SCIENTIFIC DISCUSSION

1. Introduction

This application is made to support the new indication as first-line treatment of patients with advanced gastric cancer. The applicant has performed one pivotal phase III study (ML 17032) and one supportive phase II study (M 66302) for this indication.

Gastric Cancer
Despite a sharp worldwide decline in incidence and a reduction in mortality during the last 50 years, gastric cancer remains the world's second leading cause of cancer mortality to lung cancer[1] with a remarkable variation across geographic regions. In Japan, Korea, China, and certain countries in Central and South America, the incidence is 20 to 95 cases per 100,000 men. The incidence in Western Europe ranges from 12 to 37 cases per 100,000 in men and is about 50% lower in women[2].

To date, the only potentially curative treatment for gastric cancer is surgery. Although the prognosis for gastric cancer is generally poor, better survival rates are seen in Japanese patients. An international comparison, based on population based cancer registries in developing countries and Western developed countries, shows a five year relative survival rate of about 20% while it is 40%–60% in Japan[3] most likely owing to an earlier detection. Patients with unresectable disease due to locally advanced growth or metastatic spread have a poor prognosis, with overall 5-year survival in the range of 5% to 15%. For those patients, and for patients with recurrent disease after surgery, the main option is chemotherapy as the efficacy of chemotherapy with palliative intent compared with best supportive care in patients with advanced gastric cancer has been established in terms of overall survival[4, 5].

Comparable to oesophageal, pancreatic, liver, colon and rectum cancers, 5-FU monotherapy of gastric cancer with an antineoplastic activity around 20% (ORR) was historically the cornerstone of chemotherapy treatment but has been replaced continuously (with the exception of about 6% usage of 5-FU monotherapy in 5 major EU countries - France, Germany, Italy, Spain, and the UK- as mentioned by the clinical expert of the applicant referring to data of Synovate Cancer Therapy Monitor) by 5-FU based 2 to 3 drug combinations. However, there is no unequivocal evidence for combination treatment, or specifically Cisplatin/5-FU combinations, prolonging OS as compared to 5-FU monotherapy. Please note that the quoted comparative trials comparing best supportive care vs. chemotherapy did actually investigate combination treatment (in detail 5-FU, epirubicin plus methotrexate).
Accordingly, the NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology – v. 1.2006, Gastric Cancer, recommends that: "Whenever possible, patients should be enrolled in clinical trials. Outside of clinical trials, patients may be treated with a cisplatin-based, oxaliplatin-based, 5-FU-based, taxane-based, irinotecan-based, or ECF combination chemotherapy. The decision of whether to offer best supportive care alone or with chemotherapy should be based on the patient's performance status. Patients should be offered only best supportive care if they have a Karnofsky performance score of 60 or less…"
The ESMO recommendations[6] read in similar lines: *"Patients with stage IV disease should be considered for palliative chemotherapy. Combination regimens incorporating cisplatin, 5-fluorouracil with or without anthracyclines are generally used. Epirubicin 50 mg/m^2, Cisplatin 60 mg/m^2 and protracted venous infusion 5-fluorouracil 200 mg/m^2/day (ECF) is one among the most active and well tolerated combination chemotherapy regimens. Alternate regimens including oxaliplatin, irinotecan, docetaxel, and oral fluoropyrimidines can be considered."*

[1] Journal of Clinical Epidemiology 56: 1–9, 2003
[2] IARC SciPub 157:311-26, 2004
[3] Postgrad Med J 81:419–424, 2005

[4] Cancer 72: 37-41, 1993
[5] Br J Cancer 71: 587-91, 1995
[6] Annals of Oncology 16 (Supplement 1): i22–i23, 2005

2. Clinical aspects

In order to demonstrate efficacy of capecitabine (in combination with Cisplatin) a multi-centre, international, randomised, open label phase III clinical trial comparing 1000 mg/m^2 Capecitabine bid po (for day 1-14) plus 80 mg/m^2 Cisplatin (day 1 i.v.) for a 3 weeks cycle (**Capecitabine arm**) to a **5-FU**/Cisplatin **arm** consisting in 800 mg/m^2/day continuous infusion of 5-FU (day 1-5) plus 80 mg/m^2 Cisplatin (day 1 i.v.) for a 3 weeks cycle as first line treatment of patients with advanced and/or metastatic gastric cancer has been submitted as the pivotal trial of this application. Furthermore, an open label, non-comparative trial investigating Capecitabine monotherapy as first line treatment of advanced and/or metastatic gastric cancer has been submitted as supportive data as well as results from published trials.

2.1 Clinical pharmacology

Data from an older publication[7] on a human xenograft model in mice which shows additive effects in gastric cancer while Cisplatin toxicity (nephrotoxicity, ototoxicity) is not additive to capecitabine toxicity.

Table 1: Anti-tumour activity of Xeloda in a Human Xenograft model in Mice

Combination partner	Human cancer xenograft	Percentage of growth inhibition				
		5-FU alone	Xeloda alone	Partner alone	5-FU + partner	Xeloda + partner
CPA + methotrexate	Breast cancer					
	MX-1	−11	61	40	70	102
	MAXF401	52	77	48	64	89
	ZR-75-1	35	101	59	65	112
	H-62	24	61	36	50	92
	H-71	31	79	38	29	86
CPA + doxorubicin	Breast cancer					
	MX-1	−11	61	67	104	105
	MAXF401	52	77	45	66	89
Paclitaxel	Breast cancer					
	MX-1	14	51	109	109	109
	MAXF401	36	84	118	118	119
	ZR-75-1	1	105	93	94	125
	DU4475	−2	61	48	29	75
Docetaxel	Breast cancer					
	MX-1	N/D	38	36	N/D	107
	ZR-75-1	N/D	72	65	N/D	111
Cisplatin	Gastric cancer					
	MKN45	70	84	34	77	97

CPA = Cyclophosphamide; N/D = not done.

