Clinical Pharmacology NDA Review	
NDA/Supplement No.	NDA 21743/Supplement 21
Type/Category	Efficacy supplement; Standard
Brand Name	TARCEVA
Generic Name	Erlotinib
Receipt Date	October 27, 2014
PDUFA Date	April 27, 2015
Approved Indications	• NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations • NSCLC whose disease has not progressed after four cycles of platinum-based chemotherapy • NSCLC after failure of at least one prior chemotherapy regimen • Pancreatic cancer in combination with gemcitabine
Dosage Form	25, 100, and 150 mg tablets
Route of Administration	Oral
Approved Dosing Regimen and Strength	• NSCLC: 150 mg orally, on an empty stomach, once daily • Pancreatic cancer: 100 mg orally, on an empty stomach, once daily
Applicant	OSI Pharmaceuticals, LLC
OND Division	Division of Oncology Products 2 (DOP2)
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
OCP Reviewers	Ruby Leong, Pharm.D. (DCPV), Hongshan Li, Ph.D. (DPM)
OCP Team Leaders	Hong Zhao, Ph.D. (DCPV), Qi Liu, Ph.D. (DCPV), Liang Zhao, Ph.D. (DPM)

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1 EXECUTIVE SUMMARY

TARCEVA (erlotinib) is a kinase inhibitor indicated for multiple oncology indications including non-small cell lung cancer (NSCLC) and pancreatic cancer. The recommended dosing regimen for NSCLC in adults is 150 mg once daily (QD) and for pancreatic cancer is 100 mg QD, taken orally on an empty stomach.

A Pediatric Written Request (PWR) for erlotinib was issued on May 7, 2010. The PWR specified submission of information from pharmacokinetic (PK) studies in pediatric patients with cancer and a 1:1 randomized trial of erlotinib versus etoposide in pediatric patients with recurrent ependymoma. The current pediatrics supplement contains the published literature articles for three Investigator PK and safety studies (**1**-**3**), final study reports for the randomized trial of erlotinib versus etoposide (Study OSI-774-205, PETEY) and a single arm trial (Study OSI-774-206), as well as population PK and exposure-response (E-R) analyses based on data from Study OSI-774-205 and the three Investigator studies.

The recommended Phase 2 dose (RP2D) was determined to be 85 mg/m^2 QD in pediatric patients based on the maximum tolerated dose (MTD) observed in the Jakacki study (**1**). Enrollment in the 1:1 randomized trial of erlotinib versus etoposide (Study OSI-774-205) was discontinued due to futility criteria being met at the second interim analysis for lack of efficacy of erlotinib. Twenty-five pediatric patients ranging from 3 to 20 years of age with recurrent ependymoma were enrolled (13 patients in the erlotinib arm received erlotinib 85 mg/m^2 QD orally as tablets

crushed in applesauce and 12 patients in the etoposide arm received etoposide 50 mg/m^2 QD orally for 21 days followed by a 7-day rest). All patients in the erlotinib arm experienced progressive disease.

1.2 RECOMMENDATIONS

This efficacy supplement fulfills the clinical pharmacology components of the PWR as summarized in the table below. For labeling recommendations regarding use of erlotinib in pediatric patients, please refer to **Section 3**.

Pediatric Written Request (PWR) Component	Sufficiently Supported?	Relevant Language in PWR
Pharmacokinetics	☒ Yes ☐ No Refer to **Sections 2.2.4**, **2.2.5**, **2.3.1**	Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Available Phase 1 data and the data from the Phase 2 trial must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness. The pharmacokinetic studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for erlotinib in each of the age groups (1-6, 7-16 years old).
Relative bioavailability	☒ Yes ☐ No Refer to **Section 2.5.2**	Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

1.3 PHASE 4 REQUIREMENTS AND COMMITMENTS

There are no clinical pharmacology requested postmarketing requirements (PMRs) or postmarketing commitments (PMCs).

Signatures:

Reviewer: Ruby Leong, Pharm.D. Division of Clinical Pharmacology V	Team Leaders: Hong Zhao, Ph.D., Qi Liu, Ph.D. Division of Clinical Pharmacology V
Reviewer: Hongshan Li, Ph.D. Division of Pharmacometrics	Team Leader: Liang Zhao, Ph.D. Division of Pharmacometrics

Cc: DOP2: RPM - K Boyd; MTL - S Demko; MO - A Barone
DCPV: DDD - B Booth; DD - NA Rahman

1.4 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Dose Selection: Three Investigator (Jakacki, Geoerger, Broniscer) studies have been conducted to determine the MTD/RP2D (maximum tolerated dose/recommended Phase 2 dose) of erlotinib in pediatric patients (**1**-**3**). The RP2D of erlotinib for Study OSI-774-205 was determined based on the MTD observed in the Jakacki study. In the Jakacki study, the MTD of erlotinib as a single agent in recurrent or refractory solid tumors was determined to be 85 mg/m^2 QD using an oral solution; the MTD of erlotinib in combination with temozolomide (TMZ) was determined to be 85 mg/m^2 using the tablet formulation (**1**). The Investigator suggested that the exposures of erlotinib following administration of 85 mg/m^2 as an oral solution (n=13) and as the tablet formulation (n=12) were similar. In the Geoerger study, the MTD of erlotinib as a single agent or in combination with radiotherapy was determined to be 125 mg/m^2 QD in pediatric patients with brain tumors (**2**). In the Broniscer study, the MTD was determined to be 120 mg/m^2 QD in pediatric patients with newly diagnosed high-grade glioma who did not require enzyme-inducing antiepileptic drugs (EIAEDs) (**3**).

Relative Bioavailability: A relative bioavailability study comparing the oral solution to the tablet formulation was not conducted. Population pharmacokinetic (PK) analyses including data from Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies indicated that exposure with the tablet formulation (either crushed in applesauce [n=13] or administered whole [n=79]) was 44% lower than that with the oral solution (n=13). One plausible reason for the different MTDs of 85 mg/m^2 in the Jakacki study that utilized the oral solution and 125 mg/m^2 and 120 mg/m^2 in the Geoerger and Broniscer studies, respectively, that utilized the tablet formulation could be related to the difference in exposures with the tablet formulation versus oral solution.

Exposure-Response: Exposure-response (E-R) analyses for efficacy or activity to support the clinical importance of lower exposure with the tablet formulation as compared to the oral solution based on population PK analysis were not conducted given the lack of responses in patients treated with erlotinib in Study OSI-774-205. E-R relationships were observed between AUC and the incidence of rash and diarrhea, which were consistent with those seen in adults.

Population PK: Population PK analysis was conducted using data from 105 patients of 2 to 21 years of age enrolled in Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies. The 95% CI for the geometric mean estimates of clearance and volume of distribution for erlotinib in each of the age groups (1 to 6 and 7 to 16 years of age) fell within the predefined range of 60% and 140% of the point estimate. Body surface area (BSA)-based dosing appeared to be appropriate for achieving similar erlotinib exposures across 2 to 21 years of age. Post-hoc Bayesian estimates across three age groups (2 to 6 years [n=29], 7 to 16 years [n=59], 17 to 21 years [n=17]) showed comparable apparent clearance normalized by body surface area (CL/F/BSA).

