

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212018Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

**Cross Discipline Team Leader
Review**

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212018
Priority or Standard	Priority Review
Submit Date(s)	September 18, 2018
Received Date(s)	September 18, 2018
PDUFA Goal Date	May 18, 2019
Division/Office	DOP1/OHOP/OND/CDER
Review Completion Date	April 11, 2019
Established Name	Erdafitinib
(Proposed) Trade Name	Balversa
Pharmacologic Class	Kinase inhibitor
Code name	JNJ-42756493
Applicant	Janssen Research & Development
Formulation(s)	Tablets: 3 mg, 4 mg, and 5 mg
Dosing Regimen	8 mg (two 4 mg tablets) orally once daily, with dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate levels and tolerability at 14 to 21 days
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC), that has: • susceptible FGFR3 or FGFR2 genetic alterations, and • progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA

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OSE/DMEPA	Reviewer: Tingting Gao TL: Alice Chi-Ming Tu
OSE/DRISK	Reviewer: Naomi Redd N TL: Elizabeth Everhart
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BALVERSA™ (erdafitinib)

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CDRH	Sharon Liang

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP-PLT=Division of Medical Policy Programs-Patient Labeling Team
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CDRH=Center for Devices and Radiological Health

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BIRC	Blinded Independent Review Committee
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BRIDGE	Bladder Cancer Research Initiative for Drug Targeting in Germany
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
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FGFR	Fibroblast growth factor receptor
FMI	Foundation Medicine, Inc.
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
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
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
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

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
rwBTR	real world best tumor response
rwTR	real world tumor response
RWE	real world evidence
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Erdafitinib (BALVERSA™) is a kinase inhibitor that is a new molecular entity and has not previously received marketing approval for any indication by any regulatory body. Approval of erdafitinib also represents the first approval of a drug that specifically targets genetic alterations in the fibroblast receptor growth factor (FGFR) pathway.

Erdafitinib binds to FGFR1, FGFR2, FGFR3 and FGFR4 and inhibits enzymatic activity based on in vitro data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including mutations, amplifications, and fusions. Erdafitinib demonstrated antitumor activity in FGFR-expressing cell lines and xenograft models, derived from tumor types including bladder cancer.

The clinical portion of the current application was submitted on September 18, 2018 with the proposed indication of the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, (b) (4)

The dosing regimen proposed by the Applicant is 8 mg (two 4 mg tablets) orally once daily with a dose increase to 9 mg (three 3 mg tablets) once daily if serum phosphate (PO₄) level is < 5.5 mg/dL from Days 14 to 21 and there is no drug-related toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for this application is obtained from the single arm, multicenter study BLC2001 that enrolled patients with locally advanced or metastatic urothelial cancer who had tumors with FGFR3 point mutations (R248C, S249C, G370C, Y373C) or FGFR fusions (FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1). The efficacy population for this application is obtained from a cohort of 87 patients from BLC2001 who had all previously been treated with chemotherapy, which was cisplatin or carboplatin in 97% of cases. These patients all received erdafitinib at the proposed dose of 8 mg daily with pharmacodynamically-guided dose increase possible to 9 mg daily based on serum phosphate and tolerability. Of these 87 patients, 24% also previously

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received an anti PD-L1/PD-1 therapy. The confirmed objective response rate (ORR) in the 87-patient efficacy population was 32.2% and the duration of response (DoR) was 5.4 months (95% CI: 4.2, 6.9) as determined by the Blinded Independent Review Committee (BIRC). A higher ORR was observed in patients with FGFR3 point mutations (N=64, ORR: 40.6%) than in patients with FGFR3 fusions (N=18, ORR: 11.1%) or in patients with FGFR2 fusions, in whom no responses were seen (N=6)¹.

Patients with locally advanced or metastatic urothelial cancer previously treated with a platinum-containing regimen may potentially be treated with anti PD-1/PDL 1 therapy or with chemotherapy. Pembrolizumab has shown a survival advantage over chemotherapy in this population; however, the ORR observed with pembrolizumab is lower than the ORR observed with erdafitinib and time-to-event endpoints such as overall survival (OS) cannot be assessed in BLC2001 since it is a single arm trial. Responses were also observed in patients treated with erdafitinib who had not previously responded to anti PD-L1/PD1 therapy. Additionally, the ORR in published reports of chemotherapy in patients with metastatic urothelial cancer in the second line is lower than the ORR observed with erdafitinib. For example, the chemotherapy arm in the trial that led to the regular approval pembrolizumab had an ORR of 11%. Single agent chemotherapy is also generally more toxic than erdafitinib.

Recommendation for accelerated approval for this application takes into consideration the recommended approach outlined in the Guidance for Industry- Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease. Patient subgroups with FGFR3 point mutations and one class of FGFR3 fusions showed responses. Patients with all enrolled FGFR2 fusions and certain enrolled FGFR3 fusions (FGFR3-TACC3_V3 and FGFR3-BAIAP2L1) did not demonstrate responses; however, the review team concluded that there were too few of these patients enrolled on BLC2001 to definitively demonstrate a lack of efficacy in these rare molecular subsets. Based on totality of information and biological feasibility, including the mechanism of action, results of in-vitro studies and results from study patients with other FGFR alterations, the indication statement will include patients with all enrolled FGFR3 and FGFR2 fusions in addition to the more common FGFR3 point mutations. BCL3001 is an ongoing randomized controlled trial of erdafitinib versus chemotherapy or immunotherapy in patients with urothelial cancer whose tumors harbor the same FGFR3 and FGFR2 gene alterations that were eligible for enrolment on BLC2001, with OS as the primary endpoint. Submission of BCL3001 results will be a postmarketing requirement (PMR) as a condition of approval for erdafitinib.

The Applicant presented real-world evidence to support the claim that patients with urothelial cancer and FGFR genetic alterations represents a unique subset of patients of patients who would not be expected to respond as well vs. unselected patients to anti PD-L1/PD-1 therapy, one of which (pembrolizumab) has regular approval in this setting based on a prolongation in overall survival.

¹ One patient with a FGFR2-CASP7/FGFR3-TACC3_V3 fusion is reported in both FGFR2 fusion and FGFR3 fusion numbers above

Review of the presented real-world data was inconclusive in establishing this class of patients as having a different expected response to these agents due to issues with methodology. Further, post hoc analysis of responses to prior anti PD-L1/PD-1 therapy in BLC2001 also showed a low response rate to previous anti PD-L1/PD-1 therapy (4.8%; 1 of 21) compared to responses to prior platinum-based chemotherapy (34.5%, 29 of 84). In addition, a higher response rate (59%) to erdafitinib was observed in patients who received prior the anti PD-L1/PD-1 therapy. These observations supports the claim that patients with advanced or metastatic urothelial cancer and FGFR genetic alterations represent a molecularly-defined subset in this setting. The Applicant presented real-world evidence to support the claim that patients with urothelial cancer and FGFR genetic alterations represents a unique subset of patients of patients who would not be expected to respond as well vs. unselected patients to anti PD-L1/PD-1 therapy, one of which (pembrolizumab) has regular approval in this setting based on a prolongation in overall survival. Review of the presented real-world data was inconclusive in establishing this class of patients as having a different expected response to these agents due to issues with methodology. Further, post hoc analysis of responses to prior anti PD-L1/PD-1 therapy in BLC2001 also showed a low response rate to previous anti PD-L1/PD-1 therapy (4.8%; 1 of 21) compared to responses to prior platinum-based chemotherapy (34.5%, 29 of 84). In contrast addition, a higher response rate (59%) to erdafitinib was observed in patients who received prior the anti PD-L1/PD-1 therapy . These observations supports the claim that patients with advanced or metastatic urothelial cancer and FGFR genetic alterations represent a molecularly-defined subset in this setting.

The final agreed upon indication for erdafitinib is for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has

- susceptible FGFR3 or FGFR2 genetic alterations and
- progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Accelerated approval of erdafitinib is recommended by all disciplines.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Summary and Assessment

Patients with locally advanced or metastatic urothelial cancer have a poor prognosis despite the high response rate seen with standard platinum/gemcitabine chemotherapy. While pembrolizumab has received regular approval in the second-line setting, patients whose tumors harbor FGFR alterations represent a molecularly-defined subset of patients with urothelial carcinoma. This subset may have a lower response rate to PD-L1/PD-1 inhibitors and represents a population of patients for which an unmet medical need exists.

Erdafitinib is a breakthrough-therapy designated kinase inhibitor targeting susceptible FGFR genetic alterations, that is under review for accelerated approval. Erdafitinib was evaluated in the single-arm phase 2 study BLC2001 which enrolled patients with locally advanced or metastatic urothelial cancer whose tumors were found to harbor specific FGFR3 and FGFR2 alterations. Efficacy and safety for the labeled indication was assessed via independently-determined confirmed response rate and reported adverse events in a cohort of 87 patients in BLC2001 who received prior chemotherapy, 97% of which was platinum-based. These patients received erdafitinib at a starting dose 8mg with a dose increase to 9mg based on serum phosphate levels and tolerability, which is the proposed dose for this approval.

The BICR-assessed response rate was 32% with a median duration of 5.4 months. Responses appeared to be higher in those patients with FGFR3 mutations (n=64, ORR=40.6%), compared to those with FGFR3 fusions (n=17, ORR=11.1%) and FGFR2 fusions (n=6, ORR 0%). A companion diagnostic will be approved with erdafitinib.

The safety profile of erdafitinib is acceptable in this setting. Deaths due to an adverse event occurred in 1.1% of patients while permanent treatment discontinuation occurred in 12.7%. Grade 3-4 adverse events occurred in 59% of patients and the most common (> 15%) all grade adverse events were hyperphosphatemia, stomatitis, dry mouth, decreased appetite, dry skin, alopecia, palmar-plantar erythrodysesthesia syndrome, dry eye, onycholysis, paronychia, nail dystrophy, diarrhea, constipation, nausea, fatigue, urinary tract infection, dysgeusia, musculoskeletal pain, weight decreased, and anemia. Ocular toxicity, hyperphosphatemia, and embryo-fetal toxicity are labeled as warnings and precautions for erdafitinib.

Accelerated approval of erdafitinib is recommended by all disciplines. The Applicant will be asked to submit the results of the randomized phase 3 trial BLC3001 that is underway to confirm the clinical benefit of erdafitinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Patients with locally advanced or metastatic urothelial cancer have a poor prognosis despite the high response rate seen with standard platinum/gemcitabine chemotherapy. Patients with tumors that are positive for FGFR genetic alterations appear to represent a molecularly-defined population with uniquely targetable disease.	Patients with locally advanced or metastatic urothelial cancer who have received prior platinum-based therapy have a serious and life-threatening condition.
<u>Current Treatment Options</u>	Pembrolizumab has received regular approval in this setting for an unselected population based on demonstrating an overall survival advantage over chemotherapy. Atezolizumab, avelumab, durvalumab, and nivolumab have also received accelerated approval for the treatment of patients with urothelial cancer who have received prior platinum-based therapy. Taxane-based chemotherapy, both single agent and combination, is also used in this setting. None of these treatment options specifically target the FGFR pathway.	Pembrolizumab has demonstrated an OS advantage over chemotherapy in this setting. It is not known if patients with advanced or metastatic urothelial cancer and FGFR alterations would be expected to benefit from pembrolizumab to the same extent as unselected patients.
<u>Benefit</u>	In a single-arm trial, the confirmed response rate by Blinded Independent Review Committee for erdafitinib in patients at the proposed dose and line of therapy was 32.2% (95% CI 22.4, 42.0). This included 2 patients with complete responses (2.3%). The median duration of response was 5.4 months (95% CI 4.21, 6.93).	Erdafitinib has demonstrated a good response rate with a median duration of response of approximately half a year and an acceptable safety profile.
<u>Risk and Risk Management</u>	- No REMS will be required. - The most commonly reported treatment emergent adverse events (TEAEs) were hyperphosphatemia (75.9%), stomatitis (56.3%), fatigue (54.0%), diarrhea (47.1%), dry mouth (44.8%), and onycholysis (41.4%). Ocular toxicity, hyperphosphatemia, and embryo-fetal toxicity are labeled	The risk-benefit profile of erdafitinib is acceptable in the approved patient population. Clinical trial BLC3001 is ongoing and will provide further data on the efficacy and safety of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	as warnings and precautions for erdafitinib. • Pembrolizumab has a survival advantage in this setting for an unselected patient population. Attempts to use real-world data to demonstrate that patients with FGFR-altered urothelial cancer would not be expected to respond as well to anti PD-L1/PD-1-directed therapy were inconclusive. • The Applicant will be required to complete and to submit the final report of clinical trial BLC3001 to confirm the clinical benefit of erdafitinib in urothelial cancer. In addition to confirmation of efficacy in a randomized setting, this trial is expected to further inform data on patients with FGFR2 fusions and certain FGFR3 fusions for which no responses were seen on BCL2001. Additionally, updated data from the randomized study BLC3001 will more fully inform the complete safety profile of erdafitinib.	erdafitinib in locally advanced or metastatic urothelial cancer.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Section 8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

 Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Urothelial carcinoma is the most common malignancy in the urinary tract system and accounts for approximately 17,240 deaths in 2018^{2,3}. Although most urothelial carcinomas are non-muscle invasive at diagnosis and can be managed effectively with surgical resection and/or intravesical therapies, approximately 10-15% of patients may develop invasive, locally advanced, and metastatic urothelial carcinoma⁴. In addition, approximately 10% of patients have locally advanced or metastatic disease at diagnosis. Standard of care for the first line treatment of patients with advanced disease is platinum-containing combination chemotherapy, such as gemcitabine and cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). However, almost all patients experience disease progression or intolerance to treatment during or after platinum-containing chemotherapy.

FGFR genetic alterations occur in about 20% of patients with relapsed or refractory urothelial cancer⁵. The most common alterations in this setting are FGFR point mutations, specifically point mutations in FGFR3. FGFR fusions (of FGFR3 and FGFR2) are less common in this setting, estimated to be found at a rate of ~5% in advanced urothelial cancer overall per literature and per numbers of patients screened and enrolled in BCL2001. FGFR2 fusions specifically are very rare in bladder cancer, and it is unclear if they represent molecular “drivers” in this setting, although they appear to be of clinical importance in other settings such as hepatobiliary cancers. There are no approved targeted therapies against FGFR for this molecularly-defined subset of urothelial patients.

Patients with locally advanced or metastatic urothelial carcinoma which has susceptible FGFR3 or FGFR2 genetic alterations and which has progressed during or following at least one line of prior chemotherapy are incurable. There is an unmet need for effective therapy to treat patients with this serious and life-threatening disease.

2.2. Analysis of Current Treatment Options

² Siegel RL et al. Cancer Statistics 2016. CA Cancer J Clin 2016; 66:7-30.

³ NCCN Guidelines v1 2016: Bladder Cance: Bladder Cancer.

⁴ Park JC et al. Multimodal management of muscle invasive bladder cancer. Curr Probl Cancer 2014; 38:80-108.

⁵ Gust KM, McConkey DJ, Awrey S, et al. Fibroblast growth factor receptor 3 is a rational therapeutic target in bladder cancer. Mol Cancer Ther. 2013;12(7):1245-54.

In the U.S., pembrolizumab has received regular approval for the treatment of locally advanced or metastatic urothelial carcinoma, refractory to platinum-based chemotherapy, based on an overall survival advantage demonstrated in clinical trials (10.3 months vs. 7.4, HR of 0.73; 95% CI: 0.59, 0.91, p=0.004). Other anti-PD-L1/PD1 therapies (i.e., atezolizumab, avelumab, durvalumab, and nivolumab) have received accelerated approval in the second-line setting under the provisions in 21 CFR Part 601 Subpart E (accelerated approval) and thus they do not constitute available therapy with regards to the current application. Several cytotoxic chemotherapeutics may also be used in this setting although they are not specifically approved in the U.S. for this indication and they are generally associated with low response rates and considerable toxicity. Except for vinflunine, response durations remain unknown or unreported. Nab-paclitaxel monotherapy was associated with a response rate of 28% and a longer survival time relatively to other agents. However, the results may not be reliable given the small sample size of a single-arm study. In addition, the heterogeneity of study patient populations is an issue among these studies, which may contribute to the varying response rates and survival times.

Although pembrolizumab has demonstrated a survival advantage in this setting, it is unclear if anti PD-L1/PD-1 therapy in patients with FGFR-altered urothelial cancers has the same benefit as with those with unaltered cancers, as this specific subset was not prospectively identified in the registrational trials.

Table 1: Activity and Safety of Second-Line Therapies in Urothelial Carcinoma

Regimen	Patient Population Regarding Prior Platinum Use Requirement	Number of Evaluable Patients	Overall Response Rate N (%)	Response Duration (mos), median	Overall Survival*, median	Key Safety Issues (Grade 3 or 4 Toxicity)** (%)
Pembrolizumab ^a Regular approval	Progression on prior platinum containing regimen; prior neoadjuvant/ adjuvant platinum < 12 mos of recurrence	N = 270	57 (21)	NR	10.3 months	Fatigue (4.5); Urinary tract infection (4.9); decreased appetite (3.8), Musculoskeletal pain (3.0)
Avelumab ^b Accelerated Approval	After first line platinum containing chemotherapy; no time interval specified	N = 226	30 (13)	NR	7.4 months	Anemia (7); asthenic Conditions (7), urinary tract infections (6); hyponatremia (6)
Atezolizumab ^c Accelerated Approval	Progression on prior platinum containing regimen; prior	N = 310	46 (15)	NR	7.9 months	Urinary tract infection (9); Fatigue (6); Abdominal pain

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	neoadjuvant/ adjuvant platinum < 12 mos of recurrence					(4); Dyspnea (4); Hematuria (3)
Durvalumab ^d Accelerated Approval	Progression on prior platinum containing regimen; prior neoadjuvant/ adjuvant platinum < 12 mos of recurrence	N = 182	31 (17)	NR	18.2 months	Abdominal pain (3); fatigue (6); urinary tract infection (4); Dehydration (3); Back/Neck pain (4)
Nivolumab ^e Accelerated Approval	Progression on prior platinum containing regimen; prior neoadjuvant/ adjuvant platinum < 12 mos of recurrence	N = 270	53 (20)	10.3	8.6 months	Fatigue (7); Urinary tract infection (7) Dyspnea (3.3); Diarrhea (2.6); Musculoskeletal pain (2.6)

(b) (4)

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	containing regimen					
NR: not reported; *In the relevant treatment arm or study of the enrolled patients. ** As reported from each study, which may not represent the comprehensive safety profile of each treatment based on the approved product label. a) Per FDA review of BLA 125514 (pembrolizumab), Supplement 18 b) Per FDA review of BLA 761034 (atezolizumab) c) per FDA review of BLA 761078 (avelumab) d) per FDA review of BLA 761069 (durvalumab), Supplement 8 e) Per FDA review of BLA 125554 (nivolumab), Supplement 24 f) Bellmunt J. et al. (2009) J Clin Oncol 27:4454-4461. An improvement in OS (not statistically significant) was seen. This trial led to the EMA approval of vinflunine for its use as a second-line treatment. g) Albers P et al. (2011) Annals of Oncology 22: 288–294. Results from the short-treatment arm (6 cycles) are shown for its tolerability. The prolonged treatment arm was intolerable due to safety concerns and the results are not listed. h) Choueiri TK et al (2011) J Clin Oncol 30:507-512. The results as shown were from the docetaxel + placebo arm alone. i) Ko YJ et al (2013) Lancet Oncol 2013; 14: 769–76. The preliminary results from this trial were reported in an abstract in the 2010 GUASCO meeting. The ORR at that time was 33% in 40 study patients.						

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Erdafitinib is a new molecular entity and is not currently marketed in the U.S. or in other parts of the world. There is no development program in non-malignant diseases.

3.2. Summary of Presubmission/Submission Regulatory Activity

Major regulatory activities involving the sponsor for erdafitinib and the FDA are summarized in Table 2. This summary focuses on activities relevant to the development program for erdafitinib in urothelial carcinoma.

Table 2: Key Regulatory Activities During the Clinical Development of Erdafitinib

Date	Description of Regulatory Activity
03/27/2013 (IND 117490 SDN 01)	IND 117490 was submitted for JNJ-42756493 (erdafitinib) in patients advanced or refractory solid tumors or lymphoma. The submission included a protocol for an ongoing (Spain and France initiated June 2012), first-in-human, dose-finding, clinical study 42756493EDI1001 (EDI1001) in patients with advanced or refractory solid tumors or lymphoma.
12/04/2014 (IND 117490 SDN 56)	A pre-phase 2 meeting was held to discuss the proposed design of a phase 2 clinical study (BLC2001) of erdafitinib in patients with metastatic or surgically unresectable urothelial carcinoma whose tumors harbor select FGFR genetic alterations. At this meeting, the selection of specific FGFR genetic alterations to define a molecular subset based on preliminary activity seen in EDI1001 was provided.
07/08/2016 (IND 117490 SDN 117)	A teleconference was held to obtain preliminary advice regarding Breakthrough Therapy Designation for erdafitinib (b) (4) 

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	cisplatin. The FDA advised the Sponsor that the data as presented appear premature for a BTDR and that a preliminary BTDR should be submitted again when more data are available.
09/18/2017 (IND 117490 SDN 164)	An End of Phase 2 meeting was held to obtain advice on the propose registration strategy for accelerated approval base on the preliminary results of BLC2001 and the design of the propose confirmatory phase 3 study (BLC3001).
02/16/2018 (IND 117490 SDN 190)	A pre-NDA meeting was held to obtain agreement on the proposed content, format, and planned efficacy and safety analyses for the planned NDA for erdafitinib.
03/13/2018 (IND 117490 SDN 191)	Breakthrough Therapy Designation was granted for erdafitinib for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, (b) (4) [REDACTED]
05/11/2018 (IND 117490 SDN 203)	A pre-Phase 3 meeting was held to obtain feedback on the proposed Patient Reported Outcome (PRO) endpoints in the study BLC3001.
07/24/2018 (IND 117490 SDN 212)	A pre-NDA meeting was held to share topline results from BLC2001 in preparation for the planned NDA.
07/27/2018 (IND 117490 SDN 215)	Rolling Review granted.

