Clinical Pharmacology Supplemental NDA Review

NDA	20,896 Supplement 32 (eCTD16l; SDN 1172)
Type/Category	SE8
Brand Name	Xeloda®
Generic name	Capecitabine
Applicant	Hoffman La-Roche
OCP Division	DCPV
OND Division	DOP2
Submission Date	June 10, 2013
PDUFA	December 10, 2013
Primary Reviewer	Stacy S. Shord, Pharm.D.
Team Leader	Hong Zhao, Ph.D.

Table of Contents

1 EXECUTIVE SUMMARY 2

1.1 RECOMMENDATIONS 2

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS 3

2 QUESTION BASED REVIEW 3

2.1 GENERAL ATTRIBUTES 5

2.2 GENERAL CLINICAL PHARMACOLOGY 6

2.3 INTRINSIC FACTORS 11

2.4 EXTRINSIC FACTORS 11

2.5 GENERAL BIOPHARMACEUTICS 12

2.6 ANALYTICAL SECTION 15

3 DETAILED LABELING RECOMMENDATIONS 18

List of Tables

Table 1. Description of Study NO18517, NO21125 and BP27931 7

Table 2. Summary of observed mean (± SD) plasma pharmacokinetic parameters of capecitabine and metabolites after single and multiple dose administration of capecitabine 9

Table 3. Summary of mean (± SD) plasma PK parameters of capecitabine and metabolites after single and multiple dose administration 10

Table 4. Summary statistics of PK parameters in pediatric patients derived from PPK model 11

Table 5. Comparison of the 5'DFUR exposure following the administration of the pediatric formulation to Xeloda 13

Table 6. Exposure (geometric mean (CV%)) following the administration of Xeloda and the pediatric formulation 14

Table 7. Bioanalytical methods 15

Table 8. Range of standard curves for the different analytes 16
Table 9. Lower limit of quantification for the different analytes 16
Table 10. Accuracy and precision 16

List of Figures

Figure 1. Metabolism of capecitabine 6
Figure 2. Basic structural pharmacokinetic model 11
Figure 3. Plasma concentration of 5'-FDUR following administration of Xeloda and the pediatric formulation 13

1 EXECUTIVE SUMMARY

Capecitabine as Xeloda® is a drug product approved for the treatment of patients with colorectal or breast cancer. The applicant, Roche, subsequently conducted two clinical studies: (1) a dose finding study and (2) an activity estimating study to assess the safety, activity and pharmacokinetics (PK) of capecitabine in pediatrics with newly diagnosed brainstem gliomas. No improvement in the one-year progression free survival (PFS) rate or the one-year overall survival (OS) rate was observed. The adverse event profile of capecitabine was consistent with the known adverse event profile in adults, with the exception of laboratory adverse events which occurred more commonly in pediatric patients. No pediatric indication will be approved. Pediatric exclusivity was granted on August 27, 2013.

A Pediatric Written Request (PWR) was issued and subsequently modified on March 17, 2005, January 19, 2007 (Amendment #1), May 7, 2008 (Amendment # 2), and July 1, 2011 (Amendment #3). The written request required PK characterization in at least 9 patients in each of the following two age groups: age under 6 years and age 7 years through 12 years, the use of an age-appropriate formulation and the characterization of the bioavailability of any formulation used in the clinical studies. The PK of capecitabine and its metabolites was reasonably characterized by noncompartmental and population pharmacokinetic (PPK) analyses in 25 pediatrics (median 7 years; range 3 to 17 years) enrolled into the dose finding or activity estimating studies in accordance with the written request.

A relative bioavailability study (BP27931) conducted in 31 adults which allowed for comparison of the marketed capecitabine tablets to the pediatric tablets showed that the exposure to the 5'-DFUR metabolite is similar following administration of the pediatric tablets. As such, the study failure is not likely due to poor exposure following administration of the pediatric formulation.

The approved labeling will be modified to describe these studies in limited details in section 8, Specific Populations.

1.1 RECOMMENDATIONS

This NDA supplement is acceptable from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language. The applicant adequately addressed the Pediatric Written Request (PWR) in regards to the pharmacokinetic

(PK) sampling and data analysis plan. Pediatric exclusivity was granted on August 27, 2013. No post marketing studies are being requested.

Signatures:

Stacy S. Shord, Pharm.D. Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V

Cc: DOP2: RPM **- G Davis;** MO**- M Donoghue;** MTL**- S Demko**
DCPV: DDD **- B Booth;** DD **– NA Rahman**

An OCP Office Level Briefing was not held.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

This efficacy supplement contains (1) a dose finding study; (2) an activity estimating study and a (3) relative bioavailability to assess the safety, activity and PK of capecitabine in pediatrics to support a request for pediatric exclusivity.

The PK of capecitabine and its metabolites was reasonably characterized by population pharmacokinetic (PPK) analyses in 25 pediatrics that were enrolled into the dose finding (n=10) or activity estimating (n=15) studies in accordance with the written request. The following table provides the geometric mean maximal concentrations (C_{max}) and the area under the concentration-time curve at steady-state (AUC_{ss}) for three metabolites of capecitabine derived from the PPK model.