2 QUESTION-BASED REVIEW

For brevity, only QBR questions related to the current submission are addressed below. For additional details, please refer to the original NDA 21-743 submission (SDN 15, receipt date of 07/30/2004) and the corresponding clinical pharmacology review in DAARTS (DARRTS date 10/01/2004).

PERTINENT REGULATORY HISTORY

- Pediatric study requirements under the Pediatric Research Equity Act (PREA) have been waived for the use of erlotinib tablets in the following indications:
  - Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (original NDA 21-743, 11/18/2004).
  - First-line, locally advanced, unresectable or metastatic pancreatic cancer in combination with gemcitabine (supplemental NDA [sNDA] 21-743/Supplement 3, 11/2/2005).
  - Maintenance treatment, locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy (sNDA 21-743/Supplement 16, 4/16/2010).
  - First-line, metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (sNDA 21-743/Supplement 18, 5/14/2013).
- Pediatric Written Request (PWR) for recurrent ependymoma issued on 5/7/2010 under IND 53,728.
- (b) (4)
- A revised PWR was issued on 6/23/2014 to extend the due date from 6/30/2014 to 12/31/2014 for submission of study reports to meet the terms of the PWR.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Erlotinib is currently marketed as 25, 100, and 150 mg tablets. According to the clinical pharmacology review of the original NDA, erlotinib is a Biopharmaceutics Classification System (BCS) Class 2 compound (low solubility, high permeability).

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 lists the clinical studies included in the application.

Table 1. Summary of Clinical Studies

Study Number	Study Design	Study Population	Assessments	Dosing regimen
Jakacki (1)	Open label, dose escalation of erlotinib as a single agent in the first cycle, followed by erlotinib plus TMZ in subsequent cycles	Patients < 22 years of age with recurrent or refractory CNS tumor, osteogenic sarcoma, rhabdomyosarcoma, soft tissue sarcoma, neuroblastoma or germ cell tumor (n=46)	MTD, PK, safety, antitumor activity, tumor biomarkers	First cycle: Erlotinib 35, 50, 65, 85, 110 mg/m^2 QD for 28 days Second cycle and beyond: Erlotinib 35, 50, 65, 85, 110 mg/m^2 QD plus TMZ 180 mg/m^2 (and if tolerated 200 mg/m^2 in subsequent cycles) QD for 5 days in 28-day cycles
Geoerger (2)	Open label, dose escalation (Group 1) 3+3 of erlotinib as a single agent (Group 2) continual reassessment method of erlotinib plus radiotherapy	Patients 1-21 years of age with (Group 1) brain tumors refractory to or relapsing after first-line therapy (n=30) (Group 2) newly diagnosed brainstem glioma [excluding pilocytic glioma] (n=21)	RD, safety, PK, antitumor activity, tumor biomarkers	Group 1: Erlotinib 75, 100, 125, 150 mg/m^2 QD in 21-day cycles Group 2: Erlotinib 75, 100, 125, 150 mg/m^2 QD in 21-day cycles plus radiation
Broniscer (3)	Open label, 3+3 dose escalation, erlotinib with radiotherapy	Patients 3-25 years of age with newly diagnosed high-grade glioma (n=23)	MTD, PK, antitumor activity	Erlotinib 70, 90, 120, 160 and 200 mg/m^2 QD with radiation
OSI-774-205 (PETEY)	Randomized (1:1) erlotinib vs. etoposide	Patients 1-21 years of age with recurrent or refractory ependymoma or subependymoma (n=13 in erlotinib arm, n=12 in etoposide arm)	ORR, DOR, MRR, DCR, PFS, rate of prolonged SD, duration of SD, OS, safety, PK, correlation of biomarkers with clinical outcomes	Erlotinib 85 mg/m^2 (or a maximum dose of 150 mg) QD in 28-day cycles Etoposide 50 mg/m^2 QD for 21 days followed by a 7-day rest in 28-day cycles
OSI-774-206	Open label, single arm	Patients 1-21 years of age with recurrent or refractory ependymoma previously treated with oral etoposide in Study OSI-774-205 (n=4)	Safety, ORR, treatment duration	Erlotinib 85 mg/m^2 (or a maximum dose of 150 mg) QD in 28-day cycles

DCR: Disease control rate; DOR: Duration of response; MRR: Minor response rate; MTD: Maximum tolerated dose; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetics; QD: Once daily; RD: Recommended dose; SD: Stable disease; TMZ: Temozolomide

In addition, erlotinib plasma concentration data from Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies were used for the population PK and exposure-response (E-R) analyses to fulfill the clinical pharmacology components as stated in the PWR:

> Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Available Phase 1 data and the data from the Phase 2 trial must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness. The pharmacokinetic studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for erlotinib in each of the age groups (1-6, 7-16 years old).

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy outcome measure of Study OSI-774-205 was objective response rate (ORR) according to the International Society of Pediatric Oncology Brain, Tumor Subcommittee for the Reporting of Trials criteria. Disease progression occurred in all patients (13 of 13) in the erlotinib arm and in 67% of patients (8 of 12) in the etoposide arm. In the Jakacki study of erlotinib in pediatric patients with solid tumors, no responses were observed in four patients with ependymoma (**1**). In the Geoerger study, no responses were observed in 7 patients with ependymoma (**2**).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes. Erlotinib and its metabolite (OSI-420) were appropriately identified and measured to assess PK parameters (refer to **Section 2.6**). The metabolite to parent $AUC_{0-\tau}$ ratio was approximately 10% in pediatric patients as consistent with that observed in adults. The in vitro activities of erlotinib and OSI-420 are shown in **Table 2**.

Table 2. In Vitro Activities of Erlotinib and OSI-420

	Inhibition of EGFR Tyrosine Kinase Activity: IC50 (nM)	Inhibition of Cellular EGFR Tyrosine Kinase Activity: IC50 (nM)
erlotinib	2	20
OSI-420	2.5	14

Source: Original NDA Clinical Pharmacology Review DARRTS date 10/01/2004, Table 25, Page 56.