Ethnic factors (Caucasian vs. Japanese patients) of Capecitabine PK (and its metabolites) have already been assessed in the context of a FUM, with the result labelled in sec. 5.2 of the SPC[8], and published[9].

PK interactions of Capecitabine with Cisplatin as well as PD effect of escalated dosages are available from a publication[10] in 21 patients with locally recurrent or metastatic head and neck carcinoma. Three dose levels (dose of Cisplatin and capecitabine in mg/m^2, Cisplatin at day 1 of a 21 days cycle,

[7] Oncology 57 (suppl. 1): 9-15, 1999

[8] "Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower Cmax and 24% lower AUC for capecitabine than Caucasian patients (n=22). Japanese patients had also about 25% lower Cmax and 34% lower AUC for FBAL than Caucasian patients. The clinical relevance of these differences is unknown. No significantdifferences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU)."

[9] Cancer Chemother Pharmacol 52: 193–201, 2003

[10] Annals of Oncology 14: 1578–86, 2003

Capecitabine b.i.d. for 14 days of a 21 days cycle) - level 1 80 and 1000 (three patients); level 2 100 and 1000 (12 patients); and level 3, 100 and 1125 (five patients) – were investigated. Dose limiting toxicity at first cycle was observed starting with level 2. Based on the results the authors concluded that there was no evidence of pharmacokinetic–pharmacodynamic relationships with the drugs and metabolites investigated.
The lack of PK interaction of capecitabine with other substances has been confirmed in further publications: In a trial investigating escalating doses of capecitabine (500, 825, 1000 and 1250 mg/m^2 b.i.d.) each in combination with 50 and 60 mg/m^2 Epirubicin and Cisplatin every three weeks (ECC) in 32 patients with inoperable oesophago-gastric adenocarcinoma, the authors concluded[11] that C_{max} and $AUC_{0-\infty}$ for capecitabine, DFCR, and DFUR were similar to those observed in previous capecitabine monotherapy trials. A Capecitabine dose of 1000 mg/m^2 was recommended and a phase III trial comparing ECF and ECC seemed to be justified.

A phase I trial in solid tumour patients[12] investigated Capecitabine in combination with Cisplatin and Docetaxel at overall 6 dose levels with small or even very small increments[13]. Of note is that Cisplatin and Docetaxel were repeated every 7 days while capecitabine was administered continuously (b.i.d.) for 14 days with one week rest period (cycle length 3 weeks). Main conclusions of this trial were that the recommended docetaxel, cisplatin, and capecitabine dose for phase II studies is 27/27/825 mg/m^2. An observed alteration in total and ultrafiltrate platinum disposition on cycle 2 compared with cycle 1 may be inherent to sequential Cisplatin administration; however, prior treatment with Capecitabine could not be ruled out as a factor.

2.2. Clinical efficacy
The clinical assessment is based on one pivotal phase III study (ML 17032) and on one supportive phase II study (M 66302). Published data are also discussed as supportive to the indication.

2.2.1 Main Study ML 17032

This was an open, phase III study performed in 42 centres in the 12 countries: China (14 centres, including 1 in Hong Kong), Brazil (7), Korea (4), Mexico (4), Russia (4), Argentina (2), Peru (2), Malaysia (1), Colombia (1), Guatemala (1), Panama (1), and Uruguay (1).
Approximately 300 patients were to be enrolled, 150 in each of the 2 treatment groups. All study sites and investigators were familiar with the principles of Good Clinical Practice (GCP) and clinical audits were conducted by the Clinical Quality Assurance Department of Roche. The primary objective of this study was to demonstrate that capecitabine in combination with cisplatin is non-inferior to 5-FU in combination with cisplatin in terms of progression-free survival (PFS) in previously untreated patients with advanced and/or metastatic gastric cancer. The secondary objectives were to compare the efficacy profiles of the 2 treatment groups in terms of overall response rate, complete response rate, duration of survival, time to progression, duration of response, and time to response, if PFS non-inferiority is accepted and to compare the safety profiles of the 2 treatment groups.

Patients between 18 and 75 years of age with histologically confirmed measurable advanced and/or metastatic gastric adenocarcinoma not previously treated with chemotherapy (except adjuvant or neoadjuvant treatment completed at least 6 months prior to enrollment), having creatinine clearance > 60 mL/min, Karnofsky performance status $\geq$ 70% and a life expectancy of at least 3 months, were eligible for entry into this study:

After randomization to 1:1 groups the patients received either:
- capecitabine (1000 mg/m^2 bid po) from evening of day 1 through morning of day 15 and cisplatin (80 mg/m^2 2-hour infusion with pre- and posthyper-hydration) on day 1. A 3-week cycle (2 weeks of treatment, 1-week rest) for at least 2 cycles.

[11] Annals of Oncology 13: 1469-79, 2002
[12] Clin Cancer Res 11: 5942-49, 2005
[13] The first dose level (DL1) consisted of 20 mg/m^2 docetaxel, 20 mg/m^2 cisplatin, and twice a day capecitabine at 600 mg/m^2/dose. DL2 to DL5 were 20, 20, and 825 mg/m^2; 27, 20, and 825 mg/m^2; 27, 27, and 825 mg/m^2; and 36, 27, 825 mg/m^2 for docetaxel, cisplatin, and capecitabine, respectively.

- cisplatin (80 mg/m^2 2-hour infusion with pre- and posthyper-hydration) on day 1, 5-FU (800 mg/m^2 per day, continuous infusion) on days 1 to 5. A 3-week cycle, for at least 2 cycles.

The primary objective of this study was to demonstrate that capecitabine in combination with cisplatin (capecitabine/cisplatin) is non-inferior to 5-FU in combination with cisplatin (5-FU/cisplatin) in terms of progression-free survival (PFS) in previously untreated patients with advanced and/or metastatic gastric cancer.
The secondary objectives were:
– To compare the efficacy of the 2 treatment groups in terms of overall response rate, complete response rate, duration of survival, time to progression, duration of response, and time to response, if PFS non-inferiority is accepted,
–To compare the safety profiles of the 2 treatment groups.

