SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 31 March 2005. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

XELODA contains the new chemical entity capecitabine (INN), a fluoropyrimidine carbamate.

Capecitabine is designed as a 'pro-drug' to the cytotoxic agent 5-fluorouracil (5-FU) and to be administered orally. 5-FU is a widely used cytotoxic agent. The human safety profile of 5-FU and its metabolite FBAL has been characterised through clinical trials and from many years of post-marketing experience.

The gastrointestinal absorption of capecitabine is nearly complete. Capecitabine is absorbed as unchanged parent substance but is subsequently substrate of enzymes and thus is nearly completely metabolised.

The metabolic pathway leads to production of 5'-DFCR via carboxylesterase (liver) and to 5'-DFUR via cytidine deaminase (liver and neoplastic tissue) and finally via thymidine phosphorylase to 5-FU. Thymidine phosphorylase is in higher concentration in neoplastic tissue, in comparison to healthy tissues, rendering capecitabine "tumour specific". The catabolic pathway of 5-FU comprises dihydro-5-fluorouracil (FUH2, via dihydropyrimidine dehydrogenase, DPD), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL).

Xeloda is indicated for first line monotherapy of metastatic colorectal cancer. Colorectal (adeno-) carcinoma represents a major health problem particularly in the western regions or the northern hemisphere. In these regions one of 20 persons will be affected during his life span by colorectal carcinoma rendering it with about 13% the second most common cancer in both sexes. In Europe about 376,000 new cases are diagnosed each year.

Carcinomas of the colon and rectum are differing only by their anatomic site and therefore by the local surgical techniques and radiotherapy applied, if feasible. Concerning tumour biology and systemic therapy both are considered as similar entities.

Roughly 70% of patients are presenting with (non metastatic) limited diseases, which can be resected with curative intention. Survival in node negative patients after resection is very favourable with 5-year survival rates reported in the range of 73-97%. However, relapse is a major feature in particular in patients with stage III (Dukes C) carcinoma.

About 30% of patients are primarily presenting with non resectable, advanced disease. Additional 25% of patients are relapsing after primary resection. Both groups of patients have a poor prognosis so that overall cure rates in colorectal carcinoma remain below 50%. This pattern of presentation and course leads to an estimated 5 years survival rate combined for all stages of colorectal carcinoma of only 40% in Europe.

Xeloda was granted authorisation in EU in February 2001 for first line monotherapy of patients with metastatic colorectal cancer. The indication was subsequently extended through a Type II variation to include:

- combination therapy with docetaxel in the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline

- monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Breast cancer is the most frequent malignancy in women with more than 300,000 new cases diagnosed each year in Europe and therefore a major health problem in the western world. Despite advances in the management of breast cancer, metastatic breast cancer remains an incurable disease with a median survival of 2-3 years.

Anti-neoplastic chemotherapy is the treatment of choice for patients with metastatic breast cancer who have failed endocrine therapies, or for whom hormonal treatment is not appropriate. For almost 30 years anti-neoplastic chemotherapy in breast cancer has been continuously further developed.
A number of cytotoxic agents demonstrated moderate anti-tumour activity as single compounds. The combination of active single agents was found to be more effective, and still well tolerated. Combination treatment of the CMF type demonstrated in first-line therapy approximately 50% objective tumour response.

Anthracyclines demonstrated a higher single agent activity. Their inclusion into combination regimens led to higher response rates compared to non-anthracycline-containing combination regimens in metastatic breast cancer. Therefore, anthracyclines became a standard in first-line chemotherapy for metastatic breast cancer and for adjuvant chemotherapy in suitable patients.

Taxanes as single agents have shown anti-tumour activities after failure of anthracyclines of roughly 40%. The high anti-tumour activity of taxanes leads to their widespread and earlier usage. The broad use of anthracyclines and taxanes raises the problem which cytotoxic treatment to use in patients who do not respond (any longer) to these agents, due to primary or secondary resistance while on therapy, or relapse shortly after a prior therapy for advanced or early breast cancer (adjuvant treatment).

The monoclonal antibody trastuzumab (Herceptin) was approved in EU as monotherapy for metastatic breast cancer after failure of an anthracycline and a taxane in those patients whose tumours over-express HER2.

The use of Xeloda is primarily to simplify intravenous single-agent 5-FU based therapy of metastatic colorectal carcinoma through oral route of administration. The recommended dose of Xeloda is 1250 mg/m^2 twice daily in monotherapy for two weeks followed by a one-week rest period. In combination with docetaxel, the recommended dose of Xeloda is 1250 mg/m^2 twice daily for 2 weeks followed by 1-week rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks.

2. Chemical, pharmaceutical and biological aspects

Composition

Xeloda is a conventional tablet with a film coating applied to mask the taste of the product and to avoid direct contact with the active substance. The film-coated tablets are manufactured in 2 strengths, differentiated by size and colour.

The formulations used in clinical trials differ only in the amount of the coating excipients (including the colorants). Both a dissolution study and a bioequivalence study have supported that the clinical trial formulations can be considered bioequivalent to the final composition as intended for marketing. Xeloda contains magnesium stearate and lactose. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

The packaging consists of cartons with polyvinylchloride/polyethylene/polyvinylidene lidded with aluminium foil push-through blisters.

Active substance
Capecitabine is a fluoropyrimidine carbamate with the chemical name 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine. The molecular formula is $C_{15}H_{22}FN_3O_6$ and the molecular weight 359.35. It is a chiral molecule synthesised in a 3-step process where three chiral centres come from the starting material and the fourth one is created with stereospecific synthesis. The data provided indicate that the stereochemistry is not changed during manufacture or storage of the active substance. Ten impurities have been identified, two intermediates, three degradation products and five synthetic by-products.

The particle size specification is justified by the fact that all batches of active substance that have been used for the production of the tablets have shown consistent dissolution and content uniformity data upon release.

The identification is a combination of IR and HPLC together with a test for optical rotation. The purity is controlled by chromatographic methods. The impurity limits in the specification are justified by toxicology studies. The possible related substances and the content of capecitabine are determined by a HPLC method. GC determines residual solvents (two alternative methods). All of the chromatographic methods have suitability tests. As for the tests for water, sulphated ash and heavy metals reference is given to Ph.Eur. where relevant or USP. The specified limits of particle size distribution of capecitabine reflect the quality of the material used throughout technical-pharmaceutical development. The impurity limits in the product specification are justified by toxicology studies.

The proposed specifications are supported by the batch analysis results (n = 51).

The stability studies indicate that capecitabine is a stable substance at normal conditions and the results support the proposed retest period of 3 years from initial analysis if stored below 30 °C with desiccant.

Other ingredients
All excipients comply with Ph.Eur. and the colorants comply with EU standards.

Product development and finished product
Xeloda is manufactured by conventional pharmaceutical operations (wet granulation final blending, compression and coating). In-process controls include disintegration of the kernels. There are no disintegration requirements in the finished product specification, however the dissolution requirement (min. 75% (Q) after 45 min.) controls satisfactorily the release of the drug substance.
A satisfactory process validation has been performed, including granulation, blending, compression and film coating. Reproducibility was demonstrated.

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

The control test and specifications for finished product are adequately drawn up. The identity of capecitabine is confirmed by IR-spectroscopy and high performance liquid chromatography used for the assay and the detection of degradation products.

The dissolution test is performed with a validated automatic dissolution measuring system (UV-spectrophotometer). The impurity limits in the product specification are justified by toxicology studies.

The limits for the microbial contamination are based on the requirements of Ph.Eur.

Results from 2 batches of the 150 mg strength and 3 batches of the 500 mg strength are presented. The results confirm satisfactory uniformity of the product at release and indicate reliable and consistent performance of the product in clinical use.

Stability of the product
The results from the stability studies indicate that the tablets exhibited satisfactory potency, purity and physical integrity. The physical appearance of the tablets and the dissolution data obtained show no change during storage. The results support the proposed shelf life of 3 years, as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects
In summary, the documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a product of appropriate and consistent quality. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

3. Toxico-pharmacological aspects

Pharmacodynamics

In vitro studies
Capecitabine has been designed and developed as a pro-drug to the known cytotoxic agent 5-FU. Data from cultured human cancer cell lines indicate that capecitabine becomes cytotoxic only after conversion to 5-FU. Studies on the mechanism of action of 5-FU have not been performed for this application. There is sufficient evidence suggesting that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.

In vivo studies
Efficacy and safety of capecitabine were superior to other fluoropyrimidines (5-FU, UFT, and 5'-DFUR) in xenograft models of human colon, breast, gastric, cervical, bladder, and ovarian and prostate cancer. In combination therapy, the capacitabine-based combinations (partners: standard cytostatics, dThdPase up-regulators and x-ray radiation) were more effective than 5-FU combinations in selected human breast, gastric and colon cancer xenograft models. The ratio of dThdPase/DPD (dihydropyrimidine reductase which inactivates 5-FU) in tumours seems to be an important determinant for antitumour activity of capecitabine in preclinical models. The clinical relevancy of this finding is not yet known, but is under active investigation.

Capecitabine had an antimetastatic potential and reversed cachexia in tumor-bearing animals in the Lewis Lung carcinoma and Colon 26 carcinoma models. The antitumour activity is dependent on the cumulative dose, and not on dosing schedule, when capecitabine is given for a prolonged period of time.
While the submitted data show an increased 5-FU content of colorectal tumour tissues compared with adjacent healthy tissues, the available evidence also suggests that 5-FU generation in response to capecitabine treatment is in large part localised in non-cancer cells of colorectal tumour tissues.

In conclusion, an enrichment of 5-FU in colorectal cancer cells, in particular in comparison with major target cells of fluoropyrimidine toxicity, in response to capecitabine treatment and the contribution of the 5-FU generated in stromal cells of colorectal tumour tissue to the anti-tumour effect of capecitabine remain to be established. This has been reflected in the SPC (section 5.2 *Pharmacokinetic Properties*).
Neither the mechanism of DPD activity expression, nor the intrinsic factors that affect the enzyme activity and its gene expression are known. The anticancer drugs most likely to be used together with capecitabine in combination therapy do not influence DPD activity in human colon cancer xenografts.

General and safety pharmacology programme

There were no significant effects on respiratory, nervous and gastrointestinal systems in rats and dogs.

Cardiovascular toxicity (e.g. PR- and QT-interval prolongation) was detectable after intravenous (100 mg/kg) but not after repeated dose daily oral administration to monkeys for 26/52 weeks with sufficient systemic exposure to 5'DFUR. Nevertheless, caution should be exercised when capecitabine is used in patients with pre-existing cardiovascular disorders.

Pharmacokinetics

Pharmacokinetics has been investigated in mice, rats and monkeys. In all three species systemic exposure levels were approximately proportional to dose, and did not change significantly with repeated dosing.

Like in humans, capecitabine was relatively rapidly and extensively absorbed following oral administration to monkeys (at least 81%), rats and mice (95% or greater). The plasma t_{max} for capecitabine was about 1 h (range 0.5 to 2 h) in monkeys and about 0.5 h in rodents.

In non-tumour bearing mice and rats, capecitabine levels were highest in liver, kidney, and gastrointestinal tract. Capecitabine levels in the brain were low in both species.

Plasma protein binding (primarily to the albumin fraction) of capecitabine (51-69%) and its main metabolites (20% or less, except for 5'-DFUR: 60%) were low. The half-life of capecitabine in the monkey is 0.4 h, and in man 0.5 h.

Capecitabine was rapidly and extensively metabolised to 5-FU by the monkey - presumably by hepatic/intestinal first-pass effect - with comparatively low systemic exposure to 5-FU. In contrast, generation of 5-FU in rodents was rapid but less extensive because of the differences in the 5-FU-generating enzyme distribution, as compared to monkey and man. Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs in tumour tissues by the tumour associated angiogenic factor thymidine phosphorylase (dThdPase). Capecitabine and its metabolites (5'-DFCR, 5'-DFUR, and 5-FU or metabolites of 5-FU: 5-FUH2, FUPA, and FBAL) are excreted primarily in urine. Interspecies differences are consistent with differences in the 5-FU-generating enzyme activities. Thus, cytidine deaminase activity is highest in monkey tissues.

In vivo studies in male mice indicate that there is a low potential for pharmacokinetic drug interactions due to either inhibition or induction of P450.

In pregnant and lactating mice, a considerable amount of capecitabine related material was transferred to both fetus and milk. This information is reflected in the SPC (*section 4.6 Pregnancy and lactation*).

Overall, the pharmacokinetics in monkey are similar to man. However, there are differences, some of which may relate to differences in the enzyme activities. The lower exposure to 5'-DFCR in monkey compared to man is consistent with the higher activities of cytidine deaminase in monkey tissues, as compared to human tissues. Another difference is that, the systemic exposures to 5-FU and FBAL in monkey are about half those in man at similar doses.

Toxicology

Single dose toxicity

The single dose toxicity of capecitabine has been studied in mice, rats and monkeys. In the mice study doses of 0, 1000 or 2000 mg/kg were administered by gavage and doses of 0, 250, 375 or 500 mg/kg intravenously. Animals were observed for 14 days following oral dosing. The were no deaths in any groups of both sexes. Transient clinical signs included decreased spontaneous motor activity and bradypnoea. No compound-related findings were revealed at gross necropsy. The oral lethal dose was greater than 2000 mg/kg and the maximum non-lethal intravenous dose was estimated to be greater

than 250 mg/kg for males and greater than 375 but less than 500 mg/kg for female mice. The intravenous administration is not considered to be relevant for the human situation, because the first-pass metabolism following oral administration is by-passed.

Capecitabine was given nasogastrically at doses of 500, 1000 and 2000 mg/kg in two male cynomolgus monkeys. The doses were given on days 1, 4 and 7. Animals were observed for 21 days (14 days observation after the final dosing). Necropsy was not performed. There were no deaths. After each dosing emesis, salivation and loose passage or diarrhoea was observed. The symptoms point to gastrointestinal toxicity of capecitabine**.** Due to emesis, which may have impacted exposure, the study does not allow conclusions regarding the maximal non-lethal dose.

Repeated dose toxicity
All the studies have been performed using continuous single daily dosing regimen instead of the clinical dosing regimen (two weeks of b.i.d. dosing followed by a one week off treatment). See also "Discussion on toxico-pharmacological aspects".

In a study in mice (n=6/sex/group, duration of administration=4 weeks, dose levels: 0/198/395/791 mg/kg/day, gavage), the main findings were effects on gastrointestinal and hematopoietic/lymphatic systems were shown at 395 mg/kg/day and higher: slight anemia, slight decrease in bone marrow cell count (BMC), increase in BUN, slight decrease in thymus weight and increase in spleen weight; slightly-to moderately regressive intestinal change; slightly to moderately increased extramedullary hematopoiesis in the spleen; brown pigment deposits in marrow of the femur; slight atrophic changes in thymus and the spleen. No drug-related death was observed. Effects on gastrointestinal and hematopoietic/lymphatic systems were shown at 395 mg/kg/day and higher. The maximum tolerated dose (MTD) was 198 mg/kg/day.

Another study in mice (n=15/sex/group, duration of administration=13 weeks + 4 weeks recovery, dose levels: 0/198/395/791 mg/kg/day, gavage) significant decrease in body weight, food intake, emaciation, decrease of spontaneous motor activity, and loose passage were observed at the dose level of 791 mg/kg/day. After the reduction of the dose to 593 mg/kg/day, tendency of recovery in body weight gain and clinical signs was observed. Three males and 8 females were found dead or sacrificed in this dose group after showing decreased spontaneous motor activity, loose passage, hyposthenia, hypothermia, bradypnoea or convulsion (just before death). Drug related toxicity was observed in lymphatic/hematopoietic organs, reproductive organs as well as in gastrointestinal tract and in skin in almost all dead/sacrificed animals. In the surviving animals, drug related changes were observed in lymphatic/hematopoietic organs, reproductive organs and gastrointestinal tract of the middle and high dose groups. These changes appeared to be reversible**.** There were no notable changes in the low dose group. The MTD was 198 mg/kg/day.

In a study in rats (n=5/sex/group, duration of administration=4 weeks, dose levels: 0/180/395/539 mg/kg/day, gavage), no clinical signs of exposure were evident. Body weight gain and food consumption were slightly decreased in males (at 539 mg/kg/day). Organ weights, haematology, blood chemistry, urinalysis, and necropsy examinations did not reveal drug-induced changes. Toxicologically significant organ weight changes were not observed. Slight degeneration of the rectal crypt cells was observed in both genders at 539 mg/kg/day. All rats survived. In this study MTD was 359 mg/kg/day.

Minimal increases of MCV and MCH and increase of the number of animals which showed protein positive in standard urinalysis (in the absence of renal toxicity) were observed at 539 mg/kg/day in a study in rats (n=20/sex/group, duration of administration=26 weeks, dose levels: 0/180/395/539 mg/kg/day, gavage). However, nothing abnormal was found in kidneys. Other findings included: reduced body weight and food consumption, slight decrease in RBC, total protein in serum and urine volume, slight increase of specific gravity in urine (at 359 and 539 mg/kg/day) and slight regressive changes in rectum (at 539 mg/kg/day). There were no deaths in the study. The MTD was 180 mg/kg/day.

In a 4 week study in Cynomolgus monkeys (n=3/sex/group except for the high dose, only 3 males; dose levels: 0/36/180/359, oral), loose passage or diarrhoea were evident at the two higher doses. Two animals treated with 359 mg/kg/day were sacrificed in moribund condition. Decreases of weight gain and food consumption and decreases of WBC and BMC were observed at ≥179 mg/kg/day. No toxicological significant changes in parameters relating to blood chemistry and urinalysis were found. A decrease in thymus weight (at ≥179.5 mg/kg/day) and in spleen weight (at 395 mg/kg/day) and increase in adrenal weight in the sacrificed animals has been seen. Slight to severe regressive toxicity in large intestine and small intestine as well as in lymphatic and hematopoietic organs at ≥179.5 mg/kg/day was noted. The MTD was 36 mg/kg/day.

In a 4 week study in Cynomolgus monkeys (n=3/sex/group except for the high dose, only 3 males; dose levels in mg/kg/day: 0/36/180/359 capecitabine p.o; 220/439 galocitabine p.o; 62/123 5'-DFUR p.o.), all three substances caused previously seen adverse effects on the gastrointestinal, lymphoid and hematopoietic systems. Based on clinical signs, hematological examination, organ weight, and histopathological examination, the toxic effects of capecitabine and galocitabine appear to be weaker than that of 5'-DFUR (approximately 2-4 times weaker in a molar base).

In the same species, in another study (n=3/sex/dose group + recovery 1/sex/dose group, duration of administration: 13 w + 4 w recovery; dose levels in mg/kg/day: 0/54/108/215, nasogastrically), the high dose level was decreased to 162 mg/kg/day from day 35 after 3 days cessation of dosing due to aggravation of clinical signs and decrease of body weight and food consumption. There were two deaths in the highest dosage group. The clinical symptoms were similar to those in the 4-week toxicity study. In the highest dose group animals also lost weight and their food consumption decreased. Hematological changes (decrease in RBC, HCT, Hb and WBC) were evident at > 108 mg/kg. The weights of thymus and spleen were decreased with the dosage of ≥ 108 mg/kg/day, and in the dead monkeys the weights of liver, kidneys, adrenals and brain were increased. Histopathological findings were similar to the ones found in the 4-week study. This study revealed regressive toxicity also in tonsils. Evidence of toxicity was not observed in kidneys, liver heart and brain. In the animals that died prematurely hypertrophy of cortical cells in adrenals, probably resulting from the aggravated clinical symptoms, was also observed. All changes were reversed after 4-week recovery period. MTD was 54 mg/kg/day.

In a further study (n=3/sex/ group, duration of administration: 26 weeks; dose levels in mg/kg/day: 0/18/54/144, gavage), the reversibility of the changes after the dosages was not followed. The one female at the highest dose group which was sacrificed in a moribund condition, showed diarrhoea, decreased spontaneous motor activity, loss of appetite, emaciation, hypothermia, bradypnoea; decreased body weight & food intake. In addition, toxic changes (consistent with the previous studies) were observed in lymphatic / hematopoietic systems and in gastrointestinal tract. The changes in the serum biochemistry were considered to be secondary changes caused by the aggravation of clinical signs. Weight changes were observed also in heart, liver, kidneys (low absolute weights), brain, lungs and adrenals (high relative weight). However, these were not connected with histopathological changes. In this same animal there was also evidence of skin toxicity (hypoplasia of the squamous epithelium and atrophy of the hair follicle). The clinical symptoms of the surviving animals were minor. The MTD was 54 mg/kg/day.

Finally, a study of 52 weeks of duration of administration in Cynomolgus monkeys (n=4/sex/group; dose levels in mg/kg/day: 0/36/72/108, gavage), was performed. The reversibility of the effects after the dosages was not followed in the study. Overall, the findings were consistent with previous studies**.** Clinical signs of exposure were evident at all dose levels. They included: dosage related increase in the incidence of postdosing salivation in all groups, regurgitation of small quantities of dose in all groups (including controls; however, highest incidence at 108 mg/kg/day), and transient soft faeces. There were no obvious effects of treatment on body weight, food or water consumption or on ophthalmoscopic and electrocardiographic parameters. Myelosuppression and associated effects on systemic red and white cell parameters characterised the haematopoietic toxicities. There were no treatment-related changes in blood biochemistry examinations or urinalysis. Evidence on skin toxicity was not observed. At 108 mg/kg/day, the relative weight of thymus was marginally decreased. Apart from a decrease of lymphocytes in the cortex of the thymus and proliferation of hematopoietic cells in

the bone marrow of one animal at 108 mg/kg/day, no changes attributable to treatment were seen in histopathological examinations. The MTD was 72 mg/kg/day, however, at this dosage and at 32 mg/kg changes in white cell count and myeloid left shift index were equivocal.

