NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	201292
Priority or Standard	Priority
Submit Date(s)	October 7, 2021
Received Date(s)	October 7, 2021
PDUFA Goal Date	April 7, 2022
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	April 7, 2022
Established/Proper Name	Afatinib
Trade Name	GILOTRIF
Pharmacologic Class	Kinase inhibitor
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Dosage form	Tablets: 20 mg, 30 mg, 40 mg
Applicant proposed Dosing Regimen	Not Applicable
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE(s)	adverse event(s)
AR	adverse reaction
BI	Boehringer Ingelheim Pharmaceuticals, Inc.
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	Body surface area
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
CTP	clinical trial protocol
DHOT	Division of Hematology Oncology Toxicology
DLT	Dose limiting toxicity
DMC	data monitoring committee
DoR	Duration of objective response
ECG	electrocardiogram
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
ErbB	erythroblastic leukaemia viral oncogene homolog of the human
EGF	epidermal growth factor family of
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation

IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MxR	Mixed response
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
(NSCLC)	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	Overall Survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PR	partial response
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	Progression Free Survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
VGPR	very good partial response

1 Executive Summary

Afatinib is a small molecule which covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of erythroblastic leukaemia viral oncogene homolog of the human EGF epidermal growth factor family of (ErbB) signaling. Afatinib tablets were approved on July 12, 2013 (NDA 201292) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. This indication received orphan-drug designation on December 3, 2012 and was therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA).

On December 9, 2016, BI submitted a proposed pediatric study request to study patients between ≥ 1 year to < 18 years of age with tumors with known ErbB deregulation. Under the provisions of Section 505(A) of Federal Food, Drug, and Cosmetic Act (21 U.S.C 355a) , the FDA issued the original Written Request on April 7, 2017. In order to fulfill the terms of the Written Request, Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted Supplement 17 along with a request for exclusivity to NDA 201292 on October 7, 2021 to incorporate the findings of the study conducted under the Written Request into Section 8.4 (Pediatric Use) of afatinib product labeling.

The Written Request includes Trial 1200.120 which was a dose escalation and expansion, multinational study to determine the maximum tolerated dose (MTD), safety, pharmacokinetics (PK) and efficacy of afatinib as single agent and to assess its anti-tumor activity in children ≥1 year to <18 years of age with recurrent/refractory neuroectodermal tumors, rhabdomyosarcoma and/or other solid tumors with known ErbB pathway deregulation regardless of tumor histology. Afatinib did not show substantial anti-tumor activity in pediatric patients in any of the pre-specified indications (ependymoma, high-grade glioma [HGG], and diffuse intrinsic pontine glioma [DIPG]), nor in children with recurrent or refractory malignant tumors with ErbB pathway deregulations overall. The review of safety data in Trial 1200.120 did not reveal any new safety signals compared to the established safety profile of afatinib treatment in adults. Proposed labeling submitted with the supplement included a description of the study. The FDA recommended revising the proposed labeling to shorten the summary of the study based on recommendations found in the March 2019 FDA *Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling*. At the Pediatric Exclusivity Board meeting on February 9, 2022, the Pediatric Exclusivity Board recommended granting pediatric exclusivity. The review team recommends approval of the supplemental NDA, with final labeling described in this review in Section 5.

2 Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

The original Written Request was issued on April 7, 2017. During the course of development, BI has met with FDA to obtain advice and agreement regarding the conduct of the pediatric study of afatinib described in the Written Request on November 9, 2018, January 11, 2019, and May 17, 2021.

The original Written Request contained 2 studies:

- Study 1 (Study 1200.120): A multicenter, open-label, two-part trial to identify a pediatric dose, assess the pharmacokinetics, and investigate the anti-tumor activity of afatinib when administered for the treatment of pediatric tumors with known ErbB pathway dysregulation.
    - Part 1: Dose finding to determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and pharmacokinetics of afatinib.
    - Part 2: An activity-estimating, disease-specific parallel cohort study of afatinib in patients aged 1 to <18 years with relapsed or refractory tumors with evidence of ErbB-dysregulation based upon the presence of overexpression or amplification of EGFR or HER2 using the criteria established in the companion biomarker study. The study will have three tumor-specific cohorts: HGG ≥ 5 patients; EM ≥ 5 patients, DIPG ≥ 4 patients. In addition to these three disease-specific cohorts, the trial will include a histology-agnostic cohort of patients with refractory tumors, including those which were studied for biomarker feasibility or other tumors that fulfill the biomarker screening criteria; this cohort will have a minimum of five patients.
- Study 2 was originally described as "Study(ies) designed to establish the safety and effectiveness of afatinib, as a single agent or as a component of multi- modality therapy in neuroectodermal tumors or rhabdomyosarcoma, if sufficient antitumor activity is observed in one or more tumor types in Part 2 of Study 1. …. This protocol must be reviewed and agreed upon by FDA prior to enrollment of patients."

Amendments to the Written Request are summarized below:

- Amendment 1, dated August 14, 2017
    - This amendment resolved a discrepancy in the molecular eligibility criteria between the original Written Request and BI's June 14, 2017 revision of Study 1200.120 (i.e., changed to two criteria rather than only 1 criterion)

- Amendment 2 dated June 5, 2019
    - This amendment modified the plan for the conduct of Part 2 of Study 1 such that there were 3 tumor-specific cohorts (with tumor type not specified, rather than pre-specifying these tumor types) and one histology-agnostic cohort, with a minimum of five patients each.
- Amendment 3 dated April 29, 2020
    - This amendment revised the Written Request to include the tumor types in tumor-specific cohorts based on enrollment and to change the target enrollment in the cohort of patients with diffuse intrinsic pontine glioma from a minimum of 5 to a minimum of 4 patients. The amendment was justified based on robust efforts in screening hundreds of patients and the extreme rarity of pediatric patients with the molecular aberrations eligible for the study.
- Amendment 4 dated July 26, 2021.
    - FDA agreed to the proposed amendment to this Written Request submitted on May 25, 2021, which removed Study 2 from the original Written Request due to lack of sufficient antitumor activity in Study 1 (1200.120) to support additional investigation of afatinib as a single agent in pediatric patients with cancer The study enrolled 56 patients, including 39 patients in the Part 2 expansion phase. Part 2 included 4 patients with DIPG, 8 with ependymoma and 6 with high-grade glioma; in the histology-agnostic cohort, there were 20 patients total including 4 patients with hepatocellular carcinoma, 3 with neuroblastoma, and 4 with rhabdomyosarcoma. The overall response rate (ORR) was (b) (4)% among patients in Part 2. The results of Study 1 do not support initiation of further studies to evaluate afatinib as a single agent in any of the pediatric solid tumors evaluated in expansion cohorts in Study 1.

3 Clinical Pharmacology

3.1 Executive Summary

Study 1200.120 was an open-label, dose escalation and expansion study to determine the MTD of afatinib as a single agent and to assess its antitumor activity in pediatric patients with recurrent or refractory malignant neuroectodermal tumors, rhabdomyosarcoma or other solid tumors with ErbB pathway deregulations. Patients received one of two dosages: 18 mg/m^2/day (80% of the adult dose per body surface area) or 23 mg/m^2/day. The safety and effectiveness of afatinib in pediatrics were not established (b) (4). Afatinib was administered using the commercially available tablets or an unapproved dosage form, a solution administered orally or via feeding tube. Only 3 patients received the unapproved dosage form by a feeding tube; therefore, these patients were omitted from the pharmacokinetic (PK) analysis. The population PK (PopPK) analysis suggests that the dosage form (i.e., tablets or solution administered orally) has no clinically meaningful effect on afatinib PK and supports pooling the PK data from both these dosage forms to evaluate for any differences in PK between pediatric and adult patients. The PK profile in the 37 pediatric patients aged 2 to <17 years who received 80% of the adult dose per body surface area (using either dosage form) were within range of PopPK-derived values in adults at 40 mg once daily (QD).

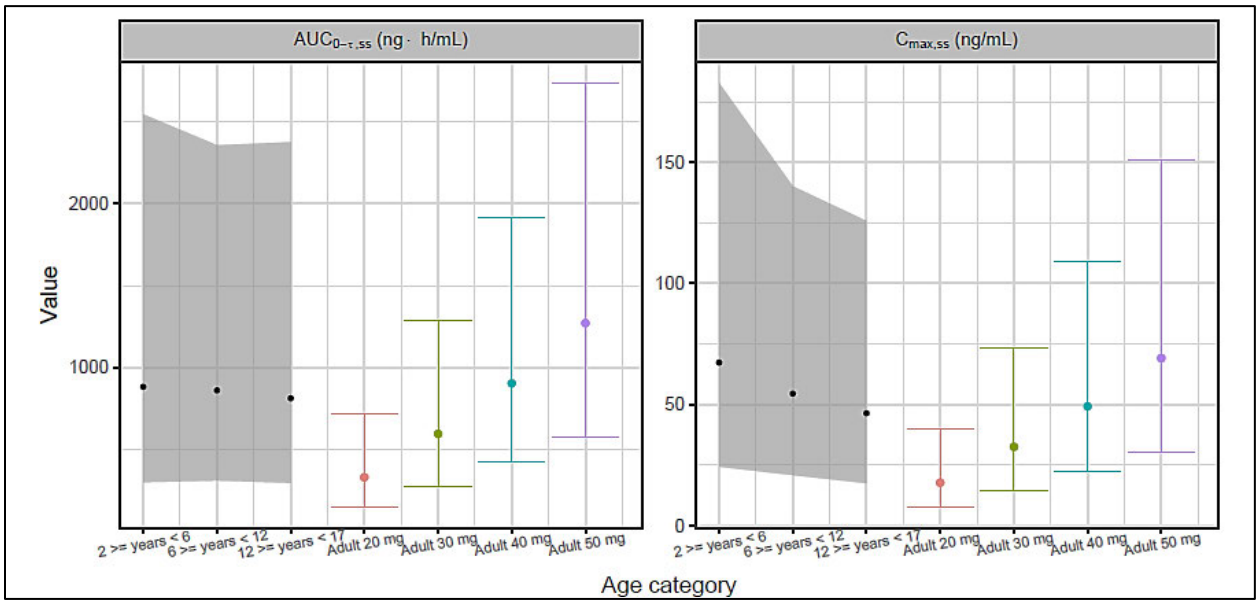
3.2 Summary of Clinical Pharmacology Assessment

Study 1200.120 has two parts, a dose finding part and an expansion part. The dose finding part included two dosage level cohorts: '0' (18mg/m^2/day) and '1' (23 mg/m^2/day). A dosage of 18 mg/m^2/day was selected for the expansion part. Pediatric patients (n=37; *see Section 5.2.1 for details*) who received afatinib at a dosage of 18 mg/m^2/day were included in the PK analysis to evaluate for any PK differences between these pediatric patients and adults at the recommended dosage of 40 mg QD. The afatinib PopPK model was acceptable and based on a previously developed 2-compartmental disposition model for adults with first-order elimination and first-order absorption and lag-time.

While two different dosage forms (excluding solution via feeding tube) were administered in the study, pooling the PK data from the solution and the tablets is acceptable as the PopPK analysis suggests that the dosage form has no clinically meaningful effect on afatinib PK.

The PopPK analysis showed that the simulated PK parameters, $AUC_{0\text{-}T,ss}$ and $C_{max,ss}$, in pediatric patients 2 to <17 years of age who received 80% of the afatinib adult dose per body surface area were within range of PopPK-derived values in adults at afatinib 40 mg QD (*Figure 1*).

