and validations of the HPLC methods used were not sufficient. Moreover, no acceptable shelf-life specification, allowing controlling the quality of the finished product over storage was presented. One major issue at the time of the withdrawal concerned the level of two impurities in this specification. The batch analysis data provided were presented for batches tested against different specification and no batch analysis results were submitted for batches tested against the proposed release specification.

Stability data generated using a matrixing design were provided for the three batches of each strength packed in HDPE bottles. Under long-term condition (25°C/40% RH) and under accelerated conditions (40°C/75% RH) respectively up to 2-year data and 6-month data are available. No batch included in the finished product stability studies was packaged in the commercial packaging. The stability data provided for batches packed in HDPE-bottles displayed a high degree of relevance for the stability of the finished product packed in PVC/Aclar/aluminium blisters. However, in the absence of any stability data under long-term and accelerated conditions for the finished product packed in the commercial packaging, it was not possible to define an acceptable shelf life and storage conditions. This was considered as a major issue at the time of the withdrawal.

2.5 Non-clinical aspects

Pharmacology

Rubitecan appeared to share many of its biological and pharmacological characteristics with other camptothecins (CPTs). There was clear evidence that CPTs, including rubitecan, act as topo-I inhibitors, even though the final events leading to cell death or inhibition of proliferation have not been fully elucidated. As suggested from *in vitro* studies, the cellular response to topo-I inhibitors is rather complex and may include additional mechanisms of action, but such mechanisms have not been confirmed *in vivo*.

The cytotoxic effect of rubitecan has been evaluated in conventional *in vitro* systems and in xenograft models with several human tumour cell lines. Most *in vitro* data point to a time and concentration-dependent induction of cell cycle arrest leading to apoptosis at nM concentrations. Once rubitecan

initiates the process of apoptosis in tumourigenic cells, these cells are irrevocably committed to apoptosis and continue to death even after removal of the drug from the culture. Protracted administration of i.v. and oral therapies in mice, where the minimum effective dose and its associated lactone plasma concentration of 9-AC causing objective regression of advanced tumours were determined, revealed that the systemic exposure of 9-AC required for anti-tumour effect was in excess of that achievable in patients. In a number of tumour cell lines, rubitecan was more potent than irinotecan and slightly more potent than topotecan with an essentially similar overall profile on the different cell-lines. *In vivo*, a convincing activity was demonstrated in nude mice xenograft models. In nearly all studies, tumour growth was inhibited and complete tumour regression was induced. Actual tumour regression following rubitecan treatment was shown to be due to massive apoptotic death rather than differentiation of the tumour cells. Still, systems using established cell lines were poorly predictive of clinical success. Unfortunately, there were no studies evaluating the effect of rubitecan on primary tumour samples from patients with solid tumours and there were no attempt to analyse the *in vivo* efficacy of rubitecan in comparison to other drugs currently used for the sought indication.

With respect to schedule dependency, *in vitro* studies showed an S-phase specificity of rubitecan, and a prolonged drug exposure at lower concentrations allowed more cells to enter apoptosis. Substantial efforts were put on the route dependency in the xenograft studies. The studies support the clinical oral posology (five-days-on, two-days-off), but a discussion regarding the efficacy of alternative treatment schedules was missing, since no other oral posologies were studied. The proposed clinical dose (1.5 mg/m^2) was substantially lower than the effective doses in nude mice.

In a number of *in vitro* studies, induction of doxorubicin resistance decreased the sensitivity to rubitecan after short, but not after long-term exposure. In cell-lines, prolonged exposure to rubitecan was reported to induce various levels of resistance to the drug. This was hypothesised to be related to gene inductions, mutations in the topo-I gene, alteration of cellular topo-I, and not related to Pgp. For example, the efficacy of the charged topotecan was inhibited by over-expression of Pgp, but CPT and its uncharged analogues (inclusion of rubitecan suggested even though not studied) did overcome MDR1-mediated resistance.

In combination studies with rubitecan and, for example, 5-FU, gemcitabine, paclitaxel, cisplatin or doxorubicin, additive or synergistic effects were observed. Despite some inconsistencies between studies (occasional antagonism), a schedule-dependence of drug combinations was implied.

No secondary pharmacodynamic studies or specific pharmacodynamic drug interaction studies were provided. This was accepted by the CHMP, since an important number of published data is available on the pharmacology and pharmacodynamics of CPTs, including rubitecan. Likewise, no safety pharmacology studies were provided. Even though this is an orphan indication, the safety profile of rubitecan was considered well characterised in a substantial number of patients. Cardiac effects were not specifically studied, but the CPTs are not identified as a class of compounds inducing QT effects and there were no signals reported from the clinical studies. However, as a clinically relevant exposure was considered not likely to be achieved in dogs, the applicant was required to perform an *in vitro* study to assess the potential for rubitecan and 9-AC to prolong the QT interval. Additional safety pharmacology studies were not considered necessary.

Pharmacokinetics

In all species, the absorption of rubitecan was rapid. Rubitecan was converted to 9-AC. In rats, mice and monkeys, this conversion was slower and was closer to that observed in humans than the conversion profile in rabbits or dogs. Overall, plasma measurements were hampered by low exposure levels and there was a large variability between individuals. Rubitican was administered by the oral route.

In rats, there was a dose-exposure-relationship. Multiple dosing did not suggest any accumulation of rubitecan, while the levels of 9-AC increased. In dogs, the pharmacokinetics of several different formulations was studied. It would have been more meaningful with an evaluation of the formulation used in the toxicity study, and a bridging study to the proposed commercial formulation. There was no information on dose-exposure-relationship, or accumulation in this species. There were no gender differences in exposure of rubitecan, while female dogs were more exposed to 9-AC. The absolute oral

bioavailability in dogs was 1 - 5 %. Presystemic, intra-luminal metabolism of rubitecan was observed in dogs, and the bioavailability for the sum of rubitecan and 9-AC was 25- 30%.