Reproduction toxicity

Fertility and early embryonic development
5-fluorouracil resulting from conversion of capecitabine has been found to target male and female reproductive organs. Decreases in testis and epididymis weights, decreased numbers of spermatocytes and spermatids, and degenerative changes were found in male mice treated with 760 mg/kg/day (about 2350 mg/m^2/day) for approximately 80 days in the fertility study. Mating conducted after a minimum of 28 days of treatment revealed a slight reduction in the ability of these males to fertilise untreated female partners. In female mice, oestrus cycles and mating were disrupted by treatment with 760 mg/kg/day. The effect was reversible as the females mated within 14 days upon withdrawal of treatment. Oestrus cycles were not evaluated at 190 and 380 mg/kg/day. Effects on female fertility may have been present at lower doses.

Embryo-foetal development
In one study mated female mice (20/group) were given daily oral doses of capecitabine (0, 198, 395 and 791 mg/kg/day by gavage) on gestation days 6 - 15. The females were killed on gestation day 17. There were no deaths attributable to the test compound. Also no drug-related toxicity was observed clinically and in gross necropsy findings. Maternal body weight development and food consumption were decreased dose-dependently from the middle of gestation. Decrease of foetus body weight, dose-related decrease of the number alive foetuses and increase of early death (resorption) and teratogenicity were observed at the dose of 198 mg/kg/day or higher. Non-toxic dose was estimated < 198 mg/kg/day in parental animals and F1 foetuses.

In a supplementary embryo-fetal development study capecitabine was given by gavage at doses of 0, 25, 50 and 100 mg/kg/day (20/dose group) from the day 6 to 15 of gestation. Inhibition of body weight development and food consumption was evident in dams at 100 mg/kg/day. No drug-related toxicity was observed in corpora lutea or implantation sites, or on fetal viability. Slight increase of rudimentary 14th rib was observed in 100-mg/kg groups. No drug-related toxicity was observed in foetus weight, external anomaly and visceral examination. Non-toxic dose was 50 mg/kg/day for parental animals and F1 foetuses.

A second supplementary Segment II study was performed with oral doses of 0, 50, 100 and 200 mg/kg/day. The study also included the examination of physical development of F1 pups after delivery. A slight prolongation of pregnant period and a slight inhibition of body weight development and food consumption were evident at 200mg/kg/day in dams. F1-pups showed embryotoxicity and teratogenicity at doses of 100 mg/kg/day or higher. No notable changes were observed in the physical development of F1-pups after delivery. Non-toxic dose level in this study was estimated to be 100 mg/kg for dams and 50 mg/kg/day for F1-pups.

Capecitabine was administered orally by gavage to mated female monkeys (5/dose level) at 0, 22.5, 45 and 90 mg/kg/day on gestation days 20 through 50. Caesarean sections were performed on day 100-102. No maternal deaths occurred. One abortion and embryolethality was noted at 90 mg/kg. Additionally, embryonic death was observed in 1 dam of the 22.5 mg/kg/day group. This may be incidental because no abortions or embryonic deaths occurred in the 45-mg/kg groups. There was no evidence of a teratogenic effect at any tested dose.

Perinatal development
No relevant effects on parturition and postnatal development or function were identified in the peri-postnatal study with doses up to 400 mg/kg/day (about 1200 mg/m^2/day). However, at this high dose a single pup developed hydrocephaly.

Genotoxicity
A standard battery of tests (3 *in vitro* tests and 1 *in vivo* test) was done to investigate the genotoxic potential of capecitabine. Capecitabine was not mutagenic *in vitro* to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). However, similar to other nucleoside analogues (i.e., 5-FU), capecitabine was clastogenic in human lymphocytes (*in vitro*) and a positive trend occurred in mouse bone marrow micronucleus tests (*in vivo).* The risk associated with exposure to capecitabine depends largely on the enzymatic conversion to 5-FU. The first step involves carboxyl esterase, which is preferentially expressed in human liver. The last step, i.e. ThdPase, which generates 5-FU is generally higher expressed in tumour tissues compared to normal human cells. It may be therefore speculated that the genotoxic risk of normal human cells after exposure to capecitabine is significantly lower compared to direct exposure to 5-FU. Repeated administration will enhance the clastogenic effect of capecitabine.

Carcinogenicity
A two-year carcinogenicity study in mice (50/sex dose group) given capecitabine in daily oral doses of 0 (Control-1), 0 (Control-2), 30, 60 or 90 mg/kg/day by dietary mixture has been performed. The study did not reveal any evidence for an oncogenic potential of capecitabine. In male mice the incidence of bronchio-alveolar adenomas and in female mice the incidence of histiocytic sarcomas were statistically significantly decreased at the dose level of 90 mg/kg/day. These findings are likely to be related to the pharmacodynamic activity of capecitabine.

Ecotoxicity/Environmental risk assessment
Data on the environmental effects and exposure of capecitabine have been presented. Exposure to the environment is considered very limited and therefore no risk of concern would be expected.

Discussion on toxico-pharmacological aspects
The pharmacodynamic profile of capecitabine as a pro-drug for 5-FU could be confirmed a) in experiments with cancer cell lines, in which capecitabine itself and its intermediate metabolites had only a low direct cytotoxic potential and b) in experiments with mice bearing human and murine tumours, in which cytotoxic effects of capecitabine appeared to be related to its conversion to 5-FU. In accordance, factors which prevent the generation of high intratumoral 5-FU levels, like e.g. low intratumoral activity of ThdPase or high intratumoral activity of DPD, may represent mechanisms of resistance to capecitabine.
Capecitabine had an antimetastatic potential and reversed cachexia in mouse tumour models. Synergistic effects of capecitabine in combination therapy with other cytotoxic drugs have been shown.

The safety pharmacology studies did not indicate significant effects on the major organ systems, but they showed a potential of capecitabine to affect cardiovascular functions in dogs and monkeys after iv. application. Although these effects were not reproduced after oral application to monkeys for up to 52 weeks, the cardiotoxic potential of capecitabine should be further characterised.

The absorption, distribution, metabolism and excretion characteristics of capecitabine and its metabolites 5´-DFCR and 5´-DFUR in rat, mouse and monkey reflected the tissue distribution pattern of the enzymes responsible for conversion of capecitabine to 5-FU.
Following oral administration, capecitabine was rapidly and extensively absorbed.
Capecitabine is first metabolised by (hepatic) carboxylesterase to 5´-DFCR, which is then converted to 5´-DFUR by cytidine deaminase, principally located in the liver and in tumour tissues. Activation of 5´-DFUR to 5-FU then occurs by ThdPase (also called tumour associated angiogenic factor), which shows high activity in tumour tissues. Accordingly, 5-FU levels were higher in colorectal cancer tissue than in the adjacent healthy tissue and in plasma. However, since ThdPase expression appears to be mainly located in the stromal cells of colorectal tumour tissues, 5-FU formation within these cells may substantially contribute to the enhanced 5-FU levels. Data about 5-FU levels produced in response to capecitabine therapy in main target cells of capecitabine toxicity, like e.g. intestinal epithelial cells, bone marrow cells and epidermal cells (related to gastrointestinal toxicity, myelosuppression and hand-foot syndrome) are not available. Therefore, conclusive evidence that 5-FU levels produced in

response to capecitabine treatment are higher in colorectal cancer cells than in main target cells of capecitabine toxicity has not been presented.

Plasma kinetics of capecitabine and its metabolites in the Cynomolgus monkey are similar to that of man. Capecitabine was rapidly and extensively metabolised to 5-FU by the monkey, however, with comparatively low plasma levels of 5-FU. Because of interspecies differences in the tissue distribution of the capecitabine metabolising enzymes, generation of 5-FU in rodents, especially in rats, was less extensive as compared to monkey and man.
Capecitabine and its metabolites are excreted primarily in urine.

Capecitabine was not lethal in monkeys at 2,000 mg/kg but conclusions on the lethal dose cannot be drawn due to a potential effect of emesis on exposure. Based on monkey data, the manifestations of acute overdosage in the human situation can be anticipated to be salivation, vomiting and diarrhoea.
In the repeated dose toxicity studies, the monkey, which shows the closest similarity to man regarding pharmacokinetics, was clearly the most sensitive species. Safety margins, as based on the systemic exposure following oral administration were low, as expected for a cytotoxic drug. The adverse effects on the gastrointestinal, lymphoid and hematopoietic system as well as on female and, in high doses, male reproductive organs were consistent with those reported for other fluoropyrmidines and appeared to be reversible.

Evidence on the hand-foot syndrome was not found in general toxicity studies. Skin toxicity was found in some dead animals (one monkey at the dose level of 144 mg/kg/day in the 26-week toxicity study, and 11 mice at the dose level of 791/593 mg/kg/day in the 13-week toxicity study). The skin toxicity was characterised by degenerative/regressive changes. Skin toxicity has been reported with other fluoropyrimidines. The applicant has performed a tissue distribution study in monkeys showing that the levels of radioactivity in skin were relatively low compared to kidney and liver. The localisation of the skin lesion in the monkey was not typical of HFS. However, the possibility that the cases of skin lesions observed in mice and monkeys only at high doses associated with lethality could represent early cases of hand-foot syndrome appears unlikely.

The dosing regimen in clinical studies, 2 weeks on/1 week off, was different from the 5 day per week dosing regimen used in some pre-clinical efficacy studies. This was done to avoid toxicity that may be caused by capecitabine metabolites with long half-lives, such as FBAL (half-live 33 hours). In addition, the intensity of this and other potential side effects, such as stomatitis, should be reduced, since this rest period is considered long enough to allow recovery from such toxicities.
Pre-clinical models are insufficient to confirm these predictions since hand-foot syndrome and stomatitis are often seen in patients treated with fluoropyrimidines but not in animals, including monkeys. Nor are they seen in tumour models (mice bearing human colon cancer xenografts) used in pre-clinical studies with capecitabine.
The database comparing the relative toxicity of each dosing regimen in animals is insufficient to recommend which regimen would be safer in clinical trials with capecitabine. The 5 days per week dosing regimen seemed to be slightly less toxic than the daily and 2 weeks-on/1 week-off regimens in a pre-clinical human colon cancer xenograft study with capecitabine. However, the difference in toxicity was not significant, and the number of mice used in this study was small.

Embryotoxicity was observed in monkeys and mice, teratogenicity was observed in mice. Therefore, pregnancy should be avoided during Xeloda therapy as long as the anticipated benefit of capecitabine treatment to the mother does not outweigh this risk consideration.

Similar to 5-FU, capecitabine was clastogenic in human lymphocytes (*in vitro*) and a positive trend was also observed *in vivo* in the mouse bone marrow micronucleus test (*in vivo*). There was no evidence of carcinogenic potential in mice.

The specifications of the impurities contained in the finished product are acceptable.
Exposure to the environment is considered very limited and therefore no risk of concern would be expected.

4. Clinical aspects

Introduction
The clinical trials were performed according to GCP standards and agreed ethical principles.

4.1 First line monotherapy of metastatic colorectal cancer

Clinical pharmacology
A total of 12 clinical pharmacology studies involving 312 cancer patients were conducted (Table 2) and submitted in the original dossier.

Table 2: Clinical pharmacology studies

Protocol no. [Report]	N*	Tumour	Treatment	Primary objective	Design/Phase
Single dose studies					
BK14561 [B-116093]	6	Cancer	Capecitabine p.o. single-dose 550 mg	Pharmacokinetics of 2 different prodrugs of 5'-DFUR	2-way cross-over randomised, Phase I
BK14824 [W-144018]	6	CRC[1]	Capecitabine p.o. single dose 5-FU i.v. single dose 1255 mg/m^2	Feasibility of NMRS to study the time course of the main metabolites	2-way cross-over Phase I
BK14822 [W-144044]	27	Cancer[2]	Capecitabine p.o. single dose 1255 mg/m^2 single dose capecitabine i.v.	Influence of hepatic impairment due to liver metastases	2-way cross-over randomised Phase I
WP15354 [W-144045]	12	Solid	Capecitabine p.o. single-dose 1250 mg/m^2 with/without Maalox	Interaction study	3-way cross-over randomised Phase I
BP15572 [W-144057]	20	Solid	Capecitabine p.o. single-dose 2000 mg/m^2	Bioequivalence between 2 different tablet formulations of capecitabine	2-way cross-over randomised Phase I
WP15353 [W-144089]	6	Solid	Capecitabine p.o. single-dose 2000 mg/m^2	Identify rates and routes of drug/metabolites excretion	Phase I
Multiple dose studies					
SO14693 [N-139256]	33	Solid	Capecitabine p.o. BID, 110-2083 mg/m^2/day 6-week continuous therapy	MTD or MAD	Uncontrolled Phase I
SO14794 [N-139257]	34	Solid	Capecitabine p.o. BID, 502-3514 mg/m^2/day 6-week intermittent therapy	MTD or MAD	Uncontrolled Phase I
SO14798 [N-139258]	31	Solid	Capecitabine p.o. BID 1004-2510 mg/m^2/day plus folinic acid 6-week continuous or intermittent therapy	MTD or MAD	Uncontrolled Phase I
BD14823 [W-144004]	19	CRC[1]	Capecitabine p.o. 1255 mg/m^2/ b.i.d. for 5 to 7 days (Colorectal cancer patients)	To determine tumour selectivity of capecitabine in tumour tissue (TT) vs. normal tissue and TT vs. plasma. Enzymatic activity. Thymidylate synthetase inhibition by 5-FU	Phase I
SO14694 [N-139259]	19	Solid	Capecitabine p.o. BID 1004-1331 mg/m^2/day plus paclitaxel 135-175 mg/m^2/3 weeks i.v.	MTD Safety, tolerability, pharmacokinetic interaction	Phase I

SO14797 [N-139265]	108	CRC[1]	Capecitabine p.o. 1331 mg/m^2 /day (continuous therapy) vs. capecitabine p.o. 1250 mg/m^{2}twice daily (intermittent therapy) vs. capecitabine p.o. 1657 mg/m^2/day (intermittent therapy) plus folinic acid	Efficacy Safety, food effects on pharmacokinetics, selection of dosage regimen for Phase III studies	Randomised, parallel group Phase II

* = evaluable patients
1 = CRC = colorectal carcinoma
2 = Cancer with/without liver metastases (with/without hepatic dysfunction)

Pharmacodynamics

Mechanism of action
Capecitabine is an orally available fluoropyrimidine carbamate prodrug, which is activated in three steps to yield 5-FU. The rationale for developing capecitabine relies on the demonstration of differences in the activities between healthy and tumour tissue of the enzymes involved in the biotransformation process to the active cytotoxic compound 5-FU.

5-FU does not demonstrate any tumour selectivity. In 8 cancer patients, 500 mg/m² i.v. bolus of 5-FU yielded similar 5-FU concentrations in plasma, primary colorectal tumour tissue and healthy adjacent tissue.

Capecitabine is claimed to produce high levels of 5-FU in tumour tissue vs. healthy tissue and plasma due to higher activity of the enzyme thymidine phosphorylase in tumours. However, further data are needed to confirm this assumption.

Dose finding studies and pharmacodynamic interactions

Introduction
In four phases I trials MTD of different capecitabine schedules have been investigated. A Phase II trial in 108 patients with advanced colorectal cancer compared 3 different schedules in terms of ORR.

The maximum tolerated dose (MTD) and the maximum acceptable dose (MAD) were determined in two phases I studies (protocols SO14693, SO14794). Two additional studies were performed to determine the MTD of capecitabine when co-administered with folinic acid (protocol SO14798) or paclitaxel (protocol SO14694).

The MTD was defined as the dose level (twice daily dose) of oral capecitabine - administered as two cycles of continuous treatment (3 weeks treatment per cycle, no rest, i.e. 6 weeks) or intermittent treatment (two weeks treatment, one week rest) - that caused drug-related grade 3-4 toxicity in one third or more of the patients treated. The MAD was defined as the dose level at which four or more patients out of six patient cohort experienced ≥ grade 2 toxicity requiring interruption of treatment for more than 14 days.

Study SO14693 (continuous, monotherapy)
A total of 33 patients with advanced and/or metastatic solid tumours (the majority of patients had colorectal carcinoma, had more than one metastasis and usually extensively pre-treated) were enrolled sequentially in cohorts of 3 to 6 patients to overall 7 escalating doses of capecitabine. Capecitabine was given orally twice daily as continuous treatment for 6 weeks at dosages of 110, 225, 502, 1003, 1331, 1657, and 2083 mg/m^2/day.

At the 1657 mg/m^2/day dose level, 8 out of 12 patients (2 cohorts of 6 patients) experienced grade 3 drug-related toxicity; this dose was considered the MTD. The dose limiting toxicity of this dose level administered as continuous capecitabine monotherapy was mostly grade 3 diarrhoea. It should be

noted that this MTD could be considered retrospectively as a too conservative estimate until further data are at hand. The recommended dose for further trials was 1331 mg/m^2/day.

Overall, a total of 255 clinical adverse events (AEs) were reported in the 33 patients, among them 27 severe (grade 3) and one life threatening (diarrhoea grade 4).
The majority of the 28 grades 3 to 4 AEs (21) were reported in the 1657 mg/m^2/day dose group representing the MTD while only 5 were reported in the 1331 mg/m^2/day dose group.

No tumour response was observed in the whole population.

Study SO14794 (intermittent, monotherapy)
A total of 34 patients with advanced and/or metastatic solid tumours (classified in the majority as adenocarcinoma, most patients had more than one metastasis and were extensively pre-treated) were enrolled sequentially in cohorts of 3 to 9 patients to 6 escalating capecitabine dose levels. Capecitabine was given orally twice daily as an intermittent treatment (two weeks treatment, one week rest) for 6 weeks at dosages of 502, 1004, 1657, 2510, 3000, 3514 mg/m^2/day.

At 2510 mg/m^2/day, 5 of 9 patient experienced grade 3 to 4 drug related toxicity, among them myelosuppression, hyperbilirubinaemia, diarrhoea and hand-foot syndrome.

At 3000 mg/m^2/day 4 of 7 patients experienced grade 4 diarrhoea and hypotension, grade 3 hand-foot syndrome and leukopenia, and 2 patients' grade 3 shifts of hyperbilirubinaemia.

At 3514 mg/m^2/day 4 of 6 patients experienced grade 3 toxicity (nausea; diarrhoea, stomatitis, abdominal discomfort; neutropenia; vomiting; hand-foot syndrome) and a grade 4 shift in hyperbilirubinaemia. This dose level was therefore above the MTD.

The MTD was considered to be 3000 mg/m^2/day. The most prominent dose-limiting toxicities were diarrhoea, hand-foot syndrome and in addition to the continuous treatment also leukopenia. The resulting recommended dose for further trials was 2510 mg/m^2/day.

A total of 349 clinical adverse events were reported in the 34 patients, among them 26 severe (grade 3) and 4 life-threatening (grade 4) event. Of the 30 grade 3 to 4 events, 25 were reported in the three highest dose groups (8, 7 and 10 events in the 2510, 3000, and 3514 mg/m^2/day dose groups, respectively).

One CR (breast cancer) and 3 PR (2 in colorectal cancer patients) were observed in the population investigated.

The intermittent schedule with 1250-mg/m^2 twice-daily capecitabine monotherapy was ultimately the schedule investigated in the two-phase III trials in colorectal carcinoma. Thus, study SO14794 has a major relevance for the assessment of the recommended dosage/schedule.

Study SO14798 (continuous or intermittent in combination with folinic acid)
A total of 31 extensively pre-treated patients with advanced and/or metastatic (most had more than 1 metastasis) solid cancer were enrolled sequentially in cohorts of six to seven patients to five escalating capecitabine dose groups. Capecitabine was given as continuous (1004 mg/m^2/day), or intermittent (1004-1657-2000-2510 mg/m^2/day) therapy in combination with folinic acid (60 mg/day).

For the continuous dose schedule of capecitabine in combination with 60-mg/day folinic acids, the MTD was just reached at the first dose level, i.e. capecitabine 1004 mg/m^2/day. Three out of 6 patients experienced grade 3 AEs (diarrhoea; nausea and vomiting; hand-foot-syndrome and asthenia each).

The MTD for the intermittent dose schedule was reached at 2000 mg/m^2/day capecitabine in combination with folinic acid 60 mg/day. Three out of 6 patients experienced grade 3 AEs (nausea and vomiting; diarrhoea; hand-foot syndrome). The recommended dose of capecitabine for further trials,

when administered in combination with folinic acid 60 mg/day, was 1657 mg/m^2/day. At this dose level 1 out of 6 patients suffered from grade 3 stomatitis and diarrhoea.

Both MTDs (in combination with folinic acid) are considerably and significantly lower than in study SO14693 (continuous monotherapy: 1657 mg/m^2/day) and study SO14794 (intermittent monotherapy: 3000 mg/m^2/day). Not fully unexpected, this indicates an interaction between capecitabine and folinic acid as a result of the known effect of 5,10-methylene-tetrahydrofolate on the stability of the binding of FdUMP (an anabolite of 5-FU) and thymidylate synthetase known from 5-FU. However, there does not seem to be any advantage in replacing a part of the capecitabine dosage by folinic acid.

Of the 229 clinical adverse events reported in this study, 25 events were severe (grade 3) and 2 events were life-threatening (grade 4). The two life-threatening events were reported in one patient in the 2510 mg/m^2/day group.
No clinically relevant myelosuppression was observed at the recommended dosages of 1657 mg/m^2/day for the intermittent schedule (plus folinic acid 60 mg/day).

Two PR (in colorectal cancer patients) were observed in the population investigated.

Study SO14694 (continuous in combination with paclitaxel)
A total of 19 patients with advanced and/or metastatic solid cancer were enrolled sequentially in cohorts of 2 to 8 patients to five different dose combinations of capecitabine as continuous therapy and paclitaxel.