2.2.4 Exposure-response

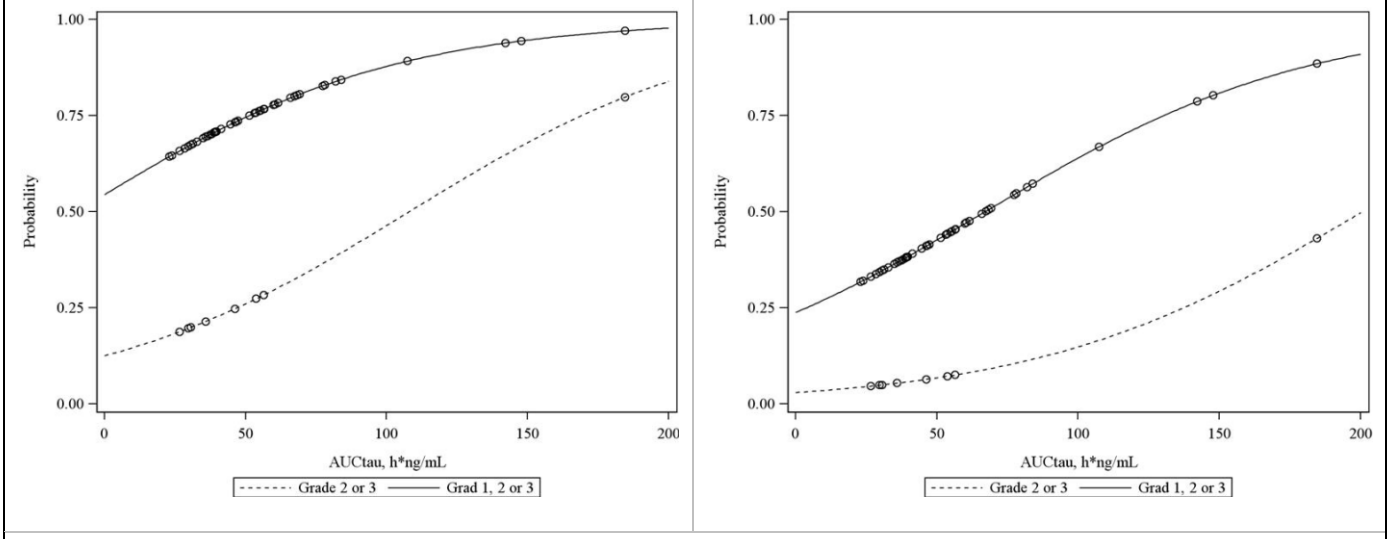
2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

Given that responses were not observed in patients treated with erlotinib in Study OSI-774-205, the planned E-R analysis for activity/efficacy was not conducted.

2.2.4.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

E-R analyses were conducted for selected adverse events including rash and diarrhea using a logistic regression model. The Pharmacometrics review concluded that an E-R relationship was observed between AUC_{tau} and the incidence of rash (p = 0.02, odds ratio of 1.6 [95% CI: 1.1, 2.3] for a 25 ng·h/mL increase in AUC_{tau}) and diarrhea (p = 0.02, odds ratio of 1.5 [95% CI: 1.1, 2.2] for a 25 ng·h/mL increase in AUC_{tau}) (**Figure 1**). These observed relationships for an increase in incidence of rash and diarrhea with increasing AUC in pediatric patients were consistent with that seen in adults (refer to clinical pharmacology review of original NDA, DARRTS date 10/01/2004).

Figure 1. Relationship Between AUC_{tau} and Rash (Left) and Diarrhea (Right) in Pediatric Patients with Recurrent Ependymoma



In the left figure, Grade 2 and 3 rash were combined because only one patient had Grade 3 rash. In the right figure, Grade 2 and 3 diarrhea were combined because only one patient had Grade 3 diarrhea.

Source: Report 5901-PK-001, Figures 42 and 44.

2.2.4.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

Three Investigator (Jakacki, Geoerger, Broniscer) studies have been conducted to determine the MTD/RP2D of erlotinib in pediatric patients (**1**-**3**). In the Jakacki study, the MTD of erlotinib as

a single agent in recurrent or refractory solid tumors was determined to be 85 mg/m^2 QD (similar to the adult recommended dose of 150 mg/day) using an oral solution; the MTD of erlotinib in combination with TMZ was determined to be 85 mg/m^2 using the tablet formulation (**1**). The Investigator suggested that the exposures of erlotinib 85 mg/m^2 following administration as an oral solution (n=13) and the tablet formulation (n=12) were similar (dose normalized $AUC_{0-\tau}$ was not statistically different for the two formulations, Wilcoxon rank sum p-value=0.9) (**1**). In the Geoerger study, the MTD of erlotinib as a single agent or in combination with radiotherapy was determined to be 125 mg/m^2 QD in pediatric patients with brain tumors, which was higher than the MTD of 150-200 mg/day in adult patients with glioblastoma/malignant glioma who received erlotinib as a single agent or in combination with radiotherapy or chemotherapy (**2**)**.** In the Broniscer study, the MTD was determined to be 120 mg/m^2 QD in pediatric patients with newly diagnosed high-grade glioma who did not require EIAEDs, which was higher than the adult recommended dose of 150 mg/day but similar to the MTD established in adult patients with recurrent high-grade glioma who did not receive EIAEDs (**3**)**.**

The RP2D for Study OSI-774-205 was determined to be 85 mg/m^2 QD based on the MTD observed in the Jakacki study (**1**). A relative bioavailability study comparing the oral solution to the tablet formulation was not conducted. Population PK analyses including data from Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies indicated that exposure with the tablet formulation (either crushed in applesauce [n=13] or administered whole [n=79]) was 44% lower than that with the oral solution (n=13) (refer to Section **2.5.2**). One plausible reason for the different MTDs of 85 mg/m^2 in the Jakacki study that utilized the oral solution and 125 mg/m^2 and 120 mg/m^2 in the Geoerger and Broniscer studies, respectively, that utilized the tablet formulation could be related to the difference in exposures with the tablet formulation versus oral solution (refer to Section **2.5.2**). E-R analyses for efficacy or activity to confirm the clinical importance of these population PK results were not conducted given the lack of responses in patients treated with erlotinib in Study OSI-774-205.

Other factors that may provide an explanation for the different MTDs include different patient populations (previously treated versus treatment naïve and various tumor histology). A study has suggested that erlotinib is able to cross the blood-brain barrier with cerebrospinal fluid (CSF) penetration of 7% for erlotinib and 9% for its metabolite OSI-420 (**4**); however, CSF samples were not collected in Study OSI-774-205 and the Investigator studies to determine if adequate erlotinib CSF concentrations were reached.

The Pharmacometrics review concluded that BSA-based dosing appeared to be appropriate for achieving similar erlotinib exposures across 2 to 21 years of age. The Jakacki study indicated that there were no correlations between age and the apparent clearance (CL/F) or dose-normalized C_{max} of erlotinib when the dose was accounted for on a mg/m^2 basis. When BSA was not taken into account, erlotinib CL/F showed a significant correlation with age ($p = 0.003$), body weight ($p = 0.002$), and BSA ($p = 0.004$) (**1**). The Geoerger study indicated a significant correlation between erlotinib CL/F and body weight and BSA (**2**).

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

The PK of erlotinib and its metabolite (OSI-420) in pediatric patients were characterized in Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies. **Table 3** shows a summary of the PK sampling plan.

Table 3. Summary of PK Sampling Plan in Study OSI-774-205 and Investigator Studies

Study	PK Sampling Time Points
Jakacki (**1**)	• Day 1: Pre-dose, 0.5, 1, 2, 4, 6, 7, 10-12, 24, 26, 30, 48 and 50 hours post-dose • Day 10 of single agent erlotinib and Day 5 of erlotinib in combination with TMZ: Pre-dose, 0.5, 1, 2, 4, 6, 7, 10-12, 24 and 26 hours post-dose
Geoerger (**2**)	• Steady-state (at various times during the first 6 cycles): Pre-dose, 30 minutes, 1, 2, 4, 6, 8, and 24 hours post-dose in the first and second cycles (Group 1) or the third cycle (Group 2) and 24 hours post-dose for subsequent cycles
Broniscer (**3**)	• Day 1: Pre-dose, and 1, 2, 4, 8, 24 (± 2), 30 (± 4) and 48 (± 4) hours post-dose • Day 8: Pre-dose, and 1, 2, 4, 8, and 24 (± 2) hours post-dose
OSI-774-205 (PETEY)	• Day 14: Pre-dose, 0.5-1.5, 2-3 and 4-8 hours post-dose

Single dose PK parameters of erlotinib administered as an oral solution and steady-state PK parameters of erlotinib administered as the tablet formulation from the Jakacki study are summarized in **Table 4**. Steady-state PK parameters of erlotinib and its metabolite OSI-420 from the Geoerger study are summarized in **Table 5**. Single dose and steady-state (day 8) PK parameters of erlotinib and its metabolite OSI-420 from the Broniscer study are shown in **Table 6**.