In rodents, rubitecan was distributed to blood/plasma and to tissues related to excretion. This distribution was similar to intravenous irinotecan and topotecan. The binding of the lactone and carboxylate forms of rubitecan and 9-AC to the various blood components is complex. In humans, most of the binding of both forms was to serum albumin. Compared to human albumin, the degree of rubitecan binding to albumin in dogs was substantially lower for both rubitecan forms. Regarding AC-9, the binding to dog albumin was substantially lower for the carboxylated form and similar for the active lactone form compared to human serum albumin. Even though rubitecan was rapidly converted to 9-AC in dogs, this may indicate that *in vivo*, dogs were exposed to a higher fraction of the unbound, pharmacologically active lactone form of rubitecan. This could explain the high toxicity in this species.

Besides the characterisation of the main metabolite 9-AC, there were no metabolism data available in toxicity species. *In vitro* data from human hepatic microsomes suggested a probable CYP-dependent metabolism. Formally, at least an *in vitro* profile of the metabolite pattern in the different species would have been required. However, since only toxic effects typical of cytotoxic anticancer drugs were seen in animals and in clinical studies (> 1400 exposed patients), the existence of a unique human metabolite associated with severe or "atypical" toxicity was thought unlikely. Urinary metabolites represented a minor proportion of the administered dose. In rat bile or faeces, a glucuronide of oxidised CPT, 9-AC and the oxidised form of CPT were identified, while in monkey bile, glucuronides were predominant. The primary route of excretion of rubitecan resembles that of irinotecan, which is excreted primarily in bile/faeces. Rubitecan was eliminated mainly in the form of metabolites and most of the radioactivity was recovered within 24 hours. No pharmacokinetic drug interaction studies were performed. Hepatic metabolism in humans was investigated in clinics (see clinical pharmacokinetics).

Toxicology

Single dose toxicity studies were not performed. Justifications were provided referring to the available published data on the toxicity of rubitecan in animals and humans. The justifications were considered acceptable. In a 4-week rat and 8-week dog studies, animals were treated per os according to the clinical posology with a 5-day on, 2-day off, dosing schedule followed by a recovery period. Rats were given doses corresponding to 1.4 to 29-fold the dose (on a body surface area basis) proposed for clinical trials. Dogs were given 1.4 to 9.4-fold the clinical dose.

In both species, the primary target organs were the gastrointestinal system, the lymphoid system and the bone marrow. Target organs were those identified for several other anti-cancer drugs including irinotecan and were predictive of the clinical adverse event profile with the exception of cystitis.

In both species, a number of animals, which received high dose of rubitecan, died or were euthanised moribund. The cause of death was attributed to gastrointestinal damage and lymphoid depletion or pancellular depletion of bone marrow. Clinical pathology changes were not marked, but consistent with anaemia and lymphocytopenia, especially in rats. In rats, there were minor variations in Alanine aminotransferase and alkaline phosphatase, and a minor increase in blood urea nitrogen after 4 weeks dosing. The latter could be indicative of dehydration, stress gastrointestinal haemorrhage or kidney damage. Gastrointestinal or renal effects were not confirmed histologically. In high dose male rats, significant decreases in heart, kidney, liver, pituitary and thyroid organ weights (absolute and relative to brain) were observed, but not discussed. There were no apparent signs of cumulative toxicity at the tolerated dose levels, but the duration of the rat study was short. At the end of the 2-week recovery period, all findings in the rats were reversed.

In dogs receiving low or mid-doses of rubitecan, few changes could be attributed to treatment. Only gastrointestinal mucosal enteropathy was observed. In dogs receiving high dose of rubitecan aimed for recovery, only one animal/gender remained and since the dogs were treated for 3 weeks only, due to poor conditions and moribund mortalities, recovery could not be assessed. On the other hand, in the two recovery animals that remained from the high dose group, the gastrointestinal changes were essentially resolved. In comparison with control animals, slight signs of anaemia were observed. The female dog had elevated mean corpuscular haemoglobin and a 7-fold increase in platelets. This could

be indicative of haemolysis or iron deficiency anaemia due to gastrointestinal bleeding, but there were no correlates with microscopy.

The limited toxicokinetic data in rats indicated a substantial variability in systemic exposure. Even at a dose causing mortalities, maximal clinical C_{max} of rubitecan was not reached in rats, especially not in the female animals. In the dog study, samples for toxicokinetic evaluation were sampled but not analysed. Dose-exposure linearity was not studied in dogs, but assuming such a relationship, it is likely that clinical exposure would not be reached.

The window between a dose free from toxicity and a severely toxic dose was very narrow. Due to overt toxicity, clinical exposure could not be reached. There were insufficient data from toxicity species to assess the activity and the potential toxicity of the metabolites of rubitecan. However, only toxic effects typical of cytotoxic anticancer drugs were observed in animals, and clinical studies confirmed that there were no specific adverse effects not identified in toxicity species. The existence of a unique human metabolite associated with severe or "atypical" toxicity was considered unlikely.

At the time of the withdrawal, the non-clinical repeat dose toxicity package did not bring any significant information to the safety evaluation of rubitecan; however, no additional information was required considering the sought indication.

As expected, rubitecan was found genotoxic in a standard battery of tests and was therefore considered as a genotoxic carcinogen. No carcinogenicity studies or studies in juvenile animals were performed. This was considered acceptable in view of the claimed indication. Teratogenicity was not observed in reprotoxicity studies in rats and rabbits. However, these findings were contradictory with irinotecan and topotecan reports, and likely due to insufficient exposure. Transplacental passage of rubitecan, 9-AC and maternal/foetal exposure ratios were not investigated. Therefore the teratogenic risk for man could not be ruled out. Further investigations on placental transfer of rubitecan and 9-AC would have been required. This issue remained unresolved at the time of withdrawal.

No studies were conducted to assess the local tolerance of rubitecan. Gastrointestinal toxicity was identified in animals and humans. No immunotoxicty studies were provided. Rubitecan being a cytotoxic drug inducing myelosuppression, further evaluation was not considered necessary.

A number of impurities were tested (proposed limit of 0.5 %). CPT is considered acceptably qualified, since it is well-characterised (including clinical testing) and described in a number of publications, and likely a metabolite. In terms of general toxicity testing, the impurities 14-NC and 12,14-diNC were considered qualified up to 0.5 %.

Rubitecan had potential effects on the environment, but considering the low prevalence of pancreatic cancers, the concentration of rubitecan in the aquatic environment would have constituted no risk.