Reviewer Comment: At the 12/04/2014 pre-phase 2 meeting, the Applicant and the FDA agreed on a specific list of FGFR genetic alterations to be included in the enrolled BLC2001 population based on preclinical and early clinical data.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For this NDA for erdafitinib, the clinical team requested that OSI verify the integrity of the submitted clinical data from Study BLC2001. Three study sites (Table 3) were selected based on the number of patients enrolled and the based on the number of reported responders and adverse reactions. The applicant (study sponsor) was also audited by OSI.

There were no significant inspectional finds at the three sites and the study sponsor. The interim classification of each site listed in the last column of Table 3. Base on the available information, OSI concluded that data from Study BLC2001 appears reliable in support of this application. For details, see Clinical Inspection Summary from OSI.

Table 3: OSI Inspected Sites and Inspectional Classification for Erdafitinib

Name of CI, Address; Site #	Protocol # and # of Subjects	Inspection Date	Classification
Tagawa, Scott 525 E. 68 th St, Rm. K615 New York, NY 10021 Email: stt2007@med.cornell.edu Site # US00014	Protocol: BLC2001 Enrolled: 6	Dec. 3-7, 2018	NAI
Siefker-Radtke, Arlene 1155 Herman Pressler Unit 1374 Houston, TX 77030 Email: asiefker@mdanderson.org Site #US00011	Protocol: BLC2001 Enrolled: 5	Dec. 4, 7, 10-11, 2018	NAI
Loriot, Yohann 114 rue Edouard Vaillant Villejuif Cedex, NA 94805 France Email: yohann.loriot@gustaveroussy.fr Site #FR00005	Protocol: BLC2001 Enrolled: 10	Jan. 14-17, 2019	NAI

Janssen Research and Development, LLC 1400 McKean Road Spring House, PA 19477 Regulatory Point of Contact: Hsiao-Ling Hung, Email: HHungl@its.jnj.com Site: Sponsor	Protocol: BLC2001	Nov. 26-30, 2018	NAI
Source: Clinical Inspection Summary for NDA 212018 by OSI.			

4.2. Product Quality

Assessment of Impurities

- **Drug Substance:** The impurity that exceeded the qualification threshold of (b) (4) % (b) (4) was qualified by nonclinical data submitted by the Applicant (13-week repeat dose studies in rats and dogs; genotoxicity studies and analysis through in silico assessment of structure-activity relationships).
- **Drug Product:** The applicant proposed the following specification limits for three specified degradants (b) (4)
 - (b) (4) in drug product - At a maximum daily clinical dose of 9 mg erdafitinib, these limits translate to a maximum daily dose of (b) (4) µg, respectively. As such, the individual specifications are below the ICHQ3B qualification threshold (b) (4) µg TDI whichever is lower).
 - (b) (4) in the drug product - These limits translate to a maximum daily dose of (b) (4) µg. As such, the individual specification is (b) (4) the ICHQ3B qualification threshold. To evaluate the potential toxicity of the impurity in question (b) (4) the Applicant conducted a 1-month repeated dose oral toxicity study in the rats (impurity evaluation; Study # TOX10565). (b) (4) was administered spiked at (b) (4) with impurity (b) (4) and compared to a group that received the same reference batch without the impurity. No adverse findings were reported following treatment with (b) (4) or the test article spiked with the impurity (b) (4). No adverse differences were reported between the two groups. As such, spiking with (b) (4)
 - (b) (4) did not result in additional toxicity. As such, the impurity specification that exceeded the qualification threshold of (b) (4) was qualified by these nonclinical data.

4.3. Clinical Microbiology

Not Applicable

4.4. Devices and Companion Diagnostic Issues

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Premarket Approval Application P180043 for theascreen® FGFR RGQ RT-PCR Kit was submitted to CDRH for evaluation as a companion diagnostic along with this NDA submission to CDER. The assay is a reverse transcription, real-time PCR test for the qualitative detection of four point mutations [p.R248C (c.742C>T, FGFR3 Exon 7), p.S249C (c.746C>G, FGFR3 Exon 7), p.G370C (c.1108G>T, FGFR3 Exon 10) and p.Y373C (c.1118A>G, FGFR3 Exon 10)] and two fusions (FGFR3:TACC3v1 and FGFR3:TACC3v3) in the fibroblast growth factor receptor 3 (FGFR3) gene in RNA samples derived from formalin-fixed paraffin-embedded (FFPE) urothelial tumor tissue. The test is indicated for use as an aid in identifying patients with cases of urothelial cancer (UC) which harbor these alterations and are therefore eligible for treatment with BALVERSA™ (erdafitinib).

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Primary Pharmacology: Erdafitinib (JNJ-42756493, BALVERSA) is an oral fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor being developed for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma whose tumors have particular FGFR2 and FGFR3 genetic alterations. In an enzymatic assay, erdafitinib inhibited the tyrosine kinase activity of FGFR1-4 with an IC₅₀ of 1.2, 2.5, 3, 5.7 nM, respectively. The binding affinity of erdafitinib was tested in a panel of 451 kinases; erdafitinib bound to all 4 members of the FGFR family (1-4) at a K_d of 0.24, 1.1, 1.4, and 2.2 nM, respectively, and to other kinases with less than or similar affinity. In the in vitro binding assay, erdafitinib also bound to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2 at clinically relevant concentrations. Erdafitinib inhibited growth of BaF3 cells expressing FGFR1, 3 or 4 (IC₅₀ of 11 to 24 nM), however showed considerably weaker inhibition against BaF3 cells expressing VEGFR2 and other kinases (IC₅₀ of 1190 to 8560 nM). Additionally, erdafitinib demonstrated antiproliferative activity in selected cancer cell lines from various tissues, including bladder cells, with FGFR1-4 alterations (amplification, mutation or fusion) at IC₅₀ values ranging from 0.1 to 129.2 nM. Erdafitinib inhibited autophosphorylation of FGFR proteins in cancer cell lines displaying activated FGFR1, 2, 3 and 4 and phosphorylation of key downstream signaling components of the FGFR signaling pathway in NCI-H1581 cells (i.e. pFRS2 -Tyr436, PLCγ 1, ERK 1/2, and pS6K). Similarly, erdafitinib demonstrated antiproliferative activity (IC₅₀ < 1 nM) in RK3E (rat kidney epithelial) cells that were transfected with constructs for FGFR2 (BICC1, AFF3, CASP7, CCDC6, OFD1) and FGFR3 (TACC3v1, TACC3v3, BAIP2L1) fusion genes and was shown to inhibit FGFR phosphorylation and phosphorylation of key downstream FGFR signaling pathway components (MAPK and S6). In vivo, erdafitinib demonstrated antitumor activity in immune-deficient rodents bearing tumors derived from multiple human cancer cell lines with FGFR1, 2 and 3 alterations (fusion or amplification) including the bladder, lung, GI and liver. Additionally, in a mouse study using patient-derived xenografts (PDX) originated from lung tumors expressing FGFR2 and FGFR3 fusion proteins, antitumor activity was associated with expression of the fusion protein in the tumor.

The in vitro and in vivo data submitted by the Applicant demonstrated that erdafitinib has antiproliferation activity in cell lines expressing FGFR with genetic alterations (i.e. mutation, fusion or amplification) and inhibits downstream signaling pathway components that play a role in cell proliferation and survival. The approved Established Pharmacologic Class (EPC) of “kinase inhibitor” is applicable to erdafitinib based on its pharmacologic activity.

Safety Pharmacology: The effect of erdafitinib on nervous system function was evaluated using the Modified Irwin’s method. Erdafitinib resulted in a higher incidence of impaired wire maneuver, flaccid body tone and clinical observations of hypotonia and paralysis in male rats at doses ≥8 mg/kg. The effects of erdafitinib on cardiovascular and respiratory systems were

evaluated in in vitro and in vivo studies. In vitro, results from the hERG (IC₅₀ 408 nM [or 182 ng/mL]) and ventricular wedge assays demonstrated that erdafitinib has potential for producing QT prolongation and arrhythmia at concentrations as low as 0.1 μM (or 44.7 ng/mL). In vivo, erdafitinib, following a single intravenous dose or oral administration to anesthetized or conscious dogs, resulted in a decreased mean heart rate and increased QTc interval, blood pressure and respiration. Additionally, idioventricular rhythm and ventricular escape rhythms were reported. The C_{max} values after single dose were less than human exposure at clinical dose of 8 mg (1399 ng/mL). Erdafitinib had no adverse effects on cardiac repolarization or other electrocardiographic parameters in patients.

ADME Studies: Irrespective of dosing regimen (daily vs intermittent dosing), systemic exposure to erdafitinib (C_{max} and AUC) following repeat oral dosing increased in a greater than dose proportional manner with accumulation in rats and dogs in the 13-week studies. Systemic exposure was greater in female rats and male dogs in the 13-week studies. Following a single oral dose of [¹⁴C]erdafitinib to male pigmented rats, radioactivity was distributed throughout the body rapidly (0.5 or 1 hours post dose) in the majority of the tissues/organs. By 24/72 hours post dose, radioactivity was either close to or below the limit of quantification in the majority of the tissues, except the eye (T_{1/2} 182.5 hours) and lacrimal gland (T_{1/2} 135.7 hours). Erdafitinib was highly bound to human plasma proteins compared to animals and extensively bound to human α1-acid glycoprotein (α1-AGP). Human metabolites were detected in at least 1 species used in erdafitinib safety studies, with the exception of the minor fecal metabolites M27 and M11 (<2%). Oxidative metabolism (O-demethylation of erdafitinib, M6) is the major metabolic pathway in human and rat. Erdafitinib was the major circulating drug-related material in human plasma; there were no circulating metabolites detected. In human and dogs, the majority of drug-related material was excreted in feces, while in rats the majority of drug-related material was excreted by both the biliary and fecal route. Erdafitinib was considered a weak inducer of CYP3A4 and did not act as a reversible CYP inhibitor in human liver microsomes.

Repeat Dose Toxicology Studies: The Applicant conducted oral repeat-dose general toxicology studies (up to 13 weeks) of erdafitinib in rats and dogs. Exposures following repeat dose at the highest dose levels in rats (32 mg/kg [human equivalent dose HED= 311 mg/day], AUC 1910 ng·h/mL) and dogs (1.5 mg/kg, [HED= 48.6 mg/day], AUC 1300 ng·h/mL) were much lower than the AUC of 29268 ng·h/mL in humans at the clinical dose of 8 mg. In the repeat-dose studies, the toxicity profile of erdafitinib in the rat and dog showed considerable overlap; however, some findings appeared to be restricted to the rat. In the rat, mortalities were reported following daily dosing at 8 mg/kg/day (HED=77.8 mg/day; 0.003 times the estimated human AUC at the clinical dose of 8 mg) and following intermittent dosing (7 days on/7 days off) at 32 mg/kg (HED=311 mg/day; 0.065 times the estimated human AUC at the clinical dose of 8 mg). The death at 32 mg/kg was attributed to the mineralization of several tissues (heart, aorta and lungs), and cause of death at 8 mg/kg/day was not determined. Clinical observations included limping, paralysis of the hind legs, hunched back, dyspnea, salivation, thin and weak appearance. The predominant microscopic findings reported in rats included atrophy of gland

structures (mammary gland), soft tissue mineralization of multiple organs (kidneys, lung, stomach, tongue, duodenum), decreased cellularity (bone marrow femur), chondroid dysplasia (larynx, trachea), degeneration of odontoblasts (teeth) and degeneration/inflammation heart. The predominant toxicities in both species included soft tissue mineralization of multiple organs (aorta and heart), eye-related findings (corneal atrophy [rats], atrophy of lacrimal gland [rat and dog], and ocular discharge, corneal opacities, thickened corneal endothelium and low tear production [dogs]), epithelial structures (tongue and oral mucosa atrophy, skin-redness crust, thin hair, and nails discolored/broken), atrophy of parotid salivary gland, chondroid dysplasia/metaplasia and abnormal dentin in teeth and degeneration of odontoblasts in rats (teeth). Tooth changes, unlikely to be of concern in an adult human population due to species difference in tooth growth pattern, may be relevant for a pediatric population. In addition, hyperphosphatemia was reported, similar to that reported in patients treated with erdafitinib. Furthermore, biomarker changes indicative of a disturbance in phosphate and vitamin D homeostasis (changes in serum phosphate, 1,25-dihydroxyvitamin D₃, FGF23, PTH, and calcium), bone turnover (increases in serum ALP and C/N-telopeptides of type I collagen [CTX and NTx]), and in urinary deoxypyridinoline were reported in both species. The microscopic findings reported in the 13-week studies (eye, salivary/hardierian gland, tongue, oral mucosa, ovaries and cervix) were not previously reported in the shorter-term toxicology studies in rats and dogs (≤1 month). In the repeat-dose study in rats, erdafitinib showed effects on female reproductive organs (necrosis of ovaries) at 32 mg/kg, indicating potential impact on fertility in patients. In dogs, decreases in relative prostate (up to 13%) and testes (up to 18%) weights were reported at doses ≥ 0.5 mg/kg/day (HED=16 mg/day; 0.058 times the estimated human AUC at the clinical dose of 8 mg).

The animal studies appeared to be predictive for a number of clinical findings. Similar to animals, in patients treated with erdafitinib, dry eye and keratitis (inflammation of cornea) were reported, although the corneal opacities and atrophy found in animals were not noted in patients (possibly due to intervention/use of lubricating drops). Retinal findings (retinal detachment and chorioretinopathy) were also reported in patients but were not reported in animal studies; possibly due to limited retinal evaluation in the general toxicology studies (i.e. limited ocular histopathology, no optical coherence tomography, lack of functional/electroretinography assessment). The findings in the eye can be attributed to the direct effect of erdafitinib on the ocular system, as was evident by the extended presence of erdafitinib ([¹⁴C]erdafitinib) in the eye and lacrimal gland in rats (up to t_{1/2} 182.5 hours), effects on the epithelia (target tissue) and pharmacological activity of erdafitinib on FGF/FGFR pathways. In peer-reviewed publications, it has been concluded that fibroblast growth factors (FGFs) and/or fibroblast growth factor receptors (FGFRs) play a key role in lens, corneal and retina

development and adult function in multiple vertebrate species.^{[1][2][3]} FGFR signaling, for example, has been implicated in lens, retina and corneal cell proliferation and differentiation. Furthermore, all four FGFR genes are expressed in the lens, and FGFR1 and FGFR2 are expressed in the retina and cornea. In addition, similar to what was reported in animals, in patients treated with erdafitinib, adverse reactions including onycholysis, paronychia, nail dystrophy, palmar-plantar erythrodysesthesia syndrome, alopecia and dry mouth were reported. The chondroid dysplasia/metaplasia reported in both species may be especially relevant for a pediatric population.

Genetic toxicology: Using the standard core battery of genetic toxicology studies recommended in ICH guidances, erdafitinib was not shown to be mutagenic, aneugenic or clastogenic.

Other Toxicology Studies (phototoxicity, skin sensitivity, eye and vascular irritation): Erdafitinib was not considered phototoxic in an in vivo study in female Long-Evans pigmented rats. Erdafitinib was considered to cause skin sensitization in the murine local lymph node assay at concentrations of $\geq 3.5\%$. Erdafitinib did not induce any vascular irritation in the HET-CAM assay. In an in vitro Bovine Corneal Opacity-Permeability Eye Irritation assay, erdafitinib induced a severe increase in corneal opacity that was associated with microscopic changes in the corneal epithelium and stroma. As such, erdafitinib scored positive as an eye irritant, which was consistent with in vivo findings reported in the general toxicology studies.

Reproductive Toxicology: Erdafitinib was reported to cross the placenta. In an embryo-fetal developmental study in rats, erdafitinib was administered during the period of organogenesis. Erdafitinib at doses $\geq 4\text{mg/kg/day}$ (HED=38.9 mg/day; less than human exposure at the clinical dose of 8 mg) produced teratogenicity (embryo-fetal death, major blood vessel malformations, multiple limb/paw malformations and increased skeletal anomalies), as well as developmental delay at 8 mg/kg/day (incomplete ossification of multiple bones with associated decreased fetal body weight). The NOAEL for maternal toxicity was the highest dose tested of 8 mg/kg/day (HED=77.8 mg/day; 0.0036 times the estimated human AUC at the clinical dose of 8 mg) and for embryo-fetal development was 1 mg/kg/day (HED=9.7 mg/day; less than human exposure at 8 mg). Females of reproductive potential should use effective contraception during treatment and for 1 month after the last dose, which is approximately 5 half-lives (the higher limit of

[1] Rosenthal R., et al., *The fibroblast growth factor receptors, FGFR-1 and FGFR-2, mediate two independent signaling pathways in human retinal pigment epithelial cells*, *Biochemical and Biophysical Research Communications* 337, 2005.

[2] Zhang J. et al., *Fibroblast Growth Factor Receptor 2 (FGFR2) Is Required for Corneal Epithelial Cell Proliferation and Differentiation during Embryonic Development*, *Plos one*, DOI:10.1371, January 2015.

[3] Robinson M., *An Essential Role for FGF Receptor Signaling in Lens Development*, *Semin Cell Dev Biol.* 17(6), December 2006.

erdafitinib $T_{1/2}$ from clinical studies was 120.5 hours). Likewise, lactating women should not breastfeed during treatment with erdafitinib and for 1 month after the last dose.

The submitted nonclinical pharmacology and toxicology data support approval of BALVERSA for the proposed indications.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary pharmacology

The Applicant conducted in vitro and in vivo pharmacology studies with JNJ-42756493.

- In an enzymatic kinase assay (time-resolved fluorescence assay), JNJ-42756493 inhibited the tyrosine kinase activities of FGFR1, FGFR2, FGFR3 and FGFR4 at an IC_{50} of 1.2, 2.5, 3 and 5.7 nM, respectively, while demonstrated lower activity for VEGFR2 (IC_{50} 36.8 nM).

Table 4: Inhibitory activity of JNJ-42756493

<u>Kinases</u>	<u>IC_{50} (nmol/L)</u>	<u>$\pm$ SD</u>
FGFR1	1.2	0.4
FGFR2	2.5	0.9
FGFR3	3	0.5
FGFR4	5.7	0.8
VEGFR2	36.8	7.1

(Excerpted from Applicant's publication [Perera et al, 2017]^[4])

- In vitro, JNJ-42756493 was tested against a panel of 451 kinases in a binding assay. JNJ-42756493 bound to all 4 members of the FGFR family at affinities (K_d) ranging between 0.24 to 2.2 nM. In comparison, JNJ-42756493 bound other kinases in the panel (CSF1R, PDGFRA, FLT4, PDGFRB, KIT, VEGFR2, TIE1, FLT1, EPHA1, LCK, LYN, ABL1, EPHB6, BLK, DDR1) at affinities ranging between 3.4 to 45 nM, with the exception of RET (at 0.94 nM). The remaining kinases tested bound at affinities over 45 nM (Study # JAN001-01-p-0001 and, Perera et al, 2017)^[4]. The C_{max} of unbound erdafitinib measure in patients at the clinical dose of 8 mg is 6.3 nM (2.8 ng/mL), suggesting binding of erdafitinib to several kinases at clinically relevant exposures.

Table 5: Kinase binding affinity for JNJ-42756493

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Kinase	K _d (nM)	Kinase	K _d (nM)	Kinase	K _d (nM)	Kinase	K _d (nM)
FGFR1	0.24	CSF1R	3.4	VEGFR2	6.6	LYN	22
RET	0.94	PDGFRA	3.4	TIE1	9	ABL1	23
FGFR3	1.1	FLT4	3.6	FLT1	12	EPHB6	32
FGFR4	1.4	PDGFRB	4.6	EPHA1	13	BLK	44
FGFR2	2.2	KIT	5.3	LCK	20	DDR1	45

*Kinases with the highest binding affinity are presented in this Table.
(Excerpted from Applicant's publication [Perera et al, 2017]^[4])*

- To demonstrate the ability of JNJ-42756493 to inhibit the proliferation of cancer cell lines, JNJ-42756493 was tested for proliferation against a panel of cell lines from different tissue organs and FGFR genetic alterations. JNJ-42756493 demonstrated antiproliferative activity in selected cancer cell lines with FGFR1, 2, 3, 4 genetic alterations (amplification, translocation, or mutation) with IC₅₀ values ranging from 0.1 to 129.2 nM. Weaker antiproliferative activity was reported in cells expressing FGFR with mutations (IC₅₀>102.4 nM) vs. fusions or amplification (IC₅₀ 0.1 nM to 71 nM). In addition, JNJ-42756493 demonstrated antiproliferative activity in other cancer cell lines that express FGFR (Caki-1, A549, HCC827, SW-620, MDA-MB-134-VI, NB-1, PC3, Hep G2 and MCF-7) with IC₅₀ values ranging from 0.236 μM to 5.33 μM. (Study # Nss-03)

Table 6: Antiproliferative activity of erdafitinib in cancer cell lines with FGFR alterations

Table 4: Antiproliferative Activity of Erdafitinib in Cancer Cell Lines with FGFR Alterations

Cell Line	Origin	FGFR Alteration	IC ₅₀ (nM)	± SEM
KATO III	Gastric	FGFR2 (Amp)	0.1	0.01
SNU-16	Gastric	FGFR2 (Amp)	0.4	0.02
RT-112	Bladder	FGFR3-TACC3 (translocation)	1.3	0.2
NCI-H1581	Large Cell Lung	FGFR1 (Amp)	2.6	0.2
A-204	Rhabdomyosarcoma	FGFR4 (Amp)	4.5	0.4
RT-4	Bladder	FGFR3-TACC3 (translocation)	5.1	0.6
DMS-114	Small Cell Lung	FGFR1 (Amp)	7	1.2
A-427	Squamous Lung	FGFR1 (Amp)	71	25.6
KMS-11	Multiple Myeloma	FGFR3 (Y377C)	102.4	53.6
MDA-MB-453	Breast	FGFR4 (Y367C)	129.2	30.4

Amp = amplification; SEM = standard error of the mean; Y377C = mutation of tyrosine to cysteine at amino acid 377; Y367C = mutation of tyrosine to cysteine at amino acid 367

(Excerpted from Applicant's study report)

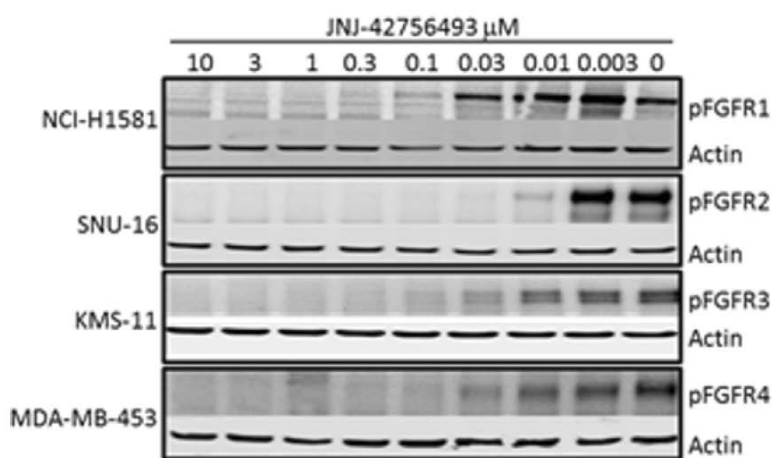
- To confirm the in vitro activity and selectivity in a cellular context, JNJ-42756493 was incubated in 96-well plates containing mouse BaF3 cells expressing various human tyrosine kinases. BaF3 cells are dependent on Interleukin 3 (IL-3) for growth. In the absence of the IL-3 cytokine in the culture medium, growth of these cells was dependent on activity of the

human tyrosine kinases. JNJ-42756493 inhibited growth of BaF3 cells expressing FGFR1, 3, or 4 (IC₅₀ ranging from 11 to 24 nM). In contrast, the inhibitory activity of JNJ-42756493 was considerably weaker against BaF3 cells expressing VEGFR2 and other kinases (IC₅₀ of 1190 to 8560 nM). The addition of IL-3, resulted in reduction in the inhibitory activity of JNJ-42756493 with higher IC₅₀ values ≥8220 nM (Study # Nss-01).