Figure 1. Simulated afatinib $AUC_{0\text{-}T,ss}$ and $C_{max,ss}$ in the pediatric population versus adult values. *(source: PopPK report - c31792800-01)*



Note: The point represent the 50th percentile and the shaded area is bounded by the 5th and 95th percentiles of the simulated data. The error bars represent the 5th and 95th percentiles of the adult data. 1000 pediatric subjects per age category were simulated.

Further, non-compartmental analysis (NCA) confirmed that afatinib exposure (geometric mean $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$) for the pediatric population is within range of those values derived for adults (derived from PopPK estimates) receiving 18 mg/m^2/day and 40 mg/day, respectively (*Figure 2 and Figure 3*).

Figure 2. Comparison of individual and gMean of $AUC_{0\text{-}24,ss}$ values of afatinib in pediatrics at 18mg/m^2 QD and adults at 40mg QD. *(source: PopPK report - c31792800-01)*

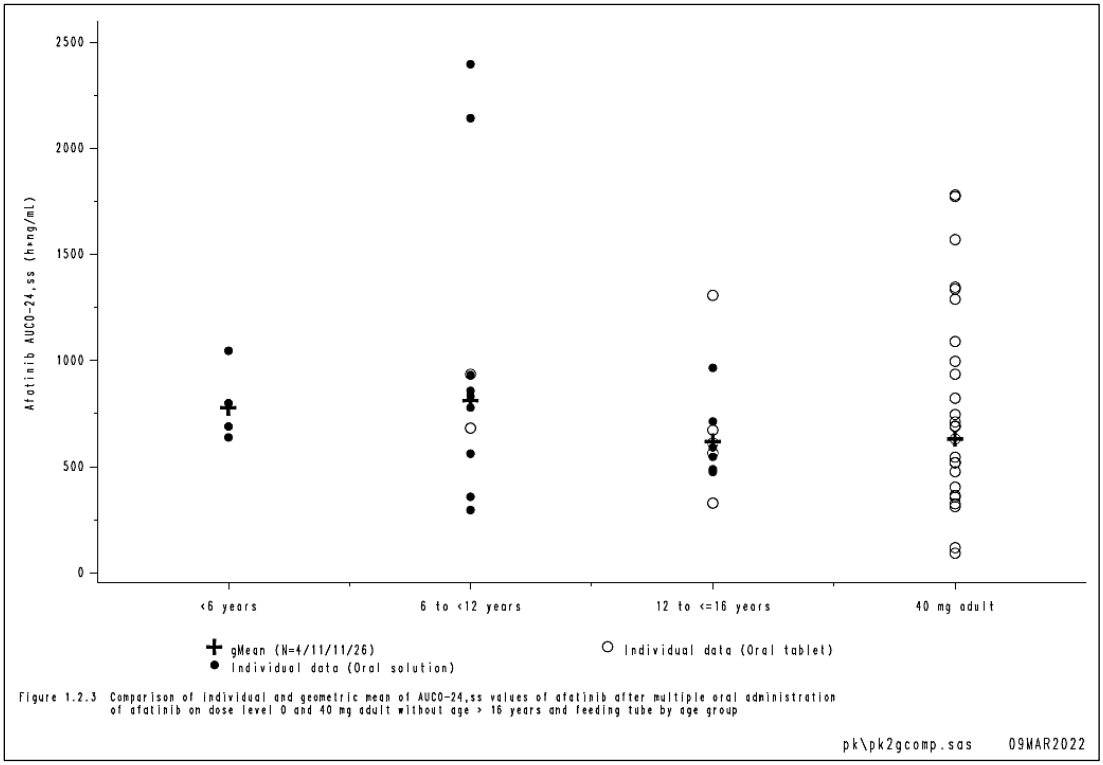
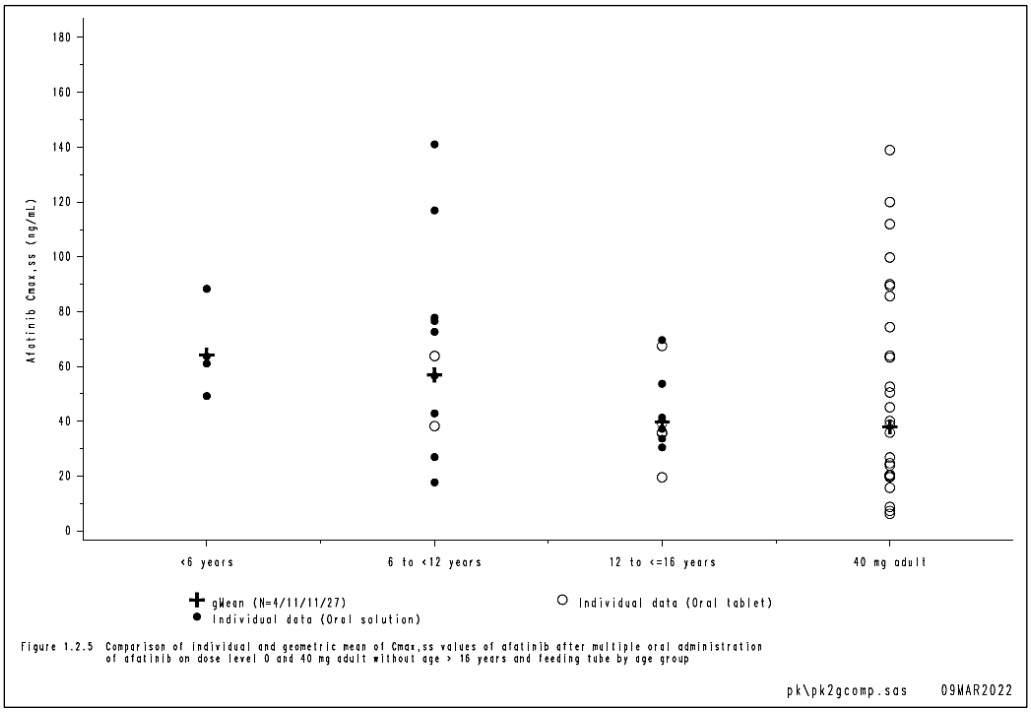


Figure 3. Comparison of individual and gMean of $C_{max,ss}$ values of afatinib at 18mg/m^2 QD and adults at 40mg QD. *(source: PopPK report - c31792800-01)*



Version date: April 2, 2018

3.2.1 **Pharmacology and Clinical Pharmacokinetics**

Analysis dataset description:

- Fifty-six patients 2 to ≤ 18 years of age were enrolled in the dose- finding part (n=17; 18mg/m^2/day or 23 mg/m^2/day) or expansion part (n=39; 18mg/m^2/day).
- Patients received afatinib as the commercially available tablets or unapproved solution, orally or using a feeding tube. Among the 56 patients, 33 and 16 patients were pediatric patients (<17 years old, n=49) who received afatinib in the form of solution or tablets, respectively. Because only 3 patients received afatinib solution using a feeding tube, clinically meaningful differences could not be evaluated between the estimated afatinib PK parameters from these patients and from those who received the commercial tablets. Therefore, these patients were omitted from the PK analysis. Nine of the 46 remaining pediatric patients received a higher dosage. Hence, only 37 pediatric patients (*Table 1*) who received a dosage of 18 mg/m^2/day were included in the PK analysis to evaluate for any PK differences between pediatric patients and adults at the recommended dosage of 40 mg QD.

Table 1. Age distribution of pediatric patients at afatinib dose level of 18mg/m^2.

Dose	Age (years)			Dosage form	
	<6	6 to <12	12 to ≤16	Tablets	Solution
18 mg/m^2 (n=37)	6	14	17	11	26

- PK samples were collected on Day 1: Predose and 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h and 24 h after administration and repeated at steady state on Day 8. An additional trough sample was taken on Day 15 (or Day 22) to confirm steady state exposure to afatinib.

Comparison of afatinib PK by dosage form:

- Among the 56 patients enrolled into the study, 22, 31 and 3 received the approved commercial tablets, the unapproved solution (orally) or unapproved solution (via feeding tube), respectively (*Figure 4 and Table 2*).

Figure 4. Distribution of patient population by age and dosage form.
(source: Report c31792800-01)

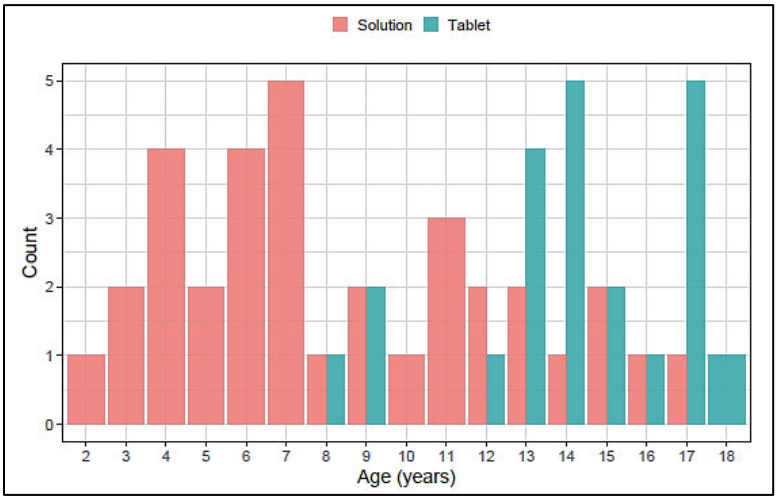


Table 2. Number of patients who received each dosage form by daily dose.
(source: Report c31792800, Table 1)

Dose (mg)	Solution	Tablet	Solution via Feeding Tube	Total subjects
10	2	0	1	3
12	2	0	0	2
14	5	0	2	7
16	4	0	0	4
18	3	0	0	3
20	1	4	0	5
22	1	0	0	1
24	6	0	0	6
26	6	0	0	6
28	1	0	0	1
30	0	14	0	14
40	0	4	0	4
All	31	22	3	56

- A NCA analysis was used to evaluate for any differences in the PK parameters of afatinib when administered as tablets or as solution (*Figure 5 and Figure 6*). The gMean $C_{max,ss}$ value of afatinib is slightly lower when administered as tablet (gMean $C_{max,ss}$ 41.8 ng/mL) compared with liquid oral solution (gMean $C_{max,ss}$ 54.1 ng/mL).

