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; CLi/F (where $i = 1,2,3$) = respective oral drug clearances.
To simplify notation, CLi instead of CLi/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

	$AUC_{SS0-12hr}$ ($\mu g \cdot hr/mL$)			C_{max} ($\mu g/mL$)		
	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 ≥ 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   (b) (4)

                                                    The dissolution data shows that   (b) (4) 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 (b) (4) within (b) (4) minutes. For the 500-mg tablets, the average percent dissolved is (b) (4) within (b) (4) minutes. Both commercial tablets   (b) (4)   dissolved   (b) (4) 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
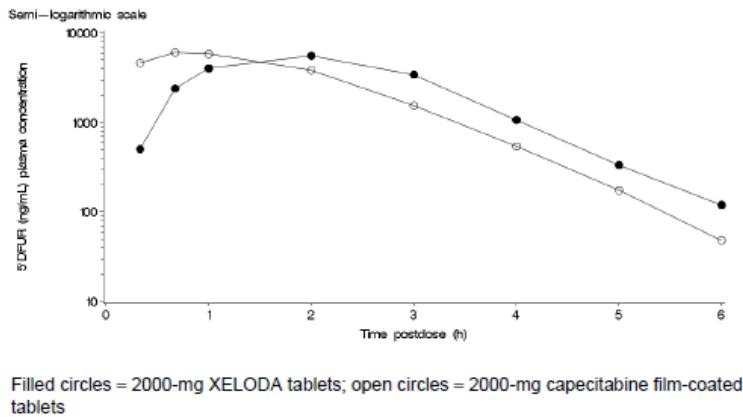

Filled circles = 2000-mg XELODA tablets; open circles = 2000-mg capecitabine film-coated tablets

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.

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).

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/s/

STACY S SHORD
11/04/2013

HONG ZHAO
11/04/2013
I concur.