- To evaluate the inhibition activity of JNJ-42756493 on FGFR autophosphorylation in cancer cell lines displaying activated FGFR1 (NCI-H1581), FGFR2 (SNU-16), FGFR3 (KMS-11) or FGFR4 (MDA-MB-453), cells were incubated and treated with a range of concentrations (0.003 to 10 μM). Protein concentrations were determined, and samples were immunoblotted. JNJ-42756493 inhibited autophosphorylation of FGFR proteins in all cancer cell lines tested displaying activated FGFR. Signal was significantly inhibited in NCI-H1581, SNU-16, KMS-11 and MDA-MB-453 cell lines, at 0.1 μM, 0.01 μM, 0.03 μM, and 0.1 μM, respectively (Study # CP100023, CP100040).

Figure 1: Activity of JNJ-42756493 on FGFR autophosphorylation in cancer cell lines

Figure 1: Western blot detection of p-FGFR (Tyr653/654) and actin in cancer cell lines with activated FGFR kinases

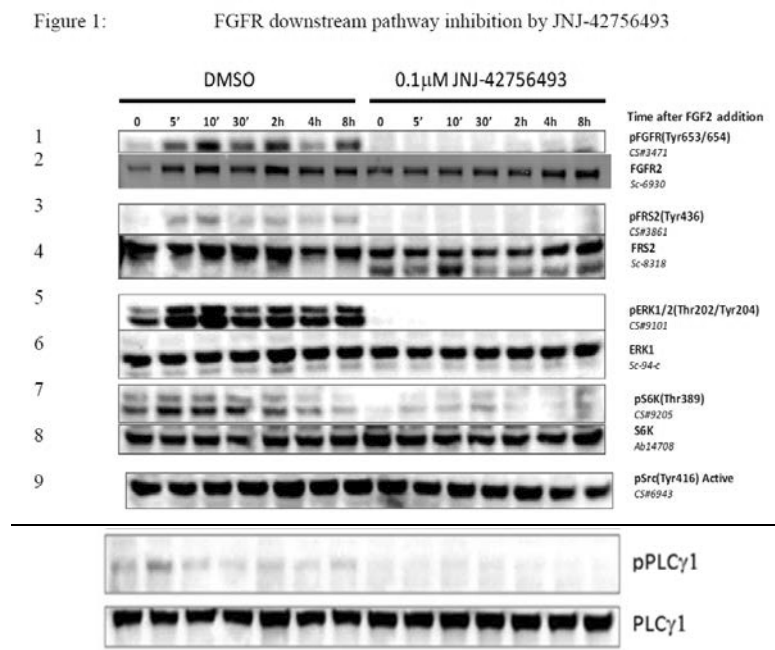


(Excerpted from Applicant's study report)

- To demonstrate that JNJ-42756493 was able to inhibit the FGFR in cellular assays leading to the blockade of key downstream signaling intermediates and pathways, NCI-H1581 NSCLC cell lines, harboring FGFR1 amplification, were pretreated with JNJ-42756493 prior to the FGF2 treatment (FGFR ligand) at different time points. Subsequently, samples were immunoblotted. The results demonstrated that the preincubation with JNJ-42756493 inhibited phosphorylation of downstream components of the FGFR signaling pathway components, up to 8 hours following the treatment with JNJ-42756493. The affected downstream components included phosphorylation of FGFR substrate 2 (pFRS2 -Tyr436),

phospholipase C gamma (PLC γ) 1, extracellular signal-regulated kinase (ERK) 1/2, and pS6K. In addition, preincubation with JNJ-42756493 inhibited FGF2 dependent activation of the FGFR downstream signaling cascades that play a role in cell proliferation and survival (Study # Nss-06).

Figure 2: FGFR downstream pathway inhibition by JNJ-42756493



(Excerpted from Applicant's study report)

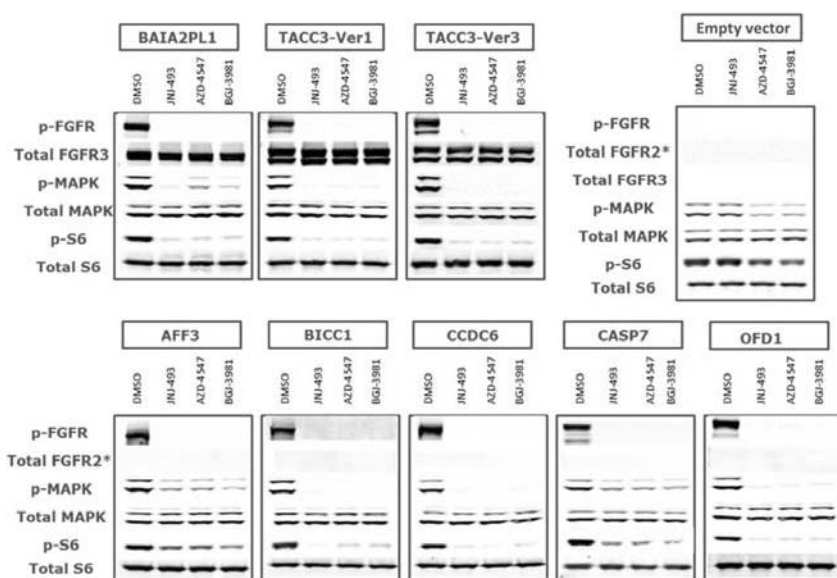
- In a peer-reviewed publication owned and provided by the Applicant^[5], the ability of JNJ-42756493 to inhibit proliferation of RK3E rat kidney epithelial cells transfected with constructs for 5 FGFR2 fusion genes (BICC1, AFF3, CASP7, CCDC6, OFD1) and 3 FGFR3 fusion genes (TACC3v1, TACC3v3, BAIP2L1) was evaluated. Cells were assayed for adenosine triphosphate content using the Cell Titer-Glo Luminescent cell viability assay. IC₅₀ values were calculated. Erdafitinib demonstrated antiproliferative activity (IC₅₀ < 1 nM) in RK3E cells overexpressing FGFR2 and FGFR3 fusion genes. Additionally, the effects of erdafitinib on the downstream signaling pathway in RK3E cells expressing FGFR2 and FGFR3 fusion genes was assessed using immunoblotting. Erdafitinib inhibited phosphorylation of downstream components of the FGFR2 and FGFR3 signaling pathway (MAPK and S6).

Table 7: Inhibition of cell proliferation in RK3E cells overexpressing FGFR2 and FGFR3 fusion genes

	Proliferation IC50
RK3E – Transgene	Erdafitinib (nM)
Vector	7010
FGFR2:AFF3	0.1133
FGFR3:BAIA2PL1	0.3211
FGFR2:BICC1	0.3303
FGFR2:CASP7	0.4718
FGFR2:CCDC6	0.1894
FGFR2:OFD1	0.2303
FGFR3:TACC3-V1	0.2915
FGFR3: TACC3-V3	0.2706

(Excerpted from Applicant's publication [Karkera et al, 2017])

Table 8: Effect of JNJ-42756493 on downstream signaling pathway in RK3E cells expressing FGFR2 and FGFR3 fusion genes



(Excerpted from Applicant's publication [Karkera et al, 2017]^[2])

- In vivo, multiple studies in immune-deficient mice and rats bearing human xenograft tumors derived from diverse human cancer cell lines with FGFR alterations (fusion or amplification) or patient-derived xenograft (PDX) originating from a variety of tissues were conducted with JNJ-42756493. JNJ-42756493 administration resulted in antitumor activity in mouse and rat tumor models of human tumors generated from multiple organs (bladder, lung, GI and liver). Additionally, in a study using PDX originated from lung tumors expressing FGFR (2 and 3) fusion proteins, the antitumor activity in mice was associated with expression levels of the fusion proteins in the tumor. Higher expression (low Δ Ct values; Table 7) was correlated with higher antitumor activity. Antitumor activity was more pronounced in lung tumors expressing FGFR3 vs. FGFR2 (Study # Nss-11).

Table 9: Xenograft tumor studies in rodents

(Representative xenograft tumor studies derived from diverse human cancer cell lines with FGFR alterations or patient-derived xenograft [PDX])

Study #	Tumor Model	FGFR Alteration	Species	Route (vehicle/ formulation) & frequency	Active/ effective dose(s) (mg/kg)	Tumor size reduction (%)	T/C (%) ¹	Antitumoral ² response based on T/C value
CSU-1325	RT-112 bladder	FGFR3-TACC3 fusion	Mouse	10% HP-β-CD/ 50XQD p.o.	6.25, 12.5 and 25	8, 35 and 68	71, 35 and -5.7	Growth reduction Growth reduction and Regression
Nss-09	RT-112 bladder	FGFR3-TACC3 fusion	Mouse	20% HP-β-CD/ 23XBID p.o.	12.5	92	8.2	Growth reduction
Nss-09	RT-112-VM (engineered variant),	FGFR3-V555M-TACC3	Mouse	20% HP-β-CD/ 23XBID p.o.	12.5	67	66.6	Growth reduction
OIV.11.4065	NCI-H1581 lung	FGFR1 (Amp)	Rat	10% HP-β-CD/ 10XQD p.o.	10 and 20	33 and 57	41.26 and 7.65	Growth reduction and Growth reduction
OIV.11.4068	NCI-H1581 lung	FGFR1 (Amp)	Rat	10% HP-β-CD/ 10XQD p.o.	10 and 20	33.7 and 37.8	47.8 and 34.4	Growth reduction and Growth reduction
OIV.10.3778	SNU-16 gastric	FGFR2 (Amp)	Mouse	10% HP-β-CD/ 7XQD p.o.	50	70	-46.6	Regression
OIV.10.3878 ³	SNU-16 gastric	FGFR2 (Amp)	Mouse	10% HP-β-CD/ 14XBID p.o.	6.25 And 12.5	68 and 86	-15.1 and -25.9	Regression and Regression
JNJ-hp-p100-Li0574	LI0574 liver PDX	unknown	Mouse	10% HP-β-CD/ 21XQD p.o.	25	63	32.5	Growth reduction
Nss-11	LUX001 Lung PDX	FGFR2 and FGFR3 fusion	Mouse	20% HP-β-CD /25XBID	3.12, 6.25 and 12.5 mg/kg	TGI of 40, 60 and 105%, respectively	--	Growth reduction and Regression at 12.5 mg/kg

¹Treated/Control (T/C) = [Average relative tumor volumes (Tlast day/Tstart day)-1.00]/[Average relative tumor volumes (Clast day/Cstart day)-1.00] (expressed as a percentage).

²Antitumoral response defined as growth reduction if T/C value ≤42% and >5% (TGI value ≥50% and <95%), stasis if T/C value ≤5% and >-5% (TGI value ≥95% and <105%), and regression if T/C value ≤-5% (TGI value ≥105%).

³C_{max} (ng/mL) and AUC (ng.h/mL) were 496 and 985, respectively for 12.5 mg/kg dose.

TGI= tumor growth inhibition; Amp=amplification; --=no data provided

Study # Nss-11:

Table 10: Antitumor activity of erdafitinib in lung cancer PDX with FGFR2 and FGFR3 fusions

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

	PDX	Ct	subtype	ΔCT	In Vivo %TGI	P value
FGFR3-TACC3 V1	LUX001	13.2	SCC	1.7	Regression	P<0.001
COL25A1-FGFR2*	LU-01-0010	18.3	Ad	12.2	50%	P<0.001
FGFR2-MCU*	LU0743	19.0	SCC	7.9	50%	0.099
FGFR2-CASP7	LU0009	31.3	SCC	23.3	0	0.946
FGFR3-TACC3 v3	LU6423	33.2	SCC	21.8	0	0.998
FGFR2-CASP7	LUN#0331	33.9	SCC	21.8	0	0.393
FGFR2-CDCC6	LU-01-0004	34.2	SCC	24.1	25	0.236
FGFR3 S249C	LU-01-0048		SCC		Regression	p<0.001

ΔCt values = Ct value of FGFR gene-CT value of GAPDH

Ct value= obtained from qRT-PCR assay are inverse to the amount of nucleic acid that is in the tumor sample and correlate to the number of copies in the sample.

(Excerpted from Applicant's study report)

Safety Pharmacology

- Nervous system function (CNS):** The Applicant evaluated the effect of JNJ-42756493 on the CNS function using the Modified Irwin's method (Study #TOX10080). The study was conducted as part of the GLP-compliant 4-week oral repeated-dose toxicity study in Sprague Dawley rats (4, 8, 16 mg/kg/day; or 32 mg/kg twice per week). The study was reviewed in support of IND 117490. At doses ≥8 mg/kg/dose, JNJ-42756493 increased the incidence of impaired wire maneuver 2 hours post-dose compared to vehicle control, and a few rats in the 32 mg/kg dose group exhibited this impairment up to 24h post-dose. Doses ≥16 mg/kg/dose resulted in flaccid body tone after 24h. In addition, males rats in the 16 mg/kg/day dose group showed clinical signs of hypotonia and paralysis in Week 4. The C_{max} values after single dose of 8, 16 mg/kg/day and 32 mg/kg were 10, 30 and 257 ng/mL, respectively, and were less than the human exposure at the clinical dose of 8 mg (1399 ng/mL).
- Cardiovascular and respiratory (single dose):** The effect of JNJ-42756493 on cardiovascular and respiratory functions were evaluated in a stand-alone GLP-compliant study in conscious non-telemetered male beagle dogs at escalating single oral doses of 1, 2.5 and 5 mg/kg (Study #TOX10104). At ≥2.5 mg/kg, mean heart rate was decreased during the first 2 hours post dose, followed by an increase in rate reported up to 6 hours postdose. At 5 mg/kg, an increase in mean QT, blood pressure and respiration were reported up to 6 hours postdose. Increases in QTcB (8% and 14.2%), QTcF (9 to 13%) and in QTcVDW (10.7% and 10.2%) were also reported. The Applicant additionally stated that idioventricular rhythm (three VPCs in a row, approximately 20 min post-dose) and ventricular escape rhythms (two VEBs in a row, approximately 2 to 3 hours post-dose) were noted. The C_{max} values after a single dose of 5

mg/kg was 265 ng/mL and was less than the human exposure at the clinical dose of 8 mg/day (1399 ng/mL).

Table 11: Cardiovascular and respiratory functions in conscious dogs

% change from pre-dosing values at different time interval

Dose (time post dose in minutes) (mean, n=4)	Heart rate (%)	QT (%)	Aortic Systolic Blood pressure (%)	Aortic Diastolic Blood pressure (%)	Mean Aortic Blood pressure (%)	Respiration rate
2.5mg/kg (0, 30, 60, 120, 180/240, 300, 360 min)	--, -6, -8, --, 11, 6, 10	--, --, --, --, 9, --, --	--, --, --, --, --, --, --	--, --, --, 7, 9, 8, --	--, --, --, --, --, --, 6	--, --, --, --, --, --, --
5mg/kg (0, 30, 60, 120, 180/240, 300, 360 min)	--, -7, -6, --, 24, 44, 26	--, 7, 7, 10, 15, --, --	12, 10, 10, 10, 5, 11, 13, 9	15, 13, 8, --, --, 9, 20, 16	14, 12, 9, 7, --, 16, 12	29, 9, 26, 12, 28, 14, 53, 32

--=no findings were reported at x minutes post dose

- Cardiovascular and respiratory (repeat dose): In the GLP-compliant 3-month repeat-dose toxicology study in male and female dogs at dose ≥ 0.5 mg/kg/day, decreases in heart rate were reported in male (up to 28%) and female dogs (up to 21%) in week 13 (Study #TOX10849). No respiratory effects were reported. The C_{max} values were less than the human exposure at the clinical dose of 8 mg (1399 ng/mL). The one-month dog study was reviewed previously under IND 117490. There were no abnormal ECG findings.
- Arterially perfused rabbit ventricular wedge: The potential electrophysiological effects of JNJ-42756493 (0.01, 0.1, 1 and 10 μ M) were evaluated in isolated arterially perfused rabbit ventricular wedge preparations to predict arrhythmogenic potential (Study #CoE2912/HRS014 [non-GLP]). JNJ-42756493 resulted in prolonged QT interval, increased rTp-Te and TdP at concentrations $\geq 0.1\mu$ M (44.7 ng/mL). Contractile force of the ventricular wedge was increased at 1 μ M. The data indicated that JNJ-42756493 has the potential to cause arrhythmia at 0.1 μ M (44.7 ng/mL) and greater.

Table 12: Effects of JNJ-42756493 on electrophysiological parameters and force of contraction in arterially-perfused rabbit ventricular wedge preparations

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Effects of vehicle and JNJ-42756493-AAA-32452371 on the electrophysiological parameters and force of contraction (FC), expressed as changes from baseline (in percentages or actual units), in arterially-perfused rabbit ventricular wedge preparations (n = 6 for compound; n = 6 for vehicle)

Parameter	Group	Baseline	Changes as	1 x 10 ⁻³ M 30 min	1 x 10 ⁻⁷ M 30 min	1 x 10 ⁻⁶ M 30 min	1 x 10 ⁻⁴ M 30 min
QT (ms)	42756493-AAA	314	Δ%	2	3	<i>10</i>	<i>29</i>
	DMSO	305		1	2	2	4
QRS (ms)	42756493-AAA	36	Δ%	0	0	0	3
	DMSO	33		0	0	0	0
Tp-Tc (ms)	42756493-AAA	54	Δ%	2	6	<i>19</i>	<i>46</i>
	DMSO	55		-2	1	0	0
rTp-Tc (%)	42756493-AAA	18	Δ%	0	2	<i>8</i>	<i>15</i>
	DMSO	18		-2	-2	-3	-4
TdP score (-)	42756493-AAA	0.0	Δ	0.0	0.0	<i>2.0</i>	<i>3.5</i>
	DMSO	0.0		0.0	0.0	<i>0.0</i>	<i>0.0</i>
QRS Rate Dependency (ms)	42756493-AAA	0	Δ	0	0	0	2
	DMSO	0		0	0	0	0
FC (mg)	42756493-AAA	5.7	Δ%	-1	-6	3	-5
	DMSO	6.0		-8	-9	<i>-16</i>	-17

Values are median values.

Statistically significant values ($p < 0.05$) are indicated in bold and italics.

(Excerpted from Applicant's study report)

- The potential cardio-hemodynamic, cardio-electrophysiological and pulmonary/respiratory effects of JNJ-42756493 were evaluated following intravenous infusion (0.32, 0.63, 1.25, 2.5, 5 and 10 mg/kg) in neuromuscular blocked, artificially ventilated, anesthetized dogs (n=4/sex) (Study #COE3030 [non-GLP]).

Table 13: The effects of JNJ-42756493 and vehicle on cardio-hemodynamic, cardio-electrophysiological and functional respiratory in anesthetized dogs at 5 minutes after onset of i.v. infusion (Median % change from baseline)

Parameter*	Treatment	0.32mg/kg	0.63mg/kg	1.25mg/kg	2.5mg/kg	5mg/kg	10mg/kg
C _{max} (ng/mL)	Compound	432	820	1860	3610	7950	14000
APD ₉₀ RV en	Compound	2	11	16	13	15	12
	Vehicle	1	3	2	4	3	2
Systolic pulmonary artery blood pressure (SPP)	Compound	-2	-3	-3	-8	-10	-10
	Vehicle	0	7	9	13	14	10
left ventricular end-diastolic pressure (LVEDP)	Compound	--	-3	0	0	0	-9
	Vehicle	--	25	39	48	58	53
PQ intervals	Compound	4	5	9	9	10	8
	Vehicle	-2	-6	-6	-7	-5	-7
	Compound	--	2	3	6	11	9

QTc interval (the highest value of QTc VDW, B, F)	Vehicle	--	-3	-4	-9	-6	-7
Left ventricular (LV) dp/dt _{min}	Compound	--	--	--	6	-1	-3
	Vehicle	--	--	--	10	12	16
Heart rate	Compound	--	--	--	--	6	22
	Vehicle	--	--	--	--	-8	-7
RR-interval	Compound	--	--	--	4	-6	-18
	Vehicle	--	--	--	20	10	8
time constant of relaxation (tau)	Compound	7	13	13	18	21	27
	Vehicle	0	0	4	10	13	11
Pressure rate (PRP)	Compound	--	--	--	--	--	21
	Vehicle	--	--	--	--	--	5
Respiratory parameters	Compound	--	--	--	--	--	--

--=no change; n=4 per group

*Median values of percentage changes at 5 minutes after onset of i.v. infusion

HERG assay: JNJ-42756493 was evaluated in the HERG assay at concentrations ranging from 30 nM to 10 µM, along with a positive control (astemizole) at one concentration (10 nM). Inhibition of HERG-mediated K current in HEK293 cells was reported at JNJ-42756493 concentrations ≥0.03µM, and IC₅₀ was calculated to be 408 nM (182 ng/mL). The IC₅₀ was lower than the human exposure at clinical dose (1399 ng/mL), suggesting a potential interference of JNJ-42756493 in cardiac repolarization in vivo (Study #COE3216-COE3317 [non-GLP]).