Figure 5. NCA - Comparison of individual and geometrical Mean (gMean) of $C_{max,ss}$ values of afatinib after multiple administrations of afatinib at 18 mg/m^2 QD by route and dosage form. *(source: Report c26541024-01)*

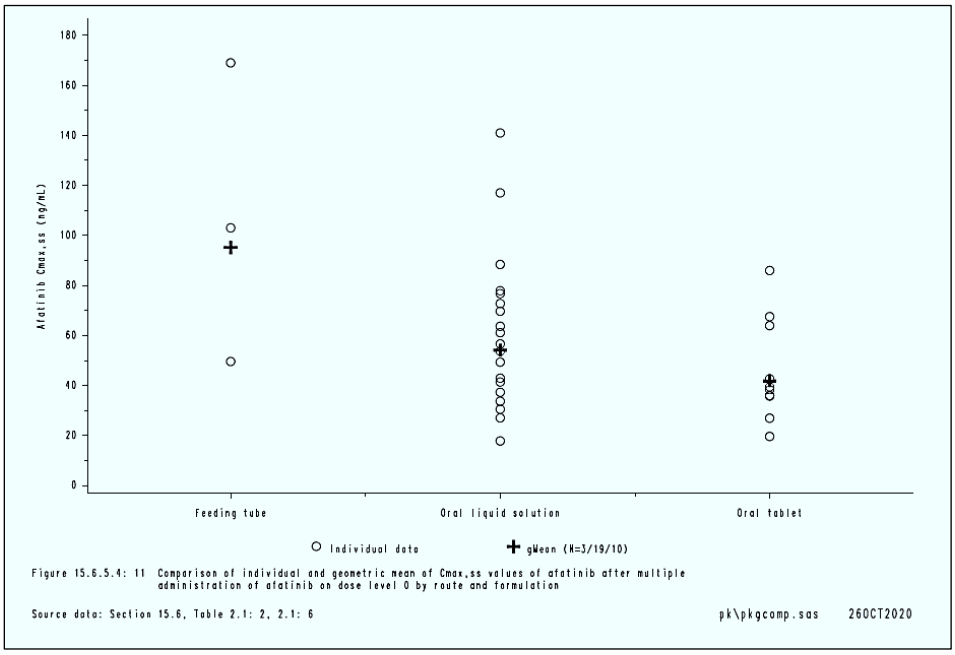
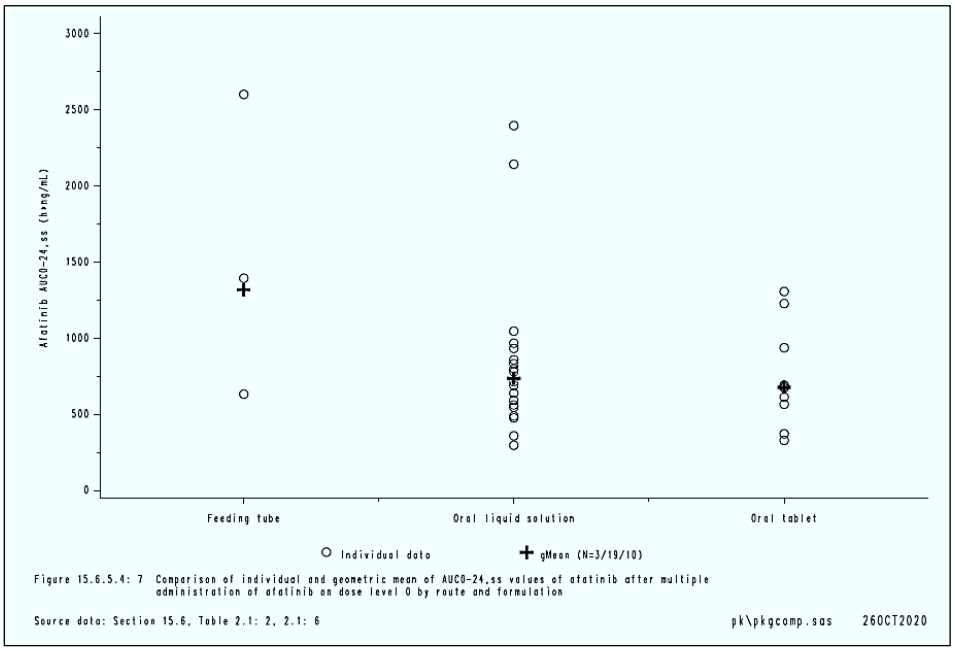


Figure 6. NCA - Comparison of individual and gMean of $AUC_{0\text{-}24h,ss}$ values of afatinib after multiple administration of afatinib at 18 mg/m^2 QD by route and dosage form. *(source: Report c26541024-01)*



- A PopPK analysis also suggests no clinically meaningful differences in exposure following administration of the tablets or solution. The PopPK analysis showed that dosage form (unapproved solution vs commercially approved tablets) was not a significant covariate that affected afatinib PK. The point estimate of F1 for commercial tablets compared to the solution (administered orally) was approximately 20% lower, and thus, no clinically meaningful differences in afatinib exposure is expected when comparing the commercial approved tablets and solution dosage forms.
- These analyses justifies and supports evaluating for differences in the PK among pediatric age groups to that in adults by combining the PK data from the pediatric patients who received the solution orally and the pediatric patients who received the approved commercial tablets.

Comparison of afatinib PK parameters among pediatric age groups versus adults:

- NCA (*Figure 7*) and PopPK analyses (*Figure 9*) were conducted using the data from 37 pediatric patients to evaluate for any differences in the PK parameters among the pediatric age groups versus adult patients. Based on the NCA analysis (*Figure 7*), afatinib exposure ($AUC_{0\text{-}24,ss}$ and $C_{max,ss}$) was similar when compared per age group in pediatric patients receiving afatinib 18mg/m^2/day.

Figure 7. gMean (gCV, N) noncompartmental PK parameters of afatinib after single and multiple administration of afatinib at 18 mg/m^2 QD by age group.

(source: Report c26541024-01)

PK parameter	Age < 6 y	Age 6-12 y	Age 12 - <17y
$AUC_{0\text{-}24}$ (ng/mL*h)	485 (75.9%; 6)	401 (77.8; 16)	317 (86.8%; 16)
C_{max} (ng/mL)	47.7 (64.5%; 6)	34.9 (81.0%; 16)	24.4 (100%; 16)
$AUC_{0\text{-}24,ss}$ (ng/mL*h)	991 (62.2%; 5)	830 (66.3%; 13)	620 (37.8%; 11)
$C_{max,ss}$ (ng/mL)	77.9 (51.0%, 5)	59.0 (63.8%; 13)	39.8 (37.4%; 11)

- The simulated multiple dose afatinib exposure ($AUC_{0\text{-}\tau,ss}$ and $C_{max,ss}$) (*Figure 8*) at a dosage of 18 mg/m^2/day in the pediatric patients was within the range of estimated values in adults at the approved recommended dosage of 40 mg QD (*Figure 9*).

Figure 8. Simulated AUC and C_{max} in a pediatric population receiving daily doses of 18mg/m^2 QD of afatinib.

(source: Available on file 1200-0120–10–study-report-body.pdf - additional documentation).

Parameter (unit)	5th Percentile	50th Percentile	95th Percentile	50th Percentile NCA[a]
2 >= years < 6				
$AUC_{0-\tau,ss}$ (ng · h/mL)	295.8	879.8	2548.3	798 (N = 5)
$C_{max,ss}$ (ng/mL)	24.3	67.3	182.8	63.7 (N = 5)
6 >= years < 12				
$AUC_{0-\tau,ss}$ (ng · h/mL)	305.8	858.2	2359.0	832 (N = 13)
$C_{max,ss}$ (ng/mL)	20.8	54.5	140.1	63.9 (N = 13)
12 >= years < 17				
$AUC_{0-\tau,ss}$ (ng · h/mL)	291.8	809.3	2377.9	590 (N = 11)
$C_{max,ss}$ (ng/mL)	17.5	46.3	125.8	37.3 (N = 11)

Figure 9. Simulated $AUC_{0-\tau,ss}$ and $C_{max,ss}$ in the pediatric patients receiving 18 mg/m^2 QD of afatinib were in range when compared to the adult values at 40 mg QD dosage.

(source: PopPK report - c31792800-01)

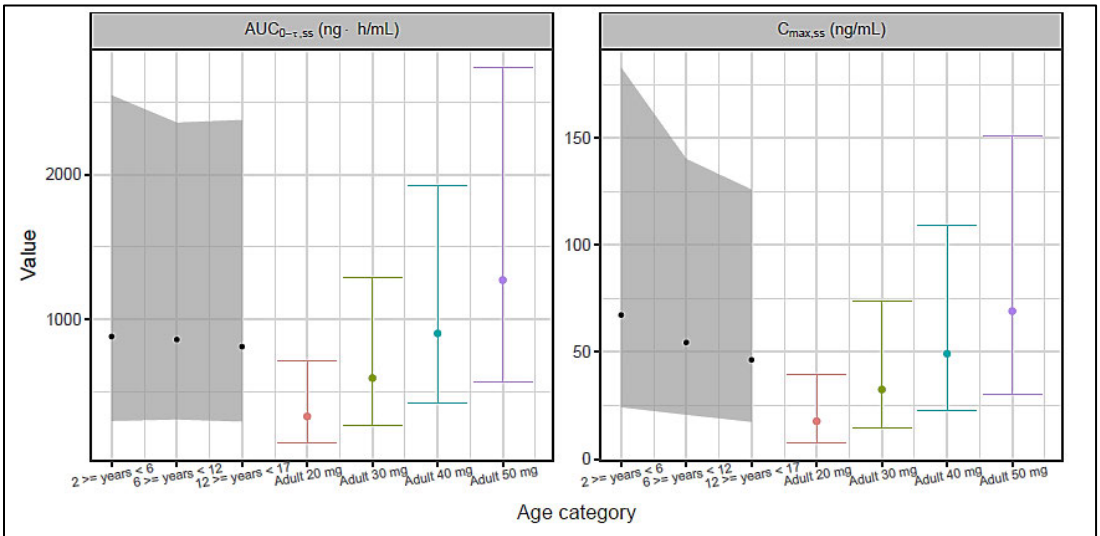


Figure A12-3: Simulated $AUC_{0-\tau,ss}$ and $C_{max,ss}$ in the pediatric population (less than 17 years of age, receiving 18 mg/m^2 afatinib) versus adult values[8]. The points represent the 50th percentile and the shaded area is bounded by the 5th and 95th percentiles of the simulated data. The error bars represent the 5th and 95th percentiles of the adult data. 1000 pediatric subjects per age category were simulated. AUC: area under the curve; SS: steady-state; τ: dosing interval; $C_{max,ss}$: maximum concentration at steady-state.

3.2.2 General Dosing and Therapeutic Individualization

General Dosing

The safety and effectiveness were not established for pediatrics [redacted] (b) (4); therefore, no dosage recommendations are needed.

Outstanding Issues

None

3.3 Comprehensive Clinical Pharmacology Review

3.3.1 General Pharmacology and Pharmacokinetic Characteristics

Bioanalytical methods used in the current study were previously validated and therefore acceptable. This submission did not include new clinical pharmacology information with exception of a description of the PK in pediatric patients described above.

3.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The safety and effectiveness of afatinib in pediatric patients has not been established.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

N/A

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

N/A

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

N/A

Question on clinically relevant specifications (TBD)?

N/A

Suryatheja Ananthula
Primary Reviewer

X Jeanne Fourie Zirkelbach
Team Leader

4 Clinical Review

Amendment 4 of the Written Request includes a single study, Trial 1200.120, entitled: "Phase 1/ 2 Open Label, Dose Escalation Trial to Determine the MTD, Safety, PK and Efficacy of Afatinib Monotherapy in Children Aged ≥1 Year to <18 Years with Recurrent/ Refractory Neuroectodermal Tumours, Rhabdomyosarcoma and/or Other Solid Tumours with Known ErbB Pathway Deregulation Regardless of Tumour Histology." The supplemental NDA contains the clinical study report for this trial.

Description of Trial

Trial 1200.120 was a Phase I/II open-label, dose escalation, multinational study to determine the maximum tolerated dose (MTD), safety, pharmacokinetics (PK) and efficacy of afatinib as single agent and to assess its anti-tumor activity in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumors, rhabdomyosarcoma and/or other solid tumors with known ErbB pathway deregulation regardless of tumor histology. The trial had two parts: a Phase I dose finding part was conducted using a rolling six design and a biomarker-specific MTD expansion cohorts/Phase II part. Specific endpoints for the study are outlined below.