Summary statistics of pharmacokinetic parameters in pediatric patients (N=25)						
	$AUC_{SS0-12hr}$ (µg • hr/mL)			C_{max} (µg/mL)		
	5'-DFUR	5-FU	FBAL	5'-DFUR	5-FU	FBAL
Geometric Mean	5.8	0.18	8.5	3.7	0.12	1.9
CV%	33.7	45.8	34.3	54.1	89.7	46.3

Roche conducted a randomized, open label, single dose, two-way crossover study in 37 adults (mean: 58 years; range: 31−79 years) with colorectal or breast cancer to assess the relative bioavailability of capecitabine following administration of pediatric tablets and commercial tablets. Patients were administered capecitabine at a dose of 2000 mg daily x 2 days. The 5′-DFUR geometric least squares means (GLSM) ratios for the C_{max} was 0.90 (0.81, 0.99) and for the AUC_{inf} was 0.97 (0.94, 1.0). Thus, 5′-DFUR had similar overall exposure achieved for both tablet formulations with the 90% confidence intervals for the GLSM ratios entirely contained within the acceptance interval criteria of 0.8, 1.25. The t_{max} is shorter for the pediatric tablet as anticipated; the formulation was developed to be readily dispersable in water.

2 QUESTION BASED REVIEW

On April 30, 1998, capecitabine as Xeloda® was approved for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing

chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated. New indications were approved on April 30, 2001 (Suppl 6), September 7, 2001 (Suppl 10) and June 15, 2005 (Suppl 16) for the use of Xeloda (1) as first-line treatment of metastatic colorectal cancer when treatment with fluoropyrimidine treatment alone is preferred, (2) in combination with Taxotere (docetaxel) for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy and (3) as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred.

A Pediatric Written Request (PWR) for Xeloda was initially issued by the FDA on March 17, 2005 under IND 45,305. The PWR was amended on January 19, 2007 (Amendment #1), May 7, 2008 (Amendment # 2), and July 1, 2011 (Amendment #3). The most recent amendment to the PWR for capecitabine specifies that Roche will conduct an open-label, dose-finding, PK, safety and efficacy study of capecitabine in combination with radiation in children with newly-diagnosed non-disseminated intrinsic diffuse brainstem gliomas. The PWR specifies that

- The PK sub-study (which can be performed across phase 1 and phase 2) will include at least 9 patients in each of the following two age groups at time of enrollment: age under 6 years and age 7 years through 12 years;
- The PK sub-study will be achieved through secondary objectives of the phase 1 and phase 2 trials, i.e. an evaluation of the PK of capecitabine and its metabolites in pediatric aged patients. Additionally, pharmacokinetic and pharmacodynamic (PK-PD) models will explore exposure-response relationships for measures of safety and effectiveness. PK sub-study must examine capecitabine PK in children using accepted procedures and methods and will attempt to model important covariates.
- Use an age-appropriate formulation in the studies described above. If the studies conducted in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you seek approval for commercial marketing.
- Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults. If appropriate, a biowaiver strategy could be used to address the relative bioavailability study.

(b) (4)

Roche believes that the terms of the PWR have been met and is requesting determination of the 6 month pediatric exclusivity extension associated with the Xeloda patent (US Patent No. 5,472,949) under Section 505A of the Federal Food, Drug, and Cosmetic Act (FD & C Act), as in effect when FDA issued the PWR on 17 March 2005 and the Best Pharmaceuticals for Children Act (BPCA), January 4, 2002 (Public Law No. 107−109).

2.1 GENERAL ATTRIBUTES

Highlights of the chemistry and physical-chemical properties

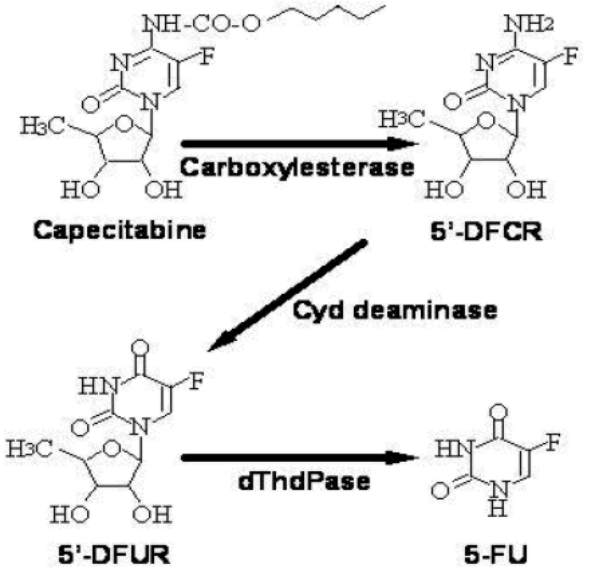
As stated in the approved labeling, capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil (5-FU). The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and it has a molecular weight of 359 grams per mole.

Xeloda is commercially available as 150-mg and 500-mg tablets for oral administration. A pediatric tablet formulation (125-mg, 175-mg, 250-mg and 350-mg) was developed for the pediatric clinical studies. The pediatric tablets were designed to quickly disperse in water so that the resulting suspension could be administered to pediatric patients who are unable to swallow tablets. The initial pediatric formulation was modified (b) (4) A relative bioavailability study (BP27931) was conducted in adults to compare the commercial tablet formulation to the pediatric tablets as described in **Section 2.5**. Roche doesn't plan to market the pediatric tablets.

Proposed mechanism(s) of action

As stated in the approved labeling, enzymes convert capecitabine to 5-FU *in vivo* as shown in **Figure 1**. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate and 5-fluorouridine triphosphate. These metabolites cause cell injury by two different mechanisms. First, the monophosphate and a folate cofactor covalently bind to thymidylate synthase to form ternary complex. This complex inhibits the formation of thymidylate; thymidylate is a necessary precursor of thymidine triphosphate, which is essential for DNA synthesis. A thymidylate deficiency subsequently inhibits cell division. Second, nuclear transcriptional enzymes mistakenly incorporate the triphosphate in place of uridine triphosphate during the synthesis of RNA, interfering with RNA processing and protein synthesis.