5.4. ADME/PK

Absorption

Abbreviated study titles and number

Pharmacokinetics of JNJ-42756493-AAA (JNJ-42756493) in mice, rats, and dogs after single oral administration of JNJ-42756493 (Study # ADME-22464, ADME-22667 & ADME-24482¹; ADME-23459², FK7511³; FK7455⁴ non-GLP).

Table 14: PK parameters of JNJ-42756493-AAA following a single oral dose across species (plasma)

Formulation/ Route	20% HP-β-CD (gavage)							API in Capsule
	Mouse ¹			Rat ²	Dog ^{3,4}			
Species (male)								
N/time point/group	3			3	4			4
Dose (mg/kg)	3	6.25	10	10	0.5	2.5	5	5
C _{max} (ng/mL)	4.99	16.6	202	5.26	1.68	64.6	208	243

AUC _{last} (ng.h/mL)	4.36	24.5	218	30.7	7.91	845	3693	4069
T _{max} (h)	0.5	0.5	1	n.d.	3.5	4.75	3.5	3
T _{1/2} (hours)	1.1	3.1	1	n.d.	3.3	8.3	7.6	7.4
Bioavailability (%)	1.1	2.3	12	1.8	--	--	100	110

n.d.= not detected
 --= was not calculated/provided by the Applicant
 20% HP-β-CD= 20% w/v hydroxypropyl-β-cyclodextrin
 Superscript ^{1,2,3,4}= Study number

Distribution
Study titles and numbers

1. Plasma kinetics and tissue distribution of JNJ-42756493-AAA after single oral administration at 10 mg/kg in the male Sprague Dawley rat (Study # ADME-22761; non-GLP).
2. [¹⁴C]JNJ-42756493: Tissue Distribution in the Male Pigmented Rat Determined by Whole-Body Autoradiography Following a Single Oral Dose (Study # FK10843; non-GLP)
3. The distribution of ³H-JNJ-42756493 in blood, plasma protein binding and microsomal binding of ³H-JNJ-42756493 in different animal species and human (Study # FK10117; non-GLP).

Results

1. Mean plasma protein binding (% bound) of JNJ-42756493-AAA averaged 89.4% with 10.6 % free/unbound. (Study # ADME-22460 and ADME-22786; non-GLP).
2. JNJ-42756493-AAA (dissolved in 20% HP-β-CD) was administered as a single dose to rats by gastric intubation (10 mL/kg or 10 mg/kg). Blood and tissue samples were collected and were quantified by LC/MS-MS (Study # ADME-22761; non-GLP):

Table 15: PK parameters of JNJ-42756493-AAA following single dose in rats (tissue and plasma)

(mean)	Plasma	Kidneys	Liver	Lung	Heart	Muscle	Skin	Eye, brain and epididymal fat.
C _{max} (ng/mL)	4.75	163	658	559	75.9	32.1	28.5	--
AUC _{0-24h} (ng.h/mL)	22.5 [#]	1227	3460	4895	296 [#]	155 [#]	135 [#]	--
T _{max} (h)	1	2	1	2	2	2	2	--
T _{1/2} (2-7 hr)	4.4 [#]	6.2	4.3	4.3	4.1 [#]	3.2 [#]	6.2 [#]	--

[#] = AUC_{0-7h} and T_{1/2} (2-7h) were provided. Plasma levels were not provided at AUC_{0-24h} or for T_{1/2} (4-24h). Values were below the limit of quantification (LOQ).
 --= The Applicant stated that levels were below the LOQ or there were not enough values reported to obtain a mean profile.

3. The distribution of radioactivity was determined in male pigmented rats (Lister-Hood; n=5) following a single oral dose (4 mg/kg) of [¹⁴C]JNJ-42756493 (dissolved in 20% HP-β-CD). (Study # FK10843; non-GLP)

Table 16: Distribution of radioactivity in tissues/organs in male rats

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Tissue/organ	0.5 hours	24 hours	72 hours
eye (lens)	BLQ	+	+
seminal vesicle, abdominal fat	BLQ	+	BLQ
uveal tract/ciliary body, kidney, liver, spleen, lacrimal gland, nasal mucosa, skin, stomach, small intestine, cecum, large intestine	+	+	+
whole blood, plasma, adrenal cortex, lung, harderian gland, mesenteric lymph node, pancreas, pituitary, thyroid, esophagus, preputial gland, prostate, testis, skeletal muscle, tongue, urinary bladder	+	+	BLQ
Aorta, vena cava, brain, pineal body, spinal cord, myocardium, adrenal medulla, mandibular lymph node, salivary gland, thymus, bulbo-urethral gland, epididymis, bone marrow, bone surface, brown fat, fur, oral cavity, nasal cavity, pharynx, larynx, rectum	+	BLQ	BLQ

+ = radioactivity was measurable

BLQ = below the lower limit of quantification

Table 17: PK parameters of radioactivity in tissues and blood (AUC tissue/blood) in male rats

Tissue type	Tissue/organ	C _{max} (µg eq/g)	T _{max} (h)	AUC (µg eq.h/g)	AUC _{0-inf} (µg eq.h/g)	t _{1/2} (h)	Tissue: Blood ratio
Circulatory	Aorta	0.245	0.5	1.48	a	-	1.7
	Plasma	0.259	0.5	0.963	0.879	8.3	1.1
	Whole blood (cardiac)	0.197	0.5	1.24	1.11	8.8	1.5
	Whole blood	0.165	0.5	0.847	0.764	8.5	1.0
	Vena cava wall	0.238	0.5	1.26	0.921 ^b	3.9 ^b	1.5
Nervous	Brain	0.016	4	0.216	a	-	0.26
	Pineal body	0.214	0.5	2.57	a	-	3.0
	Spinal cord	0.018	0.5	0.170	0.500 ^b	26.0 ^b	0.20
Ocular	Eye (lens)	0.018	24	0.972	4.92 ^b	182.5 ^b	1.1
	Uveal tract/ciliary body	0.921	24	52.2	107 ^b	67.1 ^b	61.6
Visceral organs	Kidney cortex	0.709	0.5	12.6	16.5	45.3	14.9
	Kidney inner medulla	0.577	1	5.22	5.90	39.3	6.2
	Kidney outer medulla	1.36	1	30.5	36.7	27.8	36.0
	Liver	2.61	1	46.6	55.6	31.7	55.0
	Lung	0.340	1	3.30	3.01	6.6	3.9
	Myocardium	0.206	0.5	1.01	0.632 ^b	2.4 ^b	1.2
	Spleen	0.352	1	4.75	6.64 ^b	82.1 ^b	5.6
Glandular/secretory	Adrenal cortex	0.328	1	3.68	3.33	7.2	4.3
	Adrenal medulla	0.235	0.5	2.87	27.6 ^b	81.3 ^b	3.4
	Exorbital lacrimal gland	0.178	1	2.31	2.71	28.2	2.7
	Harderian gland	0.143	4	3.27	2.94	11.1	3.9
	Intra-orbital lacrimal gland	0.134	1	2.62	6.14 ^b	135.7 ^b	3.1
	Mandibular lymph node	0.152	0.5	1.48	1.93 ^b	9.9 ^b	1.7
	Mesenteric lymph node	1.34	4	16.0	16.2	10.2	18.9
	Nasal mucosa	0.074	0.5	1.62	1.50 ^b	12.8 ^b	1.9
	Pancreas	0.321	1	4.04	5.28	61.7	4.8
	Pituitary	0.455	4	11.5	11.0 ^b	14.9 ^b	13.6
	Salivary gland	0.230	0.5	2.44	2.71 ^b	8.0 ^b	2.9
	Thymus	0.086	4	1.15	a	-	1.4
	Thyroid	0.304	0.5	3.90	3.61	12.5	4.6
	Oesophagus	3.77	0.5	4.85	4.56	6.6	5.7

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Reproductive	Bulbo-urethral gland	0.169	0.5	1.36	0.902 ^b	3.3 ^b	1.6
	Epididymis	0.055	0.5	0.388	a	-	0.46
	Preputial gland	0.175	1	6.99	a	-	8.3
	Prostate	0.130	0.5	1.77	1.58	9.7	2.1
	Seminal vesicles	0.034	4	0.765	0.696 ^b	12.3 ^b	0.90
	Testis	0.028	0.5	0.776	1.68 ^b	58.6 ^b	0.92
Musculo-skeletal	Bone marrow	0.141	0.5	1.48	1.98 ^b	10.3 ^b	1.7
	Bone surface	0.115	4	1.43	a	-	1.7
	Fat (abdominal)	0	-	0	a	-	0
	Fat (brown)	0.099	4	1.32	a	-	1.6
	Muscle (skeletal)	0.041	1	1.16	1.73 ^b	35.6 ^b	1.4
	Skin (non-pigmented)	0.105	0.5	1.63	2.31 ^b	38.5 ^b	1.9
	Skin (pigmented)	0.125	0.5	1.57	2.34 ^b	40.1 ^b	1.9
	Tongue	0.198	0.5	2.61	2.33	10.0	3.1
	Fur	0.071	1	0.140	a	-	0.17
	Extrathoracic region	Oral cavity	0.249	4	3.14	a	-
Nasal cavity		0.012	0.5	0.006	a	-	0.0071
pharynx		0.200	0.5	1.43	0.897 ^b	2.7 ^b	1.7
larynx		0.110	0.5	0.607	0.403 ^b	3.1 ^b	0.72
Excretory	Stomach wall	0.882	4	12.3	15.3	115.7	14.5
	Small intestine wall	29.3	1	90.3	91.4	23.2	107
	Caecum wall	2.31	4	34.4	36.1	24.3	40.6
	Large intestine wall	0.536	4	9.63	86.2 ^b	948.1 ^b	11.4
	Urinary bladder wall	0.506	0.5	5.44	5.02	6.3	6.4
	Rectum	0.119	0.5	0.189	0.156 ^b	0.7 ^b	0.22

(Excerpted from Applicant's study report)

- All tissues showed higher AUC values than for whole blood, except for AUC values in the brain, spinal cord, epididymis, seminal vesicles, testes, fur and rectum.
- Tissue/blood ratios were greatest in the small intestine, uveal tract/ciliary body, liver, kidney and caecum.
- Tissues with the highest T_{1/2}: Eye[lens]: 182.5 hr; Lacrimal gland: 135.7hr; Stomach: 115.7 hr; Large intestine: 948.1hr.

3. Study # FK10117; non-GLP:

Table 18: Plasma protein binding of [3H]JNJ-42756493 across species

Species	% Bound	% Free fraction
CD-1 mouse (m)	88.7	11.3
CD-1 mouse (f)	93.5	6.5
NMRI mouse (m)	94.1	5.9
SD rat (m+f)	92.8	7.2
Nude RUN rat (m)	97.8	2.2
Dog (m+f)	86.3	13.7
Human	99.38	0.6

Table 19: Binding of [3H]JNJ-42756493 to purified human proteins

Species	% Bound	% Free fraction
Human (HSA + α1-AGP)	99.61	0.39
Human (α1-AGP) at con. 0.02%-0.2%	94.1-99.5	0.52-5.87
Human (HSA) at con. 1% to 6%	53.4-83.9%	16.1-46.6

HSA=Human serum albumin
α1-AGP=α -acid glycoprotein
Con.=concentration

Table 20: Microsomal binding ([³H]-JNJ-42756493) across species

Species	% Bound	% Free fraction
SD rat-male (0.1 mg/mL protein con. and ³ H-JNJ-42756493 con. of 150 ng/mL)	2-3.6	96-98
Beagle dog -male (0.1 mg/mL protein con. and ³ H-JNJ-42756493 con. of 150 ng/mL)	23-23.6	76-77
Human (m+f) * - 0.15 mg/mL microsomal protein con. and ³ H-JNJ-42756493 con. of 150, 1500 ng/mL & 150037 ng/mL	13.9-27.3	72.7-86.1
- 1 mg/mL microsomal protein con. and ³ H-JNJ-42756493 con. of 150, 1500 ng/mL & 150037 ng/mL	45.8-75.2	24.8-54.1

- In human blood, JNJ-42756493 was mainly bound to the plasma proteins, in contrast to what was reported in animals.

Table 21: Blood distribution of JNJ-42756493 across species

Species	% bound to plasma proteins	% bound to blood cells	% present in the plasma water	Blood to plasma concentration ratio (average)
CD-1 mouse (m)	54	39	6.9	0.90
CD-1 mouse (f)	53	42	3.7	0.99
NMRI mouse (m)	56	40	3.6	0.98
SD rat (m+f)	50	47	3.8	1.1
Nude RUN rat (m)	72	25	1.7	0.80
Dog (m+f)	28	69	4.4	1.60
Human	95	4.5	0.5	0.6

Fraction of JNJ-42756493 in blood bound to plasma proteins, blood cells or present in plasma water in different species

Metabolism

Study title and number

1. *The metabolism and excretion of ³H-JNJ-42756493 in the male Sprague-Dawley rat and male Beagle dog after a single oral administration of ³H-JNJ-42756493 at 4 and 60 mg/kg (rat) and 0.25 and 1 mg/kg (dog), respectively (Study # FK10110; non-GLP).*
2. *The biliary excretion of ¹⁴C- JNJ-42756493 (Erdafitinib) in the male Sprague-Dawley rat after a single oral administration of ¹⁴C- JNJ-42756493 at 4 mg/kg (Study # FK11144; non-GLP).*
3. *The analysis of biological samples (metabolite profiling) collected in trial 42756493EDI1005, an open-label Phase I study to determine the absorption, metabolism*

and routes of excretion following oral administration of ¹⁴C-JNJ-42756493 to healthy male subjects (Study # FK12055; non-GLP).

4 & 5. Potential Induction of CYP1A2, 2B6 and 3A4 by JNJ-42756493 in Human Hepatocytes (Study # FK12003 and FK13265, non-GLP)

6. An in-vitro study on the mechanism based inhibition of five major cytochrome P-450 (CYP) activities by JNJ-42756493 (Study # FK-10109; non-GLP).

Results

1, 2 & 3. Metabolites identified and excretion of radioactivity (% of administered dose) following oral administration of erdafitinib in different species:

Table 22: Metabolites and excretion across species

Species (number (n) & sex)	Plasma*	Urine	Feces [#]	Bile
Rat (3 males) ^{1,2}	Major: JNJ-42756493, M2, Minor: M1, M4, M5, M6, M7, M8, M9	≤1%: M2, M6, M9	14%: M20, 46% ² 10% ¹ : M6, 9%: erdafitinib, 7%: M5, 7%: M9 5%: M26	NA
Rat (bile cannulated; n=4) ²	NA	≤3%: M1, M2, M6, M9, M13, M14, M15, M16, M17, M18, M25	22%: erdafitinib, 16%: M6, 2%: M20	14%: M2, 9%: M15, 4%: M13, M17, ≤3%: M3, M14, M18, M19, M20, M21, M22, M23, M25
Dog (2 males) ¹	Major: JNJ-42756493, M2, M4, M11 Minor: M3, M5, M6, M7, M8	≤1%: erdafitinib, M2	5%: erdafitinib	NA
Human (n=8) ³	erdafitinib	12%: erdafitinib, ≤2%: M6, M8, M28	16%: erdafitinib, 24%: M6 ≤3%: M5, M8, M11, M27	NA

Superscript ^{1,2,3,4}= Study number; NA=not applicable; --=not detected

**The Applicant stated: "Incomplete recovery of radioactivity after processing of sample pools resulted in insufficient radioactivity levels in UPLC injection samples for accurate calculation of plasma metabolite concentrations. Therefore, metabolite profiling based on radio chromatogram peak areas is considered qualitative."*

#The abundance of metabolites in feces is considered qualitative due to poor recovery of radioactivity after sample processing of pooled feces extracts. Total recovery of radioactivity (relative to the percent of dose recovered in feces homogenates) was approximately 58% (0-24 h) for rat, and 22% (0-24 h) and 44% (24-48 h) for dog.

4. & 5. The effects of JNJ-42756493 (0.005 to 15 µM) on the expression of cytochrome P450 enzymes (CYP1A2, CYP2B6, and CYP3A4) were evaluated in cultures of cryopreserved primary human hepatocytes from three different human donors. JNJ-42756493 was not an inducer of CYP1A2 mRNA and CYP2B6 mRNA in human hepatocytes in vitro. However, JNJ-42756493 was considered a weak inducer of CYP3A4 based on increases in mRNA.

6. The inhibition potential of JNJ-42756493 (0.1 to 100 µM) towards CYP activity was investigated using human liver microsomes. JNJ-42756493 did not inhibit the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. JNJ-42756493 exhibited weak inhibition of CYP3A4.

Excretion

Study title and number

1. The metabolism and excretion of ³H-JNJ-42756493 in the male Sprague-Dawley rat and male Beagle dog after a single oral administration of ³H-JNJ-42756493 at 4 and 60 mg/kg (rat) and 0.25 and 1 mg/kg (dog), respectively (Study # FK10110; non-GLP).

2. The biliary excretion of ¹⁴C- JNJ-42756493 (Erdafitinib) in the male Sprague-Dawley rat after a single oral administration of ¹⁴C- JNJ-42756493 at 4 mg/kg (Study # FK11144; non-GLP).

3. The analysis of biological samples (metabolite profiling) collected in trial 42756493EDI1005, an open-label Phase I study to determine the absorption, metabolism and routes of excretion following oral administration of ¹⁴C-JNJ-42756493 to healthy male subjects (Study # FK12055; non-GLP).

Results

Table 23: Excretion (%) of radioactivity across species

Species (n & sex)	Dose (mg/kg)	Collection time (hr)	Urine (%)	Feces (%)	Bile (%)	Total (%)
Rat (3m) ¹	4	0-72	2.3	88.7	--	91
Rat (3m) ¹	60	0-72	2.73	87.6	--	90.4
Dog (2m) ¹	1	0-72	6.3	75.2	--	81.5
Rat (bile cannulated; n=4) ²	4	0-48	12	31	47.9	94
Human (n=8) ³	12 mg	0-384	18.7	68.7	--	87.4

Superscript= Study number

-- = No data was collected

TK data - general toxicology studies

Study title and number

1. JNJ-42756493-AAA: 3-month Repeated Dose Oral Toxicity Study in the Rat (Study # TOX10846)
2. JNJ-42756493-AAA : 3-Month repeated dose oral toxicity study in the beagle dog/ Study # TOX10849

Rat¹ and Dog²

Exposure (AUC₀₋₂₄ and C_{max}) increased in a greater than dose proportional manner. Accumulation was reported following repeat dosing in both rats and dogs.

Table 24: TK parameters in rats following oral repeat dose (3-month)

Day	Dose (mg/kg/day)	Parameter							
		Tmax (h)*		Cmax (ng/mL)		AUC(0-t) ¹ (ng.h/mL)		AUC(0-24h) (ng.h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
Day 6	4	0.500	2.00	2.64	6.43	8.64	20.7	10.1 ¹	29.6 ²
	8	1.00	1.00	6.40	31.9	25.0	89.3	29.6 ¹	94.3 ²
	16 [#]	2.00	1.00	28.0	257	104	820	105 ¹	936
	32 [#]	2.00	2.00	524	886	2630	3620	5580	4170
Day 90	4	1.00	1.00	6.98	13.4	21.4	43.9	26.3 ²	45.2
	8	2.00 ²	1.00	26.2 ²	59.7	92.8 ²	193	99.8 ²	231 ²
	16 [#]	2.00	1.00	88.5	462	356	1640	327 ²	1780
	32 [#]	2.00	1.00	360	929	1910	10000	1910	10000

*Intermittent dosing, 7 days on/off.

#Median reported for Tmax.

¹Tlast was 4 to 24 h at 4 mg/kg/day, 1 to 7 h at 8 mg/kg/day, 7 h at 16 mg/kg/day and 7 to 24 h at 32 mg/kg/day.

²n=1

²n=2 (instead of 3)

Table 25: TK parameters in dogs following oral repeat dose (3-month)

Day	Dose (mg/kg/day)	Parameter							
		Tmax (h)*		Cmax (ng/mL)		AUC(0 t) ¹ (ng.h/mL)		AUC(0-24h) (ng.h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
Day 6	0.5	2.00	2.00	18.5	8.45	90.2	33.5	108	40.2
	0.75	2.00	2.00	27.2	20.7	218	145	218	146
	1.5 [#]	3.00	3.00	117	71.0	1130	682	1130	682
Day 90	0.5	2.00	2.00	21.6	15.9	169	91.6	172	92
	0.75	3.00	4.00	38.9	26.1	394	211	394	213
	1.5 [#]	3.00	2.00	113	98.1	1300	969	1300	969

*Intermittent dosing, 7 days on/off.

#Median reported for Tmax.

¹Tlast was 7 to 24 h at 0.5 and 0.75 mg/kg/day and 24 h at 1.5 mg/kg/day.