2.6 Clinical aspects

Pharmacokinetics

The pharmacokinetics of rubitecan has mainly been described through three phase I/II studies in patients with various advanced-stage solid tumours. Plasma concentrations of rubitecan as well as 9-AC were determined in these studies, using validated HPLC or LC/MS/MS methods. In addition, the Applicant performed a bioequivalence study comparing the clinical trial and the commercial formulation, and *in vitro* studies on permeability over CACO2 cells, protein binding and metabolism in human hepatic microsomes.

The pharmacokinetics of rubitecan and its active metabolite are incompletely understood. Factors that might affect exposure, such as organ impairment or concomitant medications, were therefore difficult to predict. The dose was individually titrated. However, individual dose-titration was viewed as a difficult procedure due to high variability and non-proportional change in exposure to 9-AC and rubitecan. Another anticipated difficulty was that the dose should not be up-titrated before 4 weeks without severe myelotoxicity; therefore, the highest possible dose for each patient would have had to be identified at the start of treatment to avoid 4 weeks of underexposure.

In vitro, rubitecan displayed a high intestinal permeability and appeared not to be a substrate for efflux proteins. The absolute bioavailability in humans is not known, but may be low due to pre-systemic metabolism. In dogs, absolute bioavailability of rubitecan was only 1-5%, while the bioavailability of rubitecan + 9-AC was 25-30%. Data on C_{max} of rubitecan and 9-AC and *in vitro* data indicated that the pre-systemic conversion to 9-AC is lower in man.

Bioavailability of rubitecan was decreased by concomitant food intake (high-fat breakfast). The applicant initially suggested that, since the dose would be individually titrated upwards or downwards based on myelotoxicity, patients could choose to take Orathecin with or without food. The starting proposed dose was 1.25 mg/m^2. However, given that the dose could not be up-titrated before 4 weeks of treatment, it was questioned whether a higher starting dose should be given to patients taking Orathecin with food. In response, the applicant suggested to increase the starting dose to 1.5 mg/m^2, which was the starting dose used in the clinical efficacy studies. In addition, recommendation to take Orathecin with a light meal and at the same time of day was made to decrease intra-individual variability. The revised dosage recommendations were considered more appropriate.

Rubitecan displays dose-dependent pharmacokinetics, with exposure to parent compound and 9-AC increasing much more than the dose (1.0 to 1.5 mg/m^2/day), although there was a large variability of the data observed. The reason for the non-linearity was not identified. There was no evidence that pharmacokinetics changed over time upon repeated dosing. Coefficient of variation (inter-individual variability) was often 90% or more. In a cross-over bioequivalence study with two different formulations, the intra-individual variability was about 50%. It was acknowledged that explaining the non-linearity and optimising the individual dose titration scheme were difficult.

Since no studies with intravenous administration were performed in humans, the volume of distribution could not be determined. Protein binding was determined separately for the lactone and the carboxylate forms of rubitecan and 9-AC. The lactone form of rubitecan was 97% bound in plasma, mainly to albumin. The lactone form of 9-AC was 65% bound. Both carboxylate forms were 100% bound. *In vitro*, this led to an almost complete shift of the equilibrium towards the carboxylate form, with very low concentrations of unbound drug.

The exposure to 9-AC (the only metabolite studied in plasma) was about one quarter of that of rubitecan, indicating that rubitecan accounted for most of the activity. However, data on protein binding were difficult to interpret, as it was difficult to know whether the free concentration of the active lactone was higher for 9-AC.

The elimination half-life was about 15-18 hours and 18-22 hours for rubitecan and 9-AC, respectively. The elimination pathways for rubitecan and its active metabolite, the plasma exposure to different metabolites, routes of excretion and the relative importance of different elimination routes were incompletely elucidated. There was no mass-balance study. *In vitro* data indicated that the conversion of rubitecan to 9-AC was mediated by cytochrome P450, and that 9-AC was further metabolised via this enzyme system. The specific isozymes involved were not identified. This made the potential metabolic drug-drug interactions difficult to predict. Animal data suggested that a major part of drug-related material was excreted in bile as glucuronidated metabolites, but this was not confirmed in humans. Cystitis was observed in patients but not in non-clinical toxicology studies, which could indicate that urinary excretion is a more important elimination pathway for active moieties in man. About 9-10% of a dose was excreted in urine as rubitecan and 9-AC. Since the bioavailability was unknown, the major route of elimination for the active compounds (urinary excretion or hepatic metabolism) could not be determined.

The applicant suggested that use of Orathecin in patients with moderate to severe renal impairment (CLcrea<50 ml/min) is contraindicated, based on medical considerations as all patients were recommended to drink at least 3 litres of fluid per day to decrease the risk for cystitis. A strict contraindication was, however, not considered appropriate. A contraindication in patients unable to maintain adequate hydration would have been more appropriate.

Hepatic impairment was expected to affect the elimination of rubitecan. In response to the list of Questions, the Applicant had suggested that severe hepatic impairment is contraindicated due to lack of data in this patient group. However, a strong warning was considered more appropriate. For mild to

moderate hepatic impairment special warnings were made due to non-proportional increases in exposure at increased doses.

There were no consistent trends towards different pharmacokinetics in men and women but this could be due to sparse data and high variability. In one study, exposure appeared to be higher in women than in men at the 1.5 mg/m^2 dose but not at 1.25 mg/m^2 dose. There were no consistent changes in pharmacokinetics with age. Patients' age ranged from 20-80 years, but data were sparse and highly variable. Other demographic factors were not studied.

Pharmacokinetic drug-drug interactions were not discussed, and no studies performed. Published data indicate that rubitecan is metabolised via CYP450 enzymes, but the applicant did not investigate which specific CYP450 isozymes were responsible for the metabolism of rubitecan and 9-AC, or whether rubitecan had the potential to inhibit CYP450. This was considered as a deficiency in the application, as no information could be given in the product information regarding potential risk for interactions with concomitantly administered drugs. The applicant had therefore agreed to perform *in vitro* studies to identify the specific isozymes responsible for rubitecan and 9-AC metabolism and the potential of rubitecan and 9-AC to inhibit or induce CYP450 enzymes.

At the time of the withdrawal, although the pharmacokinetics of rubitecan were incompletely understood, the issues raised were considered resolved based on possible amendments of the product information and further investigations of the pharmacokinetics properties (metabolism and potential interaction) of rubitecan.