Figure 1. Metabolism of capecitabine



Roche states that capecitabine has been shown to be a potential radiation sensitizer and that radiation therapy has been shown to induce thymidine phosphorylase (dTHdPase) in glioblastoma xenografts, supporting the combination of capecitabine plus radiation therapy for pediatric brain tumors.

Proposed dosage(s) and route(s) of administration

The labeled dose is 1250 mg/m^2 administered orally twice daily (BID) for the first 14 days of a 21-day treatment cycle. Xeloda is to be taken within 30 minutes of a meal, as food reduces the rate and extent of absorption.

The dose for pediatrics with brain stem gliomas in the clinical trials was 650 mg/m^2 administered orally BID with concomitant radiation therapy for a total of 9 weeks, followed by a 14-day break. After radiation therapy, the administered dose was 1250 mg/m^2 administered orally BID taken within 30 minutes of a meal for the first 14 days of a 21-day treatment cycle x 3 courses. A food effect study was not conducted with the pediatric tablets, but the approved labeling for Xeloda recommends that the commercial tablets be taken within 30 minutes of a meal as stated above. See **Section 2.5**.

2.2 GENERAL CLINICAL PHARMACOLOGY

Clinical pharmacology and clinical studies

The application contains the final study reports for a dosing finding study (NO18517), an activity estimating study (NO21125) and a relative bioavailability study (BP27931) as listed in **Table 1**.

- Study NO18517, entitled "A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas."
- Study NO21125, entitled "A Phase II Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas."

- Study BP27931, entitled "A Randomized, Open-label, Single Dose, Two-way Cross-Over Study to Investigate the Relative Bioavailability of Capecitabine in Rapid Disintegrating Tablets (RDT) Versus the Commercial Xeloda® Tablets Following Oral Administrations in Adult Patients with Solid Tumors."

Table 1. Description of Study NO18517, NO21125 and BP27931

Study Number	Indication	Study Design	Study Phase	Dose and Regimen		Number of Patients Included in PK Population
NO18517	Newly Diagnosed Brainstem Gliomas and High-Grade Gliomas in Pediatric Patients	Single center, dose-finding, open-label, multiple dose	I	RT Phase: 500, 650, or 850 mg/m^2 BID for 3 cycles [a]	Post-RT Phase: 1250 mg/m^2 BID for 3 cycles [b]	10
NO21125	Newly Diagnosed Brainstem Gliomas in Pediatric Patients	Single center, open-label, multiple dose	II	RT Phase; 650 mg/m^2 BID for 3 cycles [a]	Post-RT Phase: 1250 mg/m^2 BID for 3 cycles [b]	15
BP27931	Colorectal or Breast Cancer in Adult Patients	Multicenter, open-label, randomized, two-way crossover, relative bioavailability study	I	2000 mg capecitabine pediatric film-coated single dose [c] and 2000 mg XELODA film-coated tablet single dose [d] on 2 consecutive days		31

BID = twice a day; PK = pharmacokinetic; RT = radiation therapy.
[a] RT Phase: one cycle consists of 21 days of treatment.
[b] Post-RT Phase: one cycle is 21 days (14 days treatment followed by 7 day rest period).
[c] 8×250 mg capecitabine pediatric film-coated tablets.
[d] 4×500 mg XELODA film-coated tablets.

Table 1, Summary-Clin-Pharm

Response endpoints or biomarkers

The primary endpoint for Study NO18517 was the maximum tolerated dose (MTD).

The primary endpoint for Study NO21125 was one-year progression-free survival (PFS) rate with a secondary efficacy endpoint of one-year overall survival (OS) rate. An indication for the pediatrics with newly diagnosed brain stem gliomas was not proposed, as no improvement in survival was observed. As the pediatric tablets appear to have similar exposure to the commercial tablets [**Section 2.5**] and the MTD was identified, it is unlikely that limited systemic exposure is responsible for the absence of clinical benefit.

The primary endpoints for Study BP27931 were the relative AUC and the C_{max} of the metabolite 5'-DFUR.

Active moieties in the plasma

Plasma concentrations of capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU and FBAL) were appropriately identified using validated assays as described in **Section 2.6**.

Exposure-response

Exposure-response for clinical effectiveness and tolerability

Graphical exposure-response (E-R) analyses were performed only for patients diagnosed with intrinsic brainstem glioma from Study NO18517 (n=5) and Study NO21125 (n=15) by correlating model-based estimates of exposure (AUC) for the two main metabolites (5'-DFUR and 5-FU) with safety and efficacy measures of interest.

Exploratory graphical analysis of the relationship between exposure (AUC) for the two main metabolites (5'-DFUR and 5-FU) and PFS and tumor size was performed. Roche stated no clear relationship was observed between AUC and PFS or tumor size; however, the sample size was relatively small and no survival benefit was observed.

The adverse events reported with the greatest frequency included vomiting (80%), ALT increase (75%), lymphocyte count decrease (73%), white blood cell count decrease (61%), and platelet

count decrease (57%). Exploratory graphical analysis of the relationship of exposure (AUC) for the two main metabolites (5'-DFUR and 5-FU) with diarrhea, vomiting and PPE was performed. Roche found no clear relationship between exposure (AUC) and diarrhea, vomiting or PPE; however, the sample size was relatively small.

QT or QTc interval

The approved labeling does not describe the effect of capecitabine on the QT interval. ECGs were not assessed in Study NO18517 and NO21125.

PK characteristics of the drug and its major metabolite

The PK characteristics were assessed across Study NO18517 and Study NO21125.