Endpoints of efficacy

Primary endpoints:

- The primary endpoints in the dose finding part were a safety endpoint and PK endpoints.
- The primary endpoint in the MTD expansion cohorts/Phase II part was objective response by investigator assessment according to the institutional response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease.

Secondary endpoints:

Dose finding phase

- Objective Response by investigator assessment according to the institutional response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease.

MTD expansion cohorts/Phase II

- Progression free survival (PFS) was defined as the duration from the date of first treatment until the date of the first documented progression or death due to any cause. If a patient did not have an event, PFS was censored at the date of last adequate tumor assessment.
- Duration of objective response (DoR)

- Duration of objective response was defined as the time from first documented response of complete response (CR), very good partial response (VGPR), partial response (PR), or mixed response (MxR) until the earliest of disease progression or death among patients with objective response.

Further endpoints:

Dose finding phase and MTD expansion cohorts/Phase II

- Tumor shrinkage
- Overall Survival (OS, defined as the duration from the date of the first treatment to the date of death)
- Patient's drug acceptability
- Tumor biology and ErbB pathway deregulation assessments were an optional further endpoint in the clinical trial protocol (CTP). Given the tumor response profile observed in the trial, such analyses were not performed. Data were listed only.

MTD expansion cohorts/Phase II only

- Health-related quality of life was assessed by the PedsQL™ Measurement Model.

Safety Endpoints

Primary endpoint

The primary objective of the dose finding part was to determine the MTD of afatinib based on the number of patients with dose limiting toxicity (DLT) in a pediatric population.

No primary safety endpoint was defined for the MTD expansion cohorts/Phase II.

Trial Results

A total of 56 patients enrolled in the trial: 17 patients were treated in the Phase Ib dose finding part and 39 patients were treated in the MTD expansion cohorts/Phase II part. Thirty-two patients (57%) were male and 24 patients (43%) were female. The median age was 11.5 years (range 2 to 18 years). Table 3 below provides a summary of the distribution of tumor types that were represented in Trial 1200.120. In the dose finding part, afatinib once daily at 80% of the recommended adult dose per m^2 body surface area (BSA) using allometric scaling (18 mg/m^2/day) was identified as the MTD for pediatric patients. Exposure at this dose level was in the range considered effective in adults. Total of 56 patients enrolled, 17 patients in Part 1 and 39 in Part 2.

Table 3: Tumor Histologies Represented in Trial 1200.120

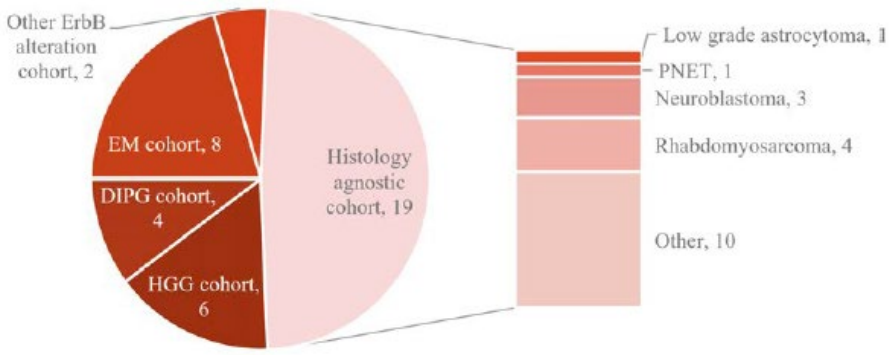
Tumour histology	N	(%)
Number of patients	56	(100.0)
High grade glioma (HGG)	13	(23.2)
Diffuse intrinsic pontine glioma (DIPG)	4	(7.1)
Low grade astrocytoma	1	(1.8)
Ependymoma (EM)	10	(17.9)
Medulloblastoma	1	(1.8)
Primitive neuroectodermal tumour (PNET)	4	(7.1)
Neuroblastoma	4	(7.1)
Rhabdomysarcoma (RMS)	7	(12.5)
Other	12	(21.4)

Source data: Table 15.1.4: 2

Source: Applicant's analysis found on pg. 77 of 1229 from the CSR

In the dose finding phase, seven patients (41%) had a diagnosis of HGG, 3 patients (18%) each had PNET or RMS, 2 patients (12%) had ependymoma, and 1 patient (6%) each had medulloblastoma or neuroblastoma. Thirty-nine patients were enrolled in the MTD expansion cohorts/Phase II portion, including 8 patients (21 %) with ependymoma, 6 patients (15 %) with HGG, and 4 patients (10%) with DIPG. The histology agnostic cohort comprised 19 patients (49%); 4 patients (10 %) had rhabdomyosarcoma, 3 patients (8 %) had neuroblastoma, 1 patient (2.6 %) each had low grade astrocytoma and PNET, and 10 patients (26%) had other tumors. Figure 10 demonstrates the different tumor histologies by cohort.

Figure 10: Representation of Tumor Histology by Cohort



Source: Applicant's analysis found on pg. 78 of 1229 from the CSR

Efficacy

None of the 17 patients treated in the Phase Ib dose finding part had an objective response. In the MTD expansion cohorts/Phase II part, 1 patient (2.6%) had a confirmed objective response. The patient had a neuronal-glial tumor of the brain with a rare CLIP2-EGFR gene fusion. Two patients had PR at a single assessment that was not confirmed at the next assessment and was therefore stable disease (SD) according to the underlying response criteria. The duration of the confirmed partial response was >170 days (duration not determined because the patient discontinued trial participation and continued afatinib treatment in a compassionate use program). The median PFS across all patients in the MTD expansion cohorts/Phase II part was 8.0 weeks (95% CI 6.4, 8.29).Overall, afatinib did not demonstrate substantial anti-tumor activity in pediatric patients in any of the pre-specified tumor types (ependymoma, high-grade glioma [HGG], and diffuse intrinsic pontine glioma [DIPG]), nor in children with other recurrent or refractory malignant tumors with ErbB pathway deregulations. Patient enrichment via selection biomarker was implemented in the maximum tolerated dose (MTD) expansion cohorts/Phase II portion.

Safety

The safety profile of afatinib has been well characterized in adults diagnosed with metastatic NSCLC. Clinically significant adverse reactions in the adult patient population associated with the use of afatinib included diarrhea, bullous and exfoliative skin disorders, (including toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome), interstitial lung disease, hepatic toxicity, and keratitis. No new safety signals were observed in pediatric patients compared to the established safety profile of afatinib treatment in adults.

In the dose finding phase of the study, two dose levels were evaluated. Dose level 1 (100% of the adult dose per body surface area based on allometric scaling) exceeded the MTD given the occurrence of DLTs in 2 of 5 evaluable patients. DLTs at dose level 1 included diarrhea, chelitis, rash, decreased appetite, hypernatremia, hypokalemia, and dehydration. Afatinib once daily at 80% of the recommended adult dose per m^2 body surface area (BSA) using allometric scaling (18 mg/m^2/day) was identified as the MTD for pediatric patients.

In Trial 1200.120 adverse events were reported for all treated patients. In 26 (46%) patients, the maximum CTCAE grade reported was Grade 3. Six patients (11%) had a Grade 4 AE and 3 patients (5%) had a fatal AE (CTCAE Grade 5, Section 12.2). The most frequently reported AEs on a system organ class level were:

- gastrointestinal disorders (52 patients, 93%) with diarrhea (43 patients, 77%) as the most frequent preferred term
- skin and subcutaneous tissue disorders (40 patients, 71%) with dry skin (16 patients, 29%) as the most frequent preferred term
- general disorders and administration site conditions (33 patients, 59%) with fatigue as the most frequently reported preferred term (15 patients, 27%)
- investigations (31 patients, 55%) with decreased weight (14 patients, 25%) as the most frequent preferred term.

A total of 33 patients (59%) had serious adverse events (SAEs). Most SAEs were considered serious because they required or prolonged hospitalization.

The most frequently reported SAEs on system organ class level were:

- nervous system disorders (15 patients, 27%) with headache (4 patients, 7%) as the most frequent preferred term
- gastrointestinal disorders (11 patients, 20%) with vomiting (7 patients, 13%) and diarrhea (3 patients, 5%) as the most frequently reported preferred terms.

Serious AEs led to discontinuation of afatinib treatment in 4 patients; the SAEs leading to treatment discontinuation were aphasia, encephalopathy, intracranial hemorrhage, headache, hypokalemia, and vomiting. Three patients were reported to have had fatal AEs during the on-treatment period; based on review of the narratives for these patients, these deaths were related to disease progression. A high-level summary of adverse events is found in Table 4 and a summary of adverse events by preferred term and system organ class is provided in Table 5.

Table 4: Summary of Adverse Events Observed in Trial 1200.120

	Dose finding – Dose level 0	Dose finding – Dose level 1	MTD expansion – Dose level 0	Total
	N (%)	N (%)	N (%)	N (%)
Number of patients	8 (100.0)	9 (100.0)	39 (100.0)	56 (100.0)
Patients with any AE	8 (100.0)	9 (100.0)	39 (100.0)	56 (100.0)
Patients with investigator-defined drug-related AEs	8 (100.0)	9 (100.0)	35 (89.7)	52 (92.9)
Patients with AEs leading to treatment discontinuation or dose reduction	4 (50.0)	2 (22.2)	7 (17.9)	13 (23.2)
Patients with AEs leading to dose reduction of afatinib	2 (25.0)	1 (11.1)	5 (12.8)	8 (14.3)
Patients with AEs leading to discontinuation of afatinib	2 (25.0)	1 (11.1)	3 (7.7)	6 (10.7)
Patients with protocol-defined AESI	2 (25.0)	2 (22.2)	7 (17.9)	11 (19.6)
Patients with SAEs	7 (87.5)	6 (66.7)	20 (51.3)	33 (58.9)
Fatal	0 (0.0)	0 (0.0)	3 (7.7)	3 (5.4)
Immediately life-threatening	0 (0.0)	1 (11.1)	1 (2.6)	2 (3.6)
Persistent or significant disability/incapacity	1 (12.5)	0 (0.0)	1 (2.6)	2 (3.6)
Required hospitalisation	5 (62.5)	6 (66.7)	19 (48.7)	30 (53.6)
Prolonged hospitalisation	0 (0.0)	1 (11.1)	6 (15.4)	7 (12.5)
Congenital anomaly or birth defect	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other medically important serious event	1 (12.5)	1 (11.1)	1 (2.6)	3 (5.4)
Patients with highest CTCAE grade				
Grade 1	0 (0.0)	1 (11.1)	4 (10.3)	5 (8.9)
Grade 2	1 (12.5)	2 (22.2)	13 (33.3)	16 (28.6)
Grade 3	5 (62.5)	4 (44.4)	17 (43.6)	26 (46.4)
Grade 4	2 (25.0)	2 (22.2)	2 (5.1)	6 (10.7)
Grade 5	0 (0.0)	0 (0.0)	3 (7.7)	3 (5.4)

A patient may be counted in more than one seriousness category.