Pharmacodynamics

Rubitecan is a semisynthetic camptothecin analogue, which exists in two forms at physiological pH 7.4, an active lactone and an inactive carboxylate form. It is highly insoluble and intravenous formulations have been unsuccessful to develop. The pharmacodynamic action is exerted mainly by interaction with the nuclear enzyme DNA topoisomerase I (topo-I).

The toxicity profile of rubitecan seemed similar to what has been observed with other topo-I interactive agents. Myelosuppression is the major dose limiting toxicity dose-limiting toxicity (DLT), as the majority of cytotoxic agents. Information regarding toxic interaction with other chemotherapeutic agents, e.g. gemcitabine, capecitabine and etoposide, was proposed to be included in the product infomation. Concerning cross-resistance with the other cytostatics, no data addressing this issue was presented, such as *in vitro* cytotoxicity assays of tumour cells.

A study in 41 patients with various histologically or cytologically confirmed solid tumours, aimed to establish the relationship between plasma pharmacokinetics with clinical response and toxicity. No PK/PD correlation was observed. The lack of correlation with effect was not surprising in a phase I study with no complete responses and only one partial response. However, a positive correlation between plasma concentration and toxicity should be possible to detect, especially in a situation where drug exposure is highly variable between patients. This lack of relationship has been further discussed and investigated, and data indicating a correlation with AUC and peripheral blood counts has been presented by the applicant.

Two phase I studies were conducted to determine the maximal tolerated dose (MTD) in patients with various solid tumours. The DLTs observed in these studies were myelosuppression, gastrointestinal effects and haemorrhagic cystitis. The MTD determined was 1.25 and 1.5 mg/m^2 given day 1-5 weekly. The lower MTD observed in one of the studies could be explained by the fasting conditions required two hours before and two hours after administration of rubitecan, as compared with just two hours before administration in the other study. All the clinical phase II/III data were collected using the higher dose. This dose was the proposed starting dose.

Clinical efficacy

Dose response studies

No formal dose-response studies have been performed with rubitecan.

Main studies

Three open-label, multi-centre study reports pertinent to the claimed indication were submitted.

RFS 2000-09 was a randomized, phase III study comparing rubitecan with best choice therapy in patients with pancreatic cancer with failure or relapse after more than one chemotherapy, except gemcitabine alone or 5-fluorouracil (5-FU) radiosensitization. RFS 2000-06 was a randomized, phase III study comparing rubitecan with 5-FU, in patients with pancreatic cancer with progression or relapse after gemcitabine. RFS 2000-01 was a phase II non-contolled study, in patients with pancreatic cancer with failure or relapse after more that one chemotherapy, other than gemcitabine alone.

Study RFS 2000-09

METHODS

Study Participants

The main inclusion criteria were histologically or cytologically confirmed diagnostic of primary adenocarcinomas of the pancreas, Karnofsky Performance Status (KPS) of ≥ 50, adequate bone marrow, hepatic and renal function (ANC ≥1500/mm^3, haemoglobin > 9g/dL, and platelets ≥ 100,000/mm^3), and sufficient recovery from previous therapy, failure or relapse after ≥1 chemotherapy regimen (other than just gemcitabin alone or low-dose radio-sensitization with 5-FU).

Treatments

Patients were randomised to rubitecan 1.5 mg/m^2/day given orally for five days each week or to the most appropriate therapy (best choice), which could consist of physician's choice of most appropriate chemotherapy or supportive care only. Rubitecan was administered together with an acidic beverage. Patients were encouraged to drink at least 3 litres of fluid daily to reduce the possibility of cystitis. Treatment was to continue for 8 weeks, or until disease progression, significant organ dysfunction or Grade 4 toxicity according to the Common Toxicity Criteria that did not resolve within 6 weeks of withholding treatment. Cross-over from the comparator arm to the Rubitecan treatment arm after disease progression was allowed. Doses were modified in order to dose patients to their individual MTD. The doses were to be increased or decreased in each patient depending on absence or occurrence of myelosuppression. All courses were to be withheld until recovery of platelets to >100,000/mm^3 and granulocytes to ≥1500/mm^3 and complete recovery of all non-hematological toxicities, except alopecia, to baseline. Dose reduction for cystitis was performed according to clinical Grade (NCI CTC criteria). Grade 1 haematuria with pain or Grade 2 haematuria resulted in withheld treatment until recovery (including resolution of any pain on urination), and a dose decrease of 0.25 mg/m^2/day. Grade 3 haematuria resulted in withheld treatment until recovery and a dose decrease of 0.50 mg/m^2/day. Grade 4 haematuria resulted in cessation of treatment. For Grade 1 haematuria without pain, the patient was closely monitored until recovery. No concomitant radiotherapy, chemotherapy, immunotherapy or hormonal therapies were allowed during these studies. However, G-CSF was permitted in the case of neutropenia <500 cells/mm^3 or neutropenic fever, and epoetin alfa was permitted.

Objectives

The primary objective was to compare overall survival in patients receiving oral rubitecan *versus* most appropriate therapy (best choice) in patients with refractory pancreatic cancer. Secondary objectives were to compare time to treatment failure, time to disease progression, objective response rate and toxicity of rubitecan *versus* best choice treatment.

Outcomes/endpoints

The primary outcome, duration of survival, was defined as the time from randomization to death from any cause.

The secondary outcome measures included progression free survival (PFS), time to radiological progression (TTRP) and tumour response. PFS was defined as the time from randomization to the date of either radiological progression or, if unavailable, symptomatic progression, or, if neither available, the date of death. TTRP was defined as time from randomization to the date of radiological progression. Patients who had not progressed at the time of last follow-up or who were lost to follow-up had observations censored at the last visit. The date of radiological progression was also assessed by an independent expert. All TTRP and PFS results were also calculated with the date of radiological progression adjusted to the next scheduled scan (every 56 days). Objective tumour response was

assessed in patients with bi-dimensionally measurable disease. Criteria for response assessments were adapted from the WHO criteria· tumour response.

Sample size

A sample size of 200 patients in each arm was selected for both pivotal studies. The log-rank equality test of survival with a two-sided p level of 0.05 had approximately 80% power to detect a difference between median survival times of 4.7 months (rubitecan) and 3.5 months (5-FU/ best choice). No references were cited in the protocols as a basis for these assumptions.