Table 4. Single Dose and Steady-State PK Parameters* of Erlotinib (Jakacki Study)

Dose	Age (years)	T_{max} (hours)	C_{max} (μg/mL)	$AUC_{0-\tau}$ (μg · hr/mL)	CL_{ss}/F (L/h/m^2)	$T_{\phi\lambda z}$ (hours)
Solution						
35 mg/m^2/d (n = 3)						(n = 2)
Minimum	5.9	0.5	1.26	6.10	2.71	2.62
Median	8.8	0.5	1.32	9.51	4.22	8.05
Maximum	9.6	2.0	1.63	12.9	5.74	13.5
50 mg/m^2/d (n = 2)						(n = 1)
Minimum	10.9	0.5	1.84	18.5	2.08	8.67
Median	15.5	0.7	1.89	21.3	2.39	8.67
Maximum	20.1	1.0	1.94	24.1	2.70	8.67
65 mg/m^2/d (n = 2)						(n = 2)
Minimum	3.2	0.5	2.81	14.1	1.58	5.94
Median	3.6	0.5	3.93	27.6	3.09	6.65
Maximum	4.0	0.6	5.05	41.2	4.61	7.36
85 mg/m^2/d (n = 4)						(n = 4)
Minimum	5.8	0.5	2.19	18.3	3.04	3.58
Median	12.0	0.7	2.67	23.3	3.65	9.75
Maximum	20.1	1.0	3.30	27.9	4.64	10.3
Tablet						
85 mg/m^2/d (n = 12)						
Minimum	5.5	1.0	1.03	7.79	1.94	NA
Median	14.7	2.0	2.02	30.4	2.80	NA
Maximum	20.5	8.0	5.20	43.8	10.9	NA

Abbreviations: T_{max}, time to maximum serum concentration; C_{max}, maximum serum concentration; $AUC_{0-\tau}$, area under the concentration-time curve over the dosing interval; CL_{ss}/F, apparent clearance at steady state; $T_{\phi\lambda z}$, Terminal half-life from single-dose data (n); NA, not applicable because single-dose data not captured for the tablet formulation.

* PK parameters were determined by noncompartmental analysis using WinNonlin version 4.1. The first dose of erlotinib was administered as an oral solution and subsequent doses were administered as the tablet formulation.
Source: Jakacki et al. (PMID: 18794549), Table 4.

Table 5. Steady-State PK Parameters of Erlotinib and Metabolite OSI-420 (Geoerger Study)

Erlotinib dose level (mg/m^2)	Cycle *n* (mean [95% CI])	Erlotinib AUC_{0-24} (mg h/L) (mean [95% CI])	Erlotinib CL/F (L/h) (mean [95% CI])	Erlotinib Vd/F (L) (mean [95% CI])	OSI-420 $AUCm_{0-24}$ (mg h/L) (mean [95% CI])	OSI-420 CL/fm (L/h) (mean [95% CI])	OSI-420 Vd/fm (L) (mean [95% CI])
75	1 ($n = 9$)	21.7 (17.2–26.3)	3.5 (3.0–4.1)	64.8 (45.9–83.8)	2.1 (1.6–2.7)	47.9 (36.8–59.0)	18.1 (14.4–21.9)
	≥2 ($n = 7$)	23.0 (14.1–31.9)	3.8 (2.5–5.1)	81.6 (45.7–117.5)	1.7 (1.2–2.2)	50.4 (34.0–56.7)	20.2 (16.8–23.6)
100	1 ($n = 8$)	26.8 (20.2–33.4)	3.9 (3.1–4.8)	85.5 (38.2–132.9)	2.8 (0.4–5.2)	45.1 (35.3–54.9)	24.3 (19.6–29.2)
	≥2 ($n = 8$)	27.5 (21.3–33.8)	3.8 (2.9–4.8)	107.9 (50.2–165.5)	2.4 (1.7–3.1)	44.9 (33.5–56.3)	21.5 (18.6–24.4)
125	1 ($n = 25$)	33.9 (25.6–42.1)	5.0 (3.7–6.4)	108.9 (85.9–132.0)	3.6 (2.8–4.4)	45.8 (36.7–54.9)	19.2 (16.7–21.8)
	≥2 ($n = 19$)	32.2 (24.6–39.8)	5.1 (3.1–7.1)	117.7 (87.2–148.2)	4.2 (2.6–5.7)	42.4 (29.7–55.0)	18.6 (15.2–21.9)
150	1 ($n = 4$)	42.4 (23.1–61.6)	3.7 (1.6–5.8)	108.3 (0–225.7)	5.2 (0–15.6)	38.8 (6.1–71.5)	13.3 (6.1–20.6)
	≥2 ($n = 4$)	40.0 (23.3–56.7)	3.9 (1.8–6.1)	123.1 (15.9–230.4)	4.1 (1.5–6.6)	41.7 (11.5–72.0)	20.0 (17.5–22.5)

Mean and 95% CI values are calculated from the post hoc parameter values (generated from individual predictions). *n*, number of patients with available data for pharmacokinetic analyses. CL/fm, apparent metabolite clearance, where fm is the fraction of erlotinib converted into OSI-420. Vd/fm, apparent metabolite volume of distribution, where fm is the fraction of erlotinib converted into OSI-420.

* PK parameters were determined by a nonlinear mixed-effects population approach using NONMEM version 1.0.
Source: Geoerger et al. (PMID: 20974795), Table 4.

Table 6. Single Dose and Steady-State PK Parameters of Erlotinib and Metabolite OSI-420 (Broniscer Study)

Dosage Level (mg/m^2)	After first dose				
	Erlotinib			OSI-420	
	C_{max} (mg/mL)	T_{max} (h)	$AUC_{0\rightarrow\infty}$ (mg·h/mL)	C_{max} (mg/mL)	$AUC_{0\rightarrow\infty}$ (mg·h/mL)
70 (*n* = 7)	1.3 (0.94-2.2)	4 (2.1-8.2)	34.9 (23.1-52.6)	0.13 (0.05-0.2)	2.1 (1.2-3.3)
90 (*n* = 2)	1.6 (1.3-1.8)	3.1 (2-4.1)	23.9 (14.4-33.3)	0.16 (0.12-0.2)	1.9 (1.4-2.3)
120 (*n* = 5)	1.2 (0.5-2)	2.2 (1-4)	27.8 (18.9-28.8)	0.14 (0.1-0.3)	2.5 (1.7-2.7)
160 (*n* = 3)	1.8 (1.3-3)	2.2 (2-2.5)	37.1 (33.1-50.6)	0.32 (0.26-0.33)	4.2 (4.1-5.2)

Day 8 of therapy				
Erlotinib			OSI-420	
C_{max} (mg/mL)	T_{max} (h)	$AUC_{0\rightarrow\infty}$ (mg·h/mL)	C_{max} (mg/mL)	$AUC_{0\rightarrow\infty}$ (mg·h/mL)
1.8 (1.7-2.8)	2.1 (1-4.1)	28.8 (21.8-30.9)	0.25 (0.2-0.6)	3.3 (2-6.9)
1.3	2.6 (1.2-4)	21.2 (18.1-24.2)	0.17	2.1 (1.7-2.4)
1.4 (1-3)	1.75 (1.3-4)	23.1 (11.8-51.2)	0.3 (0.1-0.5)	2.8 (1.9-5.9)
2 (1.3-2.4)	2.2 (1-4)	35.5 (23.7-51)	0.3	4.3 (3.8-6.1)

NOTE: Values are provided as median with range in parenthesis.
Abbreviations: C_{max}, maximal concentration; T_{max}, time for maximal concentration; $AUC_{0\rightarrow\infty}$, area under concentration time curve from zero to infinity.