Source data: c26541024, Table 15.3.1: 1, Table 15.3.1: 12, and Table 15.3.2: 1

Source: Applicant's analysis found on pg. 92 of 1229 in the CSR

Table 5: Adverse Events by System Organ Class

Table 12.1.2.2: 1 Adverse events that were reported for ≥15% of patients at the preferred term level, by CTCAE Grade, SOC, and preferred term – treated set

System organ class Preferred term	All Grades		Grade 3		Grade 4		Grade 5	
Number of patients, N (%)	56	(100.0)	56	(100.0)	56	(100.0)	56	(100.0)
Any AE	56	(100.0)	26	(46.4)	6	(10.7)	3	(5.4)
Gastrointestinal disorders	52	(92.9)	9	(16.1)	1	(1.8)	0	(0.0)
Diarrhoea	43	(76.8)	3	(5.4)	1	(1.8)	0	(0.0)
Vomiting	27	(48.2)	4	(7.1)	0	(0.0)	0	(0.0)
Nausea	18	(32.1)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	14	(25.0)	1	(1.8)	0	(0.0)	0	(0.0)
Stomatitis	14	(25.0)	1	(1.8)	0	(0.0)	0	(0.0)
Constipation	11	(19.6)	2	(3.6)	0	(0.0)	0	(0.0)
Cheilitis	10	(17.9)	1	(1.8)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	40	(71.4)	2	(3.6)	0	(0.0)	0	(0.0)
Dry skin	16	(28.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis acneiform	11	(19.6)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	33	(58.9)	8	(14.3)	0	(0.0)	0	(0.0)
Fatigue	15	(26.8)	1	(1.8)	0	(0.0)	0	(0.0)
Pyrexia	11	(19.6)	3	(5.4)	0	(0.0)	0	(0.0)
Investigations	31	(55.4)	6	(10.7)	1	(1.8)	0	(0.0)
Weight decreased	14	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	28	(50.0)	4	(7.1)	0	(0.0)	0	(0.0)
Paronychia	11	(19.6)	2	(3.6)	0	(0.0)	0	(0.0)
Nervous system disorders	28	(50.0)	10	(17.9)	1	(1.8)	1	(1.8)
Headache	17	(30.4)	3	(5.4)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	24	(42.9)	4	(7.1)	0	(0.0)	2	(3.6)
Epistaxis	12	(21.4)	0	(0.0)	0	(0.0)	0	(0.0)
Blood and lymphatic system disorders	15	(26.8)	2	(3.6)	1	(1.8)	0	(0.0)
Anaemia	11	(19.6)	2	(3.6)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	24	(42.9)	6	(10.7)	3	(5.4)	0	(0.0)
Decreased appetite	13	(23.2)	2	(3.6)	0	(0.0)	0	(0.0)

Source data: Table 15.3.1: 6

Source: Applicant's analysis found on pg. 94 of 1229 in the CSR

Conclusions

Overall, there is no data to support substantial anti-tumor activity within this pediatric patient population. The results of Trial 1200.120 did not identify any new safety signals in pediatric patients. The safety and effectiveness of afatinib in pediatric patients have not been established.

Fulfillment of Written Request

The Division of Oncology 2 reviewed the clinical study report for Trial 1200.120 as part of the labeling supplement, which was submitted to the NDA 201292 on October 7, 2021. The Division assessed that the terms of the Written Request had been met based on the information in the Written Request. The Pediatric Exclusivity Board met on February 9, 2022 and determined that exclusivity could be granted. The Annotated Written Request Amendment #4 table, which includes an assessment of how the Written Request requirements were met, is provided as an appendix to this review.

Conclusions and Regulatory Action

The Division agrees with approval of the supplement with the agreed-upon labeling and with the Pediatric Exclusivity Board's recommendation that pediatric exclusivity be granted based upon fulfillment of the terms of the Written Request. Refer to Section 5 regarding the recommended labeling language.

5 Labeling Recommendations

5.1 Prescription Drug Labeling

The following text represents the sponsor's proposed addition to Section 8.4, Pediatric Use:

Safety and effectiveness of GILOTRIF in pediatric patients have not been established.

A summary of the changes recommended by the review team are provided below:

- The FDA recommended revising the proposed labeling to shorten the summary of the study based on recommendations found in the March 2019 FDA *Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling*, which states "When it is determined that available evidence regarding safety or effectiveness does not support a pediatric indication, relevant pediatric information related to the unapproved use that is included in labeling generally should be placed only in the Pediatric Use subsection. Negative studies and inconclusive studies should be briefly summarized in this subsection... Furthermore, when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) compared with adults, a summary of this information should be included in the Pediatric Use subsection."

- The FDA recommended adding NCT number to provide an additional information source for healthcare providers.

- The FDA recommended revising the age range based on 21 CFR 201.57(c)(9)(iv)(A): The terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

- Revision of study population description were proposed for brevity.

- The FDA recommended (b) (4) }.

The agreed-upon labeling is provided below:

Safety and effectiveness of GILOTRIF in pediatric patients have not been established.

The safety and efficacy of afatinib were assessed, but not established, in a single-arm, open-label, multicenter trial [NCT02372006] which included 37 pediatric patients 2 to <17 years of age with recurrent/refractory solid tumors with known ErbB pathway deregulation who received 80% of the adult dose per body surface area. No new safety signals were observed in pediatric patients in this trial. In these 37 patients, the pharmacokinetic parameters were within range of values in adults.

6 Deputy Division Director (Clinical) Comments

I concur with the review team's findings and recommendations.

X

Martha Donoghue, MD

7 Appendices

7.1 OCP Appendices (Technical documents supporting OCP recommendations)

7.1.1 Population PK Analysis

7.1.1.1 Executive Summary

The pharmacokinetics (PK) of afatinib in 56 patients was adequately described by a two-compartment disposition model with first-order elimination and first-order absorption with lag-time. Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of afatinib in patients across different age groups and in patients administered with tablet or solution.

Simulations were performed using the developed model to compare predicted exposure with BSA based dosing in the pediatric population to an adult population. Following administration of 18 mg/m2 afatinib, simulations indicated that both AUCτ,ss and Cmax,ss were similar to the exposure with 40 mg dose in adult patients. FDA concurs with the applicant that at a dose of 18 mg/m²/day, the pharmacokinetic parameters in patients aged 2 to less than 18 years were within range of values previously observed in adults.

7.1.2.1 PPK Assessment Summary

General Information		
Objectives of PPK Analysis		• Characterize the PK of afatinib in a pediatric population with a recurrent/refractory solid tumor with known epidermal growth factor receptor (EGFR) pathway dysregulation • Perform simulation to compare pediatric and adult exposure
Study Included		Study 1200.120
Dose(s) Included		10 mg to 40 mg
Population Included		Pediatric patients with solid tumors
Population Characteristics (Table 6, Table 7)	General	Age median 11.5 yr (2-18 yr) Weight median 39.6 kg (12-125 kg) 32/56 (57%) male 52/56 (93%) white
	Pediatrics (if any)	Age 11.4 yr (2-18 yr, 2% subj <=2 yr, 21% subj <=6 yr, 32% subj <=12 yr, 45% <=18 yr)
No. of Patients, PK Samples, and BLQ		56 patients, 882 PK samples

Covariates Evaluated	Static	Sex, eGFR, ALT, status (Lansky score for patients aged ≤12 and Karnofsky score for patients aged >12)	
	Time-varying	None	
Final Model		**Summary**	**Acceptability [FDA's comments]**
Software and Version		NONMEM v7.3	Acceptable
Model Structure		The population PK of afatinib was adequately described by a two-compartment disposition model with first-order elimination and first-order absorption with lag-time.	Acceptable
Model Parameter Estimates		Table 8	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		All of the PK parameters were estimated with good precision. The IIV in PK parameters were estimated to be moderate, with a CV of 32.1% for CL/F and 59% for Vc/F. The shrinkage for CL/F and Vc/F were 15.8% and 21.1%, respectively.	Acceptable
BLQ for Parameter Accuracy		BLQ data were excluded from the analysis.	Acceptable. The BLQ percentage is low (6.3%)
GOF, VPC		Figure 11, Figure 12, Figure 13	Acceptable
Analysis Based on Simulation (optional)		Figure 14	Acceptable
Labeling Language		**Description**	**Acceptability [FDA's comments]**

8.4 Pediatric Use	Safety and effectiveness of afatinib in pediatric patients have not been established. The safety and efficacy of afatinib were assessed, but not established, in a single-arm, open-label, multicenter trial [NCT02372006] which included 37 pediatric patients 2 to <17 years of age with recurrent/refractory solid tumors with known ErbB pathway deregulation who received 80% of the adult dose per body surface area. No new safety signals were observed in pediatric patients in this trial. In these 37 patients, the pharmacokinetic parameters were within range of values previously observed in adults.	Acceptable

Table 6. Summary of Baseline Continuous Characteristics in the Analysis Dataset.

Covariate		
Age (year)	min **median** max	2.00 **11.5** 18.0
	mean (SD)	10.7 (4.57)
	N	56
WT (kg)	min **median** max	12.0 **39.6** 125
	mean (SD)	42.0 (22.5)
	N	56
AST (U/L)	min **median** max	10.0 **25.0** 95.0
	mean (SD)	29.5 (16.9)
	N	56
ALT (U/L)	min **median** max	5.00 **18.5** 74.0
	mean (SD)	25.2 (17.3)
	N	56
eGFR ($mL/min/1.73m^2$)	min **median** max	30.0 **171** 283
	mean (SD)	172 (49.6)
	N	56

WT: body weight; AST: asparate aminotransferase; ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate (Equation 1); SD: standard deviation.

Source: Table 3 in Applicant's popPK report

Table 7. Summary of Baseline Categorical Characteristics in the Analysis Dataset.

Covariate			All
Sex	Female	N	24
		Percent (%)	43
	Male	N	32
		Percent (%)	57
Race	Asian	N	1
		Percent (%)	2
	Black	N	2
		Percent (%)	4
	White	N	52
		Percent (%)	93
	Unknown	N	1
		Percent (%)	2
Disease status[a]	Karnofsky score: 60	N	2
		Percent (%)	4
	Karnofsky score: 70	N	1
		Percent (%)	2
	Karnofsky score: 80	N	11
		Percent (%)	20
	Karnofsky score: 90	N	5
		Percent (%)	9
	Karnofsky score: 100	N	6
		Percent (%)	11
	Lansky score: 50	N	2
		Percent (%)	4
	Lansky score: 70	N	6
		Percent (%)	11
	Lansky score: 80	N	5
		Percent (%)	9
	Lansky score: 90	N	7
		Percent (%)	12
	Lansky score: 100	N	11
		Percent (%)	20
Food status	Fasted	N	41
		Percent (%)	73
	Fed	N	15
		Percent (%)	27
Formulation	Solution	N	31
		Percent (%)	55
	Tablet	N	22
		Percent (%)	39
	Solution via feeding tube	N	3
		Percent (%)	5

[a] Lansky score was used for patients aged $\leq$ 12 and Karnofsky for those $>$ 12 years.