All patient analysis populations were defined and determined prior to database closure for the final analysis. One patient population was defined for the safety analysis (safety population) and two for the efficacy analysis, namely the ITT and PP populations. All demographic and baseline characteristics were summarized and all efficacy parameters were analyzed for both the ITT and PP populations. The applicant has chosen the PP population as the primary analysis population but the results have been counted for the ITT population as well and this critical assessment is mainly based on the ITT population.

Results

A total of 316 patients were enrolled into Study ML17032 at 42 centres in 12 countries. The first patient was randomized on 30 April 2003, and the last patient was randomized on 18 January 2005. Of the 316 patients, 160 were randomized to the capecitabine/cisplatin treatment group and 156 to the 5-FU/cisplatin treatment group. By the clinical cut-off date of 04 November 2005, 216 patients had died. Baseline demographic and tumour characteristics at baseline are summarised in tables 2 and 3.

Potential prognostic factors such stage, tumour histology, lymph node involvement, metastatic sites, number of metastasis, or previous anticancer treatment were overall evenly distributed in both treatment arms, both in the ITT as well as in the PP population.

Table 2: Trial ML17032: Baseline Demographic Characteristics

	Capecitabine/Cisplatin N = 160	**5-FU/Cisplatin N = 156**
Sex		
MALE	103 (64%)	108 (69%)
FEMALE n	57 (36%)	48 (31%)
	160	156
Age in years		
Mean	55.4	54.7
Median	56.0	56.0
range	26 - 74	22 - 73
n	160	156
Weight in kg		
Mean	61.2	58.8
Median	60.00	57.20
range	37.5 - 110.0	36.0 - 118.0
n	160	155
Height in cm		
Mean	164	163
Median	164	164
range	141 - 200	139 - 185
n	160	155

Ethnicity		
CAUCASIAN	31 (19%)	29 (19%)
HISPANIC	17 (11%)	15 (10%)
ORIENTAL	105 (66%)	104 (67%)
OTHER	7 (4%)	8 (5%)
n	160	156

Table 3: Trial ML17032: Baseline Tumour Characteristics

		Capecitabine/Cisplatin N=160		5-FU/Cisplatin N=156	
Histological Type					
Papillary Adenocarcinoma		9	(5.6%)	11	(7.1%) (12.8%)
Tubular Adenocarcinoma		27	(16.9%)	20	(6.4%) (17.3%)
Mucinous Adenocarcinoma		13	(8.1%)	10	(55.1%) (1.3%)
Signet Ring Cell Carcinoma		29	(18.1%)	27	
Other		79	(49.4%)	86	
Unknown		3	(1.9%)	2	
Differentiation					
Well Differentiated		9	(5.6%)	11	(7.1%) (22.4%)
Moderately Differentiated		52	(32.5%)	35	(42.3%) (1.9%)
Poorly Differentiated		65	(40.6%)	66	(26.3%)
Anaplastic		1	(0.6%)	3	
Unknown		33	(20.6%)	41	
Staging at Study Entry					
Stage 0	Tis, N0, M0		0 (0.0%)		0 (0.0%)
Stage IA	T1, N0, M0		0 (0.0%)		1 (0.6%)
Stage IB	T1, N1, M0		0 (0.0%)		0 (0.0%)
	T2, N0, M0		0 (0.0%)		0 (0.0%)
Stage II	T1, N2, M0		0 (0.0%)		0 (0.0%)
	T2, N1, M0		0 (0.0%)		1 (0.6%)
	T3, N0, M0		0 (0.0%)		1 (0.6%)
Stage IIIA	T2, N2, M0		0 (0.0%)		1 (0.6%)
	T3, N1, M0		5 (3.1%)		4 (2.6%)
	T4, N0, M0		0 (0.0%)		2 (1.3%)
Stage IIIB	T3, N2, M0		9 (5.6%)		1 (0.6%)
Stage IV	T4, N1-3, M0		3 (1.9%)		9 (5.8%)
	T1-3, N3, M0		1 (0.6%)		7 (4.5%)
	Any T, Any N, M1		141 (88.1%)		126 (80.8%)
Unknown			1 (0.6%)		3 (1.9%)

Efficacy results

The results of primary objectives are evaluated both for the PP-population and for the ITT population. The hazard ratio of capecitabine/cisplatin vs 5-FU/cisplatin was estimated by a Cox regression stratified by region and adjusted for pre-specified covariates. In the PP population, the point estimate of the hazard ratio (capecitabine/cisplatin vs 5-FU/cisplatin) was 0.85 and the upper limit of the 2-sided 95% CI was 1.11, which is below the pre-specified non-inferiority margin of 1.25. The finding was statistically significant ($p = 0.005$). Similar results were obtained for the ITT population: point estimate, 0.84; upper limit of 2-sided 95% CI, 1.09; $p = 0.003$.

Table 4: Trial ML17032: Summary of Results for Key Efficacy Parameters (PP Population)

Parameter	Median (Months) (95% CI) Capecitabine/Cisplatin (N = 139)	5-FU/Cisplatin (N = 137)	Hazard Ratio (95% CI)
Progression-free survival	5.6 (4.9, 7.3)	5.0 (4.2, 6.3)	0.81 (0.63, 1.04)* 0.85 (0.65, 1.11)**
Duration of survival	10.5 (9.3, 11.2)	9.3 (7.4, 10.6)	0.85 (0.64, 1.13)* 0.84 (0.63, 1.13)**
Time to progression	5.6 (4.8, 6.9)	5.2 (4.2, 6.6)	0.82 (0.60, 1.11)* 0.87 (0.63, 1.21)**

* Unadjusted treatment effect in Cox proportional hazards model.

** Region-stratified Cox proportional hazards model adjusted for prior chemotherapy, sex, age, Karnofsky score, bone metastases, number of metastatic sites, and serum bilirubin.