Capecitabine (mg/m^2/day):	1004	1331	1657	1657	1331
Paclitaxel (mg/m^2/every 3 weeks):	135	135	135	175	175

The MTD was capecitabine 1657 mg/m^2/day in combination with paclitaxel 175 mg/m^2/3wks. Dose-limiting toxicity in both patients recruited to this level were grade 3 neutropenia and grade 2 urinary tract infection, grade 3 fever as well as septicaemia. The recommended dose of capecitabine for further trials, when administered in combination with paclitaxel 175 mg/m^2/3wks, was 1331 mg/m^2/day.
The MTD is identical with the result of study SO14693 (continuous monotherapy: 1657 mg/m^2/day). It appears that capecitabine and paclitaxel do not have major overlapping toxicities. However, this conclusion is limited by the small number of patients (19) and in addition not very relevant for the application in view of the role taxanes have in the treatment of advanced colorectal carcinoma.

Of the 255 clinical adverse events reported in this study, 17 events were severe (grade 3) and 2 events were life-threatening (grade 4). Both life-threatening events occurred in the 1331 mg/m^2/day capecitabine plus 175 mg/m^2/3wks paclitaxel treatment group.

Phase II study SO14797 on antitumour activity in colorectal carcinoma

Introduction
This was an open-label, multicenter (21 centres in Australia, Europe, USA) randomised phase II study (Protocol SO14797) comparing the efficacy and safety of continuous and intermittent therapy with capecitabine, and intermittent capecitabine with oral leucovorin as first-line therapy in patients with advanced and/or metastatic colorectal carcinoma.

The primary objective was to evaluate antineoplastic activity (overall best objective response). Tumour responses were evaluated after 6 and 12 weeks of treatment. The dose levels were based on Phase I studies (one level below MTD). Planned treatment duration was at least 6 weeks. Patients with progressive disease were discontinued. Patients with CR or PR after 12 weeks were allowed to enter into a maintenance phase up to a total of 48 weeks. Secondary objectives included comparison of safety profiles and selection of dosing regimen for Phase III studies.

Inclusion criteria included:
- histologically or cytologically confirmed colorectal adenocarcinoma, advanced and/or metastatic

- at least one measurable lesion according to WHO criteria which had not been irradiated
- protocol defined minimum indicator lesion size
- age 18 years or above
- Karnofsky P.S. at least 70%
- life expectancy at least 3 months

Altogether 109 patients were randomised to the following treatment arms (intermittent = 2 weeks on and 1 week off treatment):

A: intermittent capecitabine 1657 mg/m^2/day+leucovorin 60 mg/day (n=35)
B: continuous capecitabine 1331 mg/ m^2/day (n=39)
C: intermittent capecitabine 2510 mg/ m^2/day (n=35)

The mean age of the patients was similar in the three groups (range 36-82 years). Mean Karnofsky performance status was also similar across the groups (range 70-100%). There were more males than females (72 vs. 36). All had advanced and/or metastatic disease, predominantly colon cancer (75%). The tumour was poorly differentiated in 81% of patients. The majority of patients (70%) had multiple metastatic sites at baseline (primarily lung and liver metastases). The disease characteristics were fairly well balanced across the groups. Ninety-four percent of patients had received previous treatment, predominantly surgery. The proportion of patients who had been treated with 5-FU based regimens was slightly higher in the continuous capecitabine group (33% vs. 26%).

The most predominant concomitant diseases were hypertension (29%), constipation (14%), abdominal pain (12%), diarrhoea (10%) and nausea (8%).

Eight patients completed 48 weeks of treatment, one hundred patients discontinued before 48 weeks. The number of patients who discontinued was similar in the three treatment arms. Nineteen patients discontinued due to adverse events. Two patients died (progressive disease). The most important reason for discontinuation was insufficient response/progressive disease.

Antineoplastic Activity
Treatment analysis was performed for ITT and standard (per protocol, at least 6 weeks of treatment) populations.

The key findings for this study are given in Table 3.

Table 3: Key findings of study SO14797

	Capecitabine; continuous regimen	**Capecitabine; intermittent regimen**	**Capecitabine plus Leucovorin**
No of patients (%) with PD as best response	8/39 (21%)	3/35 (9%)	3/35 (9%)
Median Time to Tumor Progression	127 days	230 days	165 days
Median Treatment Duration	109 days	144.5 days	130 days
Median Cumulative Dose	306.8 g	386.5 g	218.4 g
Median Actual Daily Dose	2.3 g	2.8 g	1.7 g
Number of Patients discontinuing treatment due to insufficient therapeutic response/PD	29/39 (74%)	18/35 (51.5%)	23/35 (66%)

The overall best response in the ITT population was similar (21-24%). The rate of progressive disease appears to be higher and the rate of stable disease lower in the continuous capecitabine group vs. other

treatments. No response occurred after week 12 so that best overall response at 12 and 48 weeks are identical.

Five patients experienced CR. Of these, disease progression was recorded in two patients on study days 268 and 212. The other three patients remained in CR on study days 376, 343 and 127.

Pairwise comparison of the three treatment arms (95% CI) confirmed no significant advantage of one treatment over the other.

The cumulative dose of capecitabine was highest in arm C, intermittent capecitabine (mean cumulative dose was almost 2-fold compared to intermittent capecitabine-leucovorin group). The cumulative dose was intermediate in the continuous capecitabine group. The intermittent capecitabine arm also demonstrated the highest OR rate. Dose modifications were necessary in 44-64% of patients. However, more than 95% of the planned dose was actually administered and there were no obvious differences between the groups in this respect.
Overall, the data may be indicative for the interpretation that the lower actual daily dose in arm B may be causative for the shorter TTP. Of note is the toxicity of the intermittent capecitabine + folinic acid regimen despite the low actual dose delivered.

The intermittent capecitabine regimen (2510 mg/m^2/day for 2 weeks, 1 week rest) was chosen for further studies instead of continuous capecitabine (1331 mg/m^2/day).

Safety
Most of the patients experienced adverse events (90-100%). The majority of AEs were judged to be related to treatment. Compared to continuous capecitabine, intermittent treatment appeared to have been associated with a higher frequency of grade 3-4 AEs. Grade 3 toxicities were most frequent in the combination treatment group.

Diarrhoea, nausea and hand-foot syndrome were the predominant treatment-related AEs in all groups. The incidence of treatment-related AEs was also highest in the capecitabine-leucovorin group.

Only one grade 4 treatment related AE was reported (diarrhoea and vomiting, the patient died due to sepsis).

Diarrhoea (47.1% vs. 33.3%), hand-foot syndrome (44.1% vs. 33.3%), vomiting (20.6% vs. 12.8%), nausea (44.1% vs. 23.1%) and stomatitis (20.6% vs. 12.8%) were more frequently reported in the intermittent capecitabine as opposed to continuous capecitabine group. Hand-foot syndrome and diarrhoea also appeared earlier on intermittent treatment. The incidence of hand-foot syndrome was highest in the combination group.

Approximately 65% of patients required treatment interruption and/or dose modification in the intermittent capecitabine and combination treatment groups. Only 44% required dose modifications in the continuous treatment group. The most frequent causes for modification were hand-foot syndrome, diarrhoea and vomiting.

Ten patients died during the study or within 28 days after the end of treatment. The cause of death was disease progression in nine cases (unrelated). One patient died of non-neutropenic sepsis 12 days after the end of treatment. This case was judged possibly related to treatment.

The tolerability of the combination capecitabine and leucovorin was inferior to monotherapy. The results did not suggest that this combination treatment improves antineoplastic activity.

Intermittent treatment appeared to have been associated with a higher frequency of adverse events compared to continuous treatment, which may be explained by the higher cumulative mean dose of capecitabine with this schedule.

Vital signs

Vital signs were measured at baseline and at each visit. None of the patients experienced grade 4 decrease in systolic blood pressure.

Pharmacokinetics

Nine studies including 196 patients in total deal with the absorption and metabolism of capecitabine when given as a single agent in cancer patients. A meta-analysis has been performed on the data from four Phase I studies. The objectives of the meta-analysis included (i) time-dependency of pharmacokinetics, (ii) dose proportionality, (iii) effect of gender, age, cancer type, creatinine clearance, body surface area, weight and ethnicity on the pharmacokinetics of capecitabine.

Several population pharmacokinetic analyses have been carried out on different datasets. The most important population pharmacokinetic analysis has been carried out on data from the two phases III trials in patients with metastatic colorectal cancer (SO14695 and SO14796). The results of this analysis are reviewed in the Clinical Efficacy section of this AR.

Capecitabine is rapidly and extensively absorbed and converted to its metabolites 5'-DFCR, 5'-DFUR, and 5-FU. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502-3514 mg/m^2/day. The concentrations of the metabolites 5'-DFCR and 5'-DFUR were similar on days 1 and 14. The AUC of 5-FU was 30%-35% higher on day 14. Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to non-linear pharmacokinetics for the active metabolite.

Absorption

After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-DFCR and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption, but only results in a minor effect on the AUC of 5'-DFUR and 5-FU. At 1250 mg/m^2 on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in µg/ml) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.67, 3.05, 12.1, 0.95 and 5.46 respectively. The time to peak plasma concentrations (t_{max} in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34 respectively. The $AUC_{0-\infty}$ values in µg•h/ml were 7.75, 7.24, 24.6, 2.03 and 36.3. The variability of AUC and C_{max} for capecitabine and its metabolites is high. Variability of PK translates directly in PD effects with resulting dosage adjustments. In any way, no obvious advantage of PK monitoring over the PD monitoring actually proposed in the SPC can be assumed.

Protein binding

In vitro human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound respectively, mainly to albumin.

Metabolism

Capecitabine is first metabolised by hepatic carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumour tissues but also in normal tissues, albeit usually at lower levels leading to higher concentrations of 5-FU within tumour tissue. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (0.9 - 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (3.9 - 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (3.0 - 25.8, n=8). Thymidine phosphorylase activity was 4 times greater in primary colorectal tumour than in adjacent normal tissue.

Elimination

The elimination half-life ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Faecal excretion is

minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as parent compound.

Pharmacokinetics in special populations

Introduction

Results of two population pharmacokinetic analyses have been submitted. A pharmacokinetic model was developed to describe 5'-DFUR, 5-FU and FBAL concentration vs. time data utilising extensively sampled PK data from bioequivalence study BP15572. The model was further developed utilising sparsely sampled PK data from 54 female patients with breast cancer combined with the extensively sampled data from 24 patients in a bioequivalence study (total N = 78). This model was then applied to the analysis of sparsely sampled PK data from 481 colorectal cancer patients combined with the same extensively sampled data from the 24 bioequivalence study patients (total N=505). The extensively sampled data from BP15572 were included in both population analyses to stabilise the structural PK model.

The results of the population PK analyses are fairly well in agreement with those of the individual small scale phase I studies and the PK "meta-analysis".

Age

There was no effect on the pharmacokinetics of 5'-DFUR and 5-FU, but FBAL concentrations increase with age (20% increase in age leads to 15% increase in AUC). This is explained by decrease in creatinine clearance with increasing age. Based on pharmacokinetic data, specific dose recommendations for the elderly are not necessary. However, due to increased sensitivity to the toxicity of 5-FU with increasing age, special care must be taken in elderly patients. Forty-six percent of the patients (n=234) were at least 65 years old, but only 7 were at least 80 years old. The clinical significance of the effect of age on FBAL is unclear. FBAL has no antitumour activity.

Gender

Gender did not have any clinically significant effect on the pharmacokinetics of the main metabolites of capecitabine (5'DFUR, 5-FU, FBAL). The AUC and C_{max} of FBAL are approximately 10% and 20%, respectively, higher in women than in men.

Body surface area

Body surface area (BSA) does not influence the pharmacokinetics of 5'-DFUR and 5-FU. Although BSA does influence the exposure to FBAL somewhat, the decrease in FBAL C_{max} as a function of BSA is within the inter-patient variability and this finding is not expected to have any impact on the safety or efficacy of capecitabine.

Race

Systemic exposure to 5'-DFUR, 5-FU and FBAL was higher in Caucasian than in Japanese patients, whereas systemic exposure to 5'-DFCR was lower in Caucasian patients (retrospective analysis of 7 studies). The AUC and C_{max} of 5'-DFUR were approximately 50% higher and the AUC and C_{max} of 5-FU were approximately 30% higher in Caucasian patients. To clarify this issue, the applicant has started a prospective pharmacokinetic study in altogether 40 Caucasian and Japanese cancer patients. The applicant has agreed to provide the study report as a postmarketing commitment.

Renal impairment

Pooled data from phase I studies suggested a significant influence of creatinine clearance on AUC of 5-FU. This finding was unexpected since urinary excretion is a minor pathway in 5-FU elimination. The population PK analysis of phase III trials, however, did not reveal a significant effect of the calculated creatinine clearance (Cockcroft-Gault formula) on the pharmacokinetics of 5'-DFUR or 5-FU. However, a significant effect was observed on FBAL (50% reduction in Cl_{creat} leads to a 53% increase in AUC of FBAL). A wide range of Cl_{creat} values were studied, including 217 patients with mild impairment (Cl_{creat} 51-80 ml/min) and 41 patients with moderate impairment (30-50 ml/min). There were only 3 patients with severe renal impairment. The clinical relevance of this finding is uncertain. FBAL does not have antiproliferative activity. However, the results from the concentration

effect-analyses showed a positive relationship between AUC of FBAL and treatment-related grade 3-4 diarrhoea and between C_{max} of FBAL and treatment related grade 3-4 AE's. The relationship between exposure to FBAL and safety does not necessarily mean that FBAL is causing the AE's. FBAL, as the main catabolite of 5-FU, may be a marker of the amount of 5-FU that was formed in tissues. Patients with high values of FBAL may be patients with high exposure of tissues to 5-FU, patients with poor renal function and patients with a combination of both.

The applicant has submitted the pharmacokinetic and safety data of a study in renal impairment. Preliminary results of the study indicated increased mortality in proportion to decreased creatinine clearance. Mild to severe renal impairment had no clinically significant effect on the pharmacokinetics of capecitabine and 5'-DFCR. However, the AUC of the immediate 5-FU precursor 5'-DFUR increased in patients with moderate (35% on day 1, 23% on day 14) and severe (70% on day 1) renal impairment. On day 1, AUC of 5-FU was 27% higher in patients with severe renal impairment compared to normal subjects. Renal impairment leads to a major increase in the systemic exposure to FBAL, a metabolite without antiproliferative activity (up to 255% higher AUC in patients with severe renal impairment). Despite the modest impact of renal impairment on the PK of 5'-DFUR and 5-FU, adverse events were clearly more frequent in patients with moderate or severe renal impairment.

Effect of baseline alkaline phosphatase (ALP)
ALP did not influence the pharmacokinetics of 5'-DFUR and FBAL. ALP had a low magnitude effect on AUC of 5-FU but this effect is not considered clinically important.

Effect of ALT (ALAT), AST (ASAT), bilirubin and serum albumin
These covariates did not affect the pharmacokinetics of 5'-DFUR, 5-FU and FBAL. However, patients with truly extreme values of bilirubin, ALT and AST were not included in the analyses.

Presence or absence of liver metastases
There were 364 (72%) patients with metastases and 142 (28%) without liver metastases. The presence of absence of liver metastases at baseline did not have significant effects on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL. However, in the phase I study in patients with liver metastases and abnormal aminotransferase/ALP/bilirubin values, the pharmacokinetics of capecitabine, 5'-DFUR and 5-FU were significantly affected. Hence, the presence of liver metastases and abnormal liver function tests calls for special caution.

Interaction studies
The effect of the most common concomitant medications on the pharmacokinetics was investigated in population PK analysis of the phase III trials. Nine concomitant medications (paracetamol, ranitidine, morphine, aspirin, loperamide, combination paracetamol/dextropropoxyphene, omeprazole, pyridoxine and combination oxycodone/acetaminophen) were selected for the investigation of potential effects on the pharmacokinetics of capecitabine metabolites. Three concomitant medications remained in the final population PK model and all had an effect on 5-FU clearance. Paracetamol and morphine increased 5-FU clearance by 26% and 41%, respectively, and loperamide decreased 5-FU clearance by 31%. However, the AUC of 5-FU was similar in patients with and without these concomitant medications in both treatment cycles 2 and 4. Introduction of bias (dose adjustment due to toxicity such as hand-foot syndrome requiring analgesics, or diarrhoea) may explain the lack of effect on AUC. The clinical relevance of these observations cannot be concluded with certainty from the limited data (there were 9-12 patients taking each of the medications). However, a major impact seems unlikely.

Increased phenytoin plasma concentrations have been reported during concomitant use of Xeloda with phenytoin. Patients taking phenytoin concomitantly with Xeloda should be regularly monitored for increased phenytoin plasma concentrations. This has been reflected in the SPC (See section 4.5 *Interaction with other medicinal products and other forms of interaction*).

A phase I study in patients with metastatic renal cell cancer, combination of escalating doses of capecitabine with escalating doses of *IFN-alpha-2*a did not exclude an interaction between both substances. The MTD in this study was substantially lower than that reported for intermittent

capecitabine alone, using the same schedule and the dose-limiting toxicities were those typically encountered with capecitabine. This suggested that an interaction instead of combined toxicity of capecitabine and IFN is involved and this information has been included in the SPC (Section 4.5 *Interaction with other medicinal products and other forms of interaction).*

Allopurinol: interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. A statement that concomitant use of allopurinol with Xeloda should be avoided has been included in the SPC (Section 4.5 *Interaction with other medicinal products and other forms of interaction)*.

Interaction with cytochrome P-450: during *in vitro* evaluations, at a concentration of 100 µmol/l, capecitabine and its metabolites had no significant effect on the activity of human hepatic microsomal P-450 isozymes 1A2, 2A6, 2C9, 2C19, 2E1, 2D6 and 3A4.

The applicant was committed to perform an interaction study with warfarin and to continue to closely monitor drug interactions. A clinical pharmacokinetic interaction trial with warfarin, which was stopped before reaching its accrual target, was therefore submitted. Warfarin was chosen as representative of coumarin anticoagulants metabolised by the cytochrome p450 family. Chronic capecitabine treatment increased the single warfarin dose AUC of S-warfarin by 57% with a 91% increase in INR value. This trial provides evidence that chronic administration of capecitabine down regulates CYP2C9 and causes an increase of the prothrombin time, which also resulted in a minor bleeding event after single dose of warfarin.

Bioequivalence studies

A study with 25 patients was conducted to compare the bioavailability of capecitabine formulation 3 (F3) used in the phase I clinical studies with that of capecitabine formulation 10 (F10) proposed for marketing. The two formulations were bioequivalent with regard to observed AUC of 5'-DFUR, 5'-DFCR and 5-FU but not for C_{max}. Neither the $AUC_{0\text{-}inf}$ not C_{max} of capecitabine fulfilled equivalence criteria. Although bioequivalence for capecitabine and C_{max} of the metabolites was not demonstrated, the differences are not likely to affect the relevance of phase I studies.

Clinical Efficacy

The pivotal studies are summarised in Table 4.

Table 4: Overview of pivotal studies

Number	Design	Schedule		Overall response rate (primary end point, ITT)	
		Capecitabine	**FA/5-FU**	**Capecitabine**	**FA/5-FU**
SO-14695	Open-label, Phase III	12502500 mg/m^2 twice daily/ day for two weeks followed by a one week rest period	20 mg/ m^2 i.v leucovorin followed by 425 mg/ m2 of 5-FU i.v. bolus daily from day 1 to day 5 every 28 days	78/302 (25.8%)	35/303 (11.6%)
SO-14796	Open-label, Phase III			57/301 (18.9%)	45/301 (15%)

Trial description

The indication claim is based on two phase III open, randomised, comparative (capecitabine vs. 5-FU/LV Mayo regimen, as first line treatment), multicenter trials in patients with advanced and/or metastatic colorectal cancer. The trials have identical protocols. A prospectively planned integrated analysis of these trials has also been carried out.

The primary objective of the study was to demonstrate at least non-inferiority of capecitabine with 5-FU in combination with folinic acid in terms of overall response rate (complete and partial responses)

in previously untreated patients with advanced and/or metastatic colorectal carcinoma. The objective to demonstrate non-inferiority compared to standard/established treatment in this case is appropriate.

Secondary objectives were to compare the efficacy and safety profiles of the two treatments (time to disease progression, overall survival, time to and duration of response, adverse events and time to their onset), to evaluate and to compare the medical care utilisation as well as changes in quality of life in the two treatment groups.

Male or female patients of at least 18 years of age with histologically or cytologically confirmed colorectal adenocarcinoma with advanced and/or metastatic disease, who were previously untreated by chemotherapy (except given as adjuvant or neo-adjuvant treatment more than 6 months before) and who had at least one measurable lesion according to the WHO criteria with a minimum indicator lesion size of ≥ 20 mm (in at least one diameter) in liver and soft tissue or ≥ 10 mm (in at least one diameter) in lung, skin, or lymph nodes were eligible for the study. Patients with clinically significant cardiac disease or myocardial infarction within 12 months before study entry, with evidence of CNS metastases or with a history of other malignancies within the last five years, with known hypersensitivity to fluoropyrimidines, with radiotherapy or major surgery within 4 weeks of the start of the study and patients with serious uncontrolled intercurrent infections were excluded from the study.
All patients were randomised to one of the following dosing regimens:

Capecitabine arm: Capecitabine orally at 1250 mg/m^2 twice daily within 30 minutes after the end of a meal for two weeks followed by a one week rest for at least 6 weeks. The dose had to be rounded to a combination of 500 and 150 mg tablets.

5-FU and folinic acid arm: 20 mg/m^2 folinic acid as a rapid iv injection followed by an iv bolus injection of 425 mg/m^2 5-FU, administered daily from day 1 to 5 every 28 days.