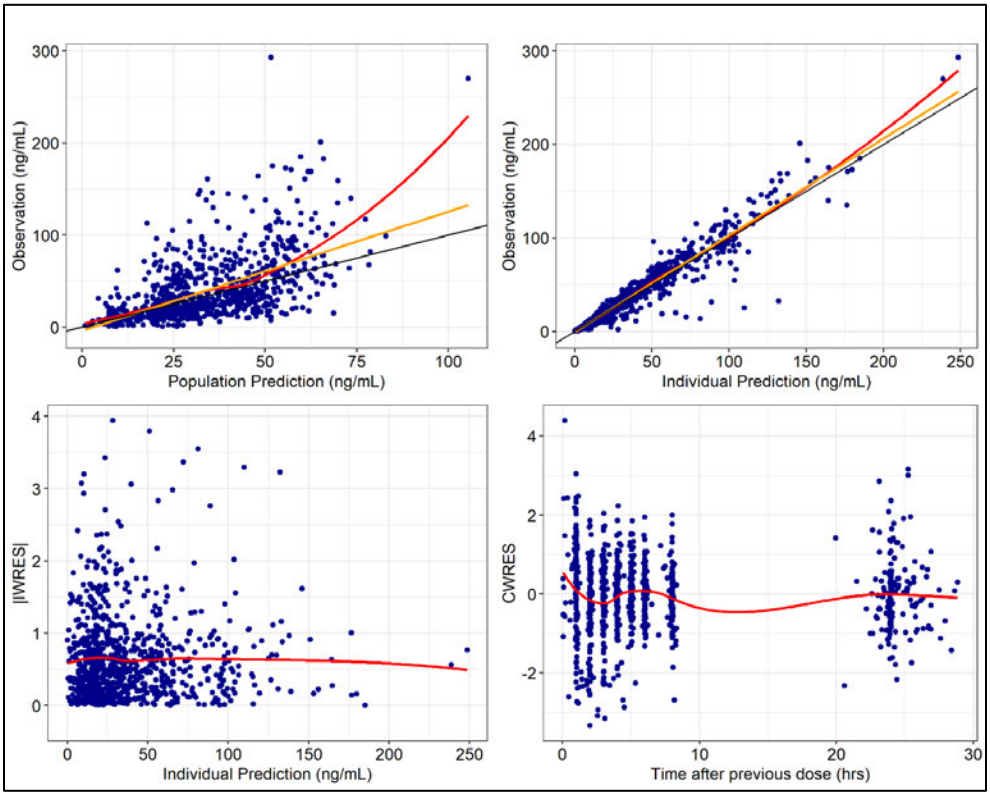
Source: Table 4 in Applicant's popPK report

Table 8. Parameter Estimates and SE from Final Population PK Model.

		Base/final model		
OFV		4904.0		
Condition number		147.9		
		Base/final model		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
CL/F	L/h	26.8	8.18	
V_c/F	L	630	11.5	
V_p/F	L	787	23.3	
Q/F	L/h	28.7	16.0	
k_a	h^{-1}	1.00	17.9	
Absorption lag time	h	0.740	6.38	
Effect of age on V_c/F and V_p/F	Exponent in power model	0.302	66.1	
Effect of weight on CL/F and Q/F	Exponent in power model	0.750	(FIX)	
Effect of weight on V_c/F and V_p/F	Exponent in power model	1.00	(FIX)	
IIV CL/F	(CV)	0.501	14.4	15.8
IIV V_c/F	(CV)	0.466	20.7	21.1
Corr. CL/F-V_c/F		0.517	20.3	
IOV KA	(CV)	1.07	12.0	9.06
IOV F1	(CV)	0.374	12.3	11.4
Prop. RUV	(CV)	0.234	6.37	12.3
Add. RUV	ug/L	0.723	60.6	12.3

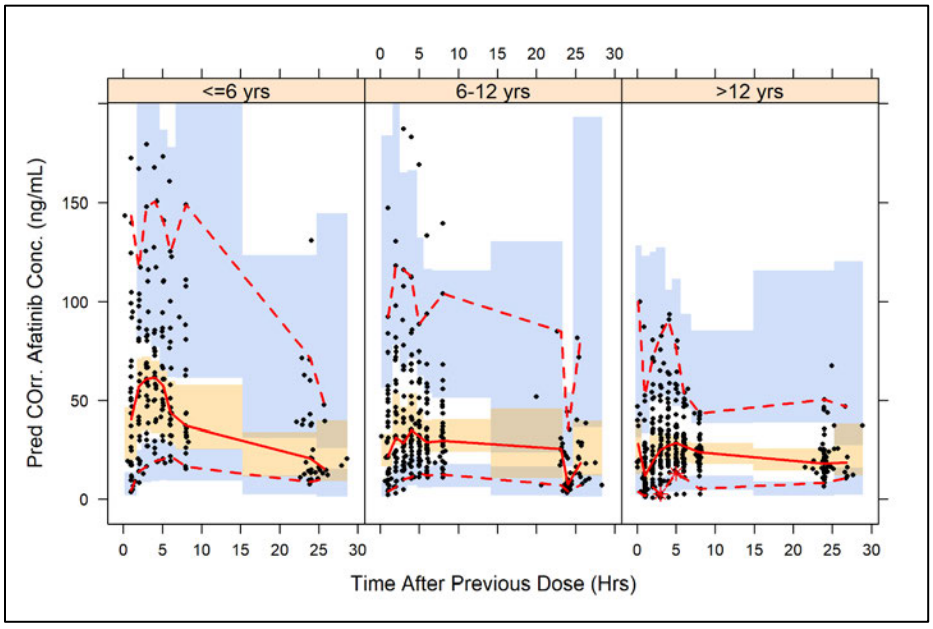
Source: Table 6 in the Applicant's popPK report

Figure 11. Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED).



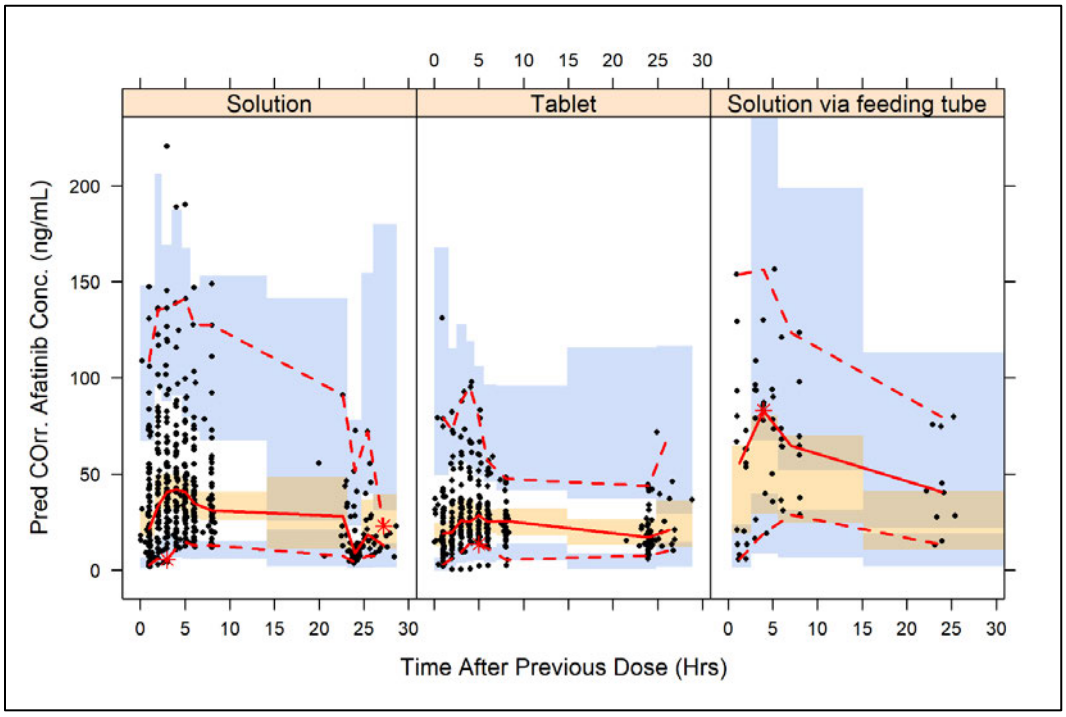
Source: Reviewer's Independent Analysis

Figure 12. VPC of Final Population PK Model, Stratified by Age Groups.



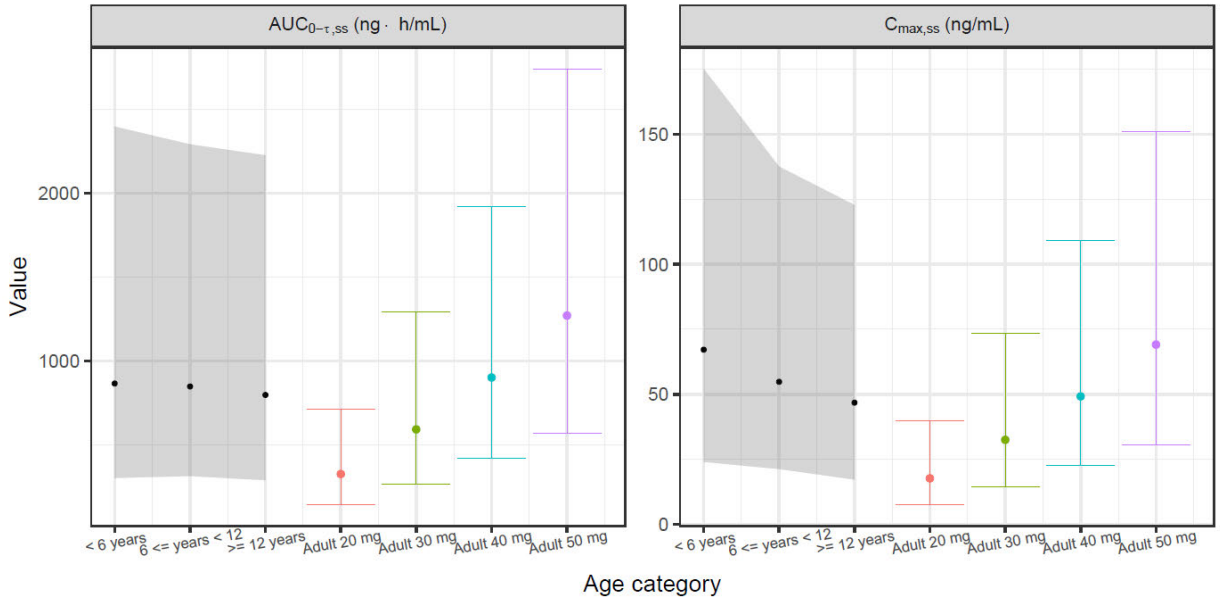
Source: Reviewer's Independent Analysis

Figure 13. VPC of Final Population PK Model, Stratified by Formulation.



Source: Reviewer's Independent Analysis

Figure 14. Simulated $AUC_{0-\tau,ss}$ and Cmax,ss in the pediatric population (receiving 18 mg/m^2 afatinib) versus adult values.



Note: The points represent the 50th percentile and the shaded area is bounded by the 5th and 95th percentiles of the simulated data. The error bars represent the 5th and 95th percentiles of

the adult data. 1000 pediatric subjects per age category were simulated. AUC: area under the curve; SS: steady-state; τ: dosing interval; Cmax,ss: maximum concentration at steady-state.
Source: Figure 16 in Applicant's popPK report

The FDA's Assessment:

The PK of afatinib in 56 pediatric patients was adequately described by a two-compartment disposition model with first-order elimination and first-order absorption with lag-time.

No signs of model misspecification were identified in the goodness-of-fit plots. Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of afatinib in patients across different age groups.

Among 56 patients included in the popPK analysis, 22, 31 and 3 patients were administered with the commercial tablet, solution and solution via feeding tube, respectively. Prediction-corrected visual predictive check also showed that the final model adequately described the observed PK profile of afatinib in patients administered with tablet or solution.