Table 5: Trial ML17032: Independent (IRC) Review: Summary of Hazard Ratios for Key Efficacy Parameters

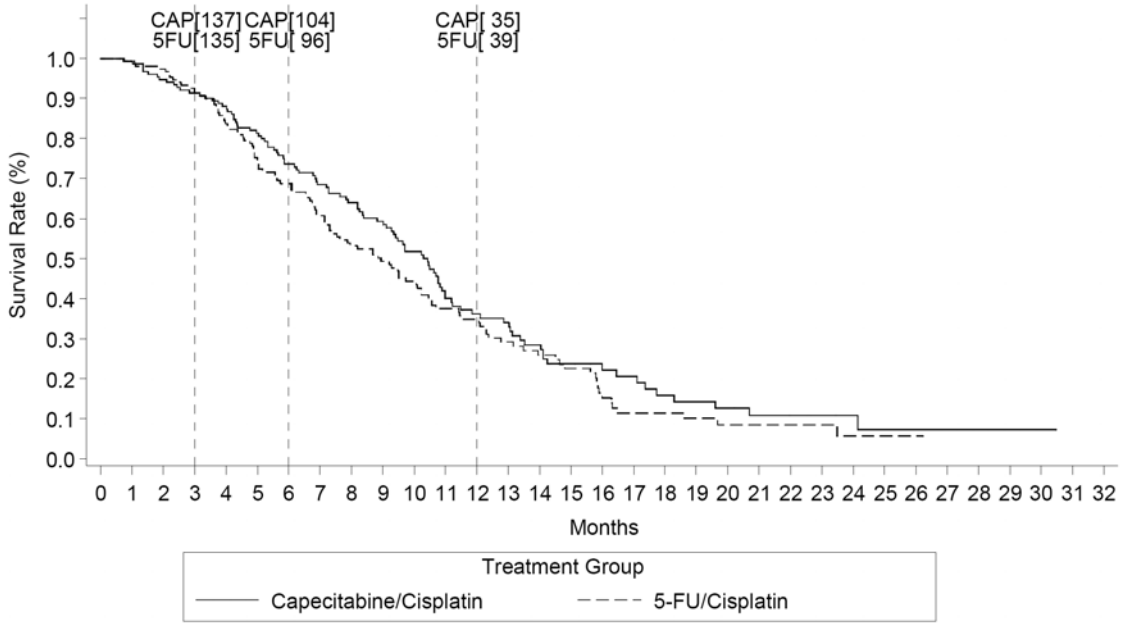
Population	Parameter	Unadjusted* Hazard Ratio (95% CI)	Adjusted** Hazard Ratio (95% CI)
PP	Progression-free survival	0.90 (0.69, 1.18)	0.93 (0.70, 1.23)
	Time to progression	0.79 (0.54, 1.15)	0.77 (0.51, 1.17)
ITT	Progression-free survival	0.89 (0.69, 1.15)	0.90 (0.69, 1.18)
	Time to progression	0.82 (0.56, 1.19)	0.80 (0.53, 1.21)

* Unadjusted treatment effect in Cox proportional hazards model.

** Region-stratified Cox proportional hazards model adjusted for prior chemotherapy, sex, age, Karnofsky score, bone metastases, number of metastatic sites, and serum bilirubin.

For all time-to-event parameters, similar results were obtained with and without adjustment for pre-specified covariates. The hazard ratios (capecitabine/cisplatin vs 5-FU/cisplatin) were similar for PFS, duration of survival, and time to progression, ranging from 0.80 to 0.88.

Figure 1: Trial ML17032: Plot of Kaplan-Meier Estimates of Survival by Treatment Group (ITT Population)



† Numbers on the top are for risk sets.

Results in pre-specified subgroups (prior chemotherapy, sex, age, Karnofsky score, bone metastases, number of metastatic sites, serum bilirubin, geographic region, and ethnicity) confirmed the overall results. No interaction was observed between treatment and subgroup variables. The hazard ratios (or odds ratios) were generally similar across subgroups, with the majority favouring capecitabine/ cisplatin over 5-FU/cisplatin. These sub-group analyses show the internal consistency and robustness of the results.

The median duration of survival was slightly longer (10.4 months vs 8.9 months) and the 1-year survival rate was slightly higher in the capecitabine/cisplatin group than in the 5-FU/cisplatin group (36.1% vs 34.8%).
The results for duration of survival in the PP population were similar to those in the ITT population.
The log-rank test of the equality of the survival functions of the 2 treatment groups was not statistically significant (p = 0.2430 in the ITT population) but the Kaplan-Meier plot of duration of survival showed a separation of the curves for the capecitabine/cisplatin and 5-FU/cisplatin groups. Survival rates were greater for the capecitabine/cisplatin group than for the 5-FU/cisplatin group across the study period except at about month 14.
The Kaplan-Meier plot of duration of survival for the PP population was similar to that for the ITT population.
The log-rank test of the equality of the survival functions of the 2 treatment groups was statistically significant in the ITT population (p = 0.0140) and in the PP population as well (p = 0.0094).

Tumour response (RECIST)
The tumour responses were assessed according to RECIST criteria. In results for the ITT population, the capecitabine/cisplatin group had a higher overall response rate (40.6%) than in the 5-FU/cisplatin group (28.8%) (p = 0.0295, stratified analysis). Patients in the capecitabine/cisplatin group had 1.41 times the chance of achieving an overall response compared with patients in the 5-FU/cisplatin group. A similar pattern was observed for partial response. Three complete responses were observed in the capecitabine/cisplatin group, and 4 in the 5-FU/cisplatin group. Similar results were observed for the PP population.
ORR was – in both arms – considerably smaller with the difference no longer reaching statistical significance following the independent assessment of the IRC: The overall response rates were 27.5% and 23.1% in the capecitabine/cisplatin and 5-FU/cisplatin groups, respectively (p = 0.3493) in the ITT and 31.7% and 25.5% (p = 0.2672) in the PP population.