* PK parameters were determined by noncompartmental methods.
Source: Broniscer et al. (PMID: 19147777), Table 3.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Population PK analysis was conducted using data from 105 pediatric patients of 2 to 21 years of age enrolled in Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies. Population PK estimates of CL/F and volume of distribution (V_d/F) were generated. The Pharmacometrics review concluded that the 95% CI for the geometric mean of CL/F and V_d/F in each age group (1 to 6 and 7 to 16 years of age) fell within the predefined range of 60% and 140% of the point estimate of the geometric mean.

Relationship between Age and Exposure

The Pharmacometrics review concluded that post-hoc Bayesian estimates across three age groups (2 to 6 years [n=29], 7 to 16 years [n=59], 17 to 21 years [n=17]) showed comparable apparent clearance normalized by body surface area (CL/F/BSA).

Relationship between Body Weight/Body Surface Area and Exposure

The Pharmacometrics review concluded that standard allometric scaling based on weight provided a good fit to the data across an age range of 2 to 21 years. BSA-based dosing appeared to be appropriate for achieving similar erlotinib exposures across 2 to 21 years of age. Other dosing methods, including weight-based dosing, were not examined.

2.4 EXTRINSIC FACTORS

2.4.2 Drug-drug interactions?

2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Erlotinib is metabolized by CYP3A4, CYP3A5, CYP1A1, and CYP1A2 and is also a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.

In Study OSI-774-205, patients were prohibited from taking strong and moderate CYP3A4 or CYP1A2 inhibitors and inducers, and proton pump inhibitors within 14 days before study entry. In the Jakacki study, patients receiving EIAEDs or CYP3A4 inducers within 4 weeks, proton pump inhibitors within 5 days, or H_2-receptor antagonists within 2 days of study entry were excluded. In the Geoerger study, EIAEDs were allowed; two patients who received EIAEDs had higher values of erlotinib CL/F (2). Dose escalation was based on patients not receiving EIAEDs or patients receiving EIAEDs who experienced dose limiting toxicity (DLT). In the Broniscer study, patients requiring use of EIAEDs were excluded. Analyses of the effect of corticosteroids on erlotinib PK have not been conducted.

In the Jakacki study, the PK of erlotinib did not appear to be affected by concomitant administration of TMZ (1).

2.5 GENERAL BIOPHARMACEUTICS

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

The RP2D of erlotinib for Study OSI-774-205 was determined to be 85 mg/m^2 QD based on the MTD of erlotinib as a single agent administered as an oral solution in recurrent or refractory solid tumors in the dose escalation phase of the Jakacki study (1). The oral solution consisted of erlotinib (10 mg/mL in 6% Captisol) and Ora-Sweet (at the same volume as erlotinib) provided in pre-filled oral syringes. Erlotinib and Ora-Sweet were mixed in a medicine cup and administered directly from the cup or the contents drawn into an oral syringe and administered. In Study OSI-774-205, erlotinib tablets were crushed and mixed with one heaped teaspoon of applesauce immediately before administration to the patient. Whole erlotinib tablets were administered in the Geoerger and Broniscer studies. In the Jakacki study, the first dose of erlotinib was administered as an oral solution and subsequent doses were administered as the tablet formulation in combination with TMZ. The Investigator suggested that the exposures of erlotinib 85 mg/m^2 following administration as an oral solution (n=13) and the tablet formulation (n=12) were similar (dose normalized $AUC_{0-\tau}$ was not statistically different for the two formulations, Wilcoxon rank sum p-value=0.9) (1).

A relative bioavailability study comparing the oral solution to the tablet formulation was not conducted. The Applicant stated that (b) (4) (b) (4) During a teleconference held with OSI Pharmaceuticals to discuss the pediatric study proposal to fulfill a PWR, FDA stated that (b) (4)

(b) (4) However, the bioavailability of any formulation used in the current protocol should be characterized. A relative bioavailability study comparing the formulation used in the current protocol to the final age appropriate formulation will need to be conducted. This bridging study may be conducted in adults. FDA also stated that PK analysis should be conducted if the formulation of crushed tablets is to be used in the current protocol. This would be needed as the PK characteristics and exposure-response relationships for the crushed tablet formulation are not known, and this could affect efficacy endpoints (meeting minutes under IND 53,728, dated 3/25/2009).

Population PK analyses including data from Study OSI-774-205 and the three Investigator (Jakacki, Geoerger, Broniscer) studies indicated that exposure with the tablet formulation (either crushed in applesauce [n=13] or administered whole [n=79]) was 44% lower than that with the oral solution (n=13). The geometric mean dose normalized AUC_{tau} determined from the individual post-hoc Bayesian estimates of the final population PK model were similar with the tablet crushed in applesauce and the tablet administered whole. One plausible reason for the different MTDs of 85 mg/m^2 in the Jakacki study that utilized the oral solution and 125 mg/m^2 and 120 mg/m^2 in the Geoerger and Broniscer studies, respectively, that utilized the tablet formulation could be related to the difference in exposures with the tablet formulation versus oral solution.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Erlotinib was taken under fasted conditions in pediatric patients as consistent with the labeling recommendation. According to the clinical pharmacology review of the original NDA, food increased erlotinib $AUC_{0\text{-}inf}$ by 2.1-fold (90% CI: 1.7, 2.6) in a single dose study and $AUC_{0\text{-}24h}$ by 1.7-fold (90% CI: 1.2, 2.3) in a multiple dose study. In Study OSI-774-205, erlotinib was taken under fasted conditions one hour before or 2 hours after meals (with the exception of one teaspoon of applesauce mixed with erlotinib crushed tablets). In the Jakacki study, erlotinib was administered at least 1 hour before or 2 hours after breakfast. The administration of erlotinib with regards to food was not specified for the Geoerger study. In the Broniscer study, erlotinib was administered one hour before or two hours after meals.