Simulations were performed using the developed model to compare predicted exposure with BSA based dosing in the pediatric population to an adult population. Following administration of 18 mg/m^2 afatinib, simulations indicated that both AUCτ,ss and Cmax,ss were similar to the exposure with 40 mg dose in adult patients. FDA concurs with the applicant that at a dose of 18 mg/m^2/day, the pharmacokinetic parameters in pediatric patients aged 2 to less than 18 years were within range of values previously observed in adults.

8 Pediatrics

8.1 Annotated Written Request Table

Written Request Items	Information Submitted (BI's Response)	Division's Comments
	The Conclusions from the synoptic interim report are: • The MTD and RP2D was determined to be 80% of the adult MTD/m2 BSA based on allometric scaling. Preliminary PK data suggest that allometric dose scaling was appropriate to provide pediatric patients with similar afatinib exposure, by accounting for age	The Division agrees with the Sponsor's response and that these terms of the WR were met.
Part 2: An activity-estimating, disease-specific parallel cohort study of afatinib in patients aged 1 to <18 years with relapsed or refractory tumors with evidence of ErbB-dysregulation based upon the presence of overexpression or amplification of EGFR or HER2 using the criteria established in the companion biomarker study.The study will have three tumor-specific cohorts: HGG ≥ 5 patients; EM ≥ 5 patients, DIPG ≥ 4 patients. In addition to these three disease-specific cohorts, the trial will include a histology-agnostic cohort of patients with refractory tumors, including those which were studied for biomarker feasibility or other tumors that fulfill the biomarker screening criteria; this cohort will have a minimum of five patients. The amendment to Part 2 of the ongoing trial 1200.120 must be reviewed and agreed upon by the FDA prior to enrollment. Efficacy in patients aged ≥1 to < 18 cannot be extrapolated and will be determined by the studies outlined in the WR.	Inclusion criteria for MTD expansion cohorts/ Phase II part: Patients aged ≥1 to <18 years with a histological diagnosis of high grade glioma (HGG), diffuse intrinsic pontine glioma (DIPG), low grade astrocytoma, medulloblastoma/PNET, ependymoma (EM), neuroblastoma, rhabdomyosarcoma and/or patients with other solid tumors (regardless of histology) but with known ErbB pathway deregulation which fulfil at least two of the below criteria: • EGFR gene amplification (FISH): Either EGFR/Cen7 ≥2.0 or ≥10% of cells with ≥15 copies or ≥40% of cells with ≥4 copies or gene cluster in ≥10% of cells • HER2 gene amplification (DDISH): Her2/CEP17 ≥2.0 • EGFR protein expression: H-score >150 (membrane staining) • HER2 protein expression: H-score >0 (membrane staining)	As referenced in the introductory portion of this document, the division met with the sponsor several times over the course of the development program and agreed with the changes to Part 2 of the trial. Part 1 of the trial was initiated in May 2015, and Part 2 of the trial was initiated April 2016. A Type C meeting was held with the division on August 8, 2016 to discuss the PPSR, at which time Part 2 of the trial was already ongoing. The language "The amendment to Part of the ongoing trial 1200.120 must be reviewed and agreed upon by FDA prior to enrollment," was included in the original Written Request and appears to refer to future amendments to Part 2. The sponsor subsequently met with FDA to discuss the conduct of Part 2 of the trial, as referenced in the background above. The division therefore considers that this term of the Written Request have been met.
		As per the written request the division specified the number of patients required for each tumor type: HGG ≥ 5 patients; EM ≥ 5 patients, DIPG ≥ 4 patients.

Written Request Items	Information Submitted (BI's Response)	Division's Comments
NONCLINICAL STUDY(IES)		
Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.	N/A	N/A
BI must submit the results of analytical validation studies for the planned biomarker assays, preferably in neuroectodermal tumor tissues and rhabdomyosarcomas, demonstrating the reliability and reproducibility of these assays.	The analytical validation studies were submitted to IND 118981. These included validation of IHC and FISH assays for Her3, Her2, and EGFR expression in pediatric neuroectodermal tumors.	Validation studies submitted under IND 118981 submission: SEQ 0114 dated 01/22/20 SEQ 0070 dated 06/15/17 SEQ 0070 dated 06/15/17 SEQ 0070 dated 06/15/17 SEQ 0070 dated 06/15/17 SEQ 0070 dated 06/15/17 The Division agrees with the Sponsor's response and that these terms of the WR were met.
CLINICAL STUDIES		
Study 1 (Study 1200.120): A multicenter, open-label, two-part trial to identify a pediatric dose, assess the pharmacokinetics, and investigate the anti-tumor activity of afatinib when administered for the treatment of pediatric tumors with known ErbB pathway dysregulation.	entitled *"Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumors, rhabdomyosarcoma and/or other solid tumors with known ErbB pathway deregulation*	The Division agrees with the Sponsor's response and that these terms of the WR were met.
Part 1:Dose finding to determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and pharmacokinetics of afatinib	entitled *"Phase I open label, dose escalation trial to determine the MTD, safety, pharmacokinetics and efficacy of afatinib monotherapy in children aged 2 years to <18 years with recurrent/refractory neuroectodermal tumors, rhabdomyosarcoma and/or other solid tumors with known ErbB pathway deregulation regardless of tumor histology*	The MTD was determined as the highest dose at which no more than 1/6 patients experienced DLTs, and was determined to be dose level 0. The incidence of DLTs and determination of the MTD is described in the study report.

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		Enrollment criteria has been met by the sponsor: High Grade Gliomas (HGG): 6 patients Ependymomas (EM): 8 patients Diffuse Intrinsic Pontine Gliomas (DIPG): 4 patients Enrollment in the study was not limited to these tumor types, but was open to patients with other tumors that met the molecular eligibility criteria. In addition, histology agnostic cohort was included as per WR with the following number of patients enrolled: 4 Rhabdomyosarcoma (RMS) 3 Neuroblastoma (NB) 1 Astrocytoma (ASTR) 1 Primitive Neuroectodermal Tumor (PNET) 10 other *2 Exploratory- Not in WR The Division agrees with the Sponsor's response and that these terms of the WR were met.
OBJECTIVES OF EACH STUDY:		
Study 1: Part 1: • Primary objectives: Determine the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), safety, and pharmacokinetics of afatinib in pediatric patients. The MTD of afatinib as monotherapy will be	Part 1: Primary Objective of the dose finding part was to determine the maximum tolerated dose (MTD), safety, and pharmacokinetics of afatinib in pediatric patients. The MTD of afatinib as single agent was determined in the pediatric patient population across all applicable tumor entities, based on the occurrence of dose limiting toxicities (DLTs). Secondary objective: To determine Objective Response	The Division notes that the determination of DOR is listed by the sponsor as a secondary objective for part 2, instead of as a primary objective. Although DOR was listed by the sponsor as a secondary objective, this is only a difference in terminology, not in study conduct. In this case, the fact that the sponsor listed DOR as a secondary objective does not reflect a difference from the terms of the WR;

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determined in the pediatric patient population across all applicable tumor types based on the occurrence of dose limiting toxicities (DLTs). • Secondary objectives: Explore the preliminary objective response by investigator assessment according to the protocol-specified response evaluation criteria for each tumor type studied. Part 2: • Primary objectives: Determine the objective response rate (ORR) and duration of response (DOR) in children age ≥1years to <18 years in three disease specific cohorts of pediatric patients with relapsed or refractory tumors. • Secondary objectives: Evaluation of progression free survival, and pharmacokinetics of afatinib.	by investigator assessment according to the institutional response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease. Part 2: Primary objective of the MTD expansion cohorts/Phase II part was objective response by investigator assessment according to the institutional response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease. Secondary objectives: To determine progression free survival (PFS), DOR, PK.	the conduct of the study was consistent with DOR being a primary objective for part 2 and thus consistent with the terms of the WR. Specifically, DOR is only considered in the context of ORR; DOR is a key component of evaluating the clinical meaningfulness of ORR, and the sponsor included ORR as a primary objective for part 2. Additionally, this is a single arm study with a descriptive statistical analysis plan. The sponsor has evaluated DOR and provided that relevant data in the CSR. Accordingly, the Division agrees with the Sponsor's response and that these terms of the WR were met.
PATIENTS TO BE STUDIED:		
Age group in which study(ies) will be performed: children ages 1 to < 18.	Children aged ≥1 year to <18 years	The Division agrees with the Sponsor's response and that these terms of the WR were met.
The 1-year lower age limit for this study was selected because it is highly unlikely that patients younger than 1 year of age would have exhausted other available treatment options at the time of entry into this study. Patients less than 1 years of age are more likely to be undergoing first line therapy for their tumors and less likely to have already	Part 1: age range 2 to 17 yrs Part 2: age range 3 to 17 yrs	Total of 56 patients enrolled. Part 1: 17 Part 2: 39 As per the written request the division specified the number of patients required for each tumor type: HGG ≥ 5 patients; EM ≥ 5 patients, DIPG ≥ 4 patients. Enrollment criteria has been met by the

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experienced recurrence or progression of disease. For this reason, neonates will not be included. • Number of patients to be studied: Study 1 • Part 1: A minimum of 17 patients • Part 2: A minimum of 5 patients each in the HGG and EM cohorts, a minimum of 4 patients in the DIPG cohort and a minimum of 5 patients in the histology-agnostic cohort, for a minimum of 20 patients in • A minimum of 50 patients in both Parts 1 and 2 is planned.		sponsor: HGG 6 patients EM 8 patients DIPG 4 patients In addition, histology agnostic cohort was included as per WR with the following number of patients enrolled: 4 RMS 3 NB 1 ASTR 1 PNET 11 other *2 Exploratory- Not in WR The Division agrees with the Sponsor's response and that these terms of the WR were met.
REPRESENTATION OF ETHNIC AND RACIAL MINORITIES:		
The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.	Study 1 was a multinational trial conducted in 28 sites (with screened patients) in 11 countries in continents Australia, Europe, and North America. The coordinating investigator was Birgit Geoerger, MD, PhD, Institut Gustave Roussy, Villejuif, France. Accordingly, a high percentage (27%) of patients were from France. Sites and investigators were selected based on their experience in treating pediatric patients in the trial indication. Because children with tumors with known ErbB pathway deregulation are rare, the selection of available sites was limited. Of the 56 treated patients, 32 patients (57.1%) were male and 24 patients (42.9%) were female. The	The Division agrees that a reasonable effort to address this requirement has been made by the sponsor and these terms of the WR were met.