Study NO18517

A total of 24 patients were enrolled into Study NO18517: 4 patients into the first cohort (500 mg/m^2 BID), 14 patients into the second cohort (650 mg/m^2 BID), and 6 patients into the third cohort (850 mg/m^2 BID). PK samples were collected on the first day of treatment and following the morning dose of capecitabine on day 14. Patients were assigned to one of two series for sample collection for up to 10 hrs after the first dose. Additional samples were collected on day 7 ± 2 days and day 21± 2 days between 1 and 4 hrs after the morning dose of capecitabine.

Ten patients provided a limited number of PK samples on days 1 and 14, but only nine patients (1 patient 3-6 years; 5 patients 7-12 years; and 3 patients 13-17 years) were included in the noncompartmental analysis (NCA). One patient who was administered a dose of 650 mg/m^2 was excluded from the NCA analysis, since only two PK samples were evaluable on day 1 and no PK samples were evaluable on day 14. Consequently, individual PK parameters could not be estimated in most patients. However, exposure (AUC and C_{max}) did not appear to increase proportionally with doses up to 850 mg/m^2 following single and multiple doses of capecitabine based on the available data. **Table 2** provides a summary of the available PK data.

Table 2. Summary of observed mean (± SD) plasma pharmacokinetic parameters of capecitabine and metabolites after single and multiple dose administration of capecitabine

Analyte	Dose (mg/m^2)	Day	n	t_{max} (hr)[a]	Mean (±SD) of Plasma PK Parameters	
					C_{max} (ng/mL)	AUC_{last} (ng • hr/mL)
Capecitabine	500	1	2	0.58 (0.17–1)	1440 ± 750	3370 ± 607
		14	2	1.33 (0.17–2.48)	2100 ± 1770	2890 ± 655
	650	1	4	0.63 (0.25–1)	3080 ± 1340	5160 ± 3700
		14	2	0.82 (0.8–0.83)	5440 ± 3270	9660 ± 3340
	850	1	3	0.85 (0.83–10)	1890 ± 1420	3470 ± 1170
		14	2	0.61 (0.5–0.72)	3710 ± 156	5670 ± 971
5'-DFCR	500	1	2	1 (1–1)	2050 ± 813	5250 ± 755
		14	2	1.49 (0.5–2.48)	2980 ± 2020	4300 ± 272
	650	1	4	0.75 (0.50–2.50)	2190 ± 626	5140 ± 3440
		14	4	1.18 (0.5–1.53)	3500 ± 1470	9250 ± 1400
	850	1	3	1.55 (0.85–10)	2180 ± 1690	4180 ± 2380
		14	2	0.61 (0.5–1.53)	3200 ± 233	6520 ± 452
5'-DFUR	500	1	2	1 (1–1)	1910 ± 834	4790 ± 784
		14	2	1.5 (0.5-2.5)	3300 ± 2800	4240 ± 929
	650	1	4	0.9 (0.7–2.5)	2640 ± 1700	4300 ± 1600
		14	2	0.82 (0.8–0.83)	3120 ± 445	8010 ± 1890
	850	1	3	1.5 (0.75–10)	3770 ± 3300	6650 ± 3740
		14	2	0.61 (0.5–0.72)	5020 ± 1220	10500 ± 445
5'-FU	500	1	2	1 (1–1)	47.8 ± 23.9	81.6 ± 29.7
		14	2	1.5 (0.5–2.5)	183 ± 196	181 ± 84.7
	650	1	4	0.75 (0.5–2.5)	77.3 ± 52.7	114 ± 40.9
		14	2	0.83 (0.8–0.83)	95.4 ± 27.8	253 ± 16.3
	850	1	3	1.5 (0.75–10)	178 ± 205	271 ± 205
		14	2	1 (0.5–1.5)	257 ± 107	499 ± 78.8
FBAL	500	1	2	2.53 (2.5–2.53)	1350 ± 134	5990 ± 951
		14	2	1.74 (1–2.5)	1770 ± 410	5720 ± 690
	650	1	4	1.5 (1.5–2.5)	1740 ± 365	8110 ± 1640
		14	2	2.2 (1.5–2.8)	2430 ± 84.9	10700 ± 574
	850	1	3	1.55 (1.42–10)	2050 ± 1640	7010 ± 4490
		14	2	2.03 (1.57–2.5)	2140 ± 304	10400 ± 1760

[a] Median (minimum-maximum)

Table 2, Summary-Clin-Pharm

Study NO21125

PK sampling was implemented in Study NO21125 to meet the requirements of the PWR. As such, patients from 2 age groups (age 3-6 years and 7-12 years) were enrolled. All patients who

were enrolled onto the primary protocol were asked to participate in the PK substudy during the first course of capecitabine. PK samples were collected on days 1 and 14 up to 6 hrs after the morning dose. Additional samples were collected on days 7 and 21. Of the 34 patients that were enrolled, 15 patients participated in the PK substudy. **Table 3** provides a summary of the mean PK parameters.