Randomization

Patients were enrolled as they entered the study and were assigned a sequential patients number for each center. Each patient was stratified by performance status (KPS 50-70 *versus* >70) and previous chemotherapy (gemcitabine *versus* 5-FU *versus* other). Stratification by center was not performed.

Blinding (masking)

There was no blinding of study drugs. Blinding reading of scans by an independent radiology panel was implemented for final assessment of best tumor response and radiological progression dates.

Statistical methods

The log-rank test was used to compare the treatment groups for each of the time-to-event variables, Fischers exact test was used to compare the objective response and toxicity between groups, and logistic regression was used to examine the effects prognostic factors on response.

RESULTS

Participant flow

Of the 409 patients enrolled, a total of 198 were randomised to rubitecan and 211 to best choice. The protocol specified dosing for 8 weeks or longer if patients tolerated the medicinal product and had no evidence of progression, with allowance for discontinuation at any time for disease progression, unacceptable toxicity or patient request; 63% of patients receiving rubitecan and 51% of best choice patients continued on treatment/care for at least 4 weeks, and 35% and 24%, respectively, for at least 8 weeks.

The most common reason for discontinuation was disease progression (43% in the rubitecan arm and 46% in the best choice arm) and symptomatic progression (25% and 27% respectively). Discontinuation for study drug toxicity was 4% in both arms, and death occurred in 11% of patients receiving rubitecan and 12% of patients receiving best choice therapy. All randomised patients were included in the ITT analyses.

Conduct of the study

None of the protocol amendments were considered to have any substantive impact on study results.

Baseline data

Demographic and disease baseline characteristics are shown in Table 1 and 2.

Table 1: Demographic and Baseline Characteristics Baseline Characteristics in Study RFS 2000-09:

	rubitecan N=198 (%)	**Best Choice N=211 (%)**	**p-Value**
Sex			
Male	105 (53)	117 (56)	0.691
Female	93 (47)	94 (45)	
Age (years)			
Mean ± SD	62.7 ± 10.5	61.0 ± 11.3	0.112
Median	64.0	61.0	
Range	37-86	31-84	

	rubitecan N=198 (%)	Best Choice N=211 (%)	p-Value
Race			
White	176 (89)	187 (89)	0.868
Black	6 (3)	8 (4)	
Asian	4 (2)	7 (3)	
Hispanic	7 (4)	5 (2)	
Other	5 (3)	4 (2)	
Karnofsky			
Mean ± SD	83.5 ± 11.7	83.7 ± 11.6	0.824
Median	90.0	90.0	
Range	50-100	50-100	
Stage of Disease			0.100
I	0	0	
II	2 (1)	6 (3)	
III	14 (7)	7 (3)	
IV	181 (91)	197 (93)	
Missing	1 (<1)	1 (<1)	

Table 2: Disease Baseline Characteristics Baseline Characteristics in Study RFS 2000-09:

	rubitecan N=198 (%)	Best Choice N=211 (%)	p-Value
Time from diagnosis (days)	N=194	N=208	
Mean ± SD	389.5 ± 443.5	379.8 ± 292.7	0.505
Median	294	294	
Range	9-4360	9-1641	
Cancer Antigen 19-9			
< 37 U/mL (Normal)	25 (13)	30 (14)	0.845
> 37 U/mL	142 (72)	151 (72)	
Missing	31 (16)	30 (9)	
Number of Prior Chemotherapies			
0	3 (2)	5 (2)	
1	64 (32)	58 (27)	ND
2	97 (49)	104 (49)	
3	26 (13)	36 (17)	
4 or more	8 (4)	8 (4)	
Prior Chemotherapy			
Gemcitabine	169 (85)	180 (85)	ND
5-FU	139 (70)	153 (73)	
Gemcitabine plus 5-FU	119 (60)	132 (63)	
Cisplatin/Carboplatin	28 (14)	40 (19)	
Mitomycin C	19 (10)	21 (10)	
Capecitabine	16 (8)	14 (7)	
Docetaxel	13 (7)	15 (7)	
Paclitaxel	13 (7)	8 (4)	
Prior Treatments			
Whipple surgery	57 (29)	65 (31)	ND
Radiotherapy	111 (56)	114 (54)	
Type of Carcinoma			
Adenocarcinoma	183 (92)	198 (94)	ND
Mucinous	8 (4)	6 (3)	
Acinar Cell	1 (1)	2 (1)	
Poorly Differentiated	3 (2)	3 (2)	
Other	1 (<1)	2 (1)	
Number of Tumour Sites			
1	90 (45)	114 (54)	ND
2	73 (37)	74 (35)	
3 or more	31 (16)	20 (9)	
0	4 (2)	3 (1)	
Tumour location (common only)			
Pancreas	116 (59)	106 (50)	ND
Pancreas + Liver	58 (29)	41 (19)	
Liver	118 (60)	118 (56)	

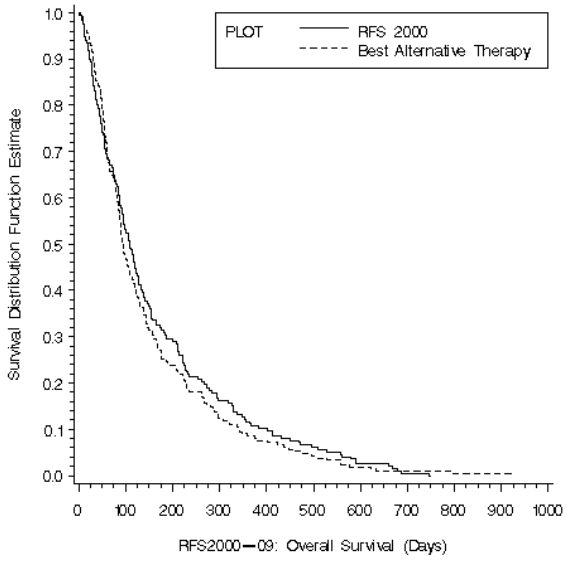
ND = Not done

Outcomes and estimation

Survival

The median survival was numerically longer with rubitecan than Best Choice therapy (108 *versus* 94 days respectively, ITT analysis), but this difference was not statistically significant (p=0.626), see figure 1. There were 49% of patients on the control treatment who crossed over to rubitecan therapy.