Superscript= Study number

(Excerpted from Applicant's study report)

TK data - reproductive toxicology study

Study title and number

JNJ-42756493-AAA: Embryo-fetal toxicity study by the oral route (gavage) in the rat (Segment II)/AB21601 (Study # tox12329)

Pregnant Rats

TK parameters collected from pregnant rats on gestation day (GD) 6 and 17 following daily dosing during organogenesis:

Pregnant rats

- Plasma exposure (AUC_{0-last} and C_{max}) increased in greater than dose-proportional manner. Accumulation was reported following repeat dosing.

Table 26: TK parameters in pregnant rats

Summary of JNJ-42756493 Toxicokinetic Parameters in Pregnant Sprague-Dawley Rats Plasma Following Daily Oral Dosing of JNJ-42756493-AAA

Parameters		Group 2 ¹	Group 3	Group 4
		1 mg/kg	4 mg/kg	8 mg/kg
G6				
t _{last}	h	n/a	7	7
t _{max}	h	1	1	1
C _{max}	ng/mL	0.679	4.93	12.7
AUC _(0-last)	h·ng/mL	n/a	14.4	47.1
AUC _(0-12h)	h·ng/mL	n/a	17.2	NR
G17				
t _{last}	h	n/a	7	7
t _{max}	h	1	1	1
C _{max}	ng/mL	0.728	10.0	38.8
AUC _(0-last)	h·ng/mL	n/a	24.1	105

¹: no full toxicokinetic evaluation was performed; t_{max} and C_{max} values were assessed directly from the measured plasma concentrations

n/a: not applicable

NR: not reported

G6 or 17= Gestation Day 6 or 17

(Excerpted from Applicant's study report)

Rat Fetuses

Plasma concentrations were measured at 1 and 2 hours postdose in fetuses on GD 17.

- Placental transfer of JNJ-42756493 occurred at 4 and 8 mg/kg/day, 2 hours postdose.

Table 27: TK parameters in fetuses on GD 17

Table 5.1 Fetuses/Dams Exposure of JNJ-42756493 in Sprague Dawley Rat after Daily Oral Administration of JNJ-42756493-AAA on G17

Groups	Time (h)					
	1			2		
	Mean plasma concentration (ng/mL)		Fetuses/Dams ratio	Mean plasma concentration (ng/mL)		Fetuses/Dams ratio
Fetuses	Dams	Fetuses		Dams		
Group 2: 1 mg/kg	<LLOQ ¹	0.827	n/c	<LLOQ ¹	0.436	n/c
Group 3: 4 mg/kg	<LLOQ ¹	10.5	n/c	0.545	5.17	0.11
Group 4: 8 mg/kg	1.34	32.2	0.04	2.63	38.2	0.07

<LLOQ: below the lower limit of quantification of 0.400 ng/mL

¹: set to 0 for ratio calculations

n/c: could not be calculated

(Excerpted from Applicant's study report)

5.5. Toxicology

5.5.1. General Toxicology

Study title/number: JNJ-42756493-AAA: 3-month Repeated Dose Oral Toxicity Study in the Rat (Study # TOX10846)

- Mortalities were reported at 8 mg/kg/day (daily dosing) and 32 mg/kg/day (intermittent dosing, 7 days on/7 days off). The cause of death at 8 mg/kg/day was

not determined, and the deaths at 32 mg/kg/day were attributed to soft tissue mineralization of the heart and aorta which were proposed to have contributed to the rat's poor condition.

- The predominant microscopic findings included atrophy of gland structures (exorbital lacrimal gland, mammary gland, salivary gland), chondroid dysplasia in multiple bones (sternum, stifle, tail), chondroid dysplasia (larynx, trachea), soft tissue mineralization of multiple organs (aorta, eye, heart, kidneys, lung, stomach, tongue, duodenum), atrophy (cornea, oral mucosa, tongue), decreased cellularity (bone marrow of femur), degeneration of odontoblasts (teeth), degeneration/inflammation (heart) and increase in hair follicles/reduced size (skin).
- Test article-related effects on female reproductive organs (necrosis of the ovarian corpora lutea and acute inflammation of the cervix) were reported at 32 mg/kg/day.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:

- 0, 4 or 8 mg/kg/day (daily dosing Day 0 to 90)
- 16 or 32 mg/kg/day (intermittent dosing, 7 days on/7 days off).

Route of administration: Orally by gavage

Formulation/Vehicle: 20% w/v hydroxypropyl-β-cyclodextrin (HP-β-CD) in demineralized water, HCl to pH 4 ± 0.1

Species/Strain: Rat [Sprague-Dawley (CrI: CD®)]

Number/Sex/Group: 10/sex/group (main study)

Age: Approximately 6 weeks

Satellite groups/unique design: 3/sex/group (TK animals)

Observations and Results: changes from control

Parameters		Major findings	
Table 28: Rat-Mortalities			
Group	Sex	Day	Findings prior to death/sacrifice
Main study rats			
4 mg/kg/day	f	67	Moribund sacrificed; cause of death gavage error confirmed by clinical observations (i.e. Blood loss from the oral cavity) and microscopic findings
32 mg/kg/day	m	34	Moribund sacrificed; clinical observations included limping and paralysis of the hind legs; microscopic findings included marked aorta mineralization and

			degeneration/inflammation of the myocardium with mineralizations that may have contributed to the rat poor condition.
32 mg/kg/day	m	49	Moribund sacrificed; clinical observations included dyspnea, reflux, slight abnormal salivation and swelling of the thorax. Cause of death gavage error confirmed by microscopic findings
Satellite groups (TK rats)			
8 mg/kg/day	m	60	The Applicant stated that the cause of death of these animals could not be determined, and as such treatment-relatedness cannot be excluded.
8 mg/kg/day	m	78	
32mg/kg/day	m	62	
32mg/kg/day	f	90	

Shaded area = drug-related mortalities

Clinical Signs

Table 29: Number of rats with clinical signs

Observation (male/female)	Cont	4 mg/kg/day	8 mg/kg/day	16 mg/kg/day	32 mg/kg/day
Tail deformation	--	--	--	2m	7m/1f
Thin/weak	--	--	--	--	1m
Hunched back	--	--	--	--	8m/10f
Paralysis-hind legs	--	--	--	--	1m
Limping	--	--	--	--	7f
Reflux	--	--	--	--	1m
Dyspnea	--	--	--	--	1m
Salivation	--	--	--	--	1m
Sternum deformation	--	--	2f	--	5m/9f
Haircoat thin	--	--	--	--	1f
Ataxia	--	1f	--	--	--
Nail/s broken	--	--	1f	--	1f
Skin abnormal (swelling/lesion)	1m	1m	6m	--	1f
Skin, irregular surface	--	--	--	--	5m/3f
Alopecia	--	--	4m	--	--

Cont= control; -- = no findings were reported; m=male; f=female

Body Weights

Table 30: Rat body weights (% change from control)

	4 mg/kg/day	8 mg/kg/day	16 mg/kg/day	32 mg/kg/day
<i>Mean body weight</i>				

Day 90	--	--	--	-12m
<i>Body weight gain</i>				
Day 90	--	--	16f	-19m
<i>-- = no findings were reported; m=male; f=female</i>				
Food Consumption				
Table 31: Rat food consumption (% change from control)				
Week	4 mg/kg/day	8 mg/kg/day	16 mg/kg/day	32 mg/kg/day
13 (Days 84-89)	--	--	--	-22m/-14f
<i>-- = no findings were reported; m=male; f=female</i>				
Ophthalmoscopy (Day 89)	No adverse test article-related findings were reported			
Hematology (Days 91-92)	8 mg/kg: 36% eosinophils (m) 16 mg/kg: 36% eosinophils (m) 32mg/kg: -24% (m)/7% (f) reticulocytes, 12% thrombocytes (m), 64%(m) /40% (f) eosinophils <i>m=male; f=female</i>			
Clinical Chemistry (Days 91-92)				
Table 32: Rat clinical chemistry (% change from control)				
(male/female)	4 mg/kg/day	8 mg/kg/day	16 mg/kg	32 mg/kg
ALT	105 (f)	48 (f)	102 (m)/41 (f)	87 (m)/86 (f)
ALP	--	45 (m)/42 (f)	73(m)/46 (f)	93 (m)/74 (f)
AST	--	25 (m)	39 (m)	34 (m)
Inorg. phosphorus	--	--	12 (m)/16 (f)	55 (m)/50 (f)
Creatinine	--	--	18 (m)	27 (m)
Globulin	--	--	14 (f)	13 (f)
Albumin/globulin	--	--	-15 (f)	-15 (f)
Calcium	--	--	--	10 (m)/7 (f)
Urea nitrogen	--	--	--	12 (m)
<i>-- = no findings were reported; m=male; f=female</i>				
Urinalysis (Days 91-92)	8 mg/kg/day: male high pH (8) 16 mg/kg: 100% (f) calcium normalized for creatinine 32 mg/kg: 600% (m)/300% (f) calcium normalized for creatinine, male high pH (8)			

Biomarkers (Day 55/91)				
Table 33: Rat biomarkers (% change from control)				
(Male/female)	4mg/kg/day	8mg/kg/day	16 mg/kg/day	32 mg/kg/day
Fibroblast growth factor (FGF-23)	32(m)/17(f)	65(m)/55(f)	44(m)/50(f)	346(m)/287 (f)
Parathyroid hormone (PTH)	--	-43(f)	-2 (m)/-49 (f)	-76 (m)/-69 (f)
1,25-dihydroxyvitamin D3	--	--	-76(m)/-51 (f)	-90 (m)/-54 (f)
C-terminal telopeptides of type I collagen (CTX)	--	--	32 (m)/25(f)	53(m)/65(f)
Deoxypyridinoline (DPD)	105/18	46/56	69/91	152/189

-- = no findings were reported; m=male; f=female

Gross Pathology

- At doses ≥ 4 mg/kg/day, deformity and discoloration of bones were reported in males and females.
- At doses ≥ 8 mg/kg, discoloration/malocclusion of the teeth were reported in males and females.
- At 32 mg/kg, firm and discolored aorta and/or discolored hearts were reported in the two moribund sacrificed males.
- At 32 mg/kg, thickened and discolored stomach wall was reported in males.
- At 32 mg/kg, irregular fur was reported in males and females.
- At 32 mg/kg, malformation, swelling and red discoloration of the paw nailbed were reported in males and females.

Organ Weights

No adverse test article-related findings were reported, except for a decrease in female heart weight at 32 mg/kg.

Histopathology

Adequate battery: Yes

Table 34: Summary of histological findings in rats at termination including deaths

Daily Dose (mg/kg) No. of Animals	0 (Vehicle)		4	8	16 ^c		32 ^c		
	M:10	F:10			M:10	F:10	M:10	F:10	
Number Examined									
Animals Examined	10	10	10	10	10	10	10	10	10
AORTA									
- No. Examined	10	10		10	10	10		10	10
- Metaplasia chondroid								3	-
Grade 1	-	-		-	-	-		3	-
- Mineralization								4*	-
Grade 2	-	-		-	-	-		1	-
Grade 3	-	-		-	-	-		1	-
Grade 4	-	-		-	-	-		2	-
BONE									
- No. Examined			1		2	2	2	6	9
- Chondroid dysplasia/metaplasia	-	-	-	-	2	2	1	6	9
Grade 1	-	-	-	-	2	1	-	1	1
Grade 2	-	-	-	-	-	-	1	1	2
Grade 3	-	-	-	-	-	1	-	2	6
Grade 4	-	-	-	-	-	-	-	2	-
BONE MARROW, FEMUR									
- No. Examined	10	9	10	1	10	10	10	10	10
- Decreased cellularity	-	-	-	-	-	-	-	9**	-
Grade 1	-	-	-	-	-	-	-	1	-
Grade 2	-	-	-	-	-	-	-	6	-
Grade 3	-	-	-	-	-	-	-	2	-
BONE, STERNUM									
- No. Examined	10	10	10	10	10	10	10	10	10
- Chondroid dysplasia/metaplasia	-	-	-	-	2	2	10**	7**	10**
Grade 1	-	-	-	-	2	2	8	5	-
Grade 2	-	-	-	-	-	-	2	2	6
Grade 3	-	-	-	-	-	-	-	-	4
BONE, STIFLE									
- No. Examined	10	9	10	1	10	10	10	10	10
- Chondroid dysplasia/metaplasia	-	-	-	-	5*	-	10**	10**	10**
Grade 1	-	-	-	-	5	-	1	6	-
Grade 2	-	-	-	-	-	-	7	4	1
Grade 3	-	-	-	-	-	-	2	-	8
Grade 4	-	-	-	-	-	-	-	1	-
- Decreased trabecular number	-	-	-	-	-	-	-	8**	-
Grade 1	-	-	-	-	-	-	-	7	-
Grade 2	-	-	-	-	-	-	-	1	-
- Hyperostosis	-	-	-	-	-	-	10**	7**	9**
Grade 1	-	-	-	-	-	-	10	7	7
Grade 2	-	-	-	-	-	-	-	2	3
Grade 3	-	-	-	-	-	-	-	-	1
- Thin cortex metaphysis	-	-	-	-	-	-	-	2	-
Grade 1	-	-	-	-	-	-	-	2	-
EXORBIT LACRIM GLDS									
- No. Examined	10	10	10	10	10	9	10	10	10
- Atrophy	-	-	-	2	4*	2	1	1	5*
Grade 1	-	-	-	2	3	2	1	1	3
Grade 2	-	-	-	-	1	-	-	2	-
EYES									
- No. Examined	10	10	10	10	10	10	10	10	10
- Atrophy cornea	-	-	-	3	2	2	7**	9**	10**
Grade 1	-	-	-	2	2	2	5	8	1
Grade 2	-	-	-	1	-	-	2	1	9
- Mineralization cornea focal	-	-	-	-	-	-	-	2	-
Grade 1	-	-	-	-	-	-	-	2	-
HARDERIAN GLANDS									
- No. Examined	10	10	10	10	10	10	10	10	10
- Dilatation acinus(i)	1	4	4	2	5	7	5	1	10**
Grade 1	1	3	4	1	4	4	3	-	5
Grade 2	-	1	-	1	1	3	2	1	4
Grade 3	-	-	-	-	-	-	-	1	1

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HEART										
- No. Examined	10	10		1	10	10	10		10	10
- Mineralization vascular	-	-		-	-	-	-		5*	-
Grade 1	-	-		-	-	-	-		2	-
Grade 2	-	-		-	-	-	-		3	-
KIDNEYS										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Mineralization artery	-	-	-	-	-	-	-	-	1	-
Grade 1	-	-	-	-	-	-	-	-	1	-
- Mineralization cortex	2	1	1	-	7*	-	5	1	9**	6*
Grade 1	2	1	1	-	7	-	5	1	4	6
Grade 2	-	-	-	-	-	-	-	-	3	-
Grade 3	-	-	-	-	-	-	-	-	2	-
- Mineralization medulla	-	2	-	-	1	1	5*	2	10**	8*
Grade 1	-	2	-	-	1	1	5	2	5	7
Grade 2	-	-	-	-	-	-	-	-	5	1
LARYNX										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Chondroid dysplasia	-	-	-	-	2	1	3	3	7**	5*
Grade 1	-	-	-	-	2	1	3	3	6	5
Grade 2	-	-	-	-	-	-	-	-	1	-
LUNG										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Mineralization	-	-	-	-	-	-	-	-	4*	-
Grade 1	-	-	-	-	-	-	-	-	4	-
- Mineralization interstitium	-	-	-	-	-	-	-	-	4*	-
Grade 1	-	-	-	-	-	-	-	-	4	-
MAMMARY GLAND(S)										
- No. Examined	9	10	10	10	10	10	10	10	10	10
- Atrophy	-	-	-	-	5*	4*	5*	7**	9**	10**
Grade 1	-	-	-	-	3	-	2	6	2	2
Grade 2	-	-	-	-	2	2	2	1	3	5
Grade 3	-	-	-	-	-	2	1	-	4	3
NOSE										
- No. Examined	10	10	-	-	10	10	10	-	10	10
- Chondroid metaplasia	-	-	-	-	-	-	-	-	2	-
Grade 1	-	-	-	-	-	-	-	-	2	-
ORAL MUCOSA										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Atrophy	-	-	-	-	-	-	2	1	7**	9**
Grade 1	-	-	-	-	-	-	2	1	7	9
OVARIES										
- No. Examined		10		1		10		10		10
- Necrosis		-		-		-		-		2
Grade 1		-		-		-		-		2
SALIVARY GLD PAROTID										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Atrophy	-	-	-	-	1	3	10**	8**	10**	10**
Grade 1	-	-	-	-	1	2	8	6	4	5
Grade 2	-	-	-	-	-	1	2	2	6	5
SKIN										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Hair follicles increased number/reduced size	-	1	-	1	4*	2	4*	4	6**	8**
Grade 1	-	1	-	1	4	2	4	4	6	8
SMALL INT. DUODENUM										
- No. Examined	10	10	-	1	10	10	10	-	10	10
- Mineralization	-	-	-	-	-	-	-	-	3	-
Grade 1	-	-	-	-	-	-	-	-	3	-
STOMACH										
- No. Examined	10	10	-	1	10	10	10	-	10	10
- Mineralization	-	-	-	-	-	-	1	-	9	-
Grade 1	-	-	-	-	-	-	1	-	5	-
Grade 2	-	-	-	-	-	-	-	-	2	-
Grade 3	-	-	-	-	-	-	-	-	1	-
Grade 4	-	-	-	-	-	-	-	-	1	-
TAIL										
- No. Examined							2		7	3
- Chondroid dysplasia/metaplasia							2		7	3
Grade 1							-		-	2
Grade 2							2		2	1
Grade 3							-		5	-

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TONGUE										
- No. Examined	10	10	-	1	10	10	10	10	10	10
- Atrophy	-	-	-	-	-	-	3	3	9**	8**
- Grade 1	-	-	-	-	-	-	3	3	5	7
- Grade 2	-	-	-	-	-	-	-	-	4	1
- Mineralization submucosa	-	-	-	-	-	-	-	-	1	-
- Grade 2	-	-	-	-	-	-	-	-	1	-
- Mineralization vascular	-	-	-	-	-	-	-	-	7**	-
- Grade 1	-	-	-	-	-	-	-	-	4	-
- Grade 2	-	-	-	-	-	-	-	-	1	-
- Grade 3	-	-	-	-	-	-	-	-	2	-
TOOTH/TEETH										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Abnormal dentin/degeneration odontoblasts	-	-	-	-	-	-	5*	-	5*	2
- Grade 1	-	-	-	-	-	-	5	-	4	1
- Grade 2	-	-	-	-	-	-	-	-	1	1
- Prominent incremental lines	-	-	-	2	-	-	7**	3	9**	10**
- Irregular (outer) dentin layer incisors	-	-	-	-	-	-	4*	3	6**	7**
TRACHEA										
- No. Examined	10	10	10	10	10	10	10	10	10	10
- Chondroid dysplasia	-	-	-	-	4*	1	6**	6**	5*	5*
- Grade 1	-	-	-	-	4	1	6	6	5	5

(Excerpted from Applicant's study report)

Table 35: Other microscopic findings in rats at terminal sacrifice including deaths

Dose (mg/kg/day)	0	4	12	16	32
Number Examined	10	10	10	10	10
Treatment-related Findings					
BONE, STIFLE					
Osteomyelitis					
- Grade 1	0	0	0	0	1m
Prominent osteoclasts					
- Grade 1	0	0	0	0	1m
EYE					
Thickening cornea endothelium					
- Grade 1	0	0	0	0	1m
HEART					
Degeneration/inflammation					
- Grade 1	1m	0	2m	4m	3m/2f
- Grade 2	1m	0	0m	1m	5m
Fibrosis					
- Grade 1	0	0	0	1m	0m
- Grade 2	0	0	0	0m	1m
LUNG					
Mineralization					
- Grade 1	0	0	0	0	4m
Mineralization interstitium					
- Grade 1	0	0	0	0	4m
Tunica media hypertrophy					
- Grade 1	0	0	1m	2m	1m
SKIN					
Hyperkeratosis epidermis					
- Grade 1	0	1m	4m	0m	1m
Hyperkeratosis follicular					
	0	0	0	0	

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- Grade 1					1m
Inflammation chronic	0	1m	2m	0m	1m
- Grade 1	0	0m	1m	0m	0m
- Grade 2					
STOMACH					
Necrosis	0	0	0	0	1m
- Grade 2					
Edema	0	0	0	0	1f
- Grade 1					
Erosion(s)	0	0	0	0	1f
- Grade 2					
TAIL					
Degeneration intervertebral disc(s)	0	0	0	1m	7m/1f
- Grade 1					
Chondroid dysplasia/metaplasia	0	0	0	0	2f
- Grade 1	0	0	0	0	1f
- Grade 2					
TRACHEA					
Chondroid dysplasia	0	0	4m/1f	6m/6f	5m/5f
- Grade 1					
Mineralization	0	0	0	0	1m
- Grade 1					
URINARY BLADDER					
Distention	0	0	2m	1m	0m
- Grade 1	0	0	0m	1m	1m
- Grade 2					
Thin urothelium	0	0	0	0	2m
- Grade 1					
CERVIX					
Inflammation acute	0	0	0	0	1f
- Grade 1	0	0	0	0	1f
- Grade 2					
GRADE 1 = Minimal / very few / very small GRADE 2 = Slight / few / small GRADE 3 = Moderate / moderate number / moderate size GRADE 4 = Marked / many / large P = Finding present, severity not scored					
<i>(Excerpted from Applicant's study report)</i>					

Study title/ number: JNJ-42756493-AAA : 3-Month repeated dose oral toxicity study in the beagle dog/ Study # TOX10849

- At doses ≥ 0.5 mg/kg/day, ocular changes consisted of bilateral watery or purulent ocular discharge, periocular alopecia, blepharospasm, diffuse corneal opacification and low tear production.
- The predominant target organs were aorta (vascular mineralization/degeneration), heart (mineralization/degeneration), bone femur and sternum (chondroid dysplasia), skin (increased hair follicles) and epithelial atrophy in the tongue, oral mucosa, parotid salivary glands, eye, teeth and lacrimal glands.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0.5 and 0.75 mg/kg/day (once daily for 3 months); or 1.5 mg/kg/day once daily every other week