Table 3. Summary of mean (± SD) plasma PK parameters of capecitabine and metabolites after single and multiple dose administration

Analyte	Day	C_{max} (ng/mL) Mean	n	t_{max} (hr) Median (Min–Max)	n	$AUC_{0\text{-}6h}$ (ng • hr/mL) Mean	n	$t_{1/2}$ (hr) Mean	n
Capecitabine	1	3030 (63.6)	15	0.658 (0.167–3.52)	15	6340 (71.5)	10	1.11 (28.8)	10
	14	5290 (94.9)	14	0.5 (0.183–1.27)	14	6180 (67.2)	10	1.83 (97)	6
5'-DFCR	1	2830 (62.3)	15	0.5 (0.25–1.27)	15	5260 (73.5)	10	1.58 (66.8)	10
	14	2450 (57.2)	14	1 (0.167–3.52)	14	5120 (53.6)	11	1.12 (33.3)	4
5'-DFUR	1	3750 (52.8)	15	0.500 (0.25–1.27)	15	5920 (53.5)	8	1.76 (59)	8
	14	3370 (79.7)	14	1 (0.25–3.52)	14	5450 (44.4)	8	1.25 (47.8)	2
5-FU	1	122 (114)	15	0.856 (0.25–3)	15	121 (33.8)	6	1.72 (47.4)	5
	14	138 (122)	14	0.883 (0.167–3.52)	14	178 (39.6)	9	1.32 (55.5)	4
FBAL	1	1580 (33.7)	15	2.43 (0.833–6)	15	5600 (35.7)	11	2.3 (42.1)	3
	14	1900 (37.4)	14	3 (0.75–6)	14	6840 (32.2)	12	1.92 (5.69)	3

Table 3, Summary-Clin-Pharm

Combined Data

The PWR states that a PK substudy (which can be performed across phase 1 and phase 2) will include at least 9 patients in each of the following 2 age groups at time of enrollment: age under 6 years and age 7 years through 12 years. The demographic data (N=25) indicate that 11 children ages 3, 4, 5 and 6; 10 children ages 7, 8, 9, 11 and 12; and 4 adolescents ages 15, 16, and 17 provided PK samples during the course of these 2 trials. Thus, the PK substudy includes the number of patients per age group as requested in the PWR.

A PPK analysis was performed on the pooled data from 25 patients enrolled into Studies NO18517 (n=10) and NO21125 (n=15) who provided at least one measurable plasma concentration and documented capecitabine dosing history. A multi-response PPK model for 3 capecitabine metabolites (5'-DFUR, 5-FU, and FBAL) that was previously built using data from 481 adult patients in 2 phase 3 studies of colorectal cancer that included sparse PK sampling (Study SO14695, n = 233; Study SO14796, n = 248) and from a bioequivalence study which included rich PK sampling (Study BP15572, n = 24) was used to obtain PK parameter estimates in pediatrics using Bayesian feedback analysis. A total of 561 observations with 106, 101, 125, 117 and 112 observations for 5'-DFUR, 5-FU, FBAL, 5'-DFCR and capecitabine concentrations were available, respectively. Roche stated that as a good agreement between the prediction and the observation was observed, it is reasonably concluded that the model previously developed in adults can accurately describe the data collected in the pediatric studies. **Figure 2** depicts the structural model for the PPK analysis and **Table 4** lists the mean PK parameters derived from the PPK model.

Figure 2. Basic structural pharmacokinetic model

Dose = capecitabine dose administered (molar units); KA = absorption rate constant; TLAG = lag time; Vi/F (where *i* = 1,2,3) = apparent volumes of distribution; CL*i*/F (where *i* = 1,2,3) = respective oral drug clearances.

To simplify notation, CL*i* instead of CL*i*/F is used to denote respective oral drug clearances or, in short, 'clearance' of the respective metabolite. Accordingly, Vi is used instead of Vi/F to denote respective apparent volumes of distribution or, in short, 'volume' of the respective metabolite.

Figure 1, Summary-Clin-Pharm

Table 4. Summary statistics of PK parameters in pediatric patients derived from PPK model

	$AUC_{SS0\text{-}12hr}$ (µg • hr/mL)			C_{max} (µg/mL)		
	5'-DFUR	5-FU	FBAL	5'-DFUR	5-FU	FBAL
Geometric Mean	5.8	0.18	8.5	3.7	0.12	1.9
CV%	33.7	45.8	34.3	54.1	89.7	46.3

2.3 INTRINSIC FACTORS

Roche reasonably did not assess the effect of intrinsic factors on the PK in this pediatric population, as the study population is relatively small. However, this submission includes a PPK report (B164836) that was previously submitted and reviewed (Suppl 6). The study report indicates that alkaline phosphatase affects 5-FU clearance; baseline creatinine clearance affects FBAL clearance and body surface area affects FBAL volume of distribution. Age, race, gender, liver metastasis, Karnofsky performance status, total bilirubin, serum albumin, AST and ALT did not appear as covariates in the final model. This model was used to estimate the PK parameters for the pediatric population as described in **Section 2.2**.

Study NO18517 and Study NO21125

Although a covariate model was not included in the revised PPK analysis, the dosage and administration (based on body surface area) and the eligibility criteria reasonably addressed previously identified intrinsic factors.

- Patients must have demonstrated adequate organ function (including a creatinine clearance or radioisotope GFR $\geq$ 70 ml/min/1.73m^2 or a serum creatinine based on age as defined by the eligibility criteria). The approved labeling recommends a dose reduction of 25% with moderate renal function. The eligibility criteria for adequate renal function would most likely prevent patients with moderate renal function from participating in the trial.
- Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency were excluded. This exclusion criterion is consistent with the contraindication listed in the approved labeling.

2.4 EXTRINSIC FACTORS

Extrinsic factors

Roche reasonably did not assess the effect of extrinsic factors on the PK in this pediatric population, as the study population is relatively small.

Drug-drug interactions

As capecitabine is not metabolized by cytochrome P450 enzymes, no drug interactions were anticipated.

2.5 GENERAL BIOPHARMACEUTICS

Biopharmaceutics classification system (BCS)

Roche states that based on its good solubility and more than 90% fraction absorbed (mass balance study), capecitabine is classified as BCS class I. FDA accepted the BCS class I designation on April 10, 2012.