Table 6: Trial ML17032: Overall Response (Partial Response + Complete Response) (RECIST) by Treatment Group

Population	Capecitabine/Cisplatin n/N Proportion (95% CI)	5-FU/Cisplatin n/N Proportion (95% CI)	p-value**
ITT	65/160 **40.6%** (32.9, 48.7)	45/156 **28.8%** (21.9, 36.6)	0.0295
PP	64/139 **46.0%** (37.6, 54.7)	44/137 **32.1%** (24.4, 40.6)	0.0182

Tumor response is (RECIST) confirmed response.
** P value is based on Cochran-Mantel-Haenszel general association statistics stratified by region.

Duration of response was determined in those patients who had RECIST confirmed partial or complete responses (in the ITT population, 65 in the capecitabine/cisplatin group and 45 in the 5-FU/cisplatin group). The median duration of response was slightly longer (7.6 months vs 6.2 months) and the 6-month rate of no progression or death was higher in the capecitabine/cisplatin group than in the 5-FU/cisplatin group (57.1% vs 55.0%). Consistent with the results of the log-rank test, which indicated that the survival curves for the 2 treatment groups were significantly different, a Kaplan-Meier plot of time to response showed a separation of the curves for the capecitabine/cisplatin and 5-FU/cisplatin groups from 1.5 months (the time of the first tumour assessment) onward. At all time points after month 2, the response rates were approximately 10% greater in the capecitabine/cisplatin group than in the 5-FU/cisplatin group

2.2.2. Efficacy results from Study M66302

This was an open-label, multi-center phase II study to evaluate the efficacy, safety and tolerability of capecitabine as first line monotherapy in previously untreated Korean patients with advanced and/or metastatic gastric cancer. The primary efficacy analysis consisted of the overall response rate which was the time from the start of treatment to progressive disease or end of study. The secondary parameters were time to disease progression, duration of response and time to response. A total of 45 patients were enrolled in this study but after one withdrawal (the patient withdrew consent) the safety/ITT population included 44 patients.
This study is considered as a supportive one because of safety parameters.

The main efficacy findings of trial M66302 can be summarised as follows:

- Objective response rate in the ITT population was 34% (CI: 20%-50%), 36% in the PP population.
- The median time to disease progression was 95 days (3.1 months) both in the ITT and in the PP population.
- Median duration of response was 251 days (8.4 months) both in the ITT and in the PP population
- OS has not been reported (and is/was obviously also not monitored)

2.2.3. Published data

Results from two Japanese phase II trials investigated a Capecitabine dosage of 828 mg/m^2 twice daily for 3 weeks of a 4-weeks cycle were provided. In the first[14], the response rate was **19%** among the 31 evaluable patients and **24%** in the subset of 25 chemotherapy-naïve patients. In the other trial[15], the response rate was **26%** among the 55 evaluable (chemotherapy-naïve) patients and 23% in the intent-to-treat (ITT) population.
Two published Korean and a Chinese trial investigated the combination of Capecitabine and Cisplatin in advanced or recurrent gastric cancer patients. Rough details on design and result are provided in table 7.

Table 7: Efficacy Results from 3 Phase II Studies of Capecitabine/ Cisplatin in Advanced Gastric Cancer

Reference	Regimen	No. of Patients/ No Evaluable	Response Rate (%)	TTP or PFS (Median, Months)	OS (Median, Months)
Kim et al. 2002[16]	Capecitabine: 1250 mg/m^2 twice daily on days 1 to 14; cisplatin: 60 mg/m^2 on day 1, 3-week cycle	42/38	55	TTP: 6.3	10.1
Kang et al. 2005[17]	Capecitabine: 1250 mg/m^2 twice daily on days 1 to 14; cisplatin: 60 mg/m^2 on day 1, 3-week cycle	32/30	28[a, b]	PFS: 5.8	11.2
Jin et al 2005[18]	Capecitabine: 1000 mg/m^2 twice daily on days 1 to 14; cisplatin: 20 mg/m^2 on days 1 to 5, 3-week cycle	154/141	46	TTP: 9	12

a) All patients had received prior adjuvant chemotherapy and had recurrent disease.
b) The authors reported the response rate as a percentage of patients enrolled. Based on the number of patients evaluable for efficacy, the response rate was 9/30 or 30%.

[14] Oncology 64: 232–36, 2003
[15] Anti-Cancer Drugs 17: 231–236, 2006
[16] Annals of Oncology 13: 1893–98, 2002
[17] British Journal of Cancer 92: 246–51, 2005
[18] Journal of Clinical Oncology 23, No 16S (June 1 Supplement): Abstract 4053, 2005

In addition to these 3 published Capecitabine/Cisplatin phase II combination trials in advanced gastric cancer the applicant is reviewing overall 7 published phase II combination trials in which the combination partner of Capecitabine was not Cisplatin but Docetaxel (3 trials[19, 20, 21]), Oxaliplatin (2 trials[22, 23]), Paclitaxel, and Irinotecan (1 trial each[24, 25]). The ORRs in these trials are high ranging from 40-65% and an OS ranging from 8.4-14.6 [or not reached] months.

In addition, a small, randomised German trial comparing Capecitabine/Cisplatin vs. capecitabine / Irinotecan is presented in table 8.

Table 8: Efficacy Results from a Randomized Phase II Trial[26] of Capecitabine-Irinotecan and Capecitabine-Cisplatin as First-line Treatment in Advanced Gastric Cancer

Regimen	No. of Patients/No. Evaluable	Response Rate (%)	PFS (Median, Months)	OS (Median, Months)
Capecitabine: 1000 mg/m^2 twice daily on days 1 to 14 Irinotecan: 250 mg/m^2 on day 1 3-week cycle	34/28	39	5.3	9
Capecitabine: 1000 mg/m^2 twice daily on days 1 to 14 Cisplatin: 80 mg/m^2 on day 1 3-week cycle	42/31	42	5.1	9.6

Concerning Capecitabine triple combination treatment an open label uncontrolled phase II and a randomized, phase III trial (REAL-2), conducted in the UK and Australia, in patients with advanced, inoperable oesophago-gastric cancer and no previous chemotherapy are reviewed.