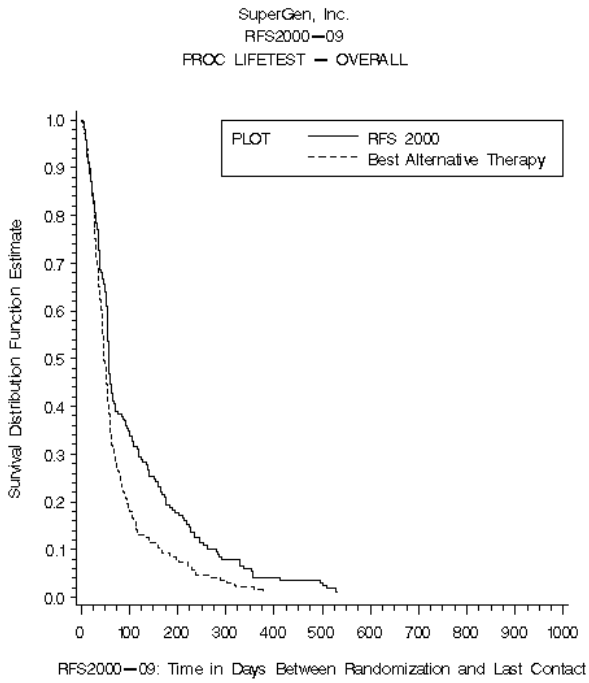
Figure 1 - Survival duration in the randomized populations (study RFS 2000-09)



Progression free survival

The ITT analysis for median (95% CI) PFS for rubitecan (58 days [56–64]) was significantly longer than for Best Choice therapy (48 days [44–55], p=0.001), see figure 2, table 3.

Figure 2 Progression-free survival per investigator assessment in study RFS 2000-09



The ITT analysis for median (95% CI) TTRP for rubitecan (58 days [57–65]) was significantly longer than for Best Choice therapy (53 days [48–58], p=0.003). The tumour response rate in the ITT analysis was 6.1% in the rubitecan arm compared with 0.5% in the Best Choice therapy arm (p=0.001). The response with rubitecan included 2 complete and 10 partial responses, with a median duration of 148 days and median survival (338 days) and PFS (269 days).

Tumour growth control was achieved in 28% of all patients receiving rubitecan compared with 13% in the Best Choice therapy are (statistical significance not tested). Patients who achieved a best response to rubitecan of stable disease had a median survival of 222 days and a PFS of 173 days.

Table 3 - Summary of unadjusted[b] analyses of secondary endpoints

Study	Treatment	Enrolled/ Treated	Unadjusted median TTRP (95% CI)	Unadjusted median PFS (95% CI)	Best response (%) /ITT pop
RFS 2000-09	**rubitecan**	198/194	58 (57-65)	58 (56-64)	2CR, 10PR (6)
	Best Choice	211/210	53 (48-58)	48 (44-55)	1CR, 0PR (<1)
	p-value[a]		p=0.003	p=0.001	p=0.001

a: Log-rank test
b: per investigators, based on actual days

Ancillary analyses

The data of study RFS 2000-09 have been analysed censoring the data from patients that crossed over to rubitecan arm at the time of crossover. The median (95% CI) survival for patients randomized to Best Choice therapy was markedly reduced to 60 (56–68) days; this was significantly less than observed in patients randomized to rubitecan (108 days [93–125], p<0.0001, ITT analysis).
The TTRP result was confirmed using independently reviewed data with adjustment to the next scheduled scan. This analysis supported the previous (114 days (62–115) vs. 64 (61-70) days, in the rubitecan vs. Best Choice groups, respectively, p=0.009). The PFS result was confirmed using independently reviewed data with exclusion of symptomatic progression and adjustment to the next

scheduled scan (median results of 113 vs. 65 days, in the rubitecan vs. Best Choice groups, respectively, p=0.026). In evaluable patients with follow-up scans on study, the response rate was 9.8% for Rubitecan compared with 0.8% for Best Choice (p<0.001) (table 4).

Table 4 - Summary of adjusted[b] analyses of secondary endpoints

Study	Treatment	Enrolled/ Treated	adjusted median TTRP (95% CI)	adjusted median PFS (95% CI)	Best response (%) /assessable
RFS 2000-09	**rubitecan**	198/123	114 (62-115)	113 (60-115)	2CR, 10PR (10)
	Best Choice	211/118	64 (61-70)	65 (63-70)	1CR, 0PR (1)
	p-value[a]		p=0.009	p=0.026	p=0.001

a: Log-rank test
b: per independent review

Study RFS 2000-06

METHODS

Study Participants

The main inclusion criteria were those listed for study RFS 2000-06. Patients enrolled had failed gemcitabine therapy only (progressive disease or relapse after response).

Treatments

Patients were randomised to Rubitecan 1.5 mg/m^2/day given orally for five consecutive days each week for eight weeks to 5-FU 600mg/m^2 IV once weekly. Patients having haematological or non-haematological toxicity which resulted in a delay of chemotherapy for > 3 weeks were to be remove from study (see study RFS 2000-09).

Objectives

The primary objective was to compare overall survival in patients receiving oral rubitecan *versus* intravenous 5-FU in patients with refractory pancreatic cancer. Secondary objectives were to compare PFS (time to treatment failure), time to disease progression, clinical benefit response rate, objective response rate and toxicity of rubitecan *versus* intravenous 5-FU.

Outcomes/endpoints

The primary outcome, duration of survival, was defined as the time from randomization to death from any cause.
The secondary outcome measures included progression free survival (PFS), objective response and clinical benefit response. PFS was defined as the time from randomization to the date of either objective evidence of progression or symptomatic progression, or the date of death. Patients who had not progressed at the time of last follow-up or who were lost to follow-up had censored observations at those times. Objective tumour response was assessed in patients with bi-dimensionally measurable disease. Criteria for response assessments were adapted from the WHO criteria. tumour response. Clinical benefit response was a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change.

Sample size, Blinding, Statistical methods
(see study RFS 2000-09).