In case of occurrence of grade 2, 3 or 4 toxicity treatment interruption until resolution to grade 0 - 1 had to be followed by a selective dose reduction of capecitabine of 25-50% or permanent discontinuation, depending on the type and severity of toxicity as further specified in the protocol Once the dose had been reduced re-escalation was not recommended. In the 5-FU/FA arm dose modifications of 5-FU were allowed in cases of >grade II non-haematological toxicity and >grade III granulocytopenia and thrombocytopenia. Furthermore, dose escalation of 5-FU by 10% of the preceding dose was allowed if no toxicity was documented on the preceding treatment cycle.

The study duration was 30 weeks (treatment phase - 211 days) with a continuation phase in responding patients (complete or partial response) for up to a total of 48 weeks. Patients with complete response had to be treated for at least an additional 12 weeks after confirmation of complete response. After 48 weeks patients with ongoing responses or stable disease might continue to receive capecitabine off study at the discretion of the investigator with a quarterly collection of survival and time to disease progression data (post-continuation phase).

Tumour assessment was done at screening, and after 6, 12, 18, 24 and 30 weeks of treatment. Response had to be confirmed a minimum of 4 weeks after the first response had been observed. The response assessment was done by the investigators as well as by an independent expert panel on the basis of a modified assessment system. For the investigation of safety, all clinical adverse events encountered during the study as well as abnormal laboratory test values and results of regular physical examinations (vital signs) had to be clearly recorded in the CRF.

The overall study population was divided into three analysis populations (Table 5): the Intent-to-treat population (all randomised patients), the Safety population (all randomised patients who received at least one dose of trial medication) and the Standard population (all patients who participated in the study according to protocol and who received at least 50% of the anticipated treatment during *at least 6 weeks of therapy,* except in case of progressive disease or death, had adequate information about tumour burden at baseline and adequate tumour assessment information).

Table 5: Overview of populations

Population	Trial 14695			Trial 14696		
	Capecitabine	5-FU + LV	All	Capecitabine	5-FU + LV	All
All Patients Randomised (ITT)	302	303	605	301	301	602
Safety Population	299	294	593	297	299	596
Standard Population	269	266	535	265	273	538

According to the non-inferiority objective efficacy was analysed primarily in the standard population, and results from the intent-to-treat analysis were regarded as supportive. All other analyses are performed on the ITT-population and are only of a descriptive nature.

The two treatment groups were balanced with respect to predefined demographic characteristics at baseline. Approximately 60% of patients were male in both groups, their mean age was 62 years, 90% were Caucasian and the mean Karnofsky PS was 89%. About two-thirds of patients in each treatment group entered the study with colon cancer and about one-third with rectal cancer. The majority of patients in each treatment group had poorly or moderately differentiated malignancies at baseline.

The majority of patients had involvement of two or more metastatic sites at baseline. A smaller proportion of patients in the capecitabine group had involvement of 4 or more metastatic sites at baseline (178 of 603 versus 202 of 604 in the 5-FU/LV group). As expected, the most frequently involved tissues/organs were the liver, lung, and lymph nodes, in that order. A similar proportion of patients had metastases in these sites in both treatment groups. Metastases to the brain (protocol exclusion) were observed in one patient, and very few patients had metastases of bone, pleura or skin.

There was an imbalance in the numbers of metastatic sites at baseline (see also Study SO14796). This difference in favour of the capecitabine group over 5-FU/LV. Cox multivariate analyses based on integrated analysis database (all randomised population) and separate Cox analyses including only treatment and number of metastatic sites at baseline have been provided. These additional analyses are in agreement with the univariate analyses of ORR, TTP and overall survival and do not change the conclusions of the data.

Most patients had received previous treatment for malignant disease in both studies. Surgery was the main previous treatment received by most patients in both treatment groups in both studies. The two treatment groups were well balanced with regard to previous treatment.

Quality of life was assessed by the patients using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 2.0). The primary time point for the analysis of the Quality of life data was chosen to be day 169.

All adverse events and abnormal laboratory parameters were assessed according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC) grading system.

The individual trials were not sufficiently powered to demonstrate non-inferiority in time to disease progression (TTP) or survival. They were sufficiently powered to demonstrate non-inferiority with regard to ORR. However, the integrated analysis was powered for demonstration of non-inferiority with regard to TTP and survival.

For the demonstration of non-inferiority in terms of time to disease progression or death ("disease free survival") and overall survival, the applicant has specified the limit 1.2. The rationale for this limit is as follows:

For an estimate of median TTP of approximately 5 months as seen in the integrated analysis, an increase of 20% in the hazard function would translate, under exponential distribution assumptions, into a 3.4 week difference in median time to disease progression as a worst case. This is regarded as a clinically meaningful limit for three reasons.

1. Usual tumour assessments are done at most every 6 weeks. A three-week difference is therefore clearly within the limits of measurement precision.
2. The active comparator in these studies (Mayo regimen) has shown improvements in median time to progression of approximately 12 weeks when compared with 5-FU alone.
3. Differences, even statistically significant ones of 3 weeks or less are generally regarded as not clinically relevant.

For survival, different limits than those set for time to disease progression may be applicable. However, with an estimated median survival of 13 months for the Mayo regimen, under ideal exponential distribution assumptions, a 20% increase in the hazard would translate into a worst survival of 10.8 months. Such a limit would rule out a median survival difference of more than 2.2 months. This is clinically relevant because:

- Median survival estimates for the Mayo regimen are in the range of 11 to 13 months. In a worst case scenario, 10.8 months median survival for Xeloda would still fall within the limits, assuming the Mayo regimen achieved a median survival of 13 months. In other words, a 2 month difference in survival is still within the range of variation seen in the median survival estimates for the Mayo regimen in the treatment of first line metastatic colon cancer, and is therefore not considered to be a clinically relevant difference.

- In some studies, the Mayo regimen has shown a 5-month improvement in survival over 5-FU monotherapy. As a worst scenario, 2.2-month survival inferiority for Xeloda would still be an improvement over 5-FU monotherapy.

For tumour response the limits were broad due to power limitations. Nevertheless, a maximum limit of 10% provides the basis for a useful clinical evaluation since most treatments for first line colorectal cancer treatment achieve tumour response rates in the range of 10% to 30%. Altogether, the applicant has sufficiently justified the non-inferiority margins.

Results
The main efficacy results are reviewed here on the basis of the pre-planned integrated analysis. The primary composite endpoint in the integrated analysis is Time to Disease Progression/Time to First Onset of Key Treatment-Related Grade 3-4 Adverse Events and Neutropenia/Granulocytopenia.

As regards the primary efficacy endpoint, non-inferiority of capecitabine compared to 5-FU/FA was demonstrated according to the prespecified margin of 1.2 for the upper limit of the confidence interval for the hazard ratio; in both the investigator and IRC (independent review committee) assessment and in both the Standard and All Randomised populations. The results of analyses of the different study populations and the investigator and IRC assessments were consistent.

The result of the investigator assessment of time to tumour progression (TTP) in the all randomised and standard population were:

Capecitabine:	140 days (median), 95% CI 131;161
5-FU/FA:	144 days, 131; 164
Hazard Ratio (CI):	1.00 (0.89; 1.12)

Capecitabine:	148 days (median), 95% CI 133;166
5-FU/FA:	144 days, 129; 165
Hazard Ratio (CI):	0.99 (0.87; 1.12)

As regards study SO-14695, TTP was a secondary endpoint and non-inferiority was not demonstrated according to IRC assessment using the prespecified 1.2 margin. Non-inferiority was not consistently demonstrated according to investigator assessment, either. However, the Kaplan-Meier TTP curves were virtually superimposable. Importantly, the study was not powered to demonstrate non-inferiority with regard to this secondary endpoint.

As regards study SO-14796, TTP was also a secondary endpoint. In this study, non-inferiority of capecitabine was demonstrated for the standard and all randomised population.

There is a large difference in the IRC and Investigator assessment of Time to Disease Progression in the integrated analysis. However, the applicant has shown that 1) the differences in assessments of PD between investigator and IRC (excluding patients with PD at follow-up) were evenly distributed in the treatment groups in the individual studies and in the integrated analysis, and that no important bias was introduced, and 2) the reasons for differences in the assessments of PD between investigator and IRC assessment were also similarly distributed in the two treatment arms, in both individual studies and the integrated analysis.

As regards the secondary efficacy endpoints in the integrated analysis:

All responses reported in the dossier (if not designated differently) refer to confirmed responses. Since tumour assessment was recommended in regular intervals of 6 weeks, most confirmation of responses did not occur exactly on day 28 but around week 6 (day 42).

Objective Response Rate (ORR): superiority of capecitabine was demonstrated in the integrated analysis in both the standard and all randomised population based on both the IRC and investigator assessment. The ORR according to IRC assessment of all randomised and standard population was 22.4% (CI 19.1;25.9) / 24.7% (21.1;28.6) in the capecitabine group and 13.3% (10.6;16.2) / 14.5 (11.6; 17.7) in the 5-FU/FA group. As regards the control group, the result is consistent with published studies.

Overall survival: non-inferiority of capecitabine was formally demonstrated for the standard population using the predefined margin of 1.2. For the all randomised population, the margin of 1.2 was slightly missed. The median survival in the standard population was as follows:

Capecitabine:	401 days
5-FU/FA:	400 days
Hazard Ratio:	1.01 (0.87; 1.18)

The most mature survival update (May 2000) confirmed clearly non-inferiority of capecitabine vs. Xeloda with a hazard ratio (standard population) of 0.96 and the upper limit of the 95% interval (0.85; 1.08) being even below 1.1.

The detailed analysis of the usage of second line therapy do exclude an effect of 2nd line treatment on the conclusion that OS in patients treated with capecitabine is at least equivalent to patients treated with 5-FU/FA.

The *median duration of response* according to the integrated analysis was slightly shorter in the capecitabine group: 246 vs. 288 days according to investigator assessment (WHO criteria). Looking at the duration of response according to investigator assessment in the two treatment arms, there is a clear difference in study SO14796 in favour of 5-FU/LV, but no difference in study 14695. The slightly shorter duration of response in the capecitabine group compared to 5-FU/LV despite a higher response rate in the former treatment could be expected. The applicant is correct in pointing out that the patient subgroups who respond to treatment in the two groups may not be totally comparable, i.e. selection may be introduced.

The *median time to treatment failure* was consistently slightly longer in both studies in the capecitabine group.

The *time to first response* analysed by the distribution of responders in time intervals and plots of Kaplan-Meier estimates showed a similar pattern in the two treatment groups, with more responders in the capecitabine group.

The *overall Quality of Life (QoL)* scores for global health were similar in both treatment groups according to both the integrated analysis and individual study analyses. The schedule of QoL assessments did not allow assessing the impact of an oral treatment versus an i.v. Treatment. The results are not necessarily comparable between the treatment groups because assessment took place at different time points in the course of treatment cycle (during 1 week rest for capecitabine patients and during 3 week rest for 5-FU/FA patients). There was no worsening in any of the parameters.

Generally, there were slight, probably clinically not relevant improvements in the QoL outcomes in patients who responded (CR/PR) in either of the treatment arms. There is a tendency for these changes to be slightly more favourable in the 5-FU/LV arm compared to capecitabine. However, the differences are unlikely to be clinically relevant. Clearly less improvement or even deterioration in QoL outcomes (especially global health and physical functioning) were observed for patients whose response was SD or PD in both treatment arms. Overall, it is important that treatment response (CR/PR) was not associated with deterioration in QoL scores in either treatment group.

In accordance with the current ICH guidelines (E9) the applicant has provided a statistical analysis, which shows that there was no study-by-treatment interaction effect on response rate, time to disease progression and survival. Including study as a factor in the model did not change estimates of the treatment effect.

In the integrated analysis not even a trend in any of the subgroup analyses could be identified. Therefore this set of analyses is reassuring for the robustness of the data concerning equivalence/non inferiority of both regimens in terms of TTP and OS.

Clinical studies in special populations

No such studies have been performed. Although there is a clear gender by treatment effect for TTP in the univariate and multivariate analysis of study SO14695 when assessed by the IRC (but not in the investigator assessment), suggesting shorter TTP in the capecitabine group compared to 5-FU/LV in male patients than in female patients, this unexpected finding was not confirmed in study SO14796 or in the integrated analysis of the two studies. Furthermore, there was no evidence of a gender by treatment effect for ORR and survival. Therefore, it can be concluded that there is no consistent evidence suggesting different treatment effect between males and females.

Discussion on clinical aspects

Pharmacokinetics

In general, absorption, distribution, metabolism and excretion of capecitabine are well investigated. The main metabolites are appropriately characterised, the recovery is nearly completely balanced and the main elimination and excretion pathways (FBAL, urinary) are described. The PK investigation are complicated by the extensive metabolism capecitabine undergoes but it appears that PK (of all major metabolites) is dose-proportional.

Overall, there were few factors identified having an impact on the PK of capecitabine. Capecitabine may have interactions with substances metabolised via CYP2C9, such as phenytoin. Potential interactions with phenytoin and warfarin were already described in the initial SmPC on the basis of postmarketing reports. An interaction trial with warfarin was submitted post-authorisation. This study provided evidence that chronic administration of capecitabine down regulates CYP2C9 and causes an increase in prothrombin time. Furthermore, sorivudine and analogues have been reported to have a clinically significant interaction with 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase. This interaction leads to increased fluoropyrimidine toxicity and is potentially fatal.

The most important single factor influencing absorption of capecitabine is administration under fasting vs. feeding conditions (fasting leads to a higher absorption while capecitabine was investigated within 30 minutes after a meal in all phase III trials).

The effects of renal impairment on the pharmacokinetics of capecitabine were evaluated on the basis of a specific pharmacokinetic study and a population pharmacokinetic analysis approach. Mild to severe renal impairment had no clinically significant effect on the pharmacokinetics of capecitabine

and 5'-DFCR. However, despite the modest impact of renal impairment on the PK of 5'-DFUR and 5-FU, adverse events were clearly more frequent in patients with moderate or severe renal impairment. This phenomenon remains unexplained and appropriate dose recommendations and contraindications have been reflected in the SPC (see section 4.2, *Posology and method of administration*; section 4.3, *Contraindications*).

Dosage schedules
Overall 4 different schedules of capecitabine have been investigated, between them two schedules ("intermittent and continuous") investigating capecitabine monotherapy. The recommended dose (i.e. a dose level lower than the MTD) determined in phase I trials was lower for the continuous (1331 mg/m^2/day) than for the intermittent schedule (2510 mg/m^2/day). Both schedules, and a schedule combining capecitabine with folinic acid, were further investigated in a randomised, parallel group phase II trial. While ORR was comparable for all schedules (in the range of about 20 to 25 %) the investigators favoured the intermittent schedule due to a numeric superiority in terms of TTP. However, the intermittent schedule appears to be more toxic (e.g. in terms of nausea and hand-foot syndrome) than the continuous so that this decision leaves space for the development of further schedules. In addition, this phase II trial demonstrated that folinic acid has strong pharmacodynamic interactions with capecitabine (in terms of Aes such as severe diarrhoea and hand-foot syndrome but not in terms of ORR, i.e. on healthy tissue).

In two large, multicentre, multinational, randomised, parallel group, open labelled phase III trials using identical protocols the intermittent monotherapeutic capecitabine schedule was compared with the well known Mayo regimen in treatment naïve patients with advanced colorectal carcinoma.

Choice of comparator
Concerns have been raised about the choice of comparator. Despite recent developments in the combination treatment of colorectal cancer (such as the combinations of 5-FU and irinotecan or oxaliplatin), monotherapy remains in wide use. Capecitabine is superior to the Mayo regimen in terms of RR (22.4 vs. 13.3%; $p<0.0001$, integrated analysis, ITT, IRC assessment) but not with respect to OS. In addition with the higher frequency of hand-foot-syndrome (or the lower frequency of neutropenia/stomatitis vice versa) it can be concluded that oral capecitabine resembles more an infusional 5-FU than a bolus regimen.

The antineoplastic activity and adverse reaction profile/pattern of 5-FU depends strongly on the schedule. The applicant has shown that there is no single standard of care in advanced colorectal cancer, and for monotherapy the Mayo regimen as comparator is acceptable. In recent years only the pattern of 5-FU schedules in use has changed slightly.

Overall, oral capecitabine tablets have the potential to replace i.v. 5-FU bolus (e.g. Mayo regimen) or to lead even to slightly improved results.

It is agreed that capecitabine, an oral fluoropyrimidine administered as a single compound, could simplify combinations with irinotecan, oxaliplatin and possibly with other therapies as well.
Although it is regrettable that there is no information on results of combining capecitabine with substances licensed most recently for the combination with 5-FU (irinotecan, oxaliplatin) this could not be expected as these substances were only investigational compounds during the development of capecitabine. The treatment of colorectal cancer has not changed very dramatically in the most recent period and flouropyrimidines have remained the backbone of the treatment.

Efficacy Results
The major results of the two pivotal trials can be briefly described as follows:
Xeloda is at least not inferior to Mayo in terms of overall survival (OS) and time to progression (TTP), and superior in terms of objective response rate (ORR). The observation of an improved ORR, which does not affect TTP and/or OS, may be surprising at the first glance. However, it has to be taken into consideration that the difference and the magnitude itself (ORR: 24.7 vs. 14.5%, standard population, IRC assessment, integrated analysis) are not "dramatic" and refer to partial response in the majority of cases. Similar patterns have been reported in relation to FA modulated 5-FU. Higher response rates for

modulated 5-FU had no effect on OS in meta-analyses. In effect, it is a usual pattern of the correlation between effect and efficacy endpoints in the treatment of advanced colorectal carcinoma.

Imbalance in number of metastatic sites
There is a clear, although not statistically significant imbalance in favour of capecitabine in the number of metastatic sites at baseline in both studies SO14796 and the integrated analysis. The applicant has conducted further analyses on the "all randomised" and standard ("per protocol") populations, taking into account this imbalance. The primary analysis population as defined by the protocol was the standard population.
With regard to Overall Response Rate and Time to Disease Progression, the conclusion of non-inferiority of capecitabine compared to 5-FU/LV was not altered by the adjusted analyses in either the all randomised or standard populations.

The applicant has analysed two different datasets for survival, the one submitted in the original dossier, and an update. The minimum follow-up time in these two datasets is very different, 11 months in the former and 21 months in the latter.

Original MAA dataset
With regard to overall survival, non-inferiority cannot be claimed in study SO14796 for the adjusted analysis of the all randomised population. However, for the standard population, the adjusted analyses allow the conclusion of non-inferiority. Similarly, for the integrated analysis non-inferiority was confirmed only for the standard population, not for the all randomised population.

Survival update
For both study SO14796, and the integrated analysis, non-inferiority can be concluded in both the all randomised and standard populations, adjusted and non-adjusted for the baseline number of metastatic sites.

The protocol specified the standard population as the primary analysis target. This is in keeping with CPMP/EWP Points to consider on biostatistical/methodological issues: superiority, non-inferiority and equivalence. According to the PtC, the primary focus in a non-inferiority study should be on the per protocol population. However, the conclusions should be similar based on analysis of the ITT population. In view of this, the survival update becomes important for the formal demonstration of non-inferiority in terms of overall survival. Altogether, it can be concluded that the baseline difference in metastatic sites did not introduce a clinically meaningful bias in favour of capecitabine.
Clinical safety

Patient exposure
The profile of adverse events, which were reported in the phase I-II studies using the intermittent capecitabine regimen, is comparable to that, reported in phase III trials.

Review of the second Periodic Safety Update Report which covers the period 01/11/98 to 30/04/99 did not suggest, besides two reports on fatal liver failure, any new signals compared to the clinical trial database included in the current dossier.

In the two-phase III trials in colorectal cancer, altogether 603 patients were treated with capecitabine and 604 were treated with 5-FU/FA. The median duration of treatment (including rest periods) was similar in the two groups (approximately 140 days), and patients received a mean of 84% of the planned dose in the capecitabine group and 89% of the planned dose in the 5-FU/FA group.

Adverse events and serious adverse events/deaths
At least 94% of patients experienced at least one AE. The majority of treatment-related AEs were graded mild or moderate.

Grade 3 (severe) treatment-related adverse events were slightly more frequent in the capecitabine group (38.1% vs. 34.1% 5-FU/FA). Grade 4 (life-threatening) treatment-related adverse events were slightly more frequent in the 5-FU/FA group (5.1% vs. 3.0% capecitabine). It should be noted that the

highest grade on the scale for hand-foot syndrome (HFS) was a grade 3 event.

The most frequent treatment-related grade 3 adverse events were as follows:

-	stomatitis:	capecitabine 2.0%	5-FU/FA 14.2%
-	neutropenia:	capecitabine 0.5%	5-FU/FA 5.4%
-	HFS:	capecitabine 17.1%	5-FU/FA 0.5%
-	diarrhoea:	capecitabine 11.6%	5-FU/FA 10.3%

The most frequent treatment-related grade 4 adverse events were as follows:

-	stomatitis:	capecitabine 0.2%	5-FU/FA 0.5%
-	neutropenia:	capecitabine 0.2%	5-FU/FA 1.9%
-	diarrhoea:	capecitabine 1.5%	5-FU/FA 1.9%

The incidence of grade 3 and 4 treatment related infections was 1.7% in the capecitabine group and 2.4% in the 5-FU/FA group. Sepsis was reported in 9 patients and one patient in the 5-FU/FA and capecitabine groups, respectively. Compared to 5-FU/FA (Mayo regimen), the most striking differences are lower frequencies (all grades considered) of diarrhoea, stomatitis, nausea, alopecia and neutropenia leading to medical intervention, and a higher frequency of HFS in capecitabine patients.