Route of administration: orally via gavage

Formulation/Vehicle: aqueous solution, containing 20% w/v Hydroxypropyl- β -cyclodextrin (HP- β -CD)

Species/Strain: Beagle dogs

Number/Sex/Group: 4/sex/group

Age: 6-8 months

Observations and Results: changes from control

Parameters	Major findings			
Mortality	None			
Clinical Signs				
Table 36: Dog clinical signs				
Number of observations N=4/sex/group (male/female)	Vehicle	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day
Haircoat abnormal (rough/piloerection)	0/0	2/3	4/4	4/4
Alopecia/hair loss	1/0	0/0	2/3	0/2
Nail long and broken nails	0/0	1/0	4/2	3/2
Ocular discharge (watery, purulent and/or mucoid)	0/0	1/0	4/4	3/4
Sclera discolored, red	0/0	0/0	0/1	0/0
Palpebral fissure narrowed (ptosis)	0/0	0/0	0/2	0/0
Skin abnormal – redness	0/0	0/0	2/2	0/1

0 =No findings were reported

Body Weight Gain				
Table 37: Dog body weight gain (% change from control)				
N=4/sex/group (male/female)	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day	
Day 90	--/-20	-10/10	-10/-20	
--=no findings were reported				
Food Consumption				
Table 38: Dog food consumption (% change from control)				
N=4/sex/group (male/female)	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day	
Days 84-89	-17/9	-24/-9	-14/4	
Ophthalmoscopy and Schirmer Tear Test (day 90):				
• Very low tear production values in one male dog of the high dose group and in some female dogs (low, medium and high dose) were reported, however without a clear dose relationship. • Number of dogs with observations on day 90:				
Table 39: Dog ophthalmoscopy and Schirmer Tear Test				
Observations N=4/sex/group (male/female)	Vehicle	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day
Blepharospasm, bilateral	0/0	0/0	2/1	0/1
Corneal opacification, diffuse, bilateral	0/0	0/0	2/3	0/1
Ocular discharge (watery, purulent, bilateral)	0/0	1/0	4/3	3/3
Periocular alopecia, bilateral	0/0	0/0	2/4	4/4
Pigmented focus/foci in tapetal fundus, bilateral	0/0	0/0	1/0	0/0
Corneal ghost vessels, bilateral	0/0	0/0	0/1	0/0
Retinal long posterior ciliary artery impression, bilateral	0/0	0/2	0/1	0/1
<i>0 =No findings were reported</i>				
ECG (week 13)				
Table 40: Dog ECG (% change from control)				
N=4/sex/group (male/female)	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day	
Heart rate	-20/-6	-30/-21	-28/-21	

Hematology (Day 91)			
Table 41: Dog hematology (% change from control)			
N=4/sex/group (male/female)	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day
Reticulocytes	-22/-46	-46/-51	-61/-36
Thrombocytes	--/--	-15/--	-8/9
White blood cells	--/-36	--/-16	-25/-33
Neutrophils	--/-41	--/-25	-27/-42
Lymphocytes	--/-24	-5/--	-26/-12
Monocytes	--/-27	--/-7	-30/-30
Fibrinogen	27/14	22/11	50/25

-- = no findings were reported

Clinical Chemistry (Day 91)			
Table 42: Dog clinical chemistry (% change from control)			
N=4/sex/group (male/female)	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day
Inorg. phosphorus	17/18	24/35	63/92
Cholesterol	--/--	-10/--	-10/-19
Creatinine	12/--	5/--	20/--
Alk. phosphatase	--/11	6/9	30/45
AST	17/14	-7/-12	11/31
ALT	--/--	--/--	11/19

-- = no findings were reported

Urinalysis (Day 91)			
Table 43: Dog urinalysis (% change from control)			
N=4/sex/group (male/female)	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day
Volume	53/22	87/--	90/121
Calcium normalized for creatinine	--/50	71/17	29/283

-- = no findings were reported

Biomarkers (Day 91)			
Table 44: Dog biomarkers (% change from control)			
(male/female)	0.5 mg/kg/day	0.75 mg/kg	1.5 mg/kg
Fibroblast growth factor (FGF-23)	51/52	44/82	74/224
Parathyroid hormone (PTH)	17/26	48/-17	-25/-63
1,25-dihydroxyvitamin D3	--/--	--/--	-45/--
N-telopeptides of type I collagen (NTX)	--/--	11/37	131/49
Deoxypyridinoline (DPD)	22/--	67/11	124/16

-- = no findings were reported; m=male; f=female

Organ Weights (relative to body weight)			
Table 45: Dog organ weight changes (% change from control)			
Day 91 (male/female)	0.5 mg/kg/day	0.75 mg/kg	1.5 mg/kg
Prostate	-13	-12	-7
Testes	-18	-18	-14
Thyroid glands	-33/-31	-33/-36	-27/-52

-- = no findings were reported; m=male; f=female

Gross Pathology				
Table 46: Dog gross pathology				
Number of observations N=4/sex/group (male/female)	Vehicle	0.5 mg/kg/day	0.75 mg/kg/day	1.5 mg/kg/day
AORTA - Irregular surface	0/0	0/0	1/1	3/4
HEART- Irregular surface	0/0	0/0	2/2	4/4
Focus/area: white-tan	0/0	0/0	0/0	1/0
SKIN- alopecia/crust	0/0	0/0	1/0	0/1
URINARY BLADDER- thickened	0/0	1/0	1/0	0/0
SKIN PERIOULAR				
alopecia	0/0	0/0	2/2	0/0
discoloration	0/0	0/0	1/0	0/0
LUNG				
Focus/area red	0/0	2/0	1/0	3/4
Focus/area white-tan	0/1	3/2	3/2	3/3
EXTREMITIES				
Broken	0/0	0/0	1/0	0/0
Discoloration/irregular surface	0/0	1/0	0/0	0/0

0 =No findings were reported

Histopathology

Adequate battery: Yes

Table 47: Summary of histological findings in dogs at termination

Daily Dose (mg/kg)	0 (Vehicle)		0.5		0.75		1.5	
	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
No. of Animals	4	4	4	4	4	4	4	4
Animals Examined	4	4	4	4	4	4	4	4
AORTA								
- No. Examined	4	4	4	4	4	4	4	4
- Mineralisation/degeneration	-	-	-	-	1	1	3	2
Grade 1	-	-	-	-	-	-	2	-
Grade 2	-	-	-	-	-	-	1	1
Grade 3	-	-	-	-	1	1	-	1
BONE, STERNUM								
- No. Examined	4	4	4	4	4	4	4	4
- Chondroid dysplasia/metaplasia	-	-	-	-	3	2	4	4
Grade 1	-	-	-	-	3	2	1	-
Grade 2	-	-	-	-	-	-	3	2
Grade 3	-	-	-	-	-	-	-	2
BONE, DISTAL FEMUR								
- No. Examined	4	4	4	4	4	4	4	4
- Closed growth plate	4	4	3	4	1	1	-	4
- Chondroid dysplasia/metaplasia	-	-	-	1	3	3	4	4
Grade 1	-	-	-	1	1	1	2	2
Grade 2	-	-	-	-	2	1	2	2
Grade 3	-	-	-	-	-	1	-	-
HEART								
- No. Examined	4	4	4	4	4	4	4	4
- Mineralization/degeneration	1	-	-	-	2	3	4	4
Grade 1	1	-	-	-	1	1	-	-
Grade 2	-	-	-	-	1	2	1	-
Grade 3	-	-	-	-	-	-	3	4
LACRIMAL GLANDS								
- No. Examined	4	4	4	4	4	4	4	4
- Atrophy	-	-	4	4	4	4	4	4
Grade 1	-	-	2	4	1	-	-	-
Grade 2	-	-	2	-	1	3	1	4

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Daily Dose (mg/kg)	0 (Vehicle)		0.5		0.75		1.5	
No. of Animals	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Grade 3					2	1	3	
SALIVARY GLD PAROTID								
- No. Examined	4	4	4	4	4	4	4	4
- Inflammation chronic	1	2	-	-	-	1	-	1
Grade 1	1	2	-	-	-	1	-	1
- Atrophy	-	-	2	2	4	4	4	4
Grade 1	-	-	1	1	1	2	-	2
Grade 2	-	-	1	1	3	2	4	2
TONGUE								
- No. Examined	4	4	4	4	4	4	4	4
- Atrophy epithelium	-	-	4	3	4	3	4	4
THYROID GLANDS								
- No. Examined	4	4	4	4	4	4	4	4
- Small follicles	-	-	-	-	-	4	-	4
Grade 1	-	-	-	-	-	4	-	1
Grade 2	-	-	-	-	-	-	-	3
TOOTH/TEETH								
- No. Examined	4	4	4	4	4	4	4	4
ORAL MUCOSA								
- No. Examined	4	4	4	4	4	4	4	4
- Atrophy epithelium	-	-	-	-	-	-	3	1
Grade 1	-	-	-	-	-	-	2	1
Grade 2	-	-	-	-	-	-	1	-

(Excerpted from Applicant's study report)

Table 48: Other microscopic findings in dogs at terminal sacrifice

Dose (mg/kg/day)	0	0.5	0.75	1.5
Number Examined/sex	4	4	4	4
Treatment-related Findings (male/female)				
SKIN PERIOULAR				
Granulomas				
- Grade 1	0/0	1/0	1/0	0/0
- Grade 2	0/0	0/0	0/0	1/0
Decreased hair follicles				
- Grade 1	0/0	0/0	1/1	0/0
SKIN EAR				
Increased hair follicles	0/0	0/0	0/0	4/0
Tooth/Teeth				
Abnormal dentin	0/0	0/0	0/0	3/4

0 = No findings were reported

GRADE 1 = Minimal / very few / very small

GRADE 2 = Slight / few / small

GRADE 3 = Moderate / moderate number / moderate size

GRADE 4 = Marked / many / large

P = Finding present, severity not scored

(Excerpted from Applicant's study report)

General toxicology; additional studies

Study title/ number: (b) (4): 1-month Repeated Dose Oral Toxicity Study in the Rat (impurity evaluation). Study # TOX10565

- No adverse findings were reported following treatment with (b) (4) or the test article spiked with the impurity (b) (4)

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- No differences were reported between both groups in regard to adverse findings.
- As such, spiking with (b) (4) did not result in additional toxicity, and the impurity would be considered qualified at (b) (4).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 4 mg/kg/day (b) (4) [Group A] or 4 mg/kg/day (b) (4) with (b) (4) [Group B] daily

Route of administration: orally by gavage

Formulation/Vehicle: 20% w/v Hydroxypropyl-β-cyclodextrin

Species/Strain: Sprague-Dawley rats

Number/Sex/Group: 10

Age: 8-9 weeks

Satellite groups/ unique design: None

Observations and Results: changes from control

Parameters	Major findings
Mortality	No mortalities were reported
Clinical Signs	No adverse test article-related observations were reported
Body Weights and Food Consumption	• Rats at group B (spiked test article) showed higher mean body weight gain (10%) than Group A (b) (4). • No test article-related effects on food consumption were reported
Clinical Pathology (Hematology, Coagulation and Clinical Chemistry)	No adverse test article-related finding differences were reported between both groups
Gross Pathology and Organ Weights	No adverse test article-related finding differences were reported between both groups.

Histopathology

Adequate battery: Yes

No adverse test article-related finding differences were reported between both groups.

Table 49: Summary of histological findings in rats at termination (impurity evaluation study)

Observations N=10/sex/group	Vehicle	Group A (4 mg/kg/day)	Group B (4 mg/kg/day-spiked)
EPIDIDYMIDES			
Infiltration mononuclear cell - Grade 1	0	1m	2m
ESOPHAGUS			
Inflammation chronic - Grade 1	0	1/0	1/2
KIDNEYS			
Dilatation pelvic - Grade 1	0	1m	3m
LUNG			
Inflammation chronic - Grade 1	1m	0	5m
Mineralization - Grade 1	0	0	1m
PROSTATE			
Infiltration granulocytic - Grade 1	0	2m	1m
SPLEEN			
Extramedullary hematopoiesis - Grade 1	0	0	1m
THYMUS			
Congestion - Grade 1	0	0	1m
BONE MARROW, STERNUM			
Atrophy - Grade 1	0	0	1f
TONGUE			
Hemorrhage - Grade 1	0	0	2f
TRACHEA			
Dilatation gland(s) - Grade 1	0	0	1f

0 =No findings were reported

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation Assay of JNJ-42756493-AAA (Study # AD88HK.502ICH.BTL)

Key Study Findings:

JNJ-42756493-AAA was not mutagenic under the condition tested.

GLP compliance: Yes

Test system: salmonella strains TA1535, TA1537, TA98, TA100 and E. coli strain WP2 *uvrA*; up to 5000 µg/plate; +/- S9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: JNJ-42756493-AAA: *In Vitro* Mammalian Cell Micronucleus Assay in TK6 Cells (Study # AD88HK.361GLP.BTL)

Key Study Findings:

JNJ-42756493-AAA was negative for the induction of micronuclei (not aneugenic and clastogenic) in both non-activated and S9-activated test systems.

GLP compliance: Yes

Test system: TK6 cells; +/- S9

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: In Vivo Micronucleus Assay in Rats for JNJ-42756493-AAA (Study # JNJ-42756493-AAA) Key Study Findings:

JNJ-42756493-AAA at doses up to and including a dose of 1000 mg/kg was negative in the bone marrow micronucleus assay.

GLP compliance: Yes

Test system: Male Sprague-Dawley rats.

Study is valid: Yes

Other Genetic Toxicity Studies: None

5.5.3. Carcinogenicity

Not conducted or required to support this NDA application of erdafitinib for patients with advanced cancer.

5.5.4. Reproductive and Developmental Toxicology

Embryo-Fetal Development

18	-5	-5	-8
20	-6	-7	-12

GD= gestation Day

Table 51: Necropsy body weight adjusted to uterus weight in rats

	Control	1 mg/kg/day	4 mg/kg/day	8 mg/kg/day
Gravid uterus (% from control)	88.4g	73.5g (-17%)	67.7g (-18%)	39g (-56%)
Adjusted BW (% from control)	312g	305g (-3%)	306g (-2%)	316 (2%)

Food Consumption

Unremarkable

Necropsy findings

Unremarkable

Cesarean Section Data

- Six females at 8 mg/kg/day group had no viable fetuses at terminal caesarean section.
- At 8 mg/kg/day, test article-related increases in post-implantation loss (early and late resorptions), decreases in number of litters with viable fetuses, number of live fetuses, litter weight and fetal weights were noted.

Table 52: Cesarean section data (rat)

Endpoint (% change from control)	Control	1 mg/kg/day	4 mg/kg/day	8 mg/kg/day
Females pregnant	22	22	22	22
Litters with viable fetuses	22	22	22	16 (-27%) ¹
Mean Number of Corpora Lutea	15.9	14.1	14	15
Mean number of early resorptions	0.7	0.9	1	8
Early resorptions (%)	4.9	7.03	9.19	54.73
Mean number of late resorptions	0	0	0.2	0.5
Late resorptions (%)	0.28	0	1.52	3.38
Mean post implantation loss	0.8	0.9	1.1	8.5 ¹
Post implantation loss (%)	5.18	7.03	10.71	58.11
Mean number of live fetuses	14.5	12.2 (-16%)	12 (-17%)	6 (-59%)
Mean total litter weight	58.3	48.9 (-16%)	45.3 (-22%)	24.2 (-59%)
Mean male & female fetal weight	4g	4g	3.8g (-5%)	2.9g (-28%)

Shading= test article-related findings

¹6 females in the group had no viable fetuses at terminal caesarean section

Offspring Anomalies (External, Visceral and Skeletal)

- Structural anomalies (great blood vessel malformations, multiple limb/paw malformations and increased skeletal anomalies) were reported at doses ≥4 mg/kg/day.
- Developmental delay at 8 mg/kg/day (incomplete ossification of multiple bones).

		Control	1 mg/kg/day	4 mg/kg/day	8 mg/kg/day
Number of litters examined		22	22	22	16
Total number of Litters with malformations (external, visceral and skeletal)		1 (0, 0, 1)	1 (0, 0, 1)	2 (0, 1, 1)	14 (4, 12, 9)
<u>External Anomalies</u>					
Paw- ectrodactyly	Litters N (%)	0	0	0	4(25)
<u>Visceral Anomalies</u>					
Aortic arch, High arched	Litters N (%)	0	0	0	1(7.1)
Subclavian artery, Retroesophageal	Litters N (%)	0	0	1(4.5)	4(28.6)
Aortic arch, Retroesophageal	Litters N (%)	0	0	0	6(42.9)
Interrupted aortic arch	Litters N (%)	0	0	0	3(21.4)
Great vessels, Multiple abnormalities	Litters N (%)	0	0	0	3(21.4)
Innominate artery, Absent	Litters N (%)	3(13.6)	2(9.1)	2(9.1)	8(57.1)
Subclavian artery, Supernumerary branch	Litters N (%)	0	0	0	1(7.1)
Umbilical artery, Transposed	Litters N (%)	2(9.1)	5(22.7)	7(31.8)	11(78.6)
Thyroid gland, Absent	Litters N (%)	0	0	0	1(7.1)
Lateral ventricle, Dilated	Litters N (%)	0	0	2(9.1)	3(21.4)
<u>Skeletal Anomalies</u>					
Limb, Multiple abnormalities (absent, bent, misshapen long bones)	Litters N (%)	1(4.5)	0	0	3(18.8)

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Paw, Multiple abnormalities (associated with ectrodactyly)	Litters N (%)	0	0	0	4(25)
Skull: Supraoccipital, Incomplete ossification	Litters N (%)	0	1(4.5)	0	5(31.3)
Forepaw: Metacarpal, Unossified, 5th digit	Litters N (%)	7(31.8)	4(18.2)	6(27.3)	15(93.8)
Hindpaw: Metatarsal, Incomplete ossification	Litters N (%)	1(4.5)	1(4.5)	0	8(50)
Hindpaw: Metatarsal, Unossified	Litters N (%)	0	0	0	8(50)
Pectoral girdle: Scapula, Short	Litters N (%)	0	0	0	1(6.3)
Pelvic girdle: Ilium, Malpositioned	Litters N (%)	0	0	0	1(6.3)
Metacarpal, Unossified, 5th digit	Litters N (%)	7(31.8)	4(18.2)	6(27.3)	15(93.8)
Ribs, Absent	Litters N (%)	0	0	0	2(12.5)
Ribs, Detached	Litters N (%)	0	0	0	1(6.3)
Ribs, Fused	Litters N (%)	0	0	0	1(6.3)
Ribs, Short	Litters N (%)	0	0	4(18.2)	8(50)
Caudal, Unossified	Litters N (%)	1(4.5)	0	0	5(31.3)
Caudal, Unossified centrum, 1st and 2nd	Litters N (%)	0	0	0	4(25)
Cervical, Incomplete ossification of arch	Litters N (%)	1(4.5)	0	0	5(31.3)
Lumbar, Number = 7	Litters N (%)	0	0	0	6(37.5)
Sternebrae, Asymmetric	Litters N (%)	0	1(4.5)	2(9.1)	8(50)
Sternebrae, Incomplete ossification, 1st/3rd	Litters N (%)	0	0	4(18.2)	15(93.8)
Sternebrae, Unossified, 1st/3rd	Litters N (%)	0	0	0	4(25)

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Sternebrae, Incomplete ossification, 2nd/4th	Litters N (%)	3(13.6)	1(4.5)	2(9.1)	11(68.8)
Sternebrae, Incomplete ossification, 6th	Litters N (%)	4(18.2)	2(9.1)	4(18.2)	11(68.8)
Sternebrae, Unossified, 6th	Litters N (%)	2(9.1)	0	0	6(37.5)
Sternebra, sternoschisis	Litters N (%)	0	0	1(4.5)	1(6.3)
Thoracic, Bipartite ossification of centrum	Litters N (%)	1(4.5)	1(4.5)	1(4.5)	4(25)
Thoracic, Incomplete ossification of centrum, 1st to 9th	Litters N (%)	4(18.2)	4(18.2)	4(18.2)	16(100)
Thoracic, Multiple abnormalities	Litters N (%)	0	0	0	4(25)
Vertebrae: Caudal, Unossified	Litters N (%)	1(4.5)	0	0	5(31.3)
Vertebrae: Caudal, Unossified centrum, 1st and 2nd	Litters N (%)	0	0	0	4(25)
Vertebrae: Cervical, Incomplete ossification of arch	Litters N (%)	1(4.5)	0	0	5(31.3)
Vertebrae: Lumbar, Number = 7	Litters N (%)	0	0	0	6(37.5)
Vertebrae: Thoracic, Bipartite ossification of centrum	Litters N (%)	1(4.5)	1(4.5)	1(4.5)	4(25)
Vertebrae: Thoracic, Incomplete ossification of centrum, 1st to 9th	Litters N (%)	4(18.2)	4(18.2)	4(18.2)	16(100)
Vertebrae: Thoracic, Multiple abnormalities	Litters N (%)	0	0	0	4(25)
Vertebrae: Thoracic, Unossified centrum, 1st to 9 th	Litters N (%)	1(4.5)	1(4.5)	0	7(43.8)

Fertility and Early Embryonic Development

Fertility and early embryonic development studies were not conducted or required to support an advanced cancer indication.

5.5.5. Other Toxicology Studies

Phototoxicity

The Applicant evaluated the effect of JNJ-42756493 on phototoxicity in in vitro and in vivo studies (Study #TOX1235; non-GLP; TOX10684, GLP).