A brief outline of the design as well as the major results of the Korean phase II trial[27] is provided :

Table 9: Efficacy Results from a Randomized Phase II Study of Capecitabine-Irinotecan and Capecitabine-Cisplatin as First-line Treatment in Advanced Gastric Cancer

Regimen	No. of Patients/No. Evaluable	Response Rate (%)	TTP (Median, Months)	OS (Median, Months)
Capecitabine: 1000 mg/m^2 twice daily on days 1 to 14 Epirubicin: 50 mg/m^2 Cisplatin: 60 mg/m^2 3-week cycle	54/50	59	6	9.6

The randomized phase III **Real-2** trial[28] used a 2 x 2 factorial design to compare 4 regimens, all of which included Epirubicin: 50 mg/m^2 IV bolus every 3 weeks. The four schedules/combinations investigated were in detail:

[19] British Journal of Cancer 90: 1329–1333, 2004
[20] Oncology 68: 190-95, 2005
[21] Am J Clin Oncol 28: 188–94, 2005
[22] British Journal of Cancer 94: 959–63: 2006
[23] Proc Am Soc Clin Oncol 23 (357s): Abstract 4199, 2005
[24] Journal of Clinical Oncology 22, No 14S (July 15 Supplement; Post-Meeting Edition): Abstract 4051, 2004
[25] British Journal of Cancer (advance online publication, 25 April 2006): 1 –5, 2006
[26] Moehler et al.: Preliminary results of a randomized German AIO phase II study, 2 abstracts submitted by the applicant, for more details see also http://www.egms.de/en/meetings/dkk2006/06dkk345.shtml
[27] Oncol 68: 333-40, 2005
[28] British Journal of Cancer 92: 1976–83, 2005

- Epirubicin, Cisplatin, 5-FU (**ECF**):
  Epirubicin plus Cisplatin (60 mg/m^2 with standard hydration every 3 weeks) and 5-FU (200 mg/m^2 daily by continuous infusion via central line)
- Epirubicin, Cisplatin, capecitabine (**ECX**):
  Epirubicin plus cisplatin (60 mg/m^2 with standard hydration every 3 weeks) and Capecitabine [500 mg/m^2 (increased to 625 mg/m^2 after results of first interim analysis) twice daily orally, continuously]
- Epirubicin, Oxaliplatin, 5-FU (**EOF**):
  Epirubicin plus Oxaliplatin (130 mg/m^2 IV infusion over 2 hours every 3 weeks) and 5-FU (200 mg/m^2 daily by continuous infusion via central line)
- Epirubicin, Oxaliplatin, Capecitabine (**EOX**):
  Epirubicin plus oxaliplatin (130 mg/m^2 IV infusion over 2 hours every 3 weeks) and Capecitabine [500 mg/m^2 (increased to 625 mg/m^2 after results of first interim analysis) twice daily orally, continuously]

Major efficacy and safety results of the REAL-2 trial are presented. Table 10 shows the result concerning overall survival. As the 95%-confidence interval for EOX does not include 1, the conclusion can be derived that EOX is statistically significantly superior to ECF in terms of OS. In table 11 referring to ORR shows only minor differences in the study arm. The results in tables 12 and 13 indicate a lower toxicity of Oxaliplatin vs. Cisplatin while the safety differences between 5-FU and Capecitabine appear negligible. With 41.7% and 51.1% grade 3/4 neutropenia both Cisplatin triple combination arms can be characterised as of pronounced myelotoxicity.

Table 10: REAL-2 Study: Median Overall Survival and Hazard Ratios by Regimen (ITT Population)

Regimen	N	Median Overall Survival (Months)	Hazard Ratio (95% CI)
ECF	263	9.9	1
ECX	245	9.3	0.95 (0.79–1.15)
EOF	250	9.9	0.92 (0.76–1.11)
EOX	244	11.2	0.80 (0.65–0.97)[a]

Table 11: REAL-2 Study: Overall Response Rates

Regimen	No. of Evaluable Patients	Response Rate (%) (95% CI)
ECF	246	40.7% (34.5–46.8)
ECX	237	46.4% (40.0–52.8)
EOF	231	42.4% (36.1–48.8)
EOX	234	47.9% (41.5–54.3)

Table 2: REAL-2 Study: Haematological Grade 3/4 Toxicity

Toxicity (% of Patients)	ECF N = 236	ECX N = 229	EOF N = 231	EOX N = 232
Leukopenia	19.5	21.0	13.4	13.8
Anemia	13.1	10.5	6.5[a]	8.6
Thrombocytopenia	4.7	4.8	4.3	5.2
Neutropenia	41.7	51.1[a]	29.9[b]	27.6[b]
Febrile neutropenia	9.3	6.7	8.5	7.8

Table 3: REAL-2 Study: Non-haematological Toxicity

Toxicity (% of Patients)	ECF N = 234	ECX N = 234	EOF N = 225	EOX N = 227
Diarrhoea	2.6	5.1	10.7 [b]	11.9 [b]
Stomatitis	1.3	1.7	4.4 [a]	2.2
Nausea/vomiting	10.2	7.7	13.8	11.4
Alopecia (grade 2)	44.2	47.4	27.7 [b]	28.8 [b]
Peripheral neuropathy	0.4	1.7	8.4 [b]	4.4 [b]
Infection	11.9	5.1 [a]	11.5	8.4
Fever	3.4	4.3	2.6	4.4
Hand-foot reaction	4.3	10.3 [a]	2.7	3.1
Lethargy	16.6	15.5	12.9	24.9 [a]
Thromboembolism	18.1	14.9	8.5 [b]	8.4 [b]

2. 3. Clinical Safety

The main data source for safety information for capecitabine for the first line treatment of advanced gastric cancer comes from the pivotal study ML 17032. In this study, all patients received treatment for at least two 3-week cycles in one of two treatment groups mentioned above. In addition, detailed safety data is also received from the supportive phase II study (M 66302).