In general, the profile of undesirable effects reported for capecitabine is similar to that reported for continuous (prolonged) 5-FU infusion especially with regard to high frequency of Hand-Foot Syndrome (HFS) and low frequency of neutropenia. Comparing the frequency of about 50% for capecitabine with literature data for continuous 5-FU infusion (rough estimate 20-30%) it appears indeed to be a high frequency. However, it has to be taken into account that in this study a grading system was used which includes “skin changes or dermatitis without pain”. This may explain the differences, or highlight the problems with the interpretation of non-randomised comparisons.
Further analyses did not suggest a relationship between exposure to the FBAL metabolite and Hand-foot syndrome

Usually hand-foot syndrome and diarrhoea did not occur concomitantly.

The phase III protocols pre-defined six treatment-related grade 3 and 4 adverse events (diarrhoea, stomatitis, nausea, vomiting, alopecia, HFS, neutropenia) as being of particular importance for evaluating comparative safety. The time to onset of prespecified adverse events was a predefined co-primary endpoint in the integrated analysis. This endpoint is valuable since it encompasses the most frequent events associated with fluoropyrimidine treatment which are also important in terms of QoL and the need for dose adjustment. A statistically significant difference (one-sided log rank test p=0.0001) favouring capecitabine was observed. Consequently, dose reductions occurred less often (66.1% vs. 57.8% of patients did not require dose reductions) and later on capecitabine than on 5-FU/FA. The median time to dose reduction was 76 days and 36 days in the capecitabine and 5-FU/FA groups, respectively.

Importantly, the median duration of treatment-related grade 3-4 adverse events was similar in the two treatment groups. Compared to 5-FU/FA, fewer capecitabine-treated patients received treatment for the treatment-related adverse events (82.3% vs. 90.5%).

Dose reductions due to adverse events occurred less often and at a later time point during treatment with capecitabine.

Treatment with capecitabine was associated with fewer treatment-related serious adverse events than 5-FU/FA (13.6% vs. 20.6%). The most frequent serious events were, for the most part, gastrointestinal. Of importance, neutropenia leading to medical intervention was reported as a serious treatment-related adverse event in 3% of patients in the 5-FU/FA group, but in only 0.3% of patients in the capecitabine group. The incidence of neutropenic fever reported as a serious AE was also lower in the capecitabine group (0% vs. 2.9%).

Importantly, HFS was reported as a serious adverse event in only two patients (0.3%) in the

capecitabine group. Despite high frequency of HFS as a treatment-related adverse event, it led to hospitalisation in only 2 cases. HFS was reported as a cause of treatment withdrawal in a low percentage of patients (1.7%) in the capecitabine group.

The incidence of premature withdrawals due to any AE (13.3% vs.10.8%) or due to treatment-related AE (9.6% vs. 6.7%) was slightly higher in the capecitabine group compared to 5-FU/FA.

In view of the potential cardiotoxicity of fluoropyrimidines, cardiac disorders have been reviewed separately. The incidence of treatment-related grade 3 and 4 cardiac events, as well as serious cardiac events reported as related to treatment was similar in the two treatment groups. However, the incidence of cardiac events of all grades and incidence of all grade 4 events (including those considered unrelated) was higher in the capecitabine group. Although the results do not suggest a clear difference in cardiotoxic potential between capecitabine and Mayo regimen, cardiac disorders must continue to be closely monitored.

Hepatobiliary disorders have been reviewed separately due to the higher incidence of hyperbilirubinemia in patients treated with capecitabine compared to 5-FU/FA. The incidence of treatment-related hepatobiliary events was slightly higher in the capecitabine group (grade 1: 0.7% vs. 0.2%; grade 2: 0.2% vs. 0.2%; grade 3: 0.5% vs. 0%). The incidence of all (including unrelated) grades 4: 1.0% vs.0.7% in the capecitabine and 5-FU/FA group, respectively. In most of the cases, liver metastases were present. One case of cholestatic hepatitis and jaundice (possibly related) and one case of jaundice (remotely related) were reported as grade 4 treatment-related events in the capecitabine group (see Section 4.8 of the SPC, *Undesirable effects*). Hepatobiliary events must continue to be closely monitored. At present, the most plausible mechanism behind hyperbilirubinemia may be the inhibition of transport molecules required for the uptake of bilirubin into hepatocytes by capecitabine. Isolated grade 3-4 hyperbilirubinemia is a frequent adverse reaction of capecitabine treatment but, based on the data presently available, without a clear association to hepato-toxicity. In the Periodic Safety Update report, two fatalities related to liver and biliary system disorders were reported. In the first case, a female patient experienced hepatic failure during treatment with capecitabine, docetaxel and diclofenac. Although confounding medications were present, a contribution of capecitabine cannot be ruled out. The other case involved a female patient who received capecitabine treatment for progressive hepatic metastases of breast cancer. Based on review of reports of hepatic failure, one or more confounding factors were present in all of the cases listed. However, a causal role of capecitabine cannot be excluded in at least two cases (see Section 4.8 of the SPC, *Undesirable effects*).

Age and renal impairment were found to be important factors in terms of frequency of adverse events. Patients who were at least 80 years old experienced a greater incidence of gastrointestinal grade 3 or 4 adverse events in both treatment groups than the overall study population. A higher incidence of grade 3 HFS compared to overall study population was observed in patients between 70 and 79 years of age (capecitabine). Patients with creatinine clearance of 30-50 ml/min at baseline experienced a greater overall incidence of treatment-related grade 3-4 adverse events relative to the overall population in both groups. The safety update did not suggest direct nephrotoxicity of capecitabine although dehydration must be avoided.

The incidence of treatment-related deaths (during treatment or within 28 days from the last dose) was 1.0% in both capecitabine and 5-FU/FA groups. The incidence of deaths (during treatment or within 28 days from the last dose) was slightly, but statistically significantly higher in the capecitabine group (8.4% vs. 5.4%). This difference was biased by the difference in treatment schedules between the two groups. The majority of deaths in both treatment groups were considered to be unrelated to treatment and most of these unrelated deaths were due to progressive disease. Importantly, the reported causes of death (during treatment, within 28 days from last dose, deaths that occurred beyond 28 days) have a very similar pattern between the two treatment groups (including cardiovascular causes, septicaemia and gastrointestinal causes).

The incidence of grade 3-4 neutropenia/granulocytopenia and leukocytopenia was clearly lower in the capecitabine group compared to 5-FU/FA (approximately 10-fold difference), whereas grade 3-4

anaemia and thrombocytopenia were reported at similar low frequencies.

Rare cases of events related to inflammation/ulceration of mucous membranes such as esophagitis, gastritis, duodenitis, colitis, and gastrointestinal haemorrhage, certain neurological disorders (encephalopathy, confusion and cerebellar signs such as ataxia, dysarthria, impaired balance and abnormal co-ordination), colitis, hepatic and cardiac failure have been reported. This is reflected in the SPC (See section 4.8, *Undesirable effects*).

There were two cases of haemolytic anemia and one case of microangiopathic haemolytic anemia. All cases were considered serious, but none was fatal. Reports of haemolytic anemia must continue to be monitored.

Laboratory findings
The incidence of grade 3-4 elevated AST (0.7-1.2%) and alkaline phosphatase (3.4-4.1%) was similar in both treatment groups. The only remarkable difference between capecitabine and 5-FU/FA in blood chemistry was the incidence of grade 3/4 hyperbilirubinemia (22.8% vs. 5.9%) and grade 4 hyperbilirubinemia (4.5% vs. 2.5%), with higher frequencies in the capecitabine group. However, the incidence of hepatobiliary events was low and not remarkably different between the two groups (see above). Furthermore, hyperbilirubinemia was generally moderate (between 1.5 and 3 x ULN) and not associated with increases in AST or alkaline phosphatase. The clinical relevance of hyperbilirubinemia during capecitabine treatment remains uncertain. However, as noted previously, hepatobiliary reactions must continue to be closely monitored and the applicant should establish the mechanism underlying increases in serum bilirubin.

A slightly higher incidence of grade 3 and 4 hyperglycaemia was observed in capecitabine-treated patients. Although the prevalence of diabetes mellitus in the two treatment arms was similar at baseline, the proportion of diabetics on insulin treatment was clearly lower in the capecitabine group (32% vs. 50%). 57% of the diabetics in the capecitabine group and 40% of the diabetics in 5-FU/LV groups used oral antidiabetic medication. This may explain the difference in the incidence of grade 3-4 hyperglycaemia and grade 3-4 shifts from baseline.

Safety in special populations
Hepatic impairment
Insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation. No information is available on hepatic impairment due to cirrhosis or hepatitis.

Renal impairment
Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min). The proposed dose reduction to 75% for patients with moderate renal impairment (creatinine clearance below 30 ml/min) is based on 25-30% increase in AUC of 5'-DFUR and on frequency of dose reductions in early cycles.

Children and adolescents (under 18 years):
The safety and efficacy of Xeloda in children and adolescents has not been studied.

Elderly
No adjustment of the starting dose is needed. However severe grade 3 or 4 treatment-related adverse events were more frequent in patients over 80 years of age compared to younger patients. Careful monitoring of elderly patients is advisable.

Discussion on clinical safety

Comparison with Mayo regimen
The safety profiles of capecitabine and Mayo regimen are clearly different. Higher frequency of hand-foot-syndrome and lower frequency of stomatitis and neutropenia are the main features of capecitabine treatment. This is, however, not unexpected. Continuous i.v. administration of 5-FU leads also to a

similar shift of adverse effects. In addition, these differences cannot be considered as unfavourable for capecitabine. Actually, stomatitis and neutropenia are risk factors for (fatal) infection while hand-foot-syndrome interferes primarily with patients' well being without being life-threatening.

A further difference to note is the frequency of isolated hyperbilirubinaemias observed for capecitabine treatment. This effect is unexpected and presently not fully explained in its last details. The knowledge available indicates that it is a pharmacodynamic effect without clinical relevance. The pathomechanism is most probably the inhibition of bilirubin uptake into hepatocytes.

The analysis of the term "death on study" resulted in a statistical significant but artificial (due to the different duration of treatment and different treatment schedules in the two trial arms) difference in favour of Mayo regimen. The applicant was asked to clarify this further by presenting a new analysis of all deaths during the first 170 days in all randomised patients. This analysis did not reveal a statistically significant difference between the treatment arms in the integrated analysis. The percentage of deaths in the two arms was similar.

A fair overall conclusion is that the safety profile of intermittent Xeloda treatment differs clearly from the Mayo regimen. It is, however, not outside of the range of known 5-FU regimens.

In conclusion, intermittent oral capecitabine treatment of naïve patients with advanced colorectal carcinoma resembles more a continuous 5-FU iv infusion than the Mayo regimen (low dose folinic acid plus 5-FU iv bolus) in terms of efficacy and safety.

Variability of DPD activity
DPD activity shows considerable inter-individual variability. Low activity could potentially lead to severe 5-FU toxicity. Therefore Xeloda is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy, or known hypersensitivity to fluorouracil (see SPC, section *4.3 Contra-indications*). In case the mechanism for fluoropyrimidine toxicity is low DPD activity, permanent discontinuation of treatment is recommended (see SPC, section 4.2 *Posology and method of administration*.

Screening for the enzyme itself has methodological limitations so that it cannot be recommended. Capecitabine is administered continuously and therefore by relative low single doses. Compared to 5-FU bolus doses this is at least theoretically an advantage in the rare situation of DPD deficiency. PK monitoring for DPD deficiency is currently not considered feasible.

The predictive value of DPD in peripheral blood mononuclear cells (PBMNC) is not yet established. In patients treated with 5-FU, the risk of developing side effects was not linked to DPD activity in PBMNC but correlated with systemic exposure to 5-FU. The correlation between DPD activity in PBMNC and 5-FU clearance was weak. Moreover, in a recent published study, measurement of DPD activity in PBMNC of patients with severe 5-FU toxicity revealed that only 36% of the patients had diminished DPD levels. These results confirm that DPD levels in PBMNC are a relatively poor predictor 5-FU toxicity.

The applicant has committed to investigate the relationship between DPD activity and capecitabine toxicity as a follow up measure.

Concomitant NSAID use

The adverse events reported in these patients (compared to patients with adverse events but no reported NSAID use) suggest a higher percentage of events possibly attributable to NSAIDs (such as dyspepsia, bloody diarrhoea, hematemesis, cerebral haemorrhage, epistaxis). However, whether there is an interaction or not cannot be concluded.

4.2. Adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer

Xeloda (capecitabine), a pro-drug of 5-FU, has granted a monotherapy indication (stage IV or metastatic) based on the demonstration of non-inferior time to disease progression (or death) compared to the Mayo regimen (a 5-FU schedule modulated by low dose folinic acid), and on the favourable fact that it can be administered by the oral route.
This application is an extension of the Xeloda indication to adjuvant treatment for patients with colon cancer. In 70% of patients with newly diagnosed colon cancer, the disease is apparently localised and potentially curable by surgical resection (i.e. stage 0 to III, see **Table 1**).

TABLE 1: UICC STAGING SYSTEM OF COLON CANCER WITH REFERENCE TO THE DUKES STAGING SYSTEM

Stage 0	Tis	N0	M0	
Stage I	T1, T2	N0	M0	(Dukes A)
Stage II	T3, T4	N0	M0	(Dukes B)
Stage III		any T	N1, N2 M0	(Dukes C)
Stage IV		any T	any N M1	

In localised (stage I to III) colon carcinoma, frequency of relapses - in most instances as a metastatic disease and infrequently as local relapse- after complete surgical resection differs considerably with stage. Relapse rates according to stage are ranging in the literature from 15% (stage I) to 90% (T4N2M0). Directly linked with the relapse rate (in terms of distant metastasis) also the survival of patients with stage I to III (and IV) tumours differs considerably.

On the basis of a meta-analysis only (Buys M et al.[1], 1988) 5-FU based adjuvant regimens (only these regimens and not e.g. adjuvant radiotherapy) result in a small survival benefit in colorectal cancer. Addition of levamisol[2,3] to 5-FU became standard of care in patients with Dukes C colon cancer in the first half of the 1990s. The issue of the benefit of adjuvant chemotherapy for high risk Dukes B colon carcinoma is still today controversial although recent evidence[4] suggests small benefit.
More recent developments comprise the head-to-head comparison 5-FU + folinic acid and 5-FU + levamisol[5,6,7] consistently showing the 5-FU + folinic acid schedules to be superior to the Moertel schedule, as well as the investigation of the benefit of combination treatment[8] in terms of the comparison of the LV5FU2 regimen (a 2-hour infusion of 200 mg/m2 LV followed by an i.v. bolus dose of 400 mg/m2 5-FU and then a 22-hour infusion of 600 mg/m^2 5-FU for 2 days every 14 days) vs. the FOLFOX4 regimen (addition of oxaliplatin to the LV5FU2 regimen). This latter MOSAIC trial argues for the potential of combination treatment offering a benefit to patients resected for Dukes B and C colon carcinoma in terms of prolonged disease free as well as overall survival (although not shown by the MOSAIC trial as published) on the expense of considerably more adverse events.

The MAH performed a trial comparing Xeloda in the schedule currently licensed for advanced colorectal carcinoma (2500 mg/m^2 total daily dose for 14 days followed by a seven day rest period in a 21 day cycle for 8 cycles) vs. the Mayo Clinic regimen (20 mg/m2 folinic acid followed by 425 mg/m^2 5-FU, both administered by rapid i.v. injection on days 1 to 5 in a 28-day cycle for 6 cycles) considered as standard, in effect a similar comparison as performed in the pivotal trials for the licensed metastatic colorectal carcinoma indication.

Clinical aspects

[1] Buys M et al, JAMA 259: 3571-78, 1988
[2] Moertel et al, Journal of Clinical Oncology 7:1447-1456, 1989
[3] Laurie et al, New England Journal of Medicine 322:352-358, 1990
[4] Journal of Clinical Oncology 22: 3395-3407, 2004
[5] Journal of Clinical Oncology 17:3553-3559, 1999
[6] Journal of Clinical Oncology 19: 1787-1794, 2001
[7] Annals of Oncology 14: 395-99, 2003
[8] New England Journal of Medicine 350: 2343-51, 2004

A single, confirmatory phase III trial is the basis for claiming the adjuvant indication. The dose finding (and the clinical pharmacology in general) was performed in (a larger) phase II trial in metastatic colorectal carcinoma (but not again in patients with stage Dukes C colon carcinoma). Trial M66001 (or X-ACT) is an ongoing open label, 1:1 randomized, international and multi-centre[9] trial comparing

- Capecitabine: (1250 mg/m^2 given orally twice daily for 14 days followed by a 7-day rest period in a 21-day cycle for 8 cycles) Vs.
- 5-FU/LV (Mayo Clinic regimen): 20 mg/m^2 leucovorin followed by 425 mg/m^2 5-FU, both administered by rapid i.v. injection on days 1 to 5 in a 28-day cycle for 6 cycles

with the primary objective to demonstrate that capecitabine is non inferior to 5-FU in combination with leucovorin in terms of disease-free survival in chemotherapy-naïve patients who underwent surgery for Dukes stage C colon carcinoma.
Secondary objectives were: to compare overall survival, safety profiles, changes in quality of life from baseline, medical care utilization of the two treatment groups.
It should be noted that the study does not comprise the attempt to demonstrate at least equivalence of both treatments in "high risk Dukes B carcinoma", which should be reflected in the wording of the indication: The inclusion criteria comprised stage Dukes C carcinoma only. Both the inclusion as well as the exclusion are aiming on (adult) patients otherwise healthy after surgery with curative intend

The primary efficacy parameter **disease-free survival,** was assessed for each patient every 6 months for the first 2 years after randomization and yearly thereafter until the end of the study. In the case of a relapse or new occurrence of colon cancer (NOCC) during the treatment phase, the patient was to be taken off treatment and followed up for survival.
Secondary efficacy parameter were **overall survival** (number of days between randomization and the date of death or the last date at which a patient was known to be alive), **relapse-free survival**, and **Quality of Life**.

The difference between disease (primary parameter) and relapse (secondary parameter) free survival is that for the latter endpoint death not related to the tumour was not considered as an event (thus, a not-tumour related death was a censored observation for determination of relapse free survival at the last date the patient was confirmed to be relapse-free).
For the assessment of QoL patients were to complete the EORTC QLQ-C30 quality of life questionnaire (version 2.0, 30 questions) at 4 time points, i.e. baseline, week 7, 16 and 25 (end of last cycle) for capecitabine and baseline, week 9, 17 and 25 (end of last cycle). According to the EORTC QLQ-C30 scoring manual[10], these questions are grouped into functional scales and symptom scales.

The primary analysis was a non-inferiority analysis of disease free survival while, as secondary analysis the statistical plan provides a test for superiority for disease free survival, an equivalence test for disease free survival rate (at 3 years), and an equivalence test for overall survival. The secondary analysis for relapse free survival was the same as performed for the primary analysis after censoring not tumour related deaths.
The sample size estimation is based on the Harrington and Fleming approach. According to this approach 632 events in the per-protocol population were required in this study to achieve a power of 80% for a non-inferiority margin of 1.25 and 63% for a margin of 1.2). According to the analysis plan, 4 populations were defined: all randomised population, per-protocol (standard) population, extended per-protocol population (all patients who received at least one dose of study drug and did not have a major violation of inclusion/exclusion criteria) and safety population.

[9] A total of 164 centres in 25 countries, including European countries, Argentina, Australia, Brazil, Canada, Israel, Singapore, Thailand, Uruguay, and USA. It has to be stated, however, that the vast majority of patients recruited were in spite of the international character Caucasians.
[10] EORTC QLQ-C30 Scoring Manual, 3rd edition. EORTC Quality of Life Group, Brussels, Belgium, 2001.

Results

Study Participants

A total of 1987 patients from 164 centres in 25 countries were randomized to M66001 trial with treatment of capecitabine (1004 patients) or 5-FU/LV (983 patients), 996 patients received at least one dose of capecitabine, and 974 patients received at least one dose of 5-FU/LV. In total, 11 randomized patients in the capecitabine arm and 9 randomized patients in the 5-FU/LV arms violated the inclusion criteria, i.e., they had metastatic disease, a non-curative resection, rectal cancer, or a stage II tumour at baseline. The first patient was randomized on November 12, 1998, and the last patient was randomized on November 02, 2001.