The in vitro phototoxic potential of JNJ- 42756493-AAA was assessed using Balb/c 3T3 mouse fibroblasts assay. JNJ-42756493-AAA was considered phototoxic in the in vitro study (Study #TOX1235; non-GLP), while in a follow-up GLP-compliant toxicology study in female Long-Evans pigmented rats, JNJ-42756493-AAA (orally 3 qd at 4, 8, and 16 mg/kg) was not considered to have phototoxic effects on the skin. Systemic exposure increased in a dose-dependent manner. AUC values were 10.1, 79.9 and 544 ng.h/mL for 4, 8 and 16 mg/kg/day, respectively. (Study # TOX10684, GLP)

Skin Sensitization

A murine local lymph node assay (LLNA) was conducted to assess the skin sensitization potential of topically applied JNJ-42756493-AAA. CBA/Ca mice (4 females/group) were administered JNJ-42756493-AAA at concentrations of 2.5%, 5%, and 10% w/v or a positive control (25% v/v hexyl cinnamic aldehyde [HCA]). Mice were treated (25 µL) daily for 3 days at the dorsal surface of both ears. No dermal irritation of the ears was reported at all doses tested. JNJ-42756493-AAA at concentrations ≥ 5% resulted in stimulation index of ≥4.1 with calculated concentration (EC3) of ≥3.5%. In conclusion, JNJ-42756493-AAA caused skin sensitization at concentrations of ≥ 3.5%. (Study # TOX10363; non-GLP)

Table 54: Skin sensitization potential

Table 1 Group DPM/node and test/control ratios

Group	Concentration	DPM	Number of lymph nodes per group	DPM/node	Stimulation Index†	Result + = positive - = negative
5	DMF	4653.75	7.0	664.82	n/a	n/a
6	2.5% w/v	14268.85	8.0	1783.61	2.7	-
7	5% w/v	21759.45	8.0	2719.93	4.1	+
8	10% w/v	40865.25	8.0	5108.16	7.7	+
9	HCA 25% v/v	57145.25	8.0	7143.16	10.7	+

† Stimulation Index of 3 or more indicates a positive result

n/a Not applicable

DPM Disintegrations per minute (less background count of 42.55 DPM)

DMF Dimethylformamide (vehicle control)

HCA Hexyl cinnamic aldehyde (positive control)

The EC3 is the concentration of test substance which would result in a stimulation index (SI) of 3.

(Excerpted from Applicant's study report)

Eye and vascular irritation

- The vascular irritation potential of JNJ-42756493-AAA was evaluated using in vitro Hen's Egg chorioallantoic membrane (CAM) irritation assay. The in vitro irritation endpoints assessed

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included hemorrhage, lysis and coagulation. No vascular irritation effect was reported at the different concentrations used (0.02, 0.1 and 0.5 mg/mL). (Study # TOX10916, non-GLP).

- In vitro Bovine Corneal Opacity-Permeability Eye irritation assay was used to assess the ocular irritation potential of JNJ-42756493-AAA when applied topically to freshly isolated bovine corneas for 4 hours at a concentration of 20%. Endpoints included measurements of opacity, permeability and histopathology of the corneas. JNJ-42756493-AAA induced severe increase in corneal opacity at approximately a similar score as that reported in the positive control. No increase in permeability was reported. Histopathology of the cornea showed epithelial and stromal changes. In conclusion, JNJ-42756493-AAA was an eye irritant in this study (Study # TOX10427, non-GLP).

Table 55: Histology analysis of the cornea

Table 5: Histology analysis (BCOP)		TOX10427									
	01	02	03	04	05	06	07	08	09	10	
Desquamation				2	2	2	1mf	2	2	1	
Epithelium: pale/swollen cytoplasm							3 mf, S, W	3 Sd, Wmf	3 S (Wmf)	3 S, W	
Epithelium: pale/swollen/vacuolated cytoplasm				4	4	4					
Epithelium: hyper eosinophilia							3 B, W	4 B, W	4 B, W	3 B (W)	
Epithelium: coagulation							2 B, W, S f	2 B, W	2 mf	2 B, (W)	
Epithelium: loss of adherence in the epithelium				4	4	5	2 B	2 B, S	2B	2B	
Epithelium: pyknosis (cell death)*							3 B	2 B	2 B	3 B	
Epithelium: nuclear condensation				3	3	3	3	3	3	3	
Loss of adherence at the epitheliostromal junction				2 mf	3 mf	2	2 mf	1 mf	3f	2	
Stroma: swelling				3 d	3 d	3 d			1d	2 d	
Keratocytes: shrunken/basophil				2	2	2	1	2	2	2	
Endothelium: absent (A) / present (P)	P	P	P	A	A	A	P	P mf	P	P	
Endothelium: loss degeneration				P	P	P					
overall grade for damage	0	0	0	4-5	4-5	4-5	3	4	4	4	

Legend
Grades: 1 / 2 / 3 / 4 / 5: minimal / slight / moderate / marked / severe/ P: present/ A: absent

W: wing cells, B: basal; S: squamous
f: focal; mf: multifocal; d: diffuse
* with cellular debris at junction

Test articles

01-03: vehicle control (0.9 % (w/v) NaCl in water)
04-06: positive control (20 % (w/w) Imidazole in vehicle)
07-10: JNJ-42765493-AAA (20% (w/w) in vehicle)

(Excerpted from Applicant's report)

Primary Reviewer

Eias Zahalka

Team Leader

Tiffany Ricks

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking accelerate approval of BALVERSA for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, (b) (4)

The proposed dosing regimen is 8 mg (two 4 mg tablets) orally once daily with a dose increase to 9 mg (three 3 mg tablets) once daily if serum phosphate (PO₄) level is < 5.5 mg/dL from Days 14 to 21 and there is no drug-related toxicity. The primary evidence of efficacy to support the proposed dosing regimen comes from Applicant's pivotal Phase 2 Study BLC2001. An ORR (CR + PR, BIRC-assessed) of 32% was observed in 87 patients in the target population who received erdafitinib treatment at the proposed dosing regimen. The safety evaluation of data from patients showed that erdafitinib at the proposed dosing regimen was managed per protocol, with a dose reduction rate of 52%, dose interruption rate of 62%, and a treatment discontinuation rate of 12%. The most common adverse reactions included hyperphosphatemia, stomatitis, dry mouth, decreased appetite, and dry skin.

The clinical pharmacology review focused on the evaluations of the proposed dosing regimen, food effect, drug-drug interactions, organ impairment, population PK modeling, and exposure-response analyses for safety and efficacy.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 212018. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal Study BLC2001 in patients with urothelial carcinoma with FGFR alterations. An ORR of 32% was observed in 87 patients who received erdafitinib treatment at the proposed dosing regimen. The safe use of the drug was managed per protocol, with dose reductions (52%) and dose interruptions (62%). The drug discontinuation rate was 12%. The most common adverse reactions included hyperphosphatemia, stomatitis, dry mouth, decreased appetite, and dry skin.
General dosing instructions	The proposed dosing regimen is 8 mg once daily with dose increase to 9 mg once daily if serum PO₄ level is < 5.5 mg/dL from Days 14 to 21 and there is no drug-related toxicity. Erdafitinib may be taken without regard to food. Dose was increased to 9 mg in 41% of patients in the pivotal Phase 2 Study BLC2001.

Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dosing recommendations should be followed: ▪ Strong CYP2C9 / CYP3A inhibitors: consider alternative agents or monitor closely for adverse reactions ▪ Strong CYP2C9 / CYP3A inducers: avoid use. A PMC trial is requested to determine the dosing strategy. ▪ Moderate CYP2C9 / CYP3A inducers: increase BALVERSA dose up to 9 mg ▪ CYP3A substrates: avoid use with sensitive CYP3A substrates with narrow therapeutic index ▪ P-gp substrates: separate dose by ≥ 6 h before or after administration of P-gp substrates with narrow therapeutic index ▪ OCT2 substrates: consider alternative agents or reducing the dose OCT2 substrates based on tolerability ▪ Serum phosphate level-altering agents: avoid use with agents that can alter serum phosphate levels before the initial dose increase period based on serum phosphate levels (Days 14 to 21)
Labeling	Overall, the proposed labeling recommendations are acceptable upon the applicant's agreement to the FDA revisions to the label. Clinical pharmacology labeling recommendations are detailed in Section 11.
Initial Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed tablets (3, 4, 5 mg film-coated tablets) was used in the proposed dosing regimen arm (Regimen 3) in pivotal Study BLC2001 and in most of the clinical pharmacology studies (i.e., no bridging is needed). Early clinical studies used oral solution, capsules, and initial film-coated tablets; the formulations showed similar erdafitinib pharmacokinetics compared to to-be-marketed tablets (see Appendix).

Post-Marketing Requirement (PMR) or Commitment (PMC)

The following issues should be addressed as PMRs and PMCs:

PMRs:

1. Complete and submit the results of your ongoing hepatic impairment study EDI1008 entitled "A Phase 1, Open-Label, Single-Dose Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Erdafitinib".
2. Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of erdafitinib on the single dose pharmacokinetics of a sensitive CYP3A substrate (e.g., midazolam), to address the potential for excessive drug toxicity or decreased drug exposure, and to determine appropriate dosing recommendations when coadministering erdafitinib with a sensitive CYP3A substrate.

PMCs

1. Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of a strong inducer (e.g., rifampin) of CYP2C9 and CYP3A on the single dose pharmacokinetics of erdafitinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations when erdafitinib is coadministered with CYP2C9 and CYP3A inducers.
2. Conduct a clinical pharmacokinetic study to evaluate the effect of repeated doses of erdafitinib (at steady-state) on the single dose pharmacokinetics of a probe

substrate of OCT2 to determine appropriate dosing recommendations for a probe substrate of OCT2 when it is coadministered with erdafitinib.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Erdafitinib is a FGFR tyrosine kinase inhibitor. The following is a summary of the clinical pharmacokinetics of erdafitinib:

Absorption: Median T_{MAX} was 2.5 h (range: 2 to 6 h). No clinically meaningful differences in erdafitinib pharmacokinetics were observed following administration of a high-fat, high-calorie meal in healthy subjects.

Distribution: Over 99% protein is bound to human plasma proteins, primarily to alpha-1-acid glycoprotein. The mean apparent volume of distribution was 29 L in patients.

Metabolism: Erdafitinib is primarily metabolized by CYP2C9 and CYP3A. The contribution of CYP2C9 and CYP3A in the total clearance of erdafitinib is estimated to be 39% and 20%, respectively.

Elimination: The mean total apparent clearance was 0.36 L/h and the mean effective half-life was 59 h in patients.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen is 8 mg once daily with dose increase to 9 mg once daily if serum phosphate (PO_4) level is < 5.5 mg/dL from Days 14 to 21 and there is no drug-related toxicity.

Therapeutic Individualization

Regarding drug-drug interactions (DDIs), the following dose modifications are recommended:

- **Strong CYP2C9 / CYP3A inhibitors:** consider alternative agents or monitor closely for adverse reactions
- **Strong CYP2C9 / CYP3A inducers:** avoid use
- **Moderate or Weak CYP2C9 / CYP3A inducers:** increase dose up to 9 mg
- **CYP3A substrates:** avoid use with sensitive CYP3A substrates with narrow therapeutic index
- **P-gp substrates:** separate dose by ≥ 6 h before or after administration of P-gp substrates with narrow therapeutic index
- **OCT2 substrates:** consider alternative agents or reducing the dose OCT2 substrates based on tolerability

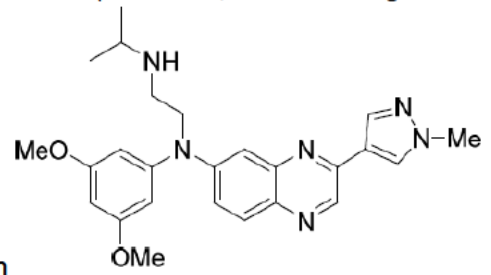
- **Serum phosphate level-altering agents:** avoid use with agents that can alter serum phosphate levels before the dose increase period based on serum phosphate levels (Days 14 to 21)

Outstanding Issues

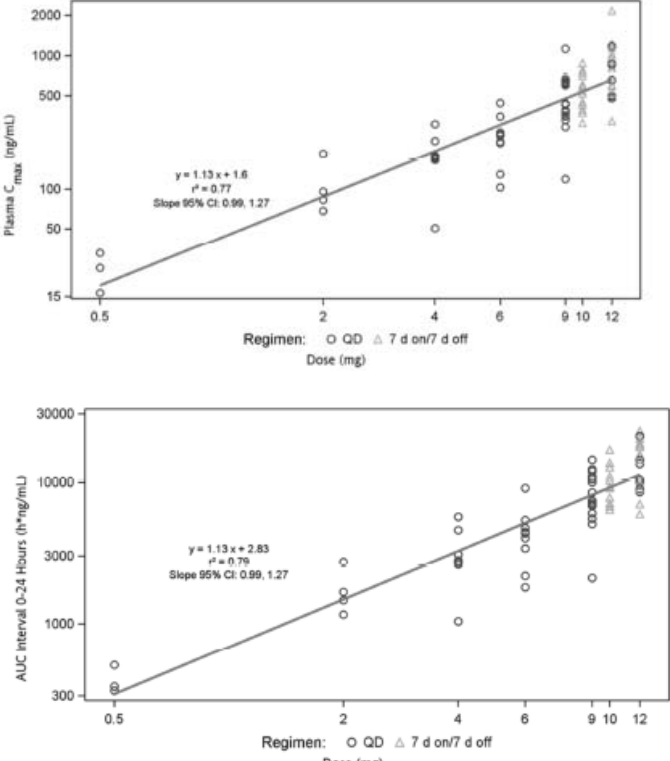
Two PMRs and two PMCs are issued, as presented in the PMR/PMC Section above. There are no other outstanding issues.

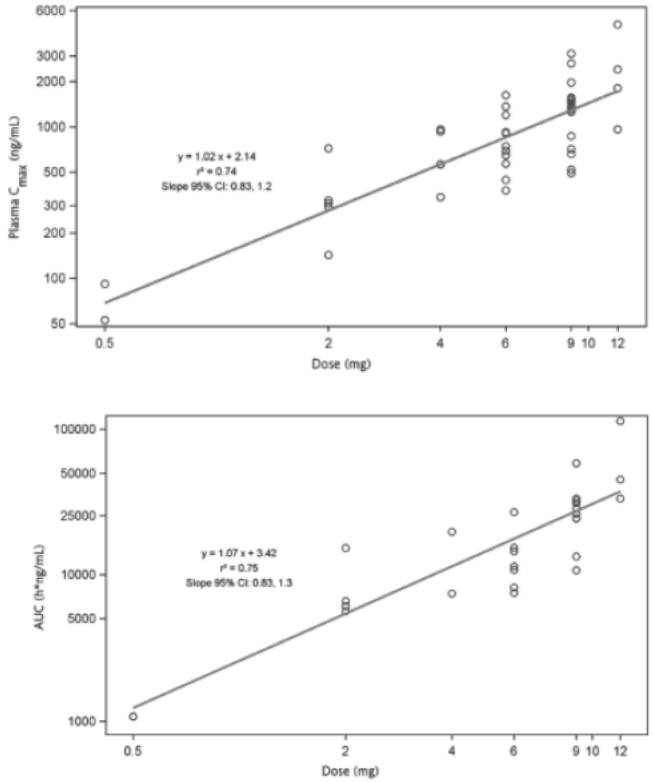
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHYSICOCHEMICAL PROPERTIES																																									
Chemical structure and molecular weight	Erdafitinib (C₂₅H₃₀N₆O₂, molecular weight = 446.56)  en																																								
Aqueous solubility	Erdafitinib has adequate solubility across the pH range of 1 to 7.4. <table border="1"> <thead> <tr> <th>Solvent</th> <th>Solubility in Solution (g/100 mL)</th> <th>pH of Solution</th> <th>Descriptive Solubility^a</th> </tr> </thead> <tbody> <tr> <td>Water</td> <td><0.001</td> <td>7.7</td> <td>Practically insoluble, or insoluble</td> </tr> <tr> <td>0.1N HCl</td> <td>0.23</td> <td>1.1</td> <td>Slightly soluble</td> </tr> <tr> <td>0.01N HCl</td> <td>0.073</td> <td>1.9</td> <td>Very slightly soluble</td> </tr> <tr> <td>Citric acid-NaOH-HCl buffer pH 2</td> <td>0.092</td> <td>1.7</td> <td>Very slightly soluble</td> </tr> <tr> <td>Citric acid-NaOH buffer pH 5</td> <td>0.037</td> <td>5.3</td> <td>Very slightly soluble</td> </tr> <tr> <td>Phosphate buffer pH 7</td> <td>0.65</td> <td>7.4</td> <td>Slightly soluble</td> </tr> <tr> <td>Boric acid-KCl-NaOH buffer pH 9</td> <td>0.001</td> <td>9.0</td> <td>Practically insoluble, or insoluble</td> </tr> <tr> <td>Phosphate-NaOH buffer pH 12</td> <td><0.001</td> <td>12.0</td> <td>Practically insoluble, or insoluble</td> </tr> <tr> <td>0.1N NaOH</td> <td><0.001</td> <td>12.9</td> <td>Practically insoluble, or insoluble</td> </tr> </tbody> </table> ^a Descriptive solubility according to USP and Ph. Eur. definitions	Solvent	Solubility in Solution (g/100 mL)	pH of Solution	Descriptive Solubility ^a	Water	<0.001	7.7	Practically insoluble, or insoluble	0.1N HCl	0.23	1.1	Slightly soluble	0.01N HCl	0.073	1.9	Very slightly soluble	Citric acid-NaOH-HCl buffer pH 2	0.092	1.7	Very slightly soluble	Citric acid-NaOH buffer pH 5	0.037	5.3	Very slightly soluble	Phosphate buffer pH 7	0.65	7.4	Slightly soluble	Boric acid-KCl-NaOH buffer pH 9	0.001	9.0	Practically insoluble, or insoluble	Phosphate-NaOH buffer pH 12	<0.001	12.0	Practically insoluble, or insoluble	0.1N NaOH	<0.001	12.9	Practically insoluble, or insoluble
Solvent	Solubility in Solution (g/100 mL)	pH of Solution	Descriptive Solubility ^a																																						
Water	<0.001	7.7	Practically insoluble, or insoluble																																						
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0.1N NaOH	<0.001	12.9	Practically insoluble, or insoluble																																						
PHARMACOLOGY																																									
Mechanism of action	Erdafitinib is an oral inhibitor of the pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor (IC ₅₀ ≈ 0.1 to 129 nM for FGFR1 to FGFR4).																																								
Active moiety	There are no major circulating metabolites. Unchanged erdafitinib was the major drug-related moiety in plasma.																																								
QT/QTc prolongation	Erdafitinib treatment has no large effects (i.e., 20 ms) on QTc interval.																																								
GENERAL INFORMATION																																									
Bioanalytical assay	Validated bioanalytical assays (LC-MS/MS) were developed to measure the concentrations of erdafitinib in the clinical studies included in this NDA (see Appendix).																																								
Patient PK vs. healthy subject (HS) PK	Erdafitinib mean C _{max} and AUC were 48% and 40%, respectively, higher in patients compared to healthy subjects—notably due to ~2-fold higher alpha-1-acid glycoprotein (AGP) in patients than in healthy subjects.																																								

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Steady-state exposure at the proposed dosing regimen	Steady-state is achieved within 14 days of QD dosing. At 9 mg QD at steady-state: • $AUC_{0-24h} \approx 2020$ ng·h/mL (41% CV) • $C_{MAX} \approx 39600$ ng/mL (44% CV)
Minimal effective dose or exposure	Unknown.
Maximum tolerated dose or exposure	Not reached, based on Phase 1 Study EDI1001 in patients with advanced or refractory solid tumors or lymphoma (highest evaluated dose = 12 mg QD).
Dose proportionality	Erdafitinib demonstrated linear PK in humans. Following multiple-dosing, erdafitinib exposures increased dose proportionally across the dose range of 0.5 to 12 mg once daily (see plots below showing beta slope close to unity). Erdafitinib PK appears to be time-independent, based on similar apparent CL (0.245 – 0.521 L/h) across the dose range of 0.5 to 12 mg once daily from Phase 1 Study EDI1001. Relationship between C_{MAX} (left) and AUC_{0-24} (right) obtained on Cycle 1 Day 1 and administered dose in patients from Study EDI1001 (once daily and intermittent doses)  Source: Figure 13 from Applicant's Summary of Clinical Pharmacology Studies Relationship between C_{MAX} (left) and AUC_{0-24} (right) obtained on Cycle 2 Day 1 (Day 21) and administered dose in patients from Study EDI1001 (once daily doses only)

	 Source: Figure 14 from Applicant's Summary of Clinical Pharmacology Studies		
Accumulation	Following once daily dosing at steady-state: • AUC ratio ≈ 4.1 • C_{MAX} ratio ≈ 3.4		
Variability	Following 9 mg QD, inter-subject variability (%CV) was 41% and 44% for steady-state AUC and C _{max} , respectively.		
ABSORPTION			
Bioavailability	The absolute bioavailability of erdafitinib is unknown.		
T_{MAX}	Median T _{max} = 3 h		
Food effect (high-fat breakfast)	AUC_{0-∞} (GMR, 90% CI)	C_{max} (GMR, 90% CI)	T_{max} (median)
	0.94 (0.89, 0.99)	0.86 (0.81, 0.92)	Fed ≈ 4.0 h
No significant food effect on the PK of erdafitinib. Erdafitinib can be administered without regard to food.			
DISTRIBUTION			
Volume of distribution (V_d)	Erdafitinib is > 99% bound to human plasma proteins, preferentially to alpha-1-acid glycoprotein. The mean apparent V _d in patients is 29 L (51% CV).		
Substrate of transporter systems	Erdafitinib is a substrate of P-gp.		
ELIMINATION			
Terminal elimination half-life and clearance	The mean effective half-life of erdafitinib in patients is 59 h. The steady-state apparent clearance is approximately 0.36 L/h, with an inter-subject variability of 51%.		
Metabolism	Erdafitinib is primarily metabolized by CYP2C9 (39% contribution of total clearance) and CYP3A (20% contribution of total clearance). Due to CYP2C9 polymorphism, patients with		

	CYP2C9*3/*3 genotype (“worst case” poor metabolizer) are expected to have higher systemic concentrations of erdafitinib.
Excretion	Based on the mass balance study, 69% of the dose is recovered in the feces (19% as unchanged) and 19% of the dose was recovered in the urine (13% as unchanged).
Drug interaction liability	Metabolism: ▪ As victim: primarily metabolized by CYP2C9 and CYP3A ▪ As perpetrator: CYP3A inhibitor and inducer Transporter: ▪ As victim: P-gp substrate ▪ As perpetrator: P-gp and OCT2 inhibitor

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes.