Randomization

Patients were stratified prior to randomisation according to the stage of the disease level, measurable disease vs. non-measurable disease and performance status (KPS 50-70 vs. >70).

RESULTS

Participant flow

All patients who were randomised, independent of whether they received treatment, were included in the survival analyses (n=224 in both arms). All randomised patients were included in the ITT analyses.

The most common reason for discontinuation was disease progression (46% in the rubitecan arm and 47% in the 5-FU arm) and symptomatic progression (22% in both arms). Discontinuation for study drug toxicity was 8% rubitecan arm and 2% in the 5-FU arm, and death occurred in 10% of patients of both arms. Discontinuation for "other" causes was 5% rubitecan arm and 10% in the 5-FU arm (which includes 20 patients never treated with 5-FU).

Baseline data

Demographic and disease baseline characteristics are shown in Table 5 and 6.

Table 5: Demographic and baseline characteristics Baseline Characteristics in study RFS 2000-06:

	rubitecan N=224 (%)	**Best Choice N=224 (%)**	**p-Value**
Sex			
Male	111(50)	128 (57)	0.107
Female	113 (50)	95 (42)	
missing	0	1 (<1)	
Age (years)			
Mean ± SD	63.1 ± 10.7	62.4 ± 10.9	0.486
Median	63.0	63.0	
Range	36-90	32-90	
Race			
White	176 (79)	179 (80)	0.298
Black	7 (3)	11 (5)	
Asian	5 (2)	3 (1)	
Hispanic	6 (3)	6 (3)	
Other	6 (3)	1 (<1)	
missing	24 (11)	24 (11)	
Karnofsky			
Mean ± SD	81.7 ± 11.7	81.9 ± 11.3	0.418
Median	80.0	80.0	
Range	50-100	50-100	
Stage of Disease			
I	0 (0)	0	0.628
II	7 (3)	8 (4)	
III	9 (4)	13 (6)	
IV	208 (93)	200 (89)	
missing	0	3 (1)	

Table 6: Disease baseline characteristics Baseline Characteristics in study RFS 2000-06:

	rubitecan N=224 (%)	**5-FU N=224 (%)**	**p-Value**
Time from diagnosis (days)	N=219	N=202	
Mean ± SD	252 ± 240	265.5 ± 252.6	0.975
Median	184	190	
Range	6-1968	5-1598	
Cancer Antigen 19-9			
< 37 U/mL (Normal)	29 (15)	26 (13)	0.239
> 37 U/mL	134 (67)	123 (57)	
Missing	37 (19)	51 (26)	
Number of Prior Chemotherapies			
0	1 (<1)	0 (0)	ND
1	210 (94)	211 (94)	
2	11 (5)	10 (4)	
3			
4 or more			

	rubitecan N=224 (%)	5-FU N=224 (%)	p-Value
Prior Chemotherapy			
Gemcitabine	222 (99)	221 (99)	ND
5-FU	2 (1)	1 (<1)	
Gemcitabine plus 5-FU			
Cisplatin/Carboplatin			
Mitomycin C	3 (1)	3 (1)	
Capecitabine			
Docetaxel			
Paclitaxel			
	4 (2)	3 (1)	
	0	1 (<1)	
Prior Treatments			
Whipple surgery	32 (14)	32 (14)	ND
Radiotherapy	30 (15)	41 (21)	
Type of Carcinoma			
Adenocarcinoma	202 (90)	201 (90)	ND
Mucinous	7 (3)	12 (5)	
Acinar Cell	2 (1)	0 (0)	
Poorly Differentiated	7 (3)	3 (1)	
Other	6 (3)	5 (2)	
Missing	0 (0)	3 (1)	
Number of Tumour Sites			
1	39 (17)	47 (21)	ND
2	88 (39)	89 (40)	
3 or more	96 (43)	84 (38)	
	1 (<1)	4 (2)	
Tumour location (common only)			
Pancreas	176 (79)	172 (77)	ND
Pancreas + Liver	123 (55)	105 (47)	
Liver	157 (70)	140 (62)	

ND = Not done

Outcomes and estimation

The median survival was numerically longer in patients treated with 5-FU (116 days) than in patients treated with rubitecan (93 days). This difference was not statistically significant (p=0.697). There were 49% of patients on the control treatment who crossed over to rubitecan therapy.
The median PFS and TTRP were similar in the two groups (see table 7). The tumour response rate was 3.1% in the rubitecan arm and 0.4% in the 5-FU arm (p=0.07). Tumour growth control rate was similar in the two groups (19% for rubitecan, 21% for 5-FU).

Table 7 - Summary of unadjusted[b] analyses of secondary endpoints

Study	Treatment	Enrolled/ Treated	Unadjusted median TTRP (95% CI)	Unadjusted median PFS (95% CI)	Best response (%) /ITT pop
RFS 2000-06	**rubitecan**	224/221	56 (54-60)	56 (54-60)	2CR, 5PR (6)
	5-FU	224/204	56 (53-63)	56 (53-63)	1CR, 0PR (<1)
	p-value[a]		p=0.868	p=0.868	p=0.07

a: Log-rank test
b: per investigators, based on actual days

Ancillary analyses

The data have been analysed censoring the data from patients that crossed over to rubitecan arm at the time of crossover. The response results from evaluable patients in study RFS 2000-06 does not differ from the results of the ITT population.

Clinical studies in special populations

Survival and PFS data for patients randomized to rubitecan treatment were examined by gender, age, race, and disease stage using the pooled data from the two phase III studies.
Gender had no statistically significant effect on survival or PFS in Rubitecan-treated patients. Both survival and PFS were comparable among patients aged 40–64 years and those aged > 64 years.
PFS (p = 0.016) and survival (not significant) was improved among patients who did not have Stage IV disease.

Supportive studies

Study RFS 2000-02

This was an open-label, randomised, multicenter, phase III study, to assess the efficacy of rubitecan *versus* gemcitabine in naïve patients with locally advanced, unresectable stage II or III or metastaic stage IV pancreatic cancer. Patients were randomised to either 8 weeks of treatment with oral rubitecan given for five consecutive days each week or 8 week of IV gemcitabine infused weekly for 7 weeks, followed by 1 week rest (cycle 1 = 8 weeks). Additional cycles of treatment were allowed for patients with disease stabilisation or regression after the initial 8 weeks.