Table 2: Demographic characteristics by randomised treatment

	Capecitabine	5-FU/LV
	N=1004	N=983
Male/female (%)	54/46	54/46
Median age, years (range)	**62 (25-80)**	**63 (22-82)**
ECOG score: 0/1 (%)	85/15	85/15
Node status: N1/N2 (%)	69/30	71/29
Baseline CEA below ULN/above ULN/missing (%)	83/9/9	85/7/8
Weight in kg Median	70.00	70.00
Height in cm Median	168.0	168.0
Body Surface Area (m^2) Median	1.795	1.800

Table 3: Summary of Baseline Tumor Staging (All Randomized Population)

Dukes (UICC) Staging Classification	**CAPECITABINE** (N=1004)	**5-FU + LEUCOVORIN** (N=983)
Primary Tumor		
PT1	12 (1.20)	6 (0.61)
PT2	90 (8.96)	92 (9.36)
PT3	763 (76.00)	746 (75.89)
PT4	138 (13.75)	139 (14.14)
Missing	1 (0.10)	
Regional Lymph node		
PN1	695 (69.22)	694 (70.60)
PN2	305 (30.38)	288 (29.30)
PNX	1 (0.10)	1 (0.10)
PN0	2 (0.20)	
Missing	1 (0.10)	
Grading		
G1	91 (9.06)	96 (9.77)
G2	652 (64.94)	620 (63.07)
G3	163 (16.24)	182 (18.51)
G4	5 (0.50)	7 (0.71)
GX	91 (9.06)	74 (7.53)
Missing	2 (0.20)	4 (0.41)

Efficacy Results

Table 4: Main Efficacy Results by Treatment Arm and Analysis Population

Endpoint Number (%) of Patients without Event[a] Hazard Ratio[b], p-value[c] (test for difference)

Population	Capecitabine	5-FU/LV	(95% CI)	p-Value[c]
Disease-free survival				
All randomized	656 (65%)	603 (61%)	0.87 (0.75, 1.00)	0.053
Per-protocol	586 (66%)	552 (63%)	0.89 (0.76, 1.04)	0.157
Extended per-protocol	636 (66%)	593 (63%)	0.87 (0.75, 1.01)	0.068
Overall survival				
All randomized	804 (80%)	756 (77%)	0.84 (0.69, 1.01)	0.071
Per-protocol	718 (81%)	694 (79%)	0.90 (0.73, 1.10)	0.298
Extended per-protocol	776 (81%)	742 (78%)	0.86 (0.71, 1.05)	0.143
Relapse-free survival				
All randomized	677 (67%)	621 (63%)	0.86 (0.74, 0.99)	0.041
Per-protocol	605 (68%)	562 (64%)	0.87 (0.74, 1.02)	0.078
Extended per-protocol	657 (69%)	608 (64%)	0.85 (0.73, 0.99)	0.041

[a] For disease-free survival, event = death, relapse, or new occurrence of colon cancer (NOCC); for overall survival, event = death (all causes); for relapse-free survival, event = death related to treatment or to disease progression, or relapse, or NOCC.
[b] Capecitabine vs. 5-FU/LV.
[c] Wald chi-square test (test for difference)

Multivariate analyses incorporating predefined prognostic factors (i.e., age, gender, lymph node status at baseline, CEA levels at baseline, time from surgery to randomization, and country) confirmed and demonstrated the robustness of the results, as well as additional subgroup analyses. In the predefined Cox regression model, treatment with capecitabine had a significant, independent impact on disease-free survival at least in the all randomized population for the per protocol population used as an example for the result in other populations; the hazard ratio in this adjusted analysis is 0.852 with a p-value of 0.0542; in this context it may be mentioned that treatment with capecitabine was also statistically significantly related with an improved outcome in terms of overall survival in the as randomized [ITT] population).

TABLE 5 MULTIVARIATE ANALYSIS OF DISEASE-FREE SURVIVAL (PER-PROTOCOL POPULATION)

Factor	Hazard Ratio	Standard Deviation	95% Confidence Interval	p-Value[a]
Trial Treatment (capecitabine vs. 5-FU/LV)	0.852	0.0835	0.723, 1.003	0.0542
Additional Covariates				
Age (in years)	0.997	0.0043	0.989, 1.006	0.5485
Time from surgery to randomization (in days)	1.003	0.0040	0.996, 1.011	0.3879
Gender (female vs. male)	0.762	0.0860	0.644, 0.902	0.0016
CEA levels at baseline (normal vs. abnormal)	0.497	0.1465	0.373, 0.663	<0.0001
Lymph nodes at baseline (N1 vs. other)	0.551	0.0870	0.465, 0.653	<0.0001
Country	--	--	--	0.5972

[a] Likelihood ratio test for country, Wald test for all other factors.

Analysis of duration of disease free survival revealed that after 3.8 years median is still not reached (3 year disease free survival rate 0.65 and 0.63 for capecitabine and 5-FU/FA respectively,

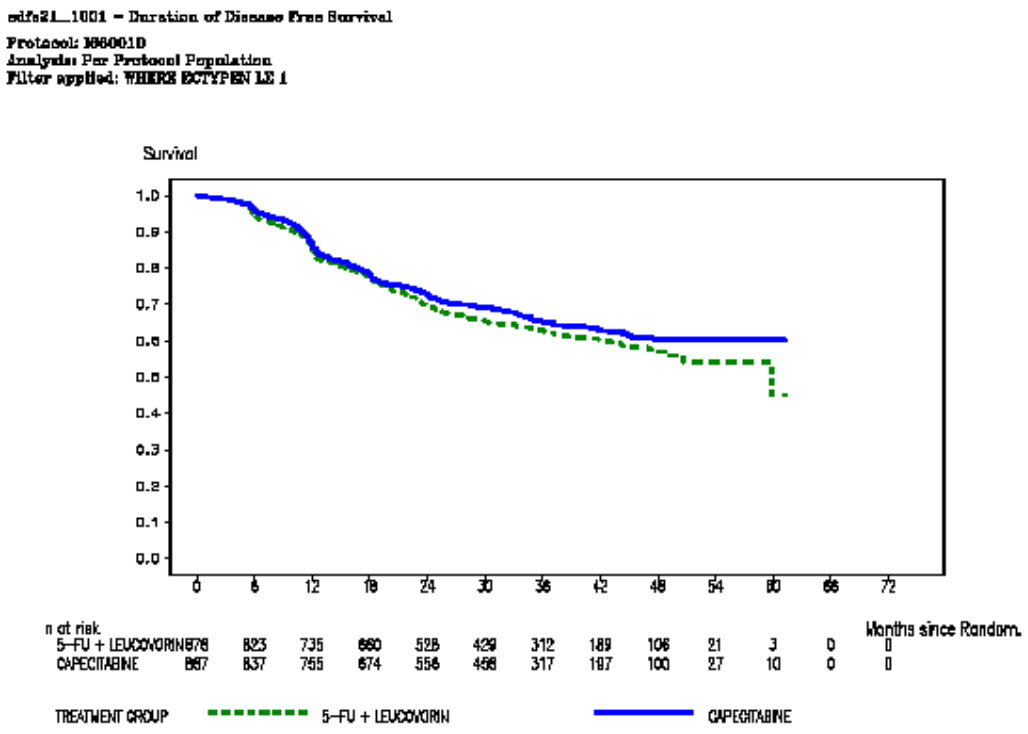
Table 6 Statistical Analysis of Disease-Free Survival (Per-Protocol Population)

	Capecitabine (N=887)		5-FU/LV (N=878)
Patients with event	301 (33.9%)		326 (37.1%)
Patients without event (a)	586 (66.1%)		552 (62.9%)
Time to event (years)			
Median (b)	.		5.0
95% CI for Median (b)	(. , .)		(4.2, .)
P-Value (Log-rank Test)		0.1569	
Hazard Ratio (c)		0.89	
95% CI for Hazard Ratio		(0.76, 1.04)	
P-Value (Wald Chi-Square Test)		0.1572	
3-Year Survival			
Rate	0.65		0.63
95% CI for Rate	(0.62, 0.69)		(0.60, 0.66)

(a) Censored.
(b) Based on Kaplan-Meier estimates. Median was not reached for the capecitabine treatment arm.
(c) Capecitabine vs. 5-FU/LV.

With upper limits for the 95% CI of 1.00 to 1.04, and corresponding low p-values, there appears to be even a trend to a superior disease free survival for the patients treated with capecitabine.

Figure 1 Kaplan-Meier Estimates of Disease-Free Survival (Per-Protocol Population)



An analysis of retention of the effect of 5-FU/FA (and odds ratio of 1.90 was supposed for 5-FU/FA vs. surgery alone) revealed that with high statistical significance the 0-hypothesis of the retention of less than 75% of the effect of 5-FU/FA by capecitabine can be rejected with sufficient statistical confidence

Table 7 Results of Testing for 75% Retention of Effect on Disease free Survival

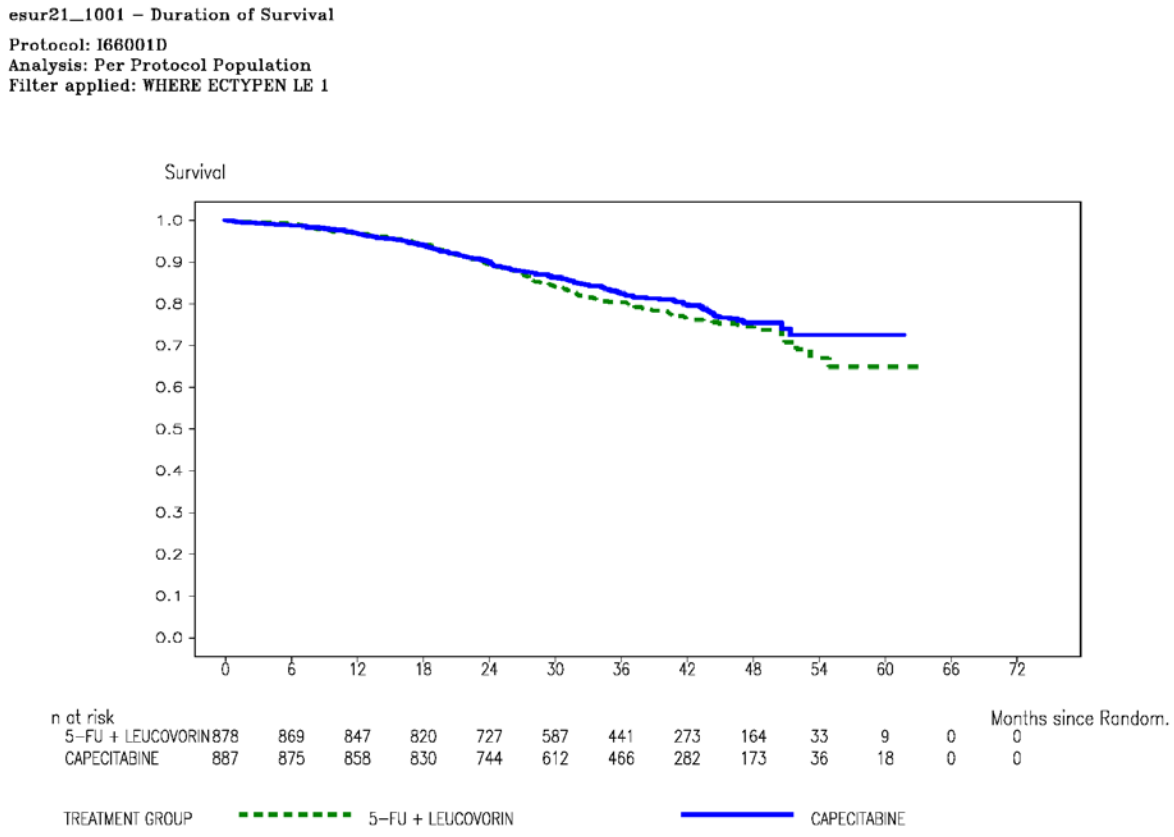
Analysis Population	p-Value from Testing for 75% Effect Retention	
	Arithmetic Definition	Geometric Definition
Per-protocol	0.000240	0.00060
All randomized	0.000025	0.00006
Extended per-protocol	0.000047	0.00012

Secondary Endpoints

- **Overall survival (OS)**

The upper limit of the 95% CI lies within 1.01 to 1.10, well below the 1.25 criteria. The duration to event, or median OS can currently not be estimated. The 3 year survival rate is 0.83 [0.80;0.85] and 0.80 [0.78; 0.83] for the per protocol population (and similar in the two other analysis populations).

Figure 2 Kaplan-Meier Estimates of Overall Survival (Per-Protocol Population)



- **Relapse free survival**

The difference between disease and relapse free survival is a very minor one (the latter censoring a non-tumour or not treatment related death in place of considering as an event). Overall 39 patients in the as randomised population were excluded from the analysis of relapse free survival (compared to disease free survival).

Table 8: Statistical Analysis of Relapse-Free Survival (Per-Protocol Population)

	Capecitabine (N=887)		5-FU/LV (N=878)
Patients with event	282 (31.8%)		316 (36.0%)
Patients without event (a)	605 (68.2%)		562 (64.0%)
Time to event (years)			
Median (b)	.		5.0
95% CI for Median (b)	(. , .)		(5.0, .)
P-Value (Log-rank Test)		0.0775	
Hazard Ratio (c)		0.87	
95% CI for Hazard Ratio		(0.74, 1.02)	
P-Value (Wald Chi-Square Test)		0.0780	
3-Year Survival			
Rate	0.67		0.64
95% CI for Rate	(0.63, 0.70)		(0.60, 0.67)

(a) Censored.
(b) Based on Kaplan-Meier estimates. Median was not reached for the capecitabine treatment arm.
(c) Capecitabine vs. 5-FU/LV.

Quality of life

Most of the patients in the safety population (91% in the capecitabine treatment arm and 88% in the 5-FU/FA treatment arm) completed a quality of life questionnaire at baseline.
The percentages of patients completing quality of life questionnaires at cycles 3 and 5 or 6 and at the end of the prescribed course of medication were slightly higher in the capecitabine treatment arm (80%, 81%, and 84%, respectively) than in the 5-FU/FA treatment arm (72%, 76%, and 76%, respectively). Similarly, the percentages of patients completing both questions in the Global Health Status scale at cycles 3 and 5 or 6 and at the end of the prescribed course of medication were slightly higher in the capecitabine treatment arm (78%, 80%, and 82%, respectively) than in the 5-FU/LV treatment arm (71%, 75%, and 76%, respectively).
In summary QoL appears to increase slightly over the time, however, there is no obvious (and also no statistical significant) difference between both arms. Thus, if the oral adjuvant treatment offers an advantage of i.v. injection, this advantage is not reflected in the QoL of the patients, at least in the QoL as measured by the EORTC QLQ-C30 instrument (sensitivity of the instrument for the question).

Discussion of efficacy

With the limitation of a median follow-up of 3.8 years, and not having a second and independent conducted trial available, it has to be stated that the well designed and well conducted trial M66001 (X-ACT) met its objective. Capecitabine was demonstrated to be non-inferior to i.v. 5-FU/LV (Mayo) in terms of disease-free survival in the all randomized per-protocol, and extended per-protocol populations, based on the pre-specified margins of 1.25 ($p < 0.001$) and 1.20 ($p < 0.001$) for the hazard ratio, corresponding to the hierarchical testing strategy specified in the protocol -in chemotherapy naïve patients who underwent surgery for stage Dukes C colon carcinoma. The upper limits of the 95% confidence interval of the hazard ratio were 1.00, 1.04, and 1.01 in the all randomized, per-protocol, and extended per-protocol populations, respectively. According to the protocol, the primary population for analysis of disease-free survival was the per-protocol population; the analysis of disease-free survival was also conducted in the all randomized and extended per-protocol populations.

With regard to disease-free survival, capecitabine retained at least 75% of the benefit that 5-FU/LV has shown over surgery alone ($p < 0.001$). In this calculation, the benefit of 5-FU/LV over surgery alone was assumed to be given by a hazard ratio of 1.90 (surgery vs. 5-FU/LV) with a 95% confidence interval of 1.53 to 2.35. In additional analyses, capecitabine was at least equivalent to 5-FU/LV in terms of overall survival, based on the protocol-specified non-inferiority margin of 1.25 in all three

populations. The upper limits of the 95% confidence intervals of the hazard ratios were 1.01, 1.10, and 1.05 for the all randomized, per-protocol, and extended per-protocol populations, respectively, and thus are all well below 1.25.

There was a trend toward superiority for capecitabine vs. 5-FU/LV with respect to disease-free survival, overall survival and relapse-free survival in the all randomized population. Superioritywith respect to relapse-free survival was demonstrated for capecitabine vs. 5-FU/LV in the all randomized and the extended per-protocol populations.

The quality of life scores for Global Health Status over time were similar for the two treatment arms. A statistically significant difference between treatment arms in the change from baseline to week 25 could not be shown.

Clinical safety

Capecitabine first became commercially available in 1998. Since then, approximately 634,000 patients worldwide have been exposed to the drug. In recent post-marketing surveillance data, the system organ class with the highest number of adverse event reports was "Gastrointestinal Disorders", followed by "Skin and Subcutaneous Tissue Disorders", and "General Disorders and Administration Site Conditions". Among the most frequently reported adverse events were palmar-plantar erythrodysesthesia, vomiting, nausea, diarrhea, dehydration, pyrexia, and febrile neutropenia.

The Applicant's Summary of Clinical Safety assessment of capecitabine is based primarily on one pivotal efficacy and safety study involving 995 patients with colon cancer in adjuvant treatment 1250 mg/m^2 of capecitabine administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a seven days rest period.

Patient exposure
Patients who received at least one dose of study medication and had at least one post-baseline safety assessment (995 patients in the capecitabine treatment arm and 974 patients in the 5-FU/LV-treatment arm) are included in the safety evaluations.

Adverse events
In the phase III study, 5252 and 5792 adverse events were reported in the capecitabine treatment arm and the 5-FU/LV-treatment arm, respectively. In both treatment arms, 91% of the patients experienced at least one adverse event during treatment or within 28 days after treatment. The proportions of patients with adverse events, which were judged related to study drug were 87% and 89% in the capecitabine and 5-FU/LV treatment arms, respectively. The total number of treatment-related adverse events was 4279 events in the capecitabine treatment arm and 4830 events in the 5-FU/LV-treatment arm. Fourty-one percent of patients in capecitabine arm and 39% in 5-FU/LV-treated patients experienced grade 3/4 adverse events. The gastrointestinal adverse events were among the most frequent adverse events in both treatment arms. The spectrum of gastrointestinal adverse events associated with capecitabine therapy was qualitatively similar to that seen with 5-FU/LV-therapy, with diarrhea, nausea, stomatitis, and vomiting being the predominant gastrointestinal adverse events.

The incidence of grade 3 treatment related palmar-plantar erythrodysesthesia was higher (17.0% in the capecitabine arm and 0.5% in the 5-FU/LV arm), whereas the incidence of treatment-related diarrhoea, nausea, vomiting, stomatitis, alopecia, and neutropenia in the capecitabine treatment arm was lower than in the 5-FU/LV-treatment arm. There was a lower incidence of treatment-related grade 3/4 neutropenia, febrile neutropenia/sepsis, and stomatitis in the capecitabine treatment arm than in the 5-FU/LV-treatment arm. There was a similar incidence of grade 3/4 diarrheas in the two treatment arms, although there were more hospitalizations due to diarrhea in the capecitabine treatment arm.

In particular, 22% of capecitabine treated patients experienced stomatitis, compared with 60% of 5-FU/LV-treated patients. Other frequently reported adverse events with a lower incidence in the capecitabine treatment arm than in the 5-FU/LV-treatment arm included alopecia (6% vs. 22%) and

neutropenia (2% vs. 8%). The incidences of all the frequently reported adverse events in the capecitabine treatment arm were either similar to or lower than those in the 5-FU/LV-treatment arm, except for the incidence of palmar-plantar erythrodysesthesia. More patients treated with capecitabine (60%) experienced palmar-plantar erythrodysesthesia than did patients treated with 5-FU/LV (9%).

The median time to first onset of the predefined treatment-related grade 3/4 adverse events was longer in capecitabine-treated patients than in 5-FU/LV-treated patients. Grade 3 palmar-plantar erythrodysesthesia was a frequent reason for premature treatment discontinuations (5%). In the capecitabine arm, the median time to onset of grade 3 treatment-related palmar-plantar erythrodysesthesia was 79 days, and the median duration was 13 days. Patients treated in capecitabine arm experienced hyperbilirubinemia, including grade 3/4 hyperbilirubinemia, more frequently than those treated with 5-FU/LV.

There were more treatment withdrawals for treatment-related adverse events in the capecitabine treatment arm (9%) than in the 5-FU/LV-treatment arm (6%), because of more palmar-plantar erythrodysesthesia in the capecitabine-treated patients.

A lower proportion of capecitabine-treated patients than 5-FU/LV-treated patients had early-onset grade 3/4 fluoropyrimidine-related toxicity (i.e., gastrointestinal toxicities, infections, neutropenia/ granulocytopenia, and thrombocytopenia).

In both treatment arms, the proportion of patients prematurely withdrawn from treatment because of adverse events was higher for older patients (≥ 65 or ≥ 70 years of age) than for younger patients (<40, 40–69, and <65 years of age). The proportions of patients experiencing treatment-related grade 3/4 adverse events and treatment-related serious adverse events were also higher for older patients than for younger patients.

Hospitalization. If the onset of an adverse event was on or before the 28th day after the last treatment dose, the hospitalization caused by this adverse event was included in the analysis even if the hospitalization itself occurred more than 28 days after the last dose. The proportion of patients with at least one hospitalization for adverse events was similar in the two treatment arms (approximately 18%). The total number of primary adverse events leading to hospitalization (215 vs. 201, capecitabine vs 5-FU/LV), the median duration of hospitalization (8 vs 6 days, capecitabine vs 5-FU/LV), and the median time to the first hospitalization (58 vs 49 days, capecitabine vs 5-FU/LV) were all comparable in the two treatment arms. Furthermore, the monthly incidence of hospitalization and the adjusted monthly incidence of hospitalization were similar in the two treatment arms.
In 2 patients was palmar-plantar erythrodysesthesia the sole reason for hospitalization.