Relative bioavailability

Biowaiver Request

Roche states that the pediatric tablets are similar to the commercial tablets [redacted] The dissolution data shows that [redacted] capecitabine dissolves from these tablets within 15 minutes in all media studied (0.1N HCl, pH 4.5 buffer, pH 6.8 buffer, and water).

The commercial tablets contain 150-mg and 500-mg of capecitabine. For the 150 -mg tablets, the average percent dissolved is [redacted] within [redacted] minutes. For the 500-mg tablets, the average percent dissolved is [redacted] within [redacted] minutes. Both commercial tablets [redacted] dissolved [redacted] when water is used as the dissolution medium as defined in the FDA Guidance for Industry "*Waiver of in vitro bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on Biopharmaceutics classification system*."

On January 23, 2013, FDA did not grant a biowaiver based on dissolution data and f2 values and instructed Roche to conduct a relative bioavailability study comparing the pediatric formulation to the approved drug formulation in adults.

Relative Bioavailability

Roche conducted a randomized, open label, single dose, two-way crossover study in 37 adults (mean 58 years; range 31 to 79 years) with colorectal or breast cancer who were planning to start treatment with Xeloda or who were being treated with Xeloda as either monotherapy or combination therapy. The primary objective of this study was to assess the relative bioavailability of capecitabine following administration of the pediatric tablets as compared to the commercial tablets. Patients were administered capecitabine at a dose of 2000 mg once daily x 2 days with a light breakfast. PK sampling was performed on days 1 and 2 up to 6 hrs post dose. The primary PK parameters were the C_{max}, the AUC_{inf}, and the t_{max} of the 5′-DFUR metabolite. The secondary PK parameters were the C_{max}, the AUC_{inf}, and the t_{max} of capecitabine and its other metabolites.

As listed in **Table 5**, similar overall exposure of 5'-FDUR was observed for the pediatric formulation as compared to Xeloda with the 90% confidence intervals (CI) for the geometric least squares means ratios that were entirely contained within the acceptance interval criteria of 0.8 to 1.25; however, the t_{max} appears shorter for the pediatric tablets [**Figure 3**]. The shorter t_{max} likely resulted from the pediatric tablet formulation, as it was designed for rapid dispersion to allow for the tablets to be administered as a suspension for pediatrics that could not swallow tablets.

Table 6 lists that geometric mean exposure to capecitabine and its other metabolites; the AUC_{inf} appears similar for these analytes; however, the C_{max} of capecitabine appears higher following

administration of the pediatric formulation compared to Xeloda. Roche states that the mean C_{max} was statistically significantly higher (~47%) for pediatric formulation, although the within-subject variability was moderately high (59%).

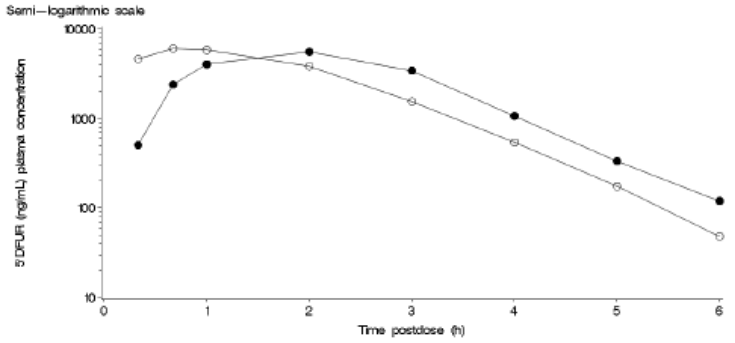
Table 5. Comparison of the 5'DFUR exposure following the administration of the pediatric formulation to Xeloda

Parameter	Treatment	N	Geometric Least Squares Means	Ratio of Geometric Least Squares Means (Pediatric Film Coated Tablets:XELODA)	90% CI for the Ratio	
					Lower	Upper
$AUC_{0-\infty}$ (ng.h/mL)	2000 mg XELODA	31	12953			
	2000 mg capecitabine pediatric film-coated tablets	31	12593	0.9722	0.9359	1.0099
C_{max} (ng/mL)	2000 mg XELODA	31	7203			
	2000 mg capecitabine pediatric film-coated tablets	31	6475	0.8991	0.8148	0.9920
t_{max} [a] (h)	2000 mg XELODA	31	2.00			
	2000 mg capecitabine pediatric film-coated tablets	31	0.67	-1.00	-1.35	-0.33

$AUC_{0-\infty}$ = area under the plasma concentration time curve extrapolated to infinity;
C_{max} = maximum observed plasma concentration; CI = confidence interval; N = number of subjects;
t_{max} = time of the maximum observed plasma concentration.
[a] Medians, median difference, and approximate 90% CI for the difference presented.

Table 3, Clinical Overview

Figure 3. Plasma concentration of 5'-FDUR following administration of Xeloda and the pediatric formulation



Filled circles = 2000-mg XELODA tablets; open circles = 2000-mg capecitabine film-coated tablets

Figure 5, Clinical Summary

Table 6. Exposure (geometric mean (CV%)) following the administration of Xeloda and the pediatric formulation

Capecitabine

	Treatment	
Parameter	**2000 mg Xeloda (N = 31)**	**2000 mg capecitabine RDT (N = 31)**
$AUC_{0\text{-tlast}}$ (ng.h/mL)	4720 (55.1)	5230 (40.2)
$AUC_{0\text{-}\infty}$[a] (ng.h/mL)	4790 (55.9)	5350 (40.1)
C_{max} (ng/mL)	3490 (81.6)	5130 (58.9)
t_{max}[b] (h)	2 (0.33-3.1)	0.33 (0.33-1)
$t_{1/2}$[a] (h)	0.43 (33.8)	0.48 (33.8)