2.6 ANALYTICAL SECTION

2.6.4 What bioanalytical methods are used to assess concentrations?

In Study OSI-774-205, erlotinib and OSI-420 concentrations were measured in human plasma using a validated atmospheric pressure chemical ionization (APCI) liquid chromatography-tandem mass spectrometry (LC-MS/MS) method [Validated Report No. 090115VSMB_OBC_R1, 20 March 2012, entitled “Method Validation for the Quantitation of OSI-906 with Erlotinib (OSI-774) and its Metabolite (OSI-420) in Human Plasma by APCI LC/MS/MS”]. The lower limits of quantification (LLOQ) were 1 ng/mL for erlotinib and OSI-420. The method and its performance during sample analysis for Study OSI-774-205 met the criteria based on the 2013 draft FDA Guidance for Industry *Bioanalytical Method Validation*

(**Table 7**).

In the Jakacki study, erlotinib and OSI-420 were measured using a validated LC-MS/MS method with a LLOQ of 1.1 ng/mL for erlotinib and 1.0 ng/mL for OSI-420 (**1**). In the Geoerger study, erlotinib and OSI-420 were measured using a validated LC-MS/MS method with a calibration range of 1-3000 ng/mL for erlotinib and 1-1000 ng/mL for OSI-420 (**2**). In the Broniscer study, erlotinib and OSI-420 were measured using a validated LC-MS/MS method with a LLOQ of 10 ng/mL for erlotinib and 1 ng/mL for OSI-420 (**3**).

Table 7. Summary of Bioanalytical Method (Study OSI-774-205)

Analytes	Erlotinib, OSI-420
Matrix	Human plasma
Anticoagulant	Dipotassium ethylenediamine tetraacetic acid (K_2EDTA)
Standard curve range (ng/mL)	1-1000
Regression Type	Linear ($1/x^2$ weighting)
Calibration standards (ng/mL)	1, 2, 5, 25, 200, 600, 900, 1000
Precision (%CV)	Erlotinib: 2.0 to 4.0 OSI-420: 2.5 to 4.2
Accuracy (%RE)	Erlotinib: -1.5 to 1.4 OSI-420: -1.8 to 1.0
Quality controls (ng/mL)	3 (QC1), 500 (QC2), 800 (QC3), 25,000 (QC4, 50-fold dilution)
Precision (%CV)	Erlotinib: 2.4 to 7.7 OSI-420: 1.8 to 3.5
Accuracy (% RE)	Erlotinib: -4.9 to -3.2 OSI-420: -6.3 to -2.3
Stability*	
Bench top	24 hours at room temperature; 146 hours (erlotinib) and 68 hours (OSI-420) at ambient temperature
Long term	170 days at -70°C, 203 days at -20°C
Freeze/thaw	5 cycles at -70°C and -20°C

* Source: Advion Method No. 100318OBC906EHPL_S_V1

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Applicant's proposed labeling changes are in BLUE and modifications made by the Agency are in RED.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of TARCEVA in pediatric patients have not been established. (b) (4) [redacted]

In an open-label, multi-center trial, 25 pediatric patients (median age 14 years, range 3-20 years) with recurrent or refractory ependymoma were randomized (1:1) to TARCEVA or etoposide. Thirteen patients received TARCEVA at a dose of 85 mg/m^2/day orally until disease progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity. Four patients randomized to etoposide also received TARCEVA following disease progression. The trial was terminated prematurely for lack of efficacy; there were no objective responses observed in these 17 TARCEVA- treated patients.

(b) (4) [redacted]

No new adverse events were identified in the pediatric population. (b) (4) [redacted]

Based on the population pharmacokinetics analysis conducted in 105 pediatric patients (2 to 21 years old) with cancer, the geometric mean estimates of CL/F/BSA (apparent clearance normalized to body surface area) were comparable across the three age groups: 2-6 years (n=29), 7-16 years (n=59), and 17-21 years (n=17).

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	021743/s21
Drug Name	Tarceva® (Erlotinib)
Dose Regimen	25, 100 and 150 mg oral tablets
Indication	A kinase inhibitor indicated for 1). NSCLC (not recommended for use in combination with platinum-based chemotherapy), and 2). Locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Sponsor	Astellas Pharma US, Inc

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1 SUMMARY OF FINDINGS

The supplementary submission of erlotinib fulfilled the pediatric written request from the perspectives of population pharmacokinetics and exposure-response analyses.

1.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

1.1.1 Does the supplementary submission fulfill the pediatric written request for population pharmacokinetics analyses?

Yes, the supplementary submission of erlotinib fulfills the pediatric written request from the perspective of population pharmacokinetics (PPK). The PPK analysis was conducted based on erlotinib pharmacokinetics (PK) data of 1 Phase II study and 3 Phase I studies as summarized in **Table 1** as described below.

- Phase 2 Study OSI-774-205 was a multi-center, randomized, open-label study of single-agent erlotinib versus oral etoposide (the active control) in patients with recurrent pediatric ependymoma. Patients were randomized 1:1 to receive either oral erlotinib at 85 mg/m^2 per day continuously or oral etoposide at 50 mg/m^2 per day for 21 days followed by a 7-day rest. Patients were on study drugs until 1 of the following occurred: progression, death, patient request, investigator decision to discontinue study drug or intolerable toxicity. Sparse PK samples (4 samples around a dose) were collected at steady-state.

- Phase 1 Study Geoerger-2011 was an open-label, multicenter, dose-escalation trial of erlotinib in pediatric patients with brainstem glioma and relapsing/refractory brain tumors. There were 2 groups of patients on erlotinib tablets. Erlotinib was administered once daily at 4 dose levels (75, 100, 125 and 150 mg/m^2) in one group with conventional 3 + 3 design. While in the other group, patients received erlotinib and local brainstem radiation (54 Gy over 6 weeks; 1.8 Gy/fraction per day), with erlotinib treatment commencing within 4 hours after the initial irradiation and continuing thereafter as a single agent until disease progression. In Group 2, dose escalation decisions were based on a continual reassessment method with likelihood inference in order to allow continuous inclusion. Intensive PK samples were collected at steady-state during the first 6 cycles of therapy.

- Phase 1 Study Jakacki-2008 utilized erlotinib as a single agent and in combination with temozolomide in children with refractory solid tumors. Erlotinib was administered orally once daily (QD) to cohorts of 3 to 6 children for a single 28-day course. Patients then received the combination (erlotinib and temozolomide) QD for 5 days for all subsequent 28-day courses. An oral erlotinib solution was administered during the dose-finding phase and a tablet formulation was subsequently studied for the maximum tolerated dose

(MTD). The erlotinib dose was escalated in cohorts of 3 to 6 patients. Intensive PK samples were collected around the first dose and at steady-state (generally day 10).

- Phase 1 Study Broniscer-2009 was a single-center MTD study of erlotinib in combination with radiation therapy. A traditional 3 + 3 dose escalation scheme was used to explore the MTD. Intensive PK samples were collected.

PPK estimates of CL/F and V/F were generated for patients 1 to 6 years and 7 to 16 years of age.

- The 95% CI for the geometric mean of each age group fell within the predefined range of 60% and 140% of the point estimate of the geometric mean.
- Standard allometric scaling based on weight provided a good fit to the data across an age range of 2 to 21 years.
- ALT was not expected to be a statistically significant covariate.
- Post-hoc Bayesian estimates between pediatric age groups (2-6 and 7-17 years) and young adults (18-21 years) showed a comparable CL/F/BSA (apparent clearance normalized by body surface area) as listed in Column 5 of **Table 2**.
- BSA based dose appeared to be appropriate for achieving similar erlotinib exposures across ages 2 to 21. Other dosing methods, including weight-based dosing, were not examined.