Gemcitabine was found to be superior to rubitecan for all efficacy parameters, as summarised in the table below:

Table 8: Efficacy results from study RFS 2000-02

Efficacy variable[a]	**rubitecan (N = 496)**	**Gemcitabine (N = 498)**	**p-value**
Median survival (days)	139	171	0.025
Median PFS (days)	58	77	<0.001
Median TTP (days)	57	60	0.019
Response rate (%)	2	4	0.039

a: see RFS 2000-06 for definitions of endpoints

Discussion on clinical efficacy

The proposed indication was supported by two phase III trials. In study RFS 2000-09, conducted in 409 patients, rubitecan was compared with Best Choice therapy. In study RFS 2000-06, conducted in 448 patients, rubitecan was compared with 5-FU. Patients involved in study RFS 2000-09 were predominantly receiving the treatment as a third line or later line therapy (66% of patients had failed two or more chemotherapies, most commonly gemcitabine, 5-FU, and gemcitabine with 5-FU). In the Best Choice therapy group, 13% of patients were receiving no active treatment. Patients involved in study RFS 2000-06 were predominantly receiving the treatment as a second line therapy following failure of gemcitabine.
The starting dose investigated in the phase II-III studies of the clinical development programme was 1.5 mg/m^2/day. The dose selection rational was not presented, and the possible influence on therapeutic results were not addressed by the applicant. In the phase III trials, rubitecan was administered orally with a starting dose of 1.5 mg/m^2/day on a five-days-on, two-days-off schedule until disease progression or lack of tolerability. The dose was adjusted to the individual MTD. The randomised groups in the pivotal studies were comparable according to demographic variables and disease characteristics. Patients randomised in study RFS 2000-06 had a more advanced disease status, e.g. more involved sites, than patients randomised in study RFS 2000-09.
Survival was the primary endpoint in both phase III studies. Secondary endpoints were progression-free survival (PFS), time to radiological progression (TTRP) and tumour response. PFS was defined as the time from randomisation to the date of either radiological progression or, if unavailable, symptomatic progression, or, if neither available, the date of death. TTRP was defined as time from randomisation to the date of radiological progression. The date of radiological progression was assessed by an independent expert (study PFS 2000-09). All TTRP and PFS results were also calculated with the date of radiological progression adjusted to the next scheduled scan (every 56 days). Tumour response was assessed in patients with bi-dimensionally measurable disease.
Survival, tumour response and radiological progression, assessed by a blinded radiologist, were considered relevant endpoints for the assessment of efficacy in open trials.

Both pivotal studies analysis failed to show a meaningful difference in terms of overall survival. A difference in survival (or significant benefits in terms of quality of life) would have been necessary to demonstrate the efficacy of rubitecan as 2nd line treatment in advanced pancreatic cancer (due to the course of the disease and the absence of available treatment improving survival). Alternative survival analyses were provided, censoring the data from patients who crossed over to the rubitecan arm. This meant excluding, from the comparator arms, the best prognosis group of patients (those considered likely to tolerate further treatment). Such alternative analyses were not considered useful to establish the fficacy of rubitecan in the proposed indication.
Analyses of secondary efficacy endpoints in study RFS 2000-06 failed to establish the clinical efficacy of rubitecan. Secondary endpoints analysis of study RFS 2000-09 showed an activity of rubetican as compared to Best Choice therapy, but this was inconsistent with the overall results. Moreover, the conclusions about PFS and TTRP results in this study was questioned due to potential ascertainment bias interpretation in the context of the open label design of the studies.
Primary and secondary endpoints observed from study 2000-06, comparing rubitecan to 5-FU (weekly IV bolus administration) in second line, showed no positive effect of rubitecan as compared to this therapy.
Survival analysis and secondary efficacy measures (tumor response and PFS) from study RFS 2000-02 shown superiority of gemcitabine as compared to rubitecan, in first line treatment.
In conclusion, based on the efficacy data presented, at the time of withdrawal there were insufficient data to establish the efficacy of Orathecin in the claimed indication.

Clinical safety

The main integrated safety database included the safety populations from the main studies in pancreatic cancer, i.e. studies RFS 2000-09, RFS 2000-06, RFS 2000-01 and RFS 2000-02. All studies employed the same dose regimen (1.5 mg/m^2 given orally for five days/week), and dose adjustments for rubitecan.

Patient exposure

Altogether 1427 patients treated with rubitecan and 892 patients treated with comparators were included in the safety database, which was considered substantial especially for an orphan indication.

Adverse events

The dosing of rubitecan was adjusted individually aiming at MTD. The total incidence of any adverse event of any grade was approximately 90%, and 70% for Grade 3-4 adverse events. The adverse event rate for any drug related events was comparable between rubitecan and the comparators (80% of patients treated with rubitecan, *vs*. 75-89% in patients treated with 5-FU, gemcitabine and best choice therapy). Chemical cystitis occurred in 23% of patients receiving rubitecan (related cases of haematuria and dysuria occurred in 15% and 7% of patients, respectively). Severe episodes of cystitis were uncommon (all-causality incidence of Grade 3-4 cystitis, haemorrhagic cystitis, dysuria and haematuria all being under 1% in the main integrated safety database). Adequate hydration (3 litres of fluid per day was recommended) appeared to reduce the risk of developing cystitis.

Serious adverse events (SAE) and deaths

The incidence of serious AEs was high. In study RFS 2000-09, drug related serious AEs affected 60 % of patients in the rubitecan arm *vs.* 36% in the best choice therapy arm. In general, incidence and cause of deaths were comparable between patients receiving rubitecan and those receiving other treatments.
In study RFS 2000-06, the rate of deaths due to other reasons than disease progression was high in the rubitecan arm as compare to other treatments (9% *vs*. 5%, respectively).

Safety conclusion

Overall, the toxicity profile of rubitecan was considered similar the other cytotoxic compounds that have the same mechanism of action. Rubitecan caused quite extensive, but manageable, gastrointestinal toxicity, myelosupression and chemical cystitis. Information regarding weekly monitoring of blood counts and urine, and contraindications for patients with low performance status

and for patients who are unable to maintain adequate hydration had to be reflected in the product information. At the time of the wirthdrawal, this issue was left unresolved.