5'-DFCR

	Treatment	
Parameter	**2000 mg Xeloda (N = 31)**	**2000 mg capecitabine RDT (N = 31)**
$AUC_{0\text{-tlast}}$ (ng.h/mL)	10800 (29.5)	10700 (26.4)
$AUC_{0\text{-}\infty}$[a] (ng.h/mL)	10800 (29.2)	10700 (26.3)
C_{max} (ng/mL)	5560 (40.7)	5350 (35.3)
t_{max}[b] (h)	2 (0.67-3.1)	0.67 (0.33-2)
$t_{1/2}$[a] (h)	0.69 (10.8)	0.67 (13.0)

5'-FU

	Treatment	
Parameter	**2000 mg Xeloda (N = 31)**	**2000 mg capecitabine RDT (N = 31)**
$AUC_{0\text{-tlast}}$ (ng.h/mL)	428 (36.6)	417 (29.8)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	433 (36.7)	421 (29.7)
C_{max} (ng/mL)	256 (59.5)	229 (42.4)
t_{max}[a] (h)	2 (0.67-3.1)	0.67 (0.33-2)
$t_{1/2}$ (h)	0.63 (22.5)	0.63 (18.7)

FBAL

	Treatment	
Parameter	**2000 mg Xeloda (N = 31)**	**2000 mg capecitabine RDT (N = 31)**
$AUC_{0\text{-tlast}}$ (ng.h/mL)	17100 (31.2)	17900 (33.6)
C_{max} (ng/mL)	5010 (29.4)	4660 (33.3)
t_{max}[a] (h)	3 (2-5.08)	2 (2-4)

Clinical Study Report

Modeling and Simulation

Roche compared the pediatric PK parameters and exposure estimates with the values predicted in an adult population at the capecitabine dose levels tested in Study NO18517. The expected exposure in adults was computed from simulations using the same formula as described above for the pediatric population, without any parameter scaling for the pediatric population. Roche states that the pediatric individual PK parameters appear to be comparable with those of adults,

except the AUC which is below the expected exposure for an adult population at the same dose level. The modeling and simulation was only briefly described in this submission. As the relative bioavailability study demonstrates similar exposure with the pediatric tablets, the modeling and simulation was not further evaluated.

Effect of food on the bioavailability

As stated in the labeling, food decreases the rate and extent of absorption and reduces exposure to the subsequent metabolite 5-FU. Consistent with the recommendation for adult dosing, the pediatric tablets were administered 30 minutes within a standard meal in the clinical studies; although the effect of food is dependent on the formulation, the relative bioavailability of capecitabine and its metabolites based on AUC_{inf} were similar when the pediatric tablets or commercial tablets were administered with food.

2.6 ANALYTICAL SECTION

Analyte selection

Capecitabine and four metabolites were measured as these metabolites lead to the active metabolite 5'-FU.

Plasma concentrations of capecitabine and its metabolites (5'-DFCR, 5'-DFUR, FU and FBAL) were determined using atmospheric pressure chemical ionization [APCI] liquid chromatography−tandem mass spectrometry [LC/MS/MS] or turbo ion spray LC/MS/MS.

Bioanalytical methods

Table 7 lists the bioanalytical methods used to measure capecitabine or metabolites for the studies included in this submission. The analytical methods appear to be reasonably well validated, suggesting the concentration data supporting the PK analyses are reliable.

Table 7. Bioanalytical methods

Study	Methods Report	Analyte	Method
NO18517	1023657	5-FU, FBAL	APCI or Turbo Ion Spray LC/MS/MS
	1023658	Capecitabine, 5'-DFCR, 5'-DFUR	Turbo Ion Spray LC/MS/MS
	1023659	Capecitabine 5-FU, FBAL, 5'-DFCR, 5'-DFUR	APCI or Turbo Ion Spray LC/MS/MS
	1055639	5-FU	APCI LC/MS/MS
NO21125 BP27931	1055537	Capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, FBAL	Turbo Ion Spray LC/MS/MS

Standard curve

Table 8 lists the standard curve used for the various analytes. The curves appear to reasonably describe the maximal concentrations observed in the patients enrolled into the different studies. Linear regression with $1/x^2$ weighting was used for capecitabine, 5'-DFCR, 5'-DFUR, and 5-FU, in human plasma for all methods. Linear (methods1023657, 1023659) or quadratic regression (1055537) with $1/x^2$ weighting was used for FBAL.

Table 8. Range of standard curves for the different analytes		
	Study NO18517	Study NO21125 Study BP27931
Capecitabine 5'-DFCR	10-5000 ng/mL	10-5000 ng/mL
5'-DFUR	50-25000 ng/mL	50-25000 ng/mL
5'-FU	2-1000 ng/mL	2-1000 ng/mL
FBAL	15-7500 ng/mL	15-7500 ng/mL

Lower and upper limits of quantification

Table 9 lists the lower limit of quantification for each analyte. The upper limit of quantification was the highest concentration included in the standard curve.

Table 9. Lower limit of quantification for the different analytes		
	Study NO18517	Study NO21125 Study BP27931
Capecitabine	10 ng/mL	10 ng/mL
5'-DFCR	10 ng/mL	10 ng/mL
5'-DFUR	50 ng/mL	50 ng/mL
5'-FU	2 ng/mL	2 ng/mL
FBAL	15 ng/mL	15 ng/mL

Accuracy, precision and selectivity

Table 10 lists the precision and accuracy for the analytical runs for the 3 studies included in this submission. The accuracy and precision is consistent with the draft guidance document entitled, "*Bioanalytical Method Validation*". Therefore, the plasma concentrations as estimated to determine the PK parameters appear reliable.