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	majority of patients were White (36 patients, 64.3%) and not Hispanic or Latino (46 patients, 82.1%). Two patients (3.6%) were Black or African American and 1 patient (1.8%) was Asian. However, 15 patients (26.8%) were from France, where information on race was not collected in accordance with local regulations. BI is of the opinion that there is no reason to believe that the population recruited in Study 1 would not adequately represent the broader pediatric patient population and therefore the data collected from the trial should be applicable to all pediatric patients with tumors with known ErbB pathway deregulation.	
STUDY ENDPOINTS:		
Safety Endpoints: **Study 1** • Primary endpoint: Identification of dose limiting toxicity, determination of the maximum tolerated dose and the recommended phase 2 dose of afatinib. • Other endpoints: overall incidence and Common Terminology Criteria for Adverse Events (CTCAE) grade of adverse events, as well as relatedness of adverse events to treatment, events leading to dose reduction, events leading to permanent treatment discontinuation, adverse events of special interest (AESI), and causes of death. The following adverse events are considered AESI and must be actively	The primary endpoint was the occurrence of DLT measured during the first course of treatment. The MTD was determined as the highest dose at which no more than 1/6 patients experienced DLT. The MTD evaluation period was defined as the initial 28 days of study treatment. Patients who completed the MTD evaluation period without missing >25% of the afatinib doses regardless of the reason were evaluable for DLT. Other safety assessments included incidence and intensity of adverse events (AEs) according to common terminology criteria for adverse events (CTCAE) version 3.0, relatedness of AEs to trial treatment, AEs leading to dose reduction, AEs leading to permanent treatment discontinuation, protocol-defined AESI, and causes of death physical examinations, and evaluation of safety clinical laboratory parameters (hematology, biochemistry, coagulation, and urine).	The following adverse events are considered AE or AESI and were actively monitored: hepatic injury, diarrhea, reduced renal function, keratitis, and cardiac failure. A schedule of assessments is provided in Table 2 below, which was taken directly from the study protocol. The MTD was determined as the highest dose at which no more than 1/6 patients experienced DLT. The MTD was determined when the last patient included into the dose finding part completed his/her 1st treatment cycle and was evaluable for DLTs. The Division agrees with the Sponsor's response and that these terms of the WR were met.

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monitored: hepatic injury, diarrhea, reduced renal function, keratitis, and cardiac failure.		
Efficacy Endpoints: **Study 1** • The primary efficacy endpoint will be ORR and duration of response (DOR) as assessed by the investigator according to the protocol-specified response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease. • Secondary endpoints: progression free survival (PFS), for descriptive purposes only, defined as the duration of time from the date of first treatment until the date of the first documented progression or death due to any cause, tumor shrinkage, and overall survival defined as the duration from the date of first treatment to the date of death.	Study 1: Part 1: The primary endpoints: safety endpoint and PK endpoints. Secondary Endpoints: Objective Response by investigator assessment according to the institutional response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease. Part 2: The primary endpoint was objective response by investigator assessment according to the institutional response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease. Secondary endpoints included progression free survival (PFS) and duration of response (DOR). Further endpoints included tumor shrinkage, overall survival, patients' drug acceptability tumor biology and ErbB pathway deregulation assessments, and health-related quality of life.	Although DOR was listed by the sponsor as a secondary endpoint, this is only a difference in terminology, not in study conduct. In this case, the fact that the sponsor listed DOR as a secondary endpoint does not reflect a difference from the terms of the WR; the conduct of the study was consistent with DOR being a primary endpoint and thus consistent with the terms of the WR. Refer to discussion above under Study Objectives regarding the inclusion of determination of DOR as a primary objective for additional information. Division considers these endpoints adequately evaluated given the descriptive nature of the analyses, therefore the Division agrees with the Sponsor's response and that these terms of the WR were met.
Pharmacokinetic Endpoints: **Study 1** Estimated apparent clearance (CL/F) and volume of distribution (Vd/F) of afatinib from pharmacokinetic (PK) samples obtained across all studies from a minimum of 20 patients ≥ 2 to < 12 years of age. • Include PK evaluation for enrolled patients < 2 years of age and ≥ 12 years of age. Population PK analysis should be performed using afatinib concentration data obtained from all	Report provided in submission: PK analysis of Afatinib in pediatric populations	All estimated PK parameters and endpoints were met from a minimum of 20 patients ≥ 2 to < 12 years of age. Twenty-eight patients 2 - < 12 years old were studied. The Division and Clinical pharmacology agrees with the Sponsor's response and that these terms of the WR were met.

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studies. • Assess the effects of age, weight, and other relevant covariates on the PK of afatinib.		
A Data Monitoring Committee (DMC) must be included.	DMC was included. See Section 6 of the CTR. As this was the first afatinib trial with pediatric patients, a DMC was appointed. The DMC was an independent multidisciplinary group consisting of 3 independent pediatrics oncologists, a BI medical representative, and an external statistician.	The Division agrees with the Sponsor's response and that these terms of the WR were met.
KNOWN DRUG SAFETY CONCERNS AND MONITORING		
The tolerability and safety of afatinib has been established in adults. Clinically significant adverse reactions associated with the use of afatinib include diarrhea, bullous and exfoliative skin disorders, (including toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome), interstitial lung disease, hepatic toxicity, and keratitis. Diarrhea is the most common adverse reaction observed in patients who received afatinib occurring in 96% of patients, with Grade 3-4 occurring in 15% or patients. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with afatinib, of which 1.3% were Grade 3. Cases of pneumonitis/ILD have been reported in 1.6% of adult patients treated with afatinib; of these, 0.4% were fatal. Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of adult patients treated with afatinib. The overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and		Patients were monitored for adverse events including: diarrhea, rash, reduced renal function, acute onset and/or unexplained worsening pulmonary symptoms, acute onset of symptoms indicative of impaired cardiac function, and keratitis and adequate management plans were in place. A schedule of assessments is provided in Table 2 below, which was taken directly from the study protocol. The Division agrees that the protocol included adequate patient safety monitoring and appropriate management guidelines; therefore, terms of the WR were met.

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the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Post marketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving afatinib. Approximately 10% of patients treated with afatinib experienced liver test abnormalities, of which 0.2% were fatal. Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with afatinib of which 0.05% of patients experienced Grade 3 keratitis. Throughout the studies described herein, all patients will be monitored for safety concerns including the adverse reactions listed above. These data will be assessed periodically along with all other safety parameters for any potential risks that may not be foreseeable from the known adult exposure or from preclinical findings. A patient whose symptoms are not manageable with allowable medications will be discontinued from the study and treated according to local treatment guidelines		
EXTRAORDINARY RESULTS:		
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected	Division Comment: No extraordinary results.	The Division agrees with the Sponsor's response and that these terms of the WR were met.

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findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.		
DRUG INFORMATION:		
Dosage Form: ○ Film coated tablets: 20 mg, 30 mg, 40 mg, and 50 mg film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent of afatinib dimaleate) ○ Capsules and solvent for oral solution: 4 mg/mL solution • Route of Administration: ○ Oral. An age-appropriate formulation will be used in Study 1. • Regimen: ○ Part 1: The starting dose was 80% of the adult dose based on allometric scaling and was increased to 100% of the adult dose based on allometric scaling. The 100% of allometric scaling exceeded the MTD of afatinib because 2 of 5 evaluable patients experienced a DLT. ○ Part 2: The MTD/RP2D determined in Part 1 was 80% of the recommended adult dose per m2 body surface using allometric scaling. This is the dose to be used in Part 2 of the trial.	Division Comment: Dosage form used: 200 mg capsule to be dissolved in aqueous solvent (2 capsules per 100 ml solvent), i.e. 4 mg/mL; dosed to achieve dose level 0 or dose level 1 for the individual patient; administration once daily	The Division agrees with the Sponsor's response and that these terms of the WR were met.

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Drug Formulation: In accordance with section 505A(e)(2) of the Federal, Food, Drug and Cosmetic Act, if 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval); 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and 3) you have not marketed the formulation within one year after the Agency publishes such notice, The Agency will publish a second notice indicating you have not marketed the new pediatric formulation. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to		

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the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-bystep compounding instructions; packaging and storage requirements; and formulation stability information. 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.		
STATISTICAL INFORMATION		
Study 1 Part 1 • A Rolling-6 dose-escalation design will be used to identify the maximum tolerated dose or RP2D and evaluate the toxicity profile of afatinib in pediatric patients. • A total of 17 patients will be enrolled and treated in the dose finding portion of Study 1. Part 2 • Given the single arm trial design and the small number of patients in each histology-defined cohort, statistics will be descriptive only.		Part 1: The dose finding part used a rolling six design to determine the MTD. Part 2: All analyses were descriptive and exploratory in nature. The Division agrees with the Sponsor's response and that these terms of the WR were met.
LABELING THAT MAY RESULT FROM THE STUDY		
You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of	The sponsor proposes the following labeling changes to **Section 8.4 Pediatric Use.** BI's proposed draft labeling text is included in Module	The Division confirms that a labeling supplement was submitted and the terms of the

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whether the study demonstrates that afatinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.	1.14.1.3 of this sNDA. **Current label:** The safety and effectiveness of GILOTRIF in pediatric patients have not been established. **Proposed label:** (b) (4) (b) (4)	WR were met. Review of the proposed labeling is ongoing.
FORMAT AND TYPES OF REPORTS TO BE SUBMITTED		
You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, an interpretation.	Full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data are submitted with this sNDA.	Full study reports were submitted by BI, which included information for of each pediatric patient that was enrolled, including country of origin, gender, ethnicity, age, race, height, and weight information. Due to certain local

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In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.	The reports included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the WR.	regulatory restrictions in France, ethnicity and racial data is listed as "missing" for patients who enrolled in a site in France; however, we note that categorizing patients using one of the specified designations for race is not a requirement in the WR. The Division agrees with the Sponsor's response and that these terms of the WR were met.
Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarket adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.	Routine periodic safety reports as described in ICH E2C are submitted to the afatinib NDA 201292.	The Division agrees with the Sponsor's response and that these terms of the WR were met.
Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards	Key safety and efficacy datasets in legacy format data are included with this sNDA submission.	The Division agrees with the Sponsor's response and that these terms of the WR were met.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Suryatheja Ananthula, PhD	CDER/OTS/OCP/DCPII Suryatheja Ananthula -S Digitally signed by Suryatheja Ananthula -S Date: 2022.04.06 14:05:35 -04'00'	Sections: 3, 7	**Select one:** _X_ Authored ___Approved
	Signature:			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 3, 7	**Select one:** ___Authored _X_ Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2022.04.06 15:25:43 -04'00'			
Clinical Pharmacology/ Pharmacometrics	Youwei Bi, PhD	CDER/OTS/OCP/DCPII	Sections: 3, 7	**Select one:** ___Authored _X_ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2022.04.06 14:10:14 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Stacy Shord, PharmD	CDER/OTS/OCP/DCPII	Sections: 3, 7	**Select one:** ___Authored _X_Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2022.04.07 09:01:06 -04'00'			
Clinical Reviewer	Marjilla Seddiq, MD	CDER/OOD/DO2	Sections: 1, 2, 4, 5, 8	**Select one:** ___Authored ___Approved
	Signature: Marjilla Seddiq -S Digitally signed by Marjilla Seddiq -S Date: 2022.04.06 14:27:21 -04'00'			
Clinical Team Leader	Diana Bradford, MD	CDER/OOD/DO2	Sections: All	**Select one:** __X_Authored __X_Approved
	Signature: Refer to CDTL signature			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	Barbara Scepura, MSN	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_ Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2022.04.05 10:02:33 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: Diana L. Bradford -S Digitally signed by Diana L. Bradford -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001559418, cn=Diana L. Bradford -S Date: 2022.04.04 18:44:08 -04'00'			
Deputy Division Director (Clinical)	Martha Donoghue, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_ Approved
	Signature: Martha Donoghue -S Digitally signed by Martha Donoghue -S Date: 2022.04.04 18:16:20 -04'00'			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ASHLEY R LANE
04/07/2022 03:24:13 PM

DIANA L BRADFORD
04/07/2022 03:24:59 PM

MARTHA B DONOGHUE
04/07/2022 03:27:14 PM