In summary, the supplementary submission of erlotinib fulfills the pediatric written request from the PPK perspective.

1.1.2 Does the supplementary submission fulfill the pediatric written request for exposure-response analyses?

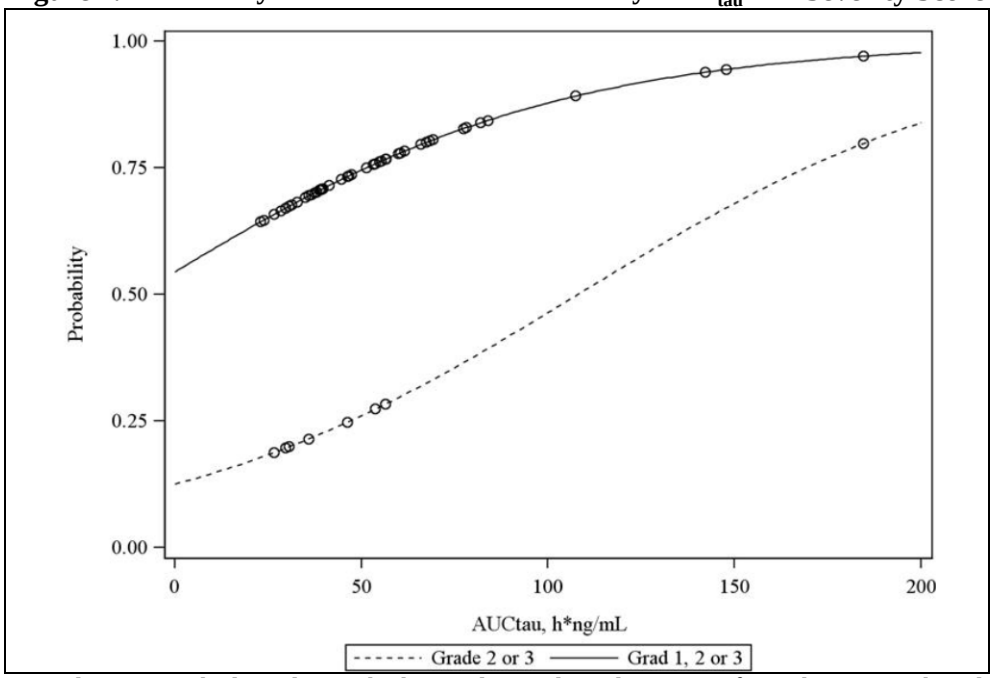
Yes, the supplementary submission of erlotinib fulfills the pediatric written request for exposure-response (ER) analyses. Exploratory analysis and logistic regression were used to examine the relationship between the occurrence of the selected AEs, rash and diarrhea, at any time during therapy and erlotinib exposures as measured by steady-state AUC_{tau}. The AUC_{tau} values were obtained from the individual post-hoc Bayesian estimates of the final PPK model. **Table 3** displays the severity grade and number of patients with rash and diarrhea across all age groups in the 4 studies as described in Section 1.1.1.

- An ER relationship was observed between AUC_{tau} and the rash probability ($p = 0.0162$), with an odds ratio of 1.567 (95% CI: 1.105, 2.337) for a 25 h·ng/mL increase in AUC_{tau} (**Figure 1**).
- An ER relationship was observed between AUC_{tau} and diarrhea probability ($p = 0.0156$), with an odds ratio of 1.544 (95% CI: 1.095, 2.194) for a 25 h·ng/mL increase in AUC_{tau}.

This relationship is likely primarily driven by patients with Grade 1 diarrhea, as Grade 2 or 3 diarrhea patients accounted for only 8 of 105 patients (**Figure 2**).

In summary, the supplementary submission of erlotinib fulfills the pediatric written request from the ER perspective.

Figure 1. Probability of the Occurrence of Rash by AUC_{tau} and Severity Score



Note: Because only 1 patient had Grade 3 rash, the Grade 2 and Grade 3 scores for rash were combined.
Source: Figure 42 of sponsor's population pharmacokinetics analysis in Page 74.

Table 1. Studies Included in the Population Pharmacokinetics Analysis						
Study	**Primary Objective**	**Treatment**	**Formulation**	**Number of Patients**	**Population**	**Sample Times**
OSI-774-205 (PETEY)	Determine the ORR of single-agent erlotinib versus oral etoposide in patients with recurrent pediatric ependymoma.	Erlotinib 85 mg/m^2 (or a maximum dose of 150 mg) once daily. Oral etoposide at 50 mg/m^2 per day for 21 days followed by a 7-day rest.	Tablet crushed in applesauce in the erlotinib arm	25 patients were randomized and 13 dosed with erlotinib 85mg/m2 per day. Note: Enrollment stopped due to futility criteria being met.	Patients had recurrent or refractory ependymoma or subependymoma and were between 1 and 21 years of age at the time of randomization/study entry Steady-state (day 14)	**Steady-state:** predose, and 0.5-1.5, 2-3 and 4-8 hrs after dose.
Jakacki 2008	To determine PK and safety/ tolerability of erlotinib alone and in combination with temozolomide in pediatric patients with recurrent or refractory solid tumors.	Dose escalation of erlotinib at 35, 50 65, 85 and 110 mg/m^2.	Oral solution or Tablet	46 enrolled 43 dosed	Patients younger than 22 years of age with a recurrent or refractory CNS tumor, osteogenic sarcoma, rhabdomyosarcoma, soft tissue sarcoma, neuroblastoma or germ cell tumor	**First dose:** Predose and 0.5, 1, 2, 4, 6, 7, 10-12, 24, 26, 30, 48 and 50 hrs after dose **Steady-state (day 10):** Predose, and 0.5, 1, 2, 4, 6, 7, 10-12, 24 and 26 hrs after dose
Broniscer 2009	To establish MTD of erlotinib administered with and after radiation therapy.	Five dosage levels were planned (70, 90, 120, 160, and 200 mg/m2 per day). A traditional 3+3 dose escalation scheme was used to estimate the MTD.	Tablet	23 enrolled 23 dosed	Patients between 3 and 25 years of age with newly diagnosed high-grade glioma	**First dose:** Predose Postdose: 1, 2, 4, 8, 24 (± 2), 30 (± 4) and 48 (± 4) hrs **Steady-state (day 8):** Predose and 1, 2, 4, 8 and 24 (± 2) hrs after dose
Geoerger 2011	To establish the RD (primary endpoint), safety, PK, and efficacy (including correlation with tumor biomarkers) of erlotinib, given as monotherapy or with radiotherapy to children with malignant brain tumors.	Group 1: Erlotinib tablets were administered orally once daily in 3-week cycles at 4 potential dose levels (75, 100, 125 and 150 mg/m2) in standard 3 + 3 dose escalation methodology Group 2: Erlotinib tablets were administered orally once daily in 3-week cycles at 4 potential dose levels (75, 100, 125 and 150 mg/m^2); dose escalation in a continual reassessment method plus radiation.	Tablet	51 enrolled, 50 dosed	Pediatric patients between 1 and 21 years of age Group 1 Patients with histologically/ cytologically confirmed malignant brain tumors refractory to, or relapsing after, first-line therapy, for whom no effective treatment exists. Group 2 Patients with newly diagnosed, histologicallyconfirmed brainstem glioma (excluding pilocytic glioma)	**Steady-state** (at various times during the first 6 cycles of therapy) 30 minutes prior to dose and 1, 2, 4, 6, 8 and 24 hrs after dose

RD: recommended dose; SD: Stable disease; MTD: Maximum Tolerable Dose; PK: pharmacokinetics
Source: Table 1 of sponsor's population pharmacokinetics analysis in Pages 15-17.