Frequently Reported (Incidence ≥ 5% in at Least One Treatment Arm) Grade 1 to 4 Treatment-Related and Treatment-Unrelated Adverse Events (Safety Population)

Adverse Event	CAPECITABINE N = 995 No. (%)	5-FU+LEUCOVORIN N = 974 No. (%)
DIARRHOEA	467 (47)	632 (65)
*STOMATITIS ALL	222 (22)	589 (60)
NAUSEA	334 (34)	460 (47)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	595 (60)	85 (9)
VOMITING	151 (15)	204 (21)
FATIGUE	156 (16)	151 (16)
ABDOMINAL PAIN	141 (14)	158 (16)
ALOPECIA	63 (6)	218 (22)
ANOREXIA	91 (9)	104 (11)
ASTHENIA	96 (10)	95 (10)
CONSTIPATION	86 (9)	105 (11)
LETHARGY	99 (10)	92 (9)
PYREXIA	71 (7)	83 (9)
RASH	70 (7)	80 (8)
DYSGEUSIA	59 (6)	89 (9)
ABDOMINAL PAIN UPPER	71 (7)	67 (7)

DIZZINESS	64 (6)	54 (6)
HEADACHE	51 (5)	9 (6)
ERYTHEMA	58 (6)	1 (5)
CONJUNCTIVITIS	7 (5)	60 (6)
DYSPEPSIA	59 (6)	48 (5)
NEUTROPENIA	22 (2)	82 (8)
EPISTAXIS	18 (2)	51 (5)

*STOMATITIS: any adverse event preferred terms starting with the strings of 'MUCOSAL', 'STOMATITIS', or 'MOUTH ULC' were combined into the new preferred term *STOMATITIS"

Discontinuation due to AES

More patients in the capecitabine treatment arm (112 patients, 11%) than in the 5-FU/LV-treatment arm (73 patients, 7%) were prematurely withdrawn from treatment for adverse events. The difference in number of premature withdrawals from treatment for adverse events between the two treatment arms was largely due to more cases of treatment withdrawal for palmar-plantar erythrodysesthesia in capecitabine-treated patients (32 patients, 3%) than in 5-FU/LV-treated patients (4 patients, <1%). Another adverse event that commonly led to premature withdrawal from treatment was diarrhea (30 capecitabine-treated patients, 3%; 28 5-FU/LV-treated patients, 3%). The incidence of premature withdrawal from treatment for any other adverse event was <1% in both treatment arms, except for stomatitis, which caused premature withdrawal in 6 capecitabine-treated patients (<1%) vs. 16 5-FU/LV-treated patients (2%). The majority of events (133 of 157 events in the capecitabine-treatment arm and 116 of 130 events in the 5-FU/LV treatment arm) that led to premature withdrawal from treatment were considered related to treatment by the investigator. The incidence of premature withdrawal from treatment because of treatment-related adverse events was higher in the capecitabine treatment arm (94 patients, 9%) than in the 5-FU/LV-treatment arm (62 patients, 6%). Because a laboratory abnormality was to be coded as an adverse event if it caused premature withdrawal from treatment, all premature withdrawals for laboratory abnormalities are included in the summary tables and listings describing premature withdrawals for adverse events.

Total number of patients with at least one treatment interruption was 150 (15.1%) in the capecitabine arm and 48 (4.9%) in the 5-FU/LV-arm. Total number of cycles interrupted was 219 and 63, respectively.

The majority of patients (57%) needed dose adjustment (treatment interruption, cycle delay, or dose reduction) at some time during treatment with capecitabine.

Serious adverse events and deaths

The two treatment groups were similar in the percentages of patients having serious AEs (capecitabine, 18%; 5-FU/LV, 19%) and in the percentages having treatment-related serious AEs (capecitabine, 11%; 5-FU/LV, 12%).

A total of 155 treatment-related serious adverse events were reported in 106 capecitabine-treated patients (11%), compared with 174 treatment-related serious adverse events reported in 115 5-FU/LV-treated patients (12%). The most common treatment-related serious adverse events included diarrhoea (incidence of 6% vs. 3%, capecitabine vs. 5-FU/LV), stomatitis (incidence of <1% vs. 3%, capecitabine vs. 5 FU/LV), and febrile neutropenia (incidence of <1% vs. 2%, capecitabine vs. 5-FU/LV). Nine patients treated with capecitabine (<1%), compared with 18 patients (2%) treated with 5-FU/LV, experienced treatment-related serious infections. Palmar-plantar erythrodysaesthesia grade 3/4 was reported in 169 patients (17%) in capecitabine arm and in 5 patients (<1%) in 5-FU/LV-arm.

Treatment-related serious palmar-plantar erythrodysesthesia was reported in 4 capecitabine-treated patients, all of whom were hospitalized. In 2 of these 4 patients, hospitalization was due solely to palmar-plantar erythrodysesthesia, whereas hospitalization in the other 2 patients was due to multiple events, including palmar-plantar erythrodysesthesia.

Mortality within 60 days after the start of treatment was <1% and similar for the two treatment arms (capecitabine, 5 patients; 5-FU/LV, 4 patients). Eight patient (0.8%) in the capecitabine treatments arm and 10 patients (1.0%) in the 5-FU/LV treatments arm died during treatment or within 28 days after the last dose of study drug administration. Of these deaths, 3 in the capecitabine treatment arm and 4 in the 5-FU/LV-treatment arm were considered probably, possibly, or remotely related to study drug treatment by the investigators. The DSMB evaluated all the relationships for the deaths within 28 days of last dose. The outcome of this evaluation resulted in a concordant assessment of relationships

(related vs. unrelated) for 15 of the total 18 cases, and an assessment of potentially related by the DSMB in 3 cases in which the investigators had judged them to be unrelated to study treatment. Thus, according to the DSMB evaluations, 5 deaths in each treatment arm were related to study treatment.

There was no predominant cause of death in either treatment arm. The causes of the 3 treatment-related deaths in the capecitabine treatment arm were aspiration pneumonia, septic shock, and multiorgan failure, and the causes of the 4 treatment-related deaths in the 5-FU/LV-treatment arm were bronchopneumonia, respiratory arrest, gastrointestinal hemorrhage, and diarrhea.

Laboratory findings

The incidences of grade 1 to 4 abnormalities of granulocyte, neutrophil, neutrophil/granulocyte and white blood cell counts were lower in the capecitabine arm. In particular, compared with patients treated with 5-FU/LV, grade 3/4 and grade 4 abnormalities of neutrophils/granulocytes in patients treated with capecitabine were relatively rare. The most prominent difference in blood chemistry between the two treatment arms was in the frequency of hyperbilirubinemia, which was more common in the capecitabine treatment arm than in the 5-FU/LV-treatment arm. The incidence of grade ¾ hyperbilirubinemia was higher in the capecitabine treatment arm (20%) than in the 5- FU/LV treatment arm (6%), utilizing the NCIC-CTC grading scale.

Safety in special populations

Safety Profile by Patients' Age

The safety profiles of capecitabine and 5-FU/LV were summarized by age of the patients, using the following two groupings: <65 and ≥ 65 years of age; <40, 40 to 69, and ≥ 70 years of age. The main findings regarding the impact of age on the safety profiles in the capecitabine and 5-FU/LV treatment arms are as follows: The difference in the safety profile between the capecitabine and 5-FU/LV treatment arms in the whole safety population was preserved in the younger and older subpopulations of patients. The lower incidence of grade 3/4 stomatitis and of neutropenia/granulocytopenia in the capecitabine treatment arm compared with the 5-FU/LV-treatment arm was observed in older as well as in younger age subgroups.
In both treatment arms, the proportion of patients prematurely withdrawn from treatment because of adverse events was higher for older patients (≥ 65 or ≥ 70 years of age) than for younger patients (<40, 40–69, and <65 years of age). The proportions of patients experiencing treatment-related grade 3/4 adverse events and treatment-related serious adverse events were also higher for older patients than for younger patients.

Safety Profile by Baseline Creatinine Clearance

Creatinine clearance at baseline was calculated according to Cockcroft and Gault. After IRB approval of protocol amendment C at individual sites, patients with severe renal impairment (creatinine clearance < 30 mL/min) were excluded from this study and 75% of the standard dose of capecitabine should have been implemented upfront in patients with a moderate renal function impairment (creatinine clearance of 30 to 50 mL/min). A total of 49 patients had a baseline creatinine clearance in the range of 30 to 50 mL/min in the capecitabine treatment group (safety population), including 15 patients enrolled under protocol amendment C, of whom 2 had capecitabine dose reduction at baseline. The general safety profile was affected by renal function in both the capecitabine and the 5-FU/LV treatment arms. The proportion of patients with treatment related grade 3 and 4 adverse events and patients with treatment-related serious adverse events increased with decreasing creatinine clearance in both treatments groups. In the 5-FU/LV-group, decreasing baseline creatinine clearance was associated with an increasing proportion of patients with grade 3/4 stomatitis.

Discussion of Safety

The profile of treatment-emergent adverse events in the phase III trial is comparable to the known safety profile of capecitabine in patients with colorectal or breast cancer.
The MAH submitted an Integrated Summary of Safety which integrates the safety data from trial M66001 (X-ACT) with trials S014695 and S014796 (the two pivotal phase III comparing capecitabine

with the Mayo regimen in first line treatment of metastatic colorectal cancer submitted with the original application) in order to discuss better the frequency of undesirable effects of Xeloda monotherapy in section 4.8.

The pooled safety data confirm the safety results of the individual studies. As expected with fluoropyrimidine therapy, gastrointestinal adverse events were among the most frequent adverse events in both treatment groups.
There was a lower incidence of treatment-related diarrhoea, nausea, vomiting, stomatitis, alopecia, and neutropenia in the capecitabine treatment group than in the 5-FU/LV treatment group.
There was a lower incidence of treatment-related grade 3/4 neutropenia and stomatitis in the capecitabine treatment group than in the 5-FU/LV treatment group. There was a similar incidence of grade 3/4 diarrhoea in the two treatment groups.
Capecitabine caused more palmar-plantar erythrodysesthesia, including more grade 3 palmar-plantar erythrodysesthesia, than 5-FU/LV.
Patients treated with capecitabine experienced hyperbilirubinemia, including grade 3/4 hyperbilirubinemia, more frequently than those treated with 5-FU/LV.
The incidences of grade 1 to 4 abnormalities of granulocyte, neutrophil, neutrophil/granulocyte, and white blood cell counts were lower in the capecitabine treatment group than in the 5-FU/LV treatment group. In particular, compared with patients treated with 5-FU/LV, grade 3/4 and grade 4 abnormalities of neutrophils/granulocytes in patients treated with capecitabine were relatively rare.
The MAH has updated section 4.8 "Undesirable Effects" of the SmPC accordingly (see response to comment 5 on SmPC section 4.8).

The overall incidence of cardiac disorders for patients treated with either capecitabine or 5-FU/LV in the adjuvant colon cancer setting was 3%, which is identical to the incidence found for the same treatments in the first-line metastatic colorectal cancer setting, and for capecitabine in the metastatic breast cancer setting. This level of cardiotoxicity is also consistent with the level reported in the fluoropyrimidine literature. Thus, no new unexpected findings emerged during study M66001.
The MAH commits to update the cumulative assessment of cardiovascular events, which was provided to CHMP with the 10th PSUR of Xeloda submitted February 2004. The update will be included with the 11th PSUR for Xeloda to be submitted January 2005.
Moreover the following statement was added in section 4 "Possible side effects" of the Patient Information Leaflet:

> *STOP taking Xeloda immediately and contact your doctor if any of these symptoms occur: Chest pain: if you experience pain localized to the centre of the chest, especially if it occurs during exercise.*

4.3 Treatment of patients with locally advanced or metastatic breast cancer

Introduction

Xeloda was granted authorisation in EU in February 2001 for first line monotherapy of patients with metastatic colorectal cancer. The indication was subsequently extended through a Type II variation for the use of capecitabine in combination with docetaxel in patients **with locally advanced or metastatic breast cancer in whom anthracycline treatment has failed.** This claim was mainly based on comparative data deriving from a large randomised controlled clinical trial (SO14999) and was supported by an additional and independent interaction trial investigating PK interactions between docetaxel and capecitabine in a population of patients with advanced solid tumours in general.

In addition to this indication a "salvage" indication: **capecitabine monotherapy after failure of prior treatment with taxanes and anthracyclines** -in breast cancer patients is claimed. This was supported by the open-label, non-controlled trials SO14697 and NO15542; both trials were of similar design.

Clinical pharmacology

Only the additional pharmacological data submitted as part of the indications in breast cancer are described here.
A phase I classical dose escalation trial with the primary objective to determine the MTD of capecitabine in combination with docetaxel, trial SO15304 has been submitted as part of the variation to include the indications in breast cancer. The trial included 36 patients with advanced solid tumours, of which 33 received at least one course of study medication, 1 died before receiving treatment, 2 did not meet entry criteria. As a conclusion, the schedule of 2500 mg/m2 capecitabine and 75-mg/m2 docetaxel could be recommended for further trials.

Pharmacodynamic effects, interactions and maximum tolerated dose (MTD) of capecitabine in combination with paclitaxel were investigated in trial SO14694 that was part of the original submission for Xeloda (for the CRC indication).

The effects of docetaxel on capecitabine and its metabolites (and vice versa) as studied in trial SO15304 are displayed in table 1. It should, however, be noted that the PK estimates for the combined treatment with capecitabine and docetaxel, capecitabine single agent and docetaxel single agent were determined on study day 1, 14 and 21 respectively. Thus, a period effect such as auto-induction of capecitabine metabolism is not excluded by the design of the trial:

TABLE 2: DOSE NORMALISED PHARMACOKINETIC PARAMETERS OF CAPECITABINE AND ITS METABOLITES, AND DOCETAXEL AFTER ADMINISTRATION OF CAPECITABINE PLUS DOCETAXEL RELATIVE TO SINGLE SUBSTANCE

	$AUC_{0-\infty}$*		C_{max}	
Analyte	Estimate in %	90% CI	Estimate in %	90% CI
Capecitabine	97	77-122	99	65-149
5'-DFCR	99	80-123	104	76-141
5'DFUR	105	93-118	106	81-138
5-FU	74	57-96	79	53-138
FBAL	102	88-118	96	79-116
Docetaxel	96	88-104	98	91-106

In summary, capecitabine has virtually no effect on the PK of paclitaxel and docetaxel. This is in line with the results of trial SO14694 where no effects of paclitaxel on a single PK estimate of a capecitabine metabolite could be found.

Being a phase I trial, efficacy assessment was not a primary objective of this trial. However tumour response assessment was conducted in 6 weeks intervals or within 72 hours after study completion, withdrawal or discontinuation of treatment and 2 CRs, 3 PRs were observed resulting in a 15% ORR in this heavily pretreated population with various solid tumours.

Clinical efficacy of capecitabine in combination with docetaxel for patients with metastatic breast cancer in whom anthracycline treatment has failed

Clinical trial SO14999

Study SO14999 is an open-label, multicenter, multinational, randomised, parallel-group phase III clinical trial. It was designed to compare the efficacy and safety profile of capecitabine (intermittent schedule) in combination with ("reduced dose") docetaxel vs. ("full dose") docetaxel administered as single agent in patients with locally advanced or metastatic breast cancer failing an anthracycline-containing (first-line) regimen. Stratification was done by previous paclitaxel treatment since paclitaxel pre-treatment, or failure, was not an exclusion criteria.

The primary objective of the study was to demonstrate superiority of combination vs. single agent treatment in terms of time to progression or death (TTP).

The sample size estimation was based, in relation to the primary endpoint of the trial (TTP), on the assumptions that TTP for docetaxel single agent will be 4.5 months and that for combination treatment 6.0 months. Assuming a strict follow up time of 9 months without drop outs, the sample size required for the intent to treat population was estimated to be 454 patients (α=0.05; power [1-β] = 0.8).
511 patients were randomised to one of the following dosing regimens:

- Combination arm (Arm A): Capecitabine orally at 1250 mg/m^2 twice daily (within 30 minutes after completing a meal) for two weeks followed by a one week rest. Docetaxel as a 1 hour infusion of 75 mg/m^2 on the first day of each cycle (every 3 weeks) together with appropriate co-medication (prophylaxis of hypersensitivity reactions by oral corticosteroid).
- Docetaxel single agent arm (Arm B): Docetaxel as a 1 hour infusion of 100 mg/m^2 on the first day of each cycle (every 3 weeks) together with appropriate co-medication (prophylaxis of hypersensitivity reactions by oral corticosteroid).

The primary endpoint was **time to progression** (TTP) calculated from the day of randomisation to progression or death. Secondary endpoints were:

Survival from the day of randomisation to the date of death or the last day the patient was known to be alive.

Objective response (OR) was determined only by bi-dimensionally measurable, previously not irradiated indicator lesions with a diameter of more than 10 mm (20 mm for hepatic lesions).OR had to be confirmed at least 4 weeks after the first observation of response. **Time to response** was defined as the time from randomisation to first record of PR or CR, duration of response as the time from first record of PR or CR to progression. Tumour assessment was done a 6 weekly basis until week 48, thereafter in 12 weekly intervals.

Quality of Life was assessed using the questionnaire EORTC QLQ-30 (version 2.0) form and its breast cancer module QLQ-BR23.

In a subgroup of 16 patients of the combination arm, the PK parameters c_{max}, t_{max}, AUC_{∞} and $t_{1/2}$ (apparent half life) were determined on study day 14 and 77. Blood samples, overall not exceeding 90 ml, were drawn pre-dose (capecitabine), and at 0.5, 1, 2, 3, 4, 5, 7, and 10 hours after administration of capecitabine at aliquots of 5 ml.

Discussion of Efficacy
Two different populations were analysed for TTP; the ITT (all-randomised) and the per protocol populations and two different analysis (primary and on treatment approach) of these populations were planned. The results are presented in table 2.

TABLE 2: ANALYSIS OF TTP

Assessment/Approach	Arm A	Arm B	Log-rank p-value	Hazard Ratio
All Randomized Patients				
• 'Primary' Approach			0.0001	0.643
Number of Events	230	247		
Median	**186 days**	**128 days**		
95% CI	[165, 198]	[105, 136]		
Standard Population				
• 'Primary' Approach			0.0001	0.632
Number of Events	182	212		
Median	**179 days**	**127 days**		
95% CI	[163, 195]	[97, 136]		
All Randomized Patients				
• 'On Treatment' Approach			0.0001	0.608

Number of Events	120	157		
Median	**188 days**	**128 days**		
95% CI	[164, 209]	[105, 136]		
Standard Population				
• 'On Treatment' Approach			0.0002	0.620
Number of Events	112	139		
Median	**180 days**	**127 days**		
95% CI	[152, 205]	[97, 136]		

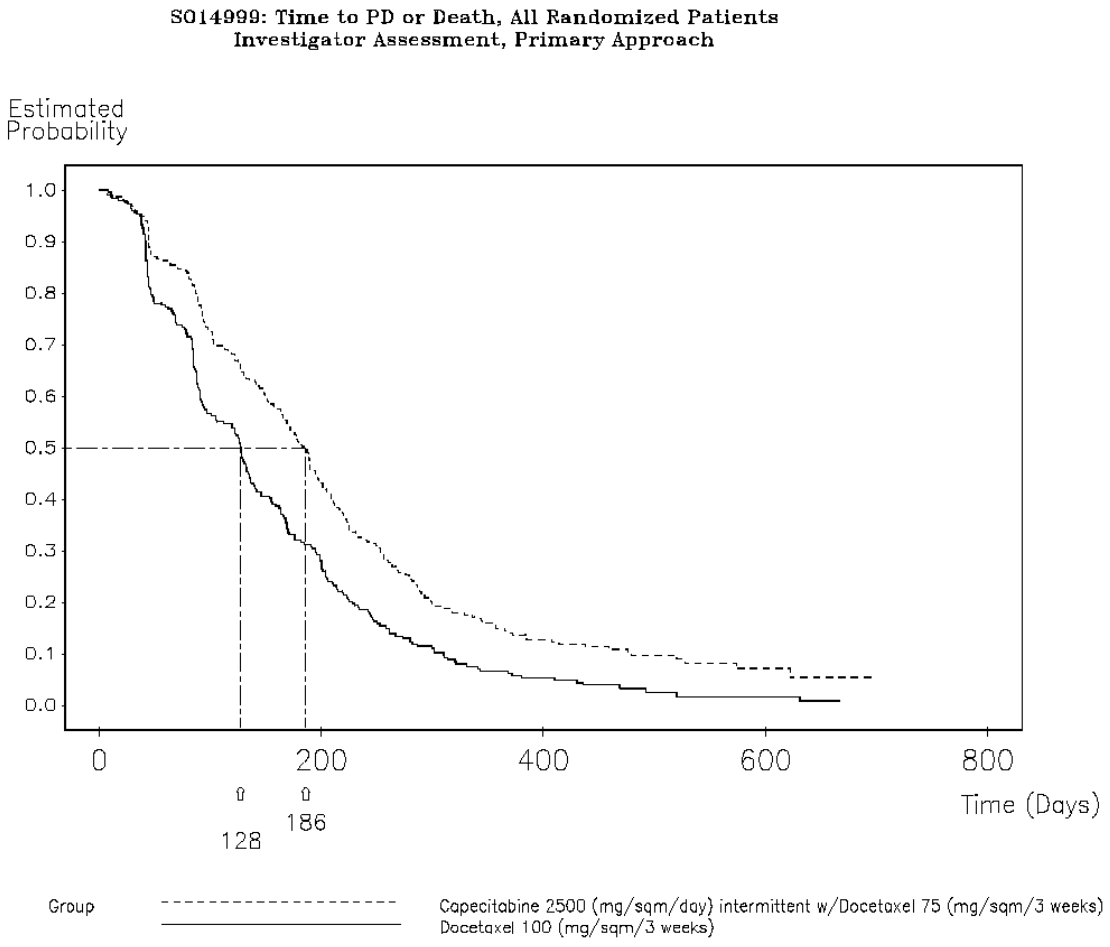
The objective of this trial to show statistically significant superiority in terms of the primary endpoint time to progression has been reached (186 vs. 128 days). This also translates into a relevant prolongation of 90 days (442 vs. 352 days) of overall survival (Table 3). There is an overall consistent pattern of significant efficacy, which clearly indicates that the combination results in more objective tumour responses, which translate into prolonged TTP and OS.