Safety results from Study ML 17032

Adverse events (AEs) were monitored throughout the study treatment phase and for 28 days after the last intake or infusion of study treatment. Related safety parameters were dose modifications and premature withdrawals from treatment due to adverse events and concomitant treatments given for AEs.

Adverse events were reported for nearly all patients (96%) in both treatment groups. Most of the patients had treatment-related AEs, and half had at least one severe or life-threatening AE. There was no difference between the two treatment groups according to the percentage of patients with severe or life-threatening adverse events or the percentage with the adverse events leading to discontinuation of trial treatment.

The capecitabine/cisplatin and 5-FU/cisplatin groups were similar in terms of the percentages of patients with all-grade adverse events, severe or life-threatening (grade 3/4) adverse events, and adverse events leading to withdrawal from trial treatment.

- Gastrointestinal adverse events were the most frequent adverse events in both treatment groups. The spectrum of gastrointestinal adverse events associated with capecitabine/cisplatin was qualitatively similar to that observed with 5FU/cisplatin, with nausea and vomiting being the predominant gastrointestinal adverse events. All grade vomiting and stomatitis were less frequent with capecitabine/cisplatin than with 5-FU/cisplatin.
- All-grade hand–foot syndrome (palmar-plantar erythrodysesthesia) was more frequent with capecitabine/cisplatin than with 5-FU/cisplatin (22% vs 4%) but led to discontinuation of trial treatment in only 1 patient (<1%) in the capecitabine/cisplatin group.
- Dose modifications due to adverse events were more frequent for capecitabine than for 5-FU (55% vs 41% of patients). However, treatment duration tended to be longer and the mean cumulative dose of cisplatin was higher in the capecitabine/cisplatin group than in the 5-FU/cisplatin group.
- Death during treatment or within 28 days after the last dose of treatment occurred in 15 patients in the capecitabine/cisplatin group and 10 in the 5-FU/cisplatin group. Of these, 7 deaths in each of the 2 groups had causes other than gastric cancer/progressive disease. One death in the capecitabine/cisplatin group and 2 deaths in the 5-FU/cisplatin group were considered by the investigator to be drug related.
- Death within 60 days after the start of treatment occurred in 8 patients in the capecitabine/cisplatin group and 5 in the 5-FU/cisplatin group. Of these, 5 deaths in the

capecitabine/cisplatin group and 3 deaths in the 5-FU/cisplatin group had causes other than gastric cancer/progressive disease.

- Treatment-related serious adverse events were reported in 10% of patients in the capecitabine/cisplatin group and 7% in the 5-FU/cisplatin group.
- There were no major differences between the treatment groups in laboratory results. The 2 treatment groups were similar with regard to the percentages of patients with grade 3/4 neutropenia/granulocytopenia (capecitabine/cisplatin, 27%; 5-FU/cisplatin, 25%) and grade 3/4 anemia (capecitabine/cisplatin, 23%; 5-FU/cisplatin, 19%). All grade bilirubin increase was more frequent in the capecitabine/cisplatin group (31%) than in the 5-FU/cisplatin group (20%). However, grade 3/4 elevations of ALAT and ASAT were present in the 5-FU/cisplatin group but not in the capecitabine/cisplatin group.

Safety results from Study M 66302

Almost all patients reported at least one AE during treatment (41/44 patients, or 93.2%, reported 185 adverse events), with the majority of these AEs being classified as related to treatment (119 events reported in 38, or 86.4%, of patients were drug-related) (Table 20).
In the majority of patients (65.9% - 50.0%), treatment-related AEs were rated by investigators as being mild (grade 1) or moderate (grade 2). About sixteen percent of patients experienced grade 3 treatment-related AEs (10 events reported by 7 patients). One (2.3%) patient reported life-threatening (grade 4) AE that was classified as being related to treatment.

Among the most common AEs were those involving the gastrointestinal tract like nausea and diarrhoea as in the study ML 17032, while palmo-plantar syndrome was the most common single event.

Most frequent drug-related AEs	Number of patients	(%)
Palmo-plantar syndrome	30	(68,2)
Nausea	12	(27,3)
Anorexia	12	(27,3)
Diarrhea	9	(20,5)
Stomatitis	6	(13,6)
Vomiting	5	(11,4)

Postmarketing Safety Data

Since capecitabine first got the marketing authorisation in 1998, it is estimated that over 1 million patients have been treated with capecitabine. Post-marketing surveillance data accumulated for capecitabine since approval have been submitted in the form of Periodic Safety Update Reports (PSURs), summarizing the worldwide safety data on capecitabine for all indications.
A Roche ADVENT Safety Database search (between 30-Apr-1998 and 08-Jan-2006) was performed for all capecitabine adverse event reports, including clinical trial cases considered to be unrelated to capecitabine by the reporting investigators, with one of the following indications: gastric cancer, gastric cancer stage III, gastric cancer stage IV, gastroesophageal cancer or metastatic gastric cancer.
A total of 270 case reports with a total of 517 adverse events and 66 co-manifestations in 268 patients, who were treated with capecitabine, were received. Of these 270 cases, 15 cases with 28 events and 4 co-manifestations were considered to be non-serious.
This is consistent with the findings in the 12th PSUR, covering the reporting period from November 1, 2004 to July 31, 2005, and included with the Renewal Application. No new safety signals were identified in this review period that necessitated a change to the Summary of Product Characteristics (SPC).

The system organ class with the highest number of adverse events is “Gastrointestinal Disorders” followed by “Skin and Subcutaneous Tissue Disorders” and “General Disorders and Administration Site Conditions”. The most frequently reported adverse events were diarrhoea, palmo-plantar erythodysthesia, vomiting and nausea.

Overall Discussion and Benefit-Risk assessment

5-FU/cisplatin is a well-established standard combination treatment of advanced and/or metastatic gastric cancer. Replacement of 5-FU by Capecitabine in this combination has only minimal effects on the safety of this combination. Concering efficacy, capecitabine is at least non-inferior with regard to the primary endpoint of the trial, PFS. The same statement applies on other secondary endpoint (including OS) and "sensitivity analysis" (such as the IRC based assessment of progression). The efficacy results proved to be rather robust in several sets of analysis performed.