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Table 2. Summary of Individual Post-hoc Bayesian Estimates from the Final Erlotinib Model by Age Group

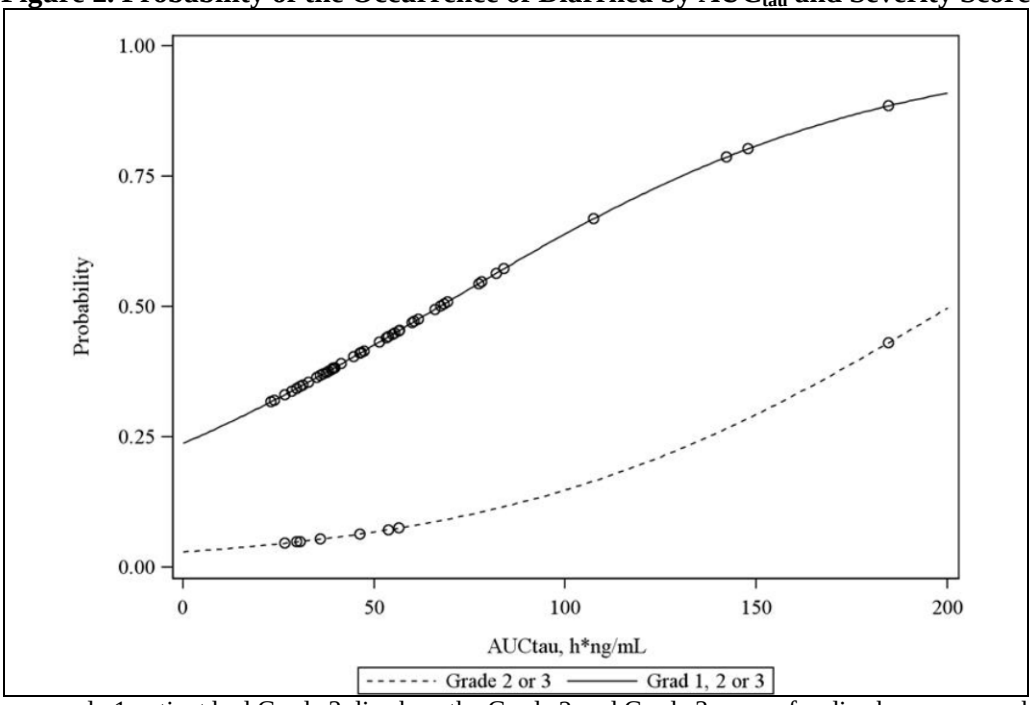
Age Group	Statistic	CL/F† (L/h)	V/F† (L)	CL/F (L/h/m^2)	V/F (L/m^2)	Ka_{slow} (h^{-1})	Ka_{fast} (h^{-1})	AUC_{tau} (µg·h/mL)	$T_{1/2}$ (h)
1 to 6 years (n = 29)	Mean	3.34	67.4	4.30	85.9	5.05	7.76	41.8	15.4
	Min	0.700	13.2	1.19	25.3	0.0038	0.997	16.2	6.73
	Median	3.12	64.0	4.18	84.9	0.252	0.997	38.4	15.8
	Max	6.86	124	7.15	147	95.3	50.0	98.1	32.0
	Geometric mean	2.98	60.9	3.90	79.7	0.298	1.71	38.0	14.2
	Lower bound of CI 95% for geometric mean	2.44	50.4	3.25	67.9	0.136	1.01	32.1	12.1
	Upper bound of CI 95% for geometric mean	3.63	73.6	4.68	93.6	0.650	2.89	44.8	16.6
	0.6 * geometric mean lower criteria	1.79	36.5						
	1.4 * geometric mean upper criteria	4.17	85.3						
7 to 16 years (n = 59)	Mean	4.63	133	3.91	104	1.21	4.32	53.2	23.3
	Min	0.403	40.1	0.240	47.8	0.0117	0.997	11.9	5.87
	Median	4.40	104	3.84	95.8	0.241	0.997	48.2	18.2
	Max	10.2	351	10.5	228	10.9	50.0	185	142
	Geometric mean	4.12	117	3.47	98.6	0.339	1.30	47.1	19.7
	Lower bound of CI 95% for geometric mean	3.59	103	3.01	90.1	0.231	1.00	41.4	17.1
	Upper bound of CI 95% for geometric mean	4.73	133	4.00	108	0.498	1.68	53.5	22.7
	0.6 * geometric mean lower criteria	2.47	70.2						
	1.4 * geometric mean upper criteria	5.77	164						
> 17 years (n = 17)	Mean	7.16	202	4.03	112	3.82	15.4	50.2	25.4
	Min	2.49	90.1	1.42	52.7	0.0273	0.997	16.4	8.65
	Median	4.90	200	2.59	112	0.697	0.997	45.9	21.9
	Max	24.3	333	13.8	175	28.5	50.0	142	47.8
	Geometric mean	5.72	187	3.23	106	0.596	3.15	43.8	22.7
	Lower bound of CI 95% for geometric mean	4.11	151	2.32	87.3	0.197	1.23	33.2	17.5
	Upper bound of CI 95% for geometric mean	7.97	231	4.49	128	1.80	8.12	57.7	29.4

CL/F: oral clearance; Max: maximum; Min: minimum; V/F: oral volume of distribution.
† CL/F and V/F values for patients receiving tablets are corrected by the relative bioavailability to the solution (e.g., CL/F = CL/relative bioavailability).

Refer to Column 5 for geometric mean of CL/F/BSA.
Source: Table 11 of sponsor's population pharmacokinetics analysis in Page 66.

Table 3. Overall Incidence of Selected Adverse Events Across All Studies by Severity Grade		
Severity Grade	**Rash (Group Term)**	**Diarrhea**
0	28	60
1	49	37
2	27	7
3	1	1
Total	105	105
Source: Table 13 of sponsor's population pharmacokinetics analysis in Page 72.		

Figure 2. Probability of the Occurrence of Diarrhea by AUC_{tau} and Severity Score



Note: Because only 1 patient had Grade 3 diarrhea, the Grade 2 and Grade 3 scores for diarrhea were combined.
Source: Figure 44 of sponsor's population pharmacokinetics analysis in Page 76.

Overall, the supplementary submission of erlotinib fulfilled the pediatric written request from the perspectives of population pharmacokinetics and exposure-response analyses.

4.2 REFERENCES

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4. Broniscer A, Panetta JC, O'Shaughnessy M, et al. Plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite OSI–420. Clin Cancer Res. 2007;13(5):1511–1515.

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RUBY LEONG
03/19/2015

HONGSHAN LI
03/19/2015

LIANG ZHAO
03/19/2015

QI LIU
03/19/2015

HONG ZHAO
03/19/2015
I concur.