TABLE 3: SUMMARY OF SURVIVAL RESULTS

Assessment/Approach	Combination Therapy	Monotherapy	Log-rank p-value	Hazard Ratio	Result of Statistical Analysis (Combination versus Monotherapy)
All Randomized Population					
• Time to Death			0.0126	0.775	Combination therapy superior
Number of Events	183	201			
Median	**442**	**352**			
95% CI	[375,497]	[298,387]			

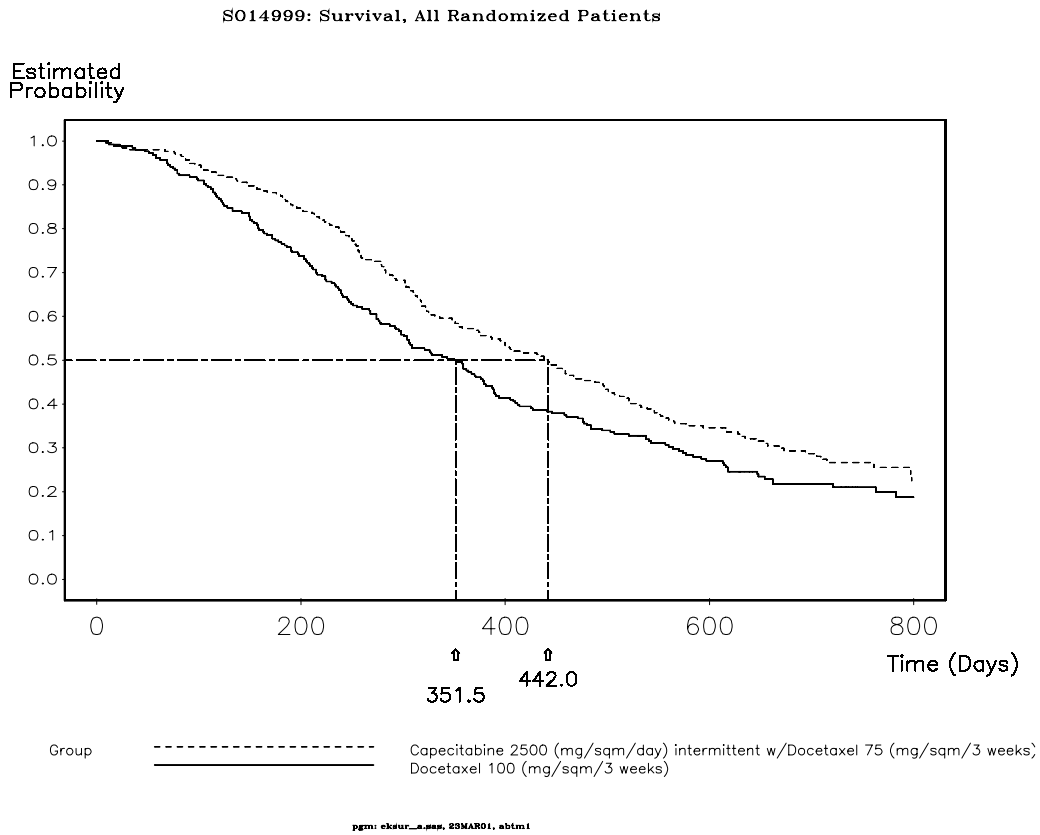
The result (of the primary approach for determination of TTP in the ITT population) is graphically displayed as the Kaplan-Meier estimate:

FIGURE 1: KAPLAN-MEIER ESTIMATES FOR TIME TO DISEASE PROGRESSION – INVESTIGATOR



ASSESSMENT - 'PRIMARY' APPROACH (ALL RANDOMIZED PATIENTS).

FIGURE 2: KAPLAN-MEIER ESTIMATES OF SURVIVAL DISTRIBUTIONS (ALL RANDOMIZED POPULATION)



An overview of ORR according to investigators and IRC assessment for all randomised patients, is presented in table 4.

TABLE 4: SUMMARY OF TUMOUR RESPONSE ASSESSED BY INVESTIGATOR AND IRC.

	Arm A N=255		**Arm B N=256**	
	Investigator	IRC	Investigator	IRC
Overall best response (CR, PR)				
N	106	82	76	59
Rate	**41.6**	**32.2**	**29.7**	**23.1**
95% C.I.	35.5 - 47.9	26.5 - 38.3	24.2 35.7	18.0 - 28.7
Complete response (CR)				
N	12	7	9	3
Rate	4.7	2.8	3.5	1.2
95% C.I.	2. 5 - 8.1	1.1 - 5.6	1.6 6.6	0.2 - 3.4
Stable disease (SD)				
N	96	117	113	131
Rate	37.7	45.9	44.1	51.2
95% C.I.	31.7 - 43.9	39.7 - 52.2	38.0 50.5	44.9 - 57.5
Progressive disease(PD)				
N	28	17	50	29
Rate	11.0	6.7	19.5	11.3
95% C.I.	7.4 - 15.5	3.9 - 10.5	14.9 24.9	7.7 – 15.9

Missing post-baseline information				
N	25	33	16	22
Rate	9.8	12.9	6.3	8.6
95% C.I.	6.5 - 14.3	9.1 - 17.7	3.6 – 10.0	5.5 – 12.7

Time to first response: The majority of responses occurred between week 6 and 12 (table 5).

TABLE 5: NUMBER OF RESPONDERS BY TIME PERIOD – INVESTIGATOR ASSESSMENTS (ALL RANDOMISED PATIENTS)

Days from Randomization to First Response	Capecitabine (12502500 mg/sqm twice daily/day) intermittent w/ Docetaxel (75 mg/sqm/3 weeks) N = 255	Docetaxel (100 mg/sqm/3 weeks) N = 256
1 – 42	21	15
43 – 84	59	43
85 – 126	18	18
127 – 168	5	0
169 – 210	2	0
211 – 252	0	0
253 – 294	1	0
Total	**106**	**76**

Taking into account that the first tumour assessments were planned to be performed "around" week 6, it becomes clear that the vast majority of responses were observed with the first tumour assessment "around" week 6, thus, this is reflecting the median time to response. In the combination arm late responses (occurring after week 18) were observed (8/106 response) while this was not the case for the monotherapy arm (0/76 responses).

The **duration of response** was similar in both arms (220 vs. 211 days, ITT population; 213 vs. 204 day, per protocol population). These data refer to the primary approach taking into account all information on progression, according to the WHO criteria.
The analysis of **Quality of Life** data is based on the safety population. From overall 511 patients, a total of 454 patients (224 on the combination therapy arm and 230 on the monotherapy arm) completed a quality of life questionnaire at least once at baseline or during the treatment phase.
The interpretation of the information derived from the quality of life questionnaires does not add further relevant information to the evaluation of the clinical efficacy of monotherapy vs. combination therapy (e.g. in terms of TTP).

Clinical efficacy of capecitabine monotherapy for breast cancer patients with failure of prior treatment with taxanes and anthracyclines

The salvage indication "failure of prior treatment with taxanes and anthracyclines in breast cancer patients" is supported by the submission of the open-label, non-controlled trial SO14697 and trial NO15542, both of which have similar designs. Two further small-randomised phase II-trials are included in the dossier: trial SO14799 for first-line chemotherapy for metastatic breast cancer in patients older than 55 years (comparison to CMF) and SO15179 in patients with metastatic breast cancer and anthracycline failure (comparison to paclitaxel). These comparative studies were not considered by the CPMP as supportive with respect to the applied indication.

Scientific Advice

With regard to this indication the applicant had obtained Scientific Advice from the CPMP in June 1996. The main issues of Scientific Advice were related to the validity of phase II trials in anthracycline and paclitaxel resistant breast cancer patients for granting authorisation, the number of patients required for efficacy, the primary endpoints (20% ORR as objective) and the acceptability of including safety data from the colorectal cancer patient population.

Clinical trial SO14697

This was an open-label, multicenter, single-arm phase II trial designed to evaluate the efficacy and safety of capecitabine in patients with metastatic breast cancer pre-treated with anthracyclines and paclitaxel. The primary objective was the overall response rate in patients with measurable disease according to the WHO criteria. An Independent Review Committee (IRC) assessed both by the investigators and tumour response. In total, 163 patients with metastatic breast cancer were included in this trial. The response to study treatment is given in the following table:

		Capecitabine (12502510 mg/m^2 twice daily/day) intermittent (n = 135)
Overall Best Response (CR, PR)	N	27
	Rate	20.00
	C.I.	13.61 – 27.75
Complete Response (CR)	N	3
	Rate	2.22
	C.I.	0.46 – 6.36
Stable Disease (SD)	N	54
	Rate	40.00
	C.I.	31.67 – 48.78
Progressive Disease (PD)	N	46
	Rate	34.07
	C.I.	26.14 – 42.72
Missing post-baseline Information	N	8
	Rate	5.93
	C.I.	2.59 – 11.34

The **overall objective response** rate (CR and PR) in the ITT population of patients with measurable disease was 20%. In the standard population of patients with measurable disease (n=117) the response rate was 23% (CI 16%-32, n=27). The majority of these patients (82%) have been pretreated with 5-FU. It should be noted that in the small subset of patients who had never received 5-FU the ORR of capecitabine was considerably higher.

Three complete objective responses were observed in patients with predominantly skin and soft tissue involvement. The objective responses were evenly distributed among the sites of disease and the number of sites involved at baseline.

- The secondary variables were:

The **median duration of response** was 241 days (range 97-324 days, ongoing) in patients with measurable disease.

The **time to response** for most of the patients followed 6 or 12 weeks of treatment.

The median **time to disease progression** was 93 days (95% CI 84, 106) in the ITT population. Approximately 34% had progressed by the time of first tumour assessment.

The median **time to treatment failure** (includes in addition to TTP patient withdrawal for any reason) was very similar, 89.5 days (95% CI 75, 100).

The median **overall survival** for all ITT patients (n=162) was 384 days. For patients with progressive disease it was 163 days, for patients with best response stable disease median survival was 391 days. Median survival was not reached by the time the study report was written.

The **overall clinical benefit response** included pain score, analgesic consumption, and Karnofsky Performance Status and was defined as follows:

- positive response: reduction of pain score to less than 50 % of baseline, reduction of analgesic consumption to less than 50 % and Karnofsky score increase of at least 20 points
- negative response: deterioration of any magnitude in any parameter in > 4 weeks
- stable: any other outcome

The overall clinical benefit was analysed in 147 patients. The response was positive in 20%, stable in 30% and negative in 50% of patients. In patients with objective tumour responses, the overall clinical benefit response was positive in 27%, stable in 19% and negative in 54%. Pain intensity response was positive in 15.3%, stable in 55.4% and negative in 29.3%. Analgesic consumption (morphine equivalents) decreased in 14.0%, was stable in 60.5% and increased in 25.5%.

Clinical trial NO15542

The trial NO15542 was an open-label, multicenter, not randomised phase II trial designed to evaluate the efficacy and safety of capecitabine in patients with metastatic breast cancer pre-treated with taxanes.
The primary objective was the overall response rate in patients with measurable disease. In total, 75 patients with metastatic breast cancer were included in this trial. Primarily, patients who had failed previous treatment with taxanes were to be included. The wording was changed to have received taxanes by an amendment.

The overall investigator assessed best **response rate (CR and PR)** in the ITT population of patients with measurable disease was 24.6% (17/67; 95 %-CI 15.0%-36.5%). In the standard population of patients with measurable disease the response rate was 27.9% (17/62, 95-CI 17.2%-40.8%).
Complete responses were not observed.

The stable disease rate in the ITT population was 30.4% (95%-CI 19.2%-42.7%, n=21).
The progressive disease rate in the ITT population was 34.8% (95%-CI 23.7%-47.2%, n=24).
The frequency of missing post-baseline information was 10.1%.

Subgroup analyses were performed on various subsets of the ITT population. Due to the sample size of the trial, the subgroups consist of small numbers of patients so that a reliable interpretation of the result is difficult.

The overall best response rate (investigators assessment) in patients with measurable disease was 27% in patients who had received paclitaxel, 20% in patients who had received docetaxel and 27% in patients who had received anthracyclines and a taxane.

Secondary variables were:

The **median duration of response** was 253 days (range 213-301 days).
The median **time to disease progression** was 98 days in the ITT population.
The median **time to treatment failure** was very similar (97 days) to TTP.
Tumour response in patients with evaluable disease was assessed clinically. For 2/5 patient's improvement is reported.
The median **overall survival** (for all ITT patients) was 373 (95% CI 244 - 467) days.
The **overall clinical benefit response** was analysed in 54 patients. It was positive in 15 %, stable in 41 % and negative in 44 % of patients.

In general, the efficacy results of this trial are in line with those of trial SO14697.

Safety

Only additional safety data derived from clinical studies in the **advanced breast cancer** indications are described in this chapter.

In the clinical trial **SO14697** the majority of patients (55%, 89/162) required treatment modification due to AEs. The most frequent event leading to treatment modification was hand-foot syndrome (44 patients). Despite the fact that several protocol modifications continuously have affected patient recruitment the patient population is considered as representative for the target population of the indication. Subgroup analysis also identified age (more than 60 years) as a risk factor for treatment related grade 3 – 4 AEs, serious AEs and withdrawals from treatment.

In a substantial number of patients in study **NO15542** dose reduction was required. Serious adverse events (SAEs) were reported in 29 patients (39 %). Forty-seven SAEs in 16 patients were judged study treatment related including the following: diarrhoea (11), nausea and vomiting (13), dehydration (6), stomatitis (5), pyrexia (1), and sepsis (1). In studies SO14697 and NO15542, several analyses performed by the MAH at the request of the CPMP confirm that the safety profile of capecitabine is acceptable in the specific population.

In combination with docetaxel, an increased incidence of grade 3 or 4 treatment-related adverse events and treatment-related serious adverse events were observed in patients 60 years of age or more. It was therefore proposed that for patients 60 years of age or more treated with the combination of Xeloda plus docetaxel, a starting dose reduction of Xeloda to 75% (950 mg/m^2 twice daily) is recommended. If no toxicity is observed in patients ≥ 60 years of age treated with a reduced Xeloda starting dose in combination with docetaxel, the dose of Xeloda may be cautiously escalated to 1250 mg/m^2 twice daily.
Besides these data, it is argued that the safety profile of Xeloda monotherapy in patients with breast cancer is similar to that observed in the phase III comparative trials in patients with colorectal cancer. It should be noted that the question of whether controlled data from patients with colorectal cancer receiving the same dose and schedule of Xeloda may be supportive for the monotherapy breast cancer claim was a subject of the Scientific Advice provided in 1996. Meanwhile, the safety database, including an extensive post-marketing experience, has become considerably larger.

Overall, the clinical trial database and the wide spread clinical use provide strong support for the notion that Xeloda can be used in the target population with acceptable tolerability.

5. Overall conclusion and benefit-risk assessment

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Pre-clinical pharmacology and toxicology
The pre-clinical pharmacology and toxicology profile of capecitabine has been sufficiently characterised.

Efficacy
It is acknowledged that the oral route of administration of capecitabine is a significant benefit compared to available anticancer medicinal products for the proposed therapeutic indication.

In general, absorption, distribution, metabolism and excretion of capecitabine are well investigated. The main metabolites are appropriately characterised, the recovery is nearly completely balanced and the main elimination and excretion pathways (FBAL, urinary) are described.

Overall 4 different schedules of capecitabine have been investigated, between them two schedules ("intermittent and continuous") investigating capecitabine monotherapy.

In two large, multicentre, multinational, randomised, parallel group, open labelled phase III trials using identical protocols the intermittent monotherapy capecitabine schedule was compared with the well known Mayo regimen in treatment naïve patients with advanced colorectal carcinoma.

The antineoplastic activity and adverse reaction profile/pattern of 5-FU depends strongly on the schedule. The applicant has shown that there is no single standard of care in advanced colorectal cancer, and for monotherapy the Mayo regimen as comparator is acceptable.

Xeloda is at least not inferior to Mayo in terms of overall survival (OS) and time to progression (TTP), and superior in terms of objective response rate (ORR).

For patients with advanced or metastatic breast cancer failing anthracyclines, a comparative phase III trial was submitted, investigating the question whether the addition of capecitabine to (standard) docetaxel monotherapy can improve the therapeutic results. The trial showed statistically significant superiority in terms of the primary endpoint time to progression (186 vs. 128 days). This also translates into a relevant prolongation of 90 days (442 vs. 352 days) of overall survival.

For capecitabine monotherapy of patients failing anthracyclines and taxanes two large phase II trials were submitted with a response rate of 20 - 25%, and consistent time to disease progression as well as overall survival.

Safety

The safety profiles of capecitabine and Mayo regimen in the indication of colorectal cancer are clearly different. Higher frequency of hand-foot-syndrome and lower frequency of stomatitis and neutropenia are the main features of capecitabine treatment.
A further difference to note is the frequency of isolated hyperbilirubinaemias observed for capecitabine treatment. This effect is unexpected and presently not fully explained in its last details. The knowledge available suggests that it is a pharmacodynamic effect without clinical relevance.

The analysis of the term "death on study" resulted in a statistical significant but artificial (due to the different duration of treatment and different treatment schedules in the two trial arms) difference in favour of Mayo regimen. A further analysis did not reveal a statistically significant difference between the treatment arms in the integrated analysis. The percentage of deaths in the two arms was similar.

A fair overall conclusion is that the safety profile of intermittent Xeloda treatment differs clearly from the Mayo regimen. It is, however, not outside of the range of known 5-FU regimens.

An analysis of safety data in patients ≥ 60 years of age treated with Xeloda monotherapy and an analysis of patients treated with Xeloda plus docetaxel combination therapy showed an increase in the incidence of treatment-related grade 3 and 4 adverse events and treatment-related serious adverse events compared to patients < 60 years of age. Patients ≥ 60 years of age treated with Xeloda plus docetaxel also had more early withdrawals from treatment due to adverse events compared to patients < 60 years of age. This was addressed in the SPC by the inclusion of dose reduction / escalation recommendations.

Furthermore, safety of monotherapy in breast cancer was discussed in the context of the initial colorectal cancer submission. In overall, the clinical trial safety database and widespread clinical use provide additional support that Xeloda can be used in the target population of breast cancer patients with acceptable tolerability.

Benefit/risk assessment

The applicant has discussed the role of 5-FU based monotherapy particularly taking into account recent developments in the combination treatment of colorectal cancer in an oral explanation before the CPMP. The applicant also provided justifications for the dose recommendations for the treatment with Xeloda of patients with impaired renal function.

The CPMP acknowledged that 5-FU regimens in general are considered to have a modest benefit in terms of overall survival in patients with advanced colorectal cancer. The benefit is so modest that larger meta-analysis are required to show it. The non-inferior OS for capecitabine treatment vs. the Mayo regimen is insofar not unexpected. It is primarily reassuring in terms of safety. However, concerns have been raised about the choice of comparator particularly in view of recent developments in the combination treatment of colorectal cancer. Currently, no comparative data are available on Xeloda monotherapy in comparison with first line combination regimens and this was reflected in the SPC. However, it was also acknowledged that 5-FU based monotherapy regimens remain in wide use.

The non-inferiority, or lack of superiority more precisely, in terms of TTP is to some extent disappointing in view of the superiority capecitabine has on the endpoint ORR.
If one acknowledges that patients may directly benefit from tumour shrinkage (partial response, ORR), capecitabine treatment has to be considered as more beneficial than the Mayo regimen. But direct benefits deriving from partial responses are always disputable as long as they are not reflected in other endpoints (e.g. quality of life, symptom control etc.).

Capecitabine is not simply an "oral 5-FU". The metabolism which capecitabine undergoes may represent theoretically an advantage in comparison with i.v. 5-FU administration (e.g. tumour specificity). However, the 5-FU anabolic pathway of capecitabine makes this substance also more complex in relation to safety. E.g., the isolated hyperbilirubinaemias may potentially be due to a capecitabine metabolite. Thus, also based on theoretical grounds, capecitabine may bear the risk of unexpected AEs. However, capecitabine has also the potential to be slightly safer than bolus i.v. 5-FU administration.

In summary, the data show that capecitabine has a benefit-risk ratio in the range of the Mayo regimen.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Xeloda for first line monotherapy of metastatic colorectal cancer was favourable and therefore recommended the granting of the marketing authorisation.

Subsequently, capecitabine was demonstrated to be non-inferior to i.v. 5-FU/LV (Mayo) in terms of disease-free survival in the all randomized per-protocol, and extended per-protocol populations, based on the pre-specified margins, specified in the protocol -in chemotherapy naïve patients who underwent surgery for stage Dukes C colon carcinoma. There was a trend toward superiority for capecitabine vs. 5-FU/LV with respect to disease-free survival, overall survival and relapse-free survival in the all randomized population. Superiority with respect to relapse-free survival was demonstrated for capecitabine vs. 5-FU/LV in the all randomized and the extended per-protocol populations.

With the limitation of a median follow-up of 3.8 years, and not having a second and independent conducted trial available, it has to be stated that the well designed and well conducted trial M66001 (X-ACT) met its objectives. The MAH committed to report on 5 years overall and disease free survival rates for the X-ACT trial not later than in the 3rd quarter of 2006.

Based on the CPMP review of data on safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Xeloda in the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer is positive.

In the indication of breast cancer in patients who have failed anthracyclines the results were consistent, indicating that the combination of capecitabine and docetaxel offers a clinically relevant benefit in terms of TTP, OS and ORR. In assessing the benefit-risk, the CPMP considered the somewhat higher toxicity of the combination arm as of no major concern, manageable, and compensated by the efficacy data.

The CPMP considered that the agreed objective in terms of response rate for the monotherapy -in patients who have failed both anthracyclines and taxanes- has been reached. Data on overall survival indicate a potential survival benefit. The ORR is consistent at the level of 20% in the phase II trials submitted which reflects an active treatment. The safety profile in breast cancer monotherapy is comparable to Xeloda monotherapy in colorectal cancer and it can be considered that it resembles the acceptable profile of the infusional 5-FU.

Based on the CPMP review of data on safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Xeloda in the indications:

- in combination with docetaxel in locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy containing an anthracycline.

- as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Was also favourable and therefore recommended the extension of the indication.

The MAH committed to report the results of the EORTC trial (study number 10001) entitled " A randomised phase III trial evaluating the efficacy of capecitabine and vinorelbine in anthracycline and taxane pre-treated metastatic breast cancer" once they become available.