Table 10. Accuracy and precision				
	Study NO18517		Study NO21125 Study BP27931	
	Precision	Accuracy	Precision	Accuracy
Capecitabine	2.9%−4.2%	−2.5 to 4.3%	1.6%−3.1%	−0.3 to 2.3%
5'-DFCR	2.1%−4.7%	−2.8 to 3.3%	2.2%−5.8%	−2.3 to 0.8%
5'-DFUR	3.2%−7.8%	−1.0 to 2.0%	3.1%−5.9%	−2.5 to −0.7%
5-FU	3.1%−7.8%	−4.9 to −1.7%	4.3%−8.4%	0.5 to 4.6%
FBAL	2.9%−10.7%	−1.7 to 5.1%	6.2%−8.2%	−0.3 to 4.2%

Sample stability

Method 1023657

- In human plasma at room temperature, 5-FU is stable for up to 4 hrs and FBAL is stable for up to 24 hrs. 5-FU and FBAL are stable in human plasma prepared in an ice bath and stored at 4°C for up to 24 hrs.
- 5-FU and FBAL was stable for up to three freeze/thaw cycles.
- The report referenced a long-term stability report of June 29, 2004 for capecitabine and its metabolites, including stability of 5-FU and FBAL in human plasma at -70° C and of these analytes in stock and working solutions.

Method 1023658

- In human plasma at room temperature, capecitabine and 5'-FDUR are stable and 5'-DFCR is stable for up to 4 hrs.
- Capecitabine, 5'-DFCR, and 5'-DFUR are stable in human plasma for up to 24 hrs at 4°C.
- Capecitabine, 5'-DFCR, and 5'-DFUR are stable in human plasma for up to three freeze/thaw cycles.
- The report referenced a long-term stability report of June 29, 2004 for capecitabine and its metabolites, including stability of 5-FU and FBAL in human plasma at -70°C and of these analytes in stock and working solutions.

Methods 1023659 and 1055639

- No stability data was provided in the report.

Method 1055537

- The stability of the analytes in processed human plasma samples was determined by processing the QC samples in replicates of six and storing the extracts at room temperature. After storage, fresh standard curves were prepared and extracted along with run acceptance QC samples. The processed, stored samples were then injected with this analytical run. The processed sample stability for capecitabine, 5'-DFCR, 5-FU, and FBAL was acceptable after 161 hrs and after 22 hrs for 5'-DFUR.
- Capecitabine, 5'-DFUR, 5-FU, and FBAL were stable after standing for 24 hrs at room temperature, but 5'-DFCR was stable for only up to 4 hrs standing at room temperature.
- Capecitabine, 5'-DFUR, 5'-DFUR, 5-FU, and FBAL were stable after being subjected to five freeze/thaw cycles at –70°C.
- Capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, and FBAL were stable in whole blood samples after storage for one hour at room temperature and after storage for one hour in an ice bath.
- The analytes were stable in stock and working solutions stored for 24 hrs at room temperature.

QC sample plan

Most reports specified that run acceptance QC samples were analyzed with each validation run that required a calibration curve. Some reports indicated that 3 QCs were assayed in replicates of six.

3 DETAILED LABELING RECOMMENDATIONS

Roche only proposes labeling changes to section 8.4 Pediatrics.

Roche Proposed Labeling	FDA Proposed Labeling
(b) (4)	The safety and effectiveness of XELODA in pediatric patients have not been established. (b) (4) In both trials, pediatric patients received an investigational pediatric formulation of capecitabine concomitantly with and following completion of radiation therapy (total dose of 5580 cGy in 180 cGy fractions). The relative bioavailability of the investigational formulation to XELODA was similar. The first trial was conducted in 22 pediatric patients (median age 8 years, range 5-17 years) with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas and high grade gliomas. In the dose-finding portion of the trial, patients received capecitabine with concomitant radiation therapy at doses ranging from (b) (4) mg/m^2 to 850 mg/m^2 every 12 hours for up to 9 weeks. After a 2 week break, patients received 1250 mg/m^2 capecitabine every 12 hours on Days 1-14 of a 21-day cycle for up to 3 cycles. The maximum tolerated dose of capecitabine administered concomitantly with radiation therapy was 650 mg/m^2 every 12 hours. The major dose limiting toxicities were palmar-plantar erythrodysesthesia and alanine aminotransferase (ALT) elevation. The second trial was conducted in 34 additional pediatric patients with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas (median age 7 years, range 3-16 years) and 10 pediatric patients who received the maximum tolerated dose of capecitabine identified in the dose-finding trial who met the eligibility criteria for this trial. All patients received 650 mg/m^2 capecitabine every 12 hours with concomitant radiation therapy for up to 9 weeks. After a 2 week break, patients received 1250 mg/m^2 capecitabine every 12 hours on Days 1-14 of a 21-day cycle for up to 3 cycles.

(b) (4)	There was no improvement in one-year progression-free survival rate and one-year overall survival rate in pediatric patients with newly diagnosed intrinsic brainstem gliomas who received capecitabine relative to a similar population of pediatric patients who participated in other clinical trials. The adverse reaction profile of capecitabine was consistent with the known adverse reaction profile in adults, with the exception of laboratory (b) (4) which occurred more commonly in pediatric patients. The most common laboratory (b) (4) (per-patient incidence ≥40%) were increased alanine aminotransferase (75%), lymphocytopenia (73%), leukopenia (b) (4); thrombocytopenia (57%), hypoalbuminemia (b) (4) and hypokalemia (b) (4).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY S SHORD
11/04/2013

HONG ZHAO
11/04/2013
I concur.