In summary, considering also that Capecitabine is for oral (for 14 days) administration and 5-FU is for continuous infusion (for 5 days), benefit-risk relationship of Capecitabine/Cisplatin is "at least comparable" to 5-FU/Cisplatin. Rather, there is some evidence that efficacy of Capecitabine/Cisplatin may be even better (e.g. ORR based on investigators' assessment or the range of the different 95%-CIs of the primary and secondary endpoints). As 5-FU/Cisplatin represents standard of care of advanced gastric cancer so that Capecitabine/Cisplatin has at least the potential to improve standard of care (at minimum by replacing 5-FU continuous infusion by [ambulatory] intake of tablets without recognisably affecting safety).
In study Real-2 in ECF, Cisplatin can be replaced by Oxaliplatin, 5-FU can be replaced by Xeloda and EOX is statistically significantly superior to ECF in terms of OS. In addition there was a trend to an improved safety profile in Oxaliplatin arms. At both dosages of 200 mg/m^2 5-FU and 625 mg/m^2 Xeloda had a comparable safety profile.

Taking into account also the published trials it could even be argued that restricting capecitabine in the treatment of advanced gastric cancer patient to the combination partner cisplatin is a suboptimal regulatory result. Capecitabine/Cisplatin reflects appropriately the well established character of 5-FU and the already broad experience with Capecitabine in advanced gastric cancer not limited to the Cisplatin combination only but to platinum regimens.

Both the two published Japanese phase II trials as well as the submitted trial M66302 characterise Capecitabine as an active substance in the treatment of advanced and/or metastatic chemotherapy naïve gastric cancer patients deserving further investigation (in the year 2002, when trial M66302 was performed). This is no surprise in view of Capecitabine being an oral pro-drug of 5-FU, 5-FU and Capecitabine are active as monotherapy in colorectal cancer, and 5-FU is the backbone of the treatment of advanced intestinal cancers since decades. However, the evidence from these trials was not sufficient to support a monotherapy indication for Xeloda in gastric cancer.

Also the safety profile of Xeldoda in advanced gastric cancer is no surprise. For underlining the well established character of Xeloda's safety profile, AEs frequently reported in (the phase II) trial M66302 were compared with SPC statements. The differences are minor.
The MAH was requested to perform a meta-analysis of all finalised phase III Roche sponsored trials investigating Capecitabine. Subject of the meta-anlysis should be relevant fluoropyrimidine AEs (HFS, Gastrointestinal AEs, Grade 3/4 neutropenia). Factors to be analysed should comprise capecitabine starting dose, cumulative capecitabine dose and/or treatment duration, combination partner, intend and/or line of treatment.

The MAH has revised the section 4.8 of the SPC adverse effects. Concerning monotherapy (adjuvant colon and treatment of advanced colorectal) this simplification has actually already taken place. For the new posology applied for (Xeloda in combination with platinum regimen) it is considered that AEs of Xeloda in these combinations are clinically relevant and should be described.

3. CONCLUSION

- On 22 February 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

Area[1]	Description	Due date[2]
Clinical	**NO16966** A phase III randomised, open-label study comparing the effect of first-line treatment with intermittent Xeloda versus fluorouracil/leucovorin, both in combination with oxaliplatin (i.e. XELOX versus FOLFOX) with or without bevacizumab, on tumour progression in patients with metastatic colorectal cancer. This study is currently planned to be submitted to the CHMP in April 07 as part of a Type II variation to extend the currently approved indication for Xeloda to metastatic colorectal cancer. Study NO16966 and NO16967 (see below) will both be submitted as part of the submission dossier. **Meta-analysis:** The MAH commits to provide the Follow Up Measure in two parts: – Part 1 – A proposed analysis plan for conducting a meta-analysis of the large database represented by the studies that are currently described in the approved SPC as well as the additional studies to be submitted (NO16966 and NO16967) will be submitted to CHMP end-April 07. Part II – Results of the meta-analysis will be submitted with the Responses to the Request for Supplementary Information for the above-mentioned Type II variation to extend the currently approved indication for Xeloda to metastatic colorectal cancer.	Part I – to be submitted end-April 07 Part II - To be submitted with the Responses to the Request for Supplementary Information.
Clinical	**NO16967** A Phase III randomised, open-label study of the effect of intermittent Xeloda versus iv fluorouracil/leucovorin, both in combination with oxaliplatin (i.e. XELOX versus FOLFOX), on tumour progression in patients with metastatic colorectal cancer who received prior CPT-11 and 5-fluorouracil/leucovorin. This study is currently planned to be submitted to the CHMP in April 07 as part of a Type II variation to extend the currently approved indication for Xeloda to metastatic colorectal cancer. Study NO16966 (see above) and NO16967 will both be submitted as part of the submission dossier.	

	Meta-analysis: It is proposed that the FUM will be submitted in 2 parts as described above for study NO16966.	As for NO16966
Clinical	**NO16968** A randomised, open-label study of the effect of intermittent Xeloda in combination with oxaliplatin, versus fluorouracil/leucovorin, on disease-free survival in patients who have undergone surgery for colon cancer. This study is currently planned to be submitted in 2008 as part of a Type II variation to extend the currently approved indication for Xeloda in the adjuvant treatment of colon cancer. Formal confirmation of the submission date still required. **Meta-analysis:** The MAH commits to provide the Follow Up Measure in two parts: Part 1 – A proposed analysis plan for conducting a meta-analysis of the large database represented by the studies that are currently described in the approved SPC as well as the additional study to be submitted (NO16968) will be submitted to CHMP end-April 07. Part II – Results of the meta-analysis will be submitted with the initial submission for the above-mentioned Type II variation to extend the currently approved indication for Xeloda in the adjuvant treatment of colon cancer.	Part I – to be submitted end-April 07 Part II - To be submitted in 2008 with the initial submission of this variation

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.