Evidence of effectiveness was obtained from Applicant’s pivotal Study BLC2001.

Study BLC2001 was a Phase 2, multi-center, open-label study to evaluate multiple dosing regimens of erdafitinib in patients with metastatic or surgically unresectable urothelial cancer with FGFR genetic alterations (N=210). The primary objective was to evaluate ORR (CR + PR) of the selected dosing regimen of erdafitinib. Erdafitinib was administered without regard to food.

The following dosing regimens were evaluated (1 cycle = 28 days):

- Initial randomization (1:2)
 - **Regimen 1 (n=33):** 10 mg QD 7 days on/7 days off with potential dose increase* to 12 mg QD 7 days on/7 days off on Cycle 2, Day 1
 - **Regimen 2 (n=78):** 6 mg QD with potential dose increase* to 8 mg QD on Cycle 2, Day 1
- Dose Selection (following interim analysis of Regimen 1 and Regimen 2 data, including population PK/PD modeling)
 - **Regimen 3 (n=87):** 8 mg QD with potential dose increase* to 9 mg QD on Cycle 1, Day 15—*proposed dosing regimen for this NDA*

*Dose increase was based on whether the measured serum PO₄ level < 5.5 mg/dL (Regimen 1: measured on Cycle 1, Day 21; Regimen 2: measured on Cycle 2, Day 1; Regimen 3: measured on Cycle 1, Day 14), in addition to consideration of any drug-related toxicity. Treatment with Regimen 3 resulted in an BIRC-assessed ORR of 32% (95% CI: 22%, 42%).

Overall, the clinical pharmacology information was adequate to provide supportive evidence of effectiveness of erdafitinib based on ORR in the intended patient population. The clinical pharmacology program, including the exposure-response analyses (refer to Dose Rationale Section below and Pharmacometrics Review in the Appendix), supported the following:

- The proposed dosing regimen of 8 mg once daily with dose increase to 9 mg once daily if serum PO₄ level is < 5.5 mg/dL from Days 14 to 21 and there is no drug-related toxicity
- There was a positive exposure-response relationship for safety (higher dose leads to more adverse events)
- Exposure-response analysis for efficacy indicated that 9 mg appears to be at the plateau for efficacy
- Clinical safety profile was manageable with dose reductions (52%) and dose interruptions (62%)
- Exploratory subgroup analyses of limited clinical data suggest heterogeneity in response to erdafitinib according to the FGFR alteration type
- Refer to Clinical Pharmacology Sections below for details regarding PK, food effect, DDIs and effect of FGFR alteration type on response

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

Yes. The Applicant’s proposed dosing regimen of 8 mg once daily with dose increase to 9 mg once daily, if serum PO₄ level is < 5.5 mg/dL from Days 14 to 21 and there is no drug-related toxicity. The proposed dosing regimen is reasonable and appropriate for the intended patient population for which the indication is being sought. The proposed dosing regimen is supported by the observed efficacy, safety, and PK data from pivotal Study BLC2001, as noted below.

Dose Selection Rationale

Erdafitinib dose of 8 mg daily is the proposed starting dose with the potential for increasing to 9 mg daily on Day 14 based on whether serum phosphate concentration meet a pre-defined threshold of 5.5 mg/dL. There is only one chance for each patient to increase to the 9 mg daily dose. No further dose increase is allowed but dose interruption is possible based on tolerability. The proposed dosing adjustment schedules is shown in Table 56.

Table 56: Dose Adjustment Schedule for the Proposed Pharmacodynamically-Guided Dosing Algorithm Based on Regimen 3 (BLC2001)

Phosphate concentration	< 5.5 mg/dL	5.5 – 7 mg/dL	7 – 9 mg/dL	> 9 mg/dL
Individualized dose titration at Day 14	9 mg QD	8 mg QD	Interruption ^a	Interruption ^a
			Interruption ^a	Interruption ^a
Individualized dose titration after Day 14	Same dose	Same dose	Restart lower dose ^b if treatment had to be interrupted twice for the same reason; otherwise restart same dose	Restart lower dose ^b

a Until PO₄ < 5.5 mg/dL

b Dose reduction levels: 8 mg (if up-titrated) – 6 mg – 5 mg – 4 mg – 0 mg

Erdafitinib dose up-titration from 8 to 9 mg daily is to optimize benefit-risk ratio in individual patients based on their serum phosphate concentrations. Both the continuous and the intermittent schedules were evaluated for safety and efficacy in the Phase 2 study BLC2001, with a 6 mg and 8 mg starting dose with intra-subject up-titration to 8 mg and to 9 mg respectively for the continuous schedule and 10 mg starting dose with intra-subject up-titration to 12 mg for intermittent schedule based on serum phosphate levels.

Serum phosphate concentration is a marker of FGFR target engagement in early cycles of erdafitinib treatment. In Study BLC2001, analysis of anti-tumor response versus serum phosphate concentration in the first 3 months in the 8 mg daily regimen showed that responses were achieved both above and below 5.5 mg/dL, with a small advantage to subjects who achieved serum phosphate concentrations above 5.5 mg/dL.

Table 57: Best Overall Response by Maximum Serum Phosphate (<5.5, ≥5.5 mg/dL) within First 3 Months -Investigator Assessment; Regimen 3 (BLC2001)

	Maximum serum phosphate within first	Maximum serum phosphate within
	3 months: < 5.5 mg/dL	first 3 months: ≥ 5.5 mg/dL
Total number of subjects	26	72
Objective response rate (CR+PR)	9 (34.6%)	31 (43.1%)
95% CI	(16.3%, 52.9%)	(31.6%, 54.5%)
Disease control rate (CR+PR+SD)	17 (65.4%)	62 (86.1%)
95% CI	(47.1%, 83.7%)	(78.1%, 94.1%)
Best overall response		
Confirmed complete response (CR)	0	3 (4.2%)
Confirmed partial response (PR)	9 (34.6%)	28 (38.9%)
Stable disease (SD)	8 (30.8%)	31 (43.1%)
Progressive disease (PD)	9 (34.6%)	9 (12.5%)
Inevaluable (NE)	0	1 (1.4%)

95% CI are 95% confidence interval calculated with normal approximation.

Source: Table 21 on page 65 of Applicant's study report 42756493BLC2001

Simulations reflecting a dose increase based on serum phosphate levels and a serum phosphate-based dose modification algorithm confirmed a higher proportion of subjects achieved target serum phosphate levels (≥ 5.5 mg/dL) with a starting dose of 8 mg once daily than with 6 mg once daily.

The PK/PD modeling was performed to assess different scenarios for dosing, including up-titration to 8 mg from a starting dose of 6 mg, or a starting dose of 8 mg with potential up-titration to 9 mg. Based on the PK/PD modeling, the starting dose of 8 mg daily was selected at the interim analysis, with a provision for up-titration to 9 mg for subjects with serum phosphate levels <5.5 mg/dL on Day 14. Approximately 41% of subjects starting at 8 mg were up-titrated to 9 mg daily dose (Table 1; Mod2.7.3/SCE/Table 28). This approach of intra-subject up-titration based on their individual serum phosphate levels (rather than down-titration from a 9 mg

starting dose) was deemed appropriate to increase the tolerability of erdafitinib and improve the chances of treatment success.

The efficacy results for the individualized up-titration to 9 mg daily dose based on Day 14 serum phosphate concentration showed improvement in the objective response rate (ORR: complete + partial response [CR+PR]) and best overall response compared to 8 mg daily dose. The results for disease control rate (CR+PR+ stable disease [SD]), duration of response, progression free and overall survival (PFS, OS) are comparable for 8 mg and 9 mg daily doses (Table 1).

Table 58: Summary of Efficacy by Dose Titration- Investigator Assessment; Regimen 3 (BLC2001)

	8-mg Daily Non-uptitrated ^a	8-mg Daily Uptitrated to 9-mg Daily ^b
Total number of subjects, 8-mg daily regimen	58	41
Objective response rate (CR+PR)	20 (34.5%)	20 (48.8%)
95% CI	(22.3%, 46.7%)	(33.5%, 64.1%)
Disease control rate (CR+PR+SD)	48 (82.8%)	31 (75.6%)
95% CI	(73%, 92.5%)	(62.5%, 88.8%)
Best overall response		
Complete response (CR)	1 (1.7%)	2 (4.9%)
Partial response (PR)	19 (32.8%)	18 (43.9%)
Stable disease (SD)	28 (48.3%)	11 (26.8%)
Progressive disease (PD)	8 (13.8%)	10 (24.4%)
Inevaluable (NE)	2 (3.4%)	0
Duration of response (months)		
Number of responders	20	20
Median (95% CI)	5.59 (4.21, 7.39)	5.98 (4.21, 13.37)
Range	(2.7, 10.0+)	(1.4+, 14.3+)
Progression-free survival (months)		
Median (95% CI)	5.52 (3.06, 7.39)	5.55 (3.98, 6.64)
12-month PFS rate (95% CI)	0.19 (0.10, 0.31)	0.21 (0.08, 0.37)
Overall survival (months)		
Median (95% CI)	14.03 (9.82, NE)	13.80 (7.49, NE)
12-month overall survival rate (95% CI)	0.58 (0.43, 0.71)	0.50 (0.30, 0.67)

CI=confidence interval.

+ indicates subjects censored

^a For subjects whose serum phosphate level were ≥ 5.5 mg/dL on Day 14

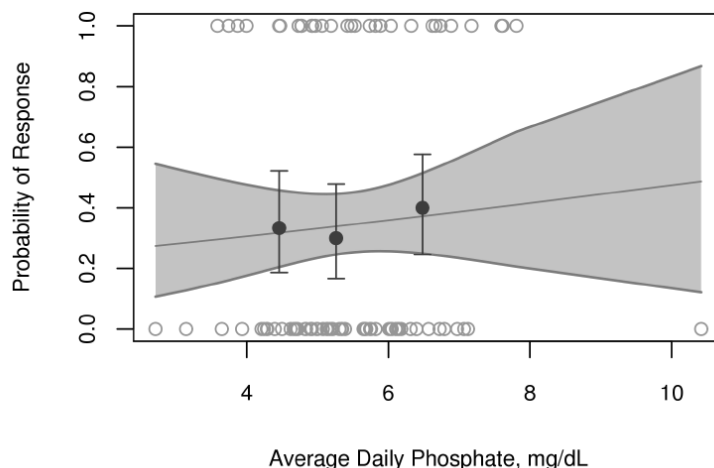
^b For subjects whose serum phosphate level were < 5.5 mg/dL on Day 14

Source: Table 1 on page 5 of Applicant's Response to Information Request to Clinical Pharmacology Dated Nov 16, 2018

Exposure-response analysis characterized a significant relationship of higher investigator-assessed ORR, DCR, and PFS with increasing serum phosphate concentrations (Figure 3). The incidence of eye disorders, central serous retinopathy, nail disorders, palmar-plantar erythrodysesthesia, and skin disorders, at any grade, had a significant relationship with mean serum phosphate levels up to the day of the adverse event (for details, please refer pharmacometrics review in the Appendix). Treatment with 8 mg erdafitinib once daily was associated with clinically manageable events that were reversible upon temporary treatment

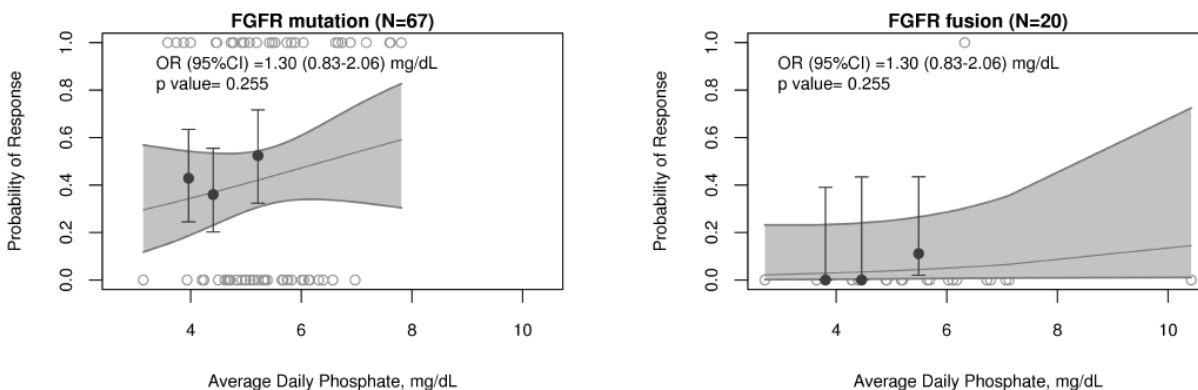
interruption. The totality of the data including the exposure-response analysis support the 8 mg once daily starting dose with potential for a pharmacodynamically-guided individualized up-titration to 9 mg once daily and a stepwise dose reduction and/or interruption for tolerability.

Figure 3: Probability of Response (ORR by BIRC) as a Function of Average Daily Phosphate



Source: Figure 10 on page 39 of Applicant's population exposure response report

Figure 4: Probability of Response (ORR by BIRC) as a Function of Average Daily Phosphate and Stratified by FGFR Alteration (Prognostic Factor)



Source: Figure 11 on page 40 of Applicant's population exposure response report

Note: The blue points represent observed ORR at tertiles of average daily phosphate. Solid blue line represents model-predicted response. The blue area are 95% prediction intervals.

Overall, erdafitinib dose up-titration from 8 to 9 mg daily appears to provide a strategy to optimize benefit-risk ratio in individual patients based on their serum phosphate concentrations. Further increase erdafitinib dose beyond 9 mg daily may have no further benefits based on

exposure-response analysis for efficacy. And safety of daily dose of 12 mg is a serious concern based on safety data from Phase I study EDI1001. In addition to serum phosphate concentration, FGFR alteration was also a significant predictor for efficacy. Patients with FGFR fusion had much lower response rate than patients with FGFR3 point mutation. See Table 77.

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

No. Population PK analysis indicated that age (21 – 88 years old), sex, race, body weight (36 – 132 kg) are not significant covariates for erdafitinib clearance. The relevance of the covariate effects was limited (<30%). Furthermore, since erdafitinib dosing is individualized based on phosphate concentrations, dose adjustments based on age, body weight, gender, race are not needed in adult subjects with bladder cancer. In addition, no dose adjustment is proposed in patients with renal or hepatic impairment (see below).

Note that patients with CYP2C9*3/*3 genotypes may have higher erdafitinib plasma concentrations due to reduced metabolic clearance. Monitor for increased adverse reactions in patients who are known or suspected to have CYP2C9*3/*3 genotype.

Renal Impairment (RI)

No dose adjustment is needed in patients with RI.

Population PK analysis indicated that there was no clinically meaningful effect of mild (eGFR [estimated glomerular filtration rate, using modification of diet in renal disease equation] 60 – 89 mL/min/1.73 m², N=156) or moderate (eGFR 30 – 59 mL/min/1.73 m², N=95) RI on the systemic exposure of erdafitinib. The PK of erdafitinib in patients with severe RI or RI requiring dialysis is unknown due to lack of clinical data.

Hepatic Impairment (HI)

No dose adjustment can be recommended in patients with mild HI at this time.

The PK of erdafitinib in subjects with moderate or severe HI is unknown. Population PK analysis indicated that there was no clinically meaningful effect of mild (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1.0 – 1.5 x ULN and any AST) HI on the systemic exposure of erdafitinib (n=69, from combined clinical Studies). A clinical study to evaluate single-dose PK of erdafitinib in subjects with mild, moderate, or severe HI, and normal hepatic function is currently ongoing. A PMR is issued to ensure that this study is completed and a final clinical study report is submitted.

Tumor FGFR alteration type

To determine molecular eligibility in Study BLC2001, patients were centrally screened for 5 fusions (FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3_V1, FGFR3-TACC3_V3, FGFR3-BAIAP2L1) and 4 FGFR3 point mutations (exon 7 [R248C, S249C], exon 10 [G370C, Y373C]) in archival tumor tissue using a RNA-based polymerase chain reaction (PCR) clinical trial assay (CTA). See

Table 59 for the distribution of FGFR alterations and investigator-assessed objective response rates (INV-ORR) of the enrolled chemo-relapsed/refractory population receiving 8 mg, 6 mg, or 10 mg erdafitinib. The most commonly detected point mutation and fusion corresponded to S249C and FGFR3-TACC3_V1, respectively. Patients with point mutations had higher response rates than patients with fusions in all 3 dosing cohorts (recognizing only 2 patients with fusions without co-occurring FGFR3 point mutations were treated in the 10 mg cohort). Responses were seen across all 4 FGFR3 point mutation subgroups in the 8 mg and 6 mg dosing cohorts. All responders with FGFR3 fusions had a FGFR3-TACC3_V1 fusion. Six patients had FGFR2 fusions as the only alteration detected; of these, one patient with a FGFR2-BICC1 fusion receiving erdafitinib 6 mg exhibited a partial response (PR). Of note, the Blinded Independent Review Committee (BIRC) assessment of disease for this patient was performed in response to a Clinical Information Request of 16 November 2018 leading to a response assessment of progressive disease (PD).

Table 59: Investigator-Assessed Objective Response Rate by FGFR Alteration type, Relapsed/Refractory Population (N=189)

FGFR POINT MUTATIONS / FUSIONS	8 mg QD Efficacy Dataset		6 mg QD		10 mg 7on/7off	
	Patients (N)	Responses (N)	Patients (N)	Responses (N)	Patients (N)	Responses (N)
Total - Chemo Relapsed/Refractory	87	35[§]	73	27	29	6
INV-ORR (%)	40.2[§]		37.0		20.7	
FGFR3 Point Mutations Only *	64	31[§]	59	22	24	5
INV-ORR (%)	48.4[§]		37.3		20.8	
G370C	4	2	11	3	5	0
R248C	9	5	14	6	5	0
S249C	40	18 [§]	19	7	8	2
Y373C	11	6	13	5	3	1
G370C/S249C	0	0	1	0	1	1
R248C/Y373C	0	0	1	1	1	1
S249C/Y373C	0	0	0	0	1	0
FGFR Fusions Only *	23	4	10	2	2	0
INV-ORR (%)	17.4		20.0		0	
FGFR2-BICC1	2	0	1	1	0	0
FGFR2-CAPS7	3	0	0	0	0	0
FGFR3-BAIAP2L1	1	0	1	0	1	0
FGFR3-TACC3_V1	10	4	7	1	1	0
FGFR3-TACC3_V3	6	0	0	0	0	0
FGFR2-CASP7/FGFR3-BAIAP2L1	0	0	1	0	0	0
FGFR2-CASP7/FGFR3-TACC3_V3	1	0	0	0	0	0
Point Mutations and Fusions	0	0	4	3	3	1

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INV-ORR (%)	NA		75.0		33.3	
G370C/FGFR2-BICC1	0	0	1	1	0	0
G370C/FGFR3-TACC3_V1	0	0	1	1	0	0
R248C/FGFR3-TACC3_V1	0	0	1	0	1	1
S249C/FGFR3-BAIAP2L1	0	0	0	0	1	0
R248C/S249C/FGFR3-TACC3_V1	0	0	1	1	0	0
S249C/Y373C/FGFR2-CASP7/FGFR3-BAIAP2L1/FGFR3-TACC3_V1/FGFR3-TACC3_V3	0	0	0	0	1	0

*Source: Reviewer table adapted from Applicant's exploratory subgroup analysis; Attachment TEFRSF02B-C, Study BLC2001 Clinical Study Report. Responses as submitted by the applicant. §The investigator-assessed response for one patient (8mg; S249C) was changed from PR to SD by FDA review resulting in an INV-ORR of 46.9% for the subset of FGFR3 Point Mutations Only (39.1% for the 8 mg dosing cohort). See Section 8 for additional details and for BIRC assessments (8mg). *Only refers to the only FGFR alteration(s) detected in the tumor sample as assessed by the CTA assay. INV-ORR: Investigator-assessed objective response rate= (CR+PR).*

Results of an exploratory multivariate analysis conducted by the reviewer by combining data of patients with either point mutations or fusions enrolled in the 6 mg and 8 mg dosing cohorts showed that FGFR alteration type (point mutation vs fusion) remained independently associated with INV-ORR (P=0.05), considering other factors that may be associated with response (smoking status [never/previous/current], TNM stage at diagnosis [0A-II/III-IV], and dosing cohort [6 mg/8 mg]).

Exploratory Biomarker analysis – Circulating Tumor DNA

Plasma for circulating tumor DNA (ctDNA) was collected in study BCL2001 to explore whether FGFR alterations analyzed using next generation sequencing (NGS) could be detected in blood as a potential replacement for tumor tissue testing in the future. Samples from 155 patients for whom ctDNA was detected at screening (baseline) were included in the analyses (cutoff date of 7 May 2018). The concordance between ctDNA and the tissue-based assay used to determine eligibility in the study was 63.1% for point mutations and 24.1% for fusions; all concordant fusion samples were FGFR3-TACC3 positive. Based on the applicant exploratory analyses, patients with FGFR3 point mutations confirmed by both methods had a higher likelihood of clinical response. Additional FGFR point mutations (e.g., FGFR3 G380R, FGFR2 R664W) were detected in samples of a few patients with the use of NGS.

Reviewer comment: FGFR3 point mutations and fusions are considered important driver events in bladder/urothelial cancer. Data on the pathogenicity of FGFR2 variants in urothelial cancer are sparse. Exploratory subgroup analyses of limited clinical data suggest heterogeneity in response to erdafitinib according to the FGFR alteration type that persists after considering other factors that may influence responsiveness. Whether this heterogeneity reflects a differential sensitivity of FGFR alterations to erdafitinib or is due to small numbers and the exploratory nature of the analyses remains to be determined.

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

There are no clinically relevant food-drug interactions—erdafitinib may be taken without regard to food.

There are clinically relevant DDIs—the following dose modifications are recommended (details provided in Sections below):

- **Strong CYP2C9 / CYP3A inhibitors:** consider alternative agents or monitor closely for adverse reactions
- **Strong CYP2C9 / CYP3A inducers:** avoid use
- **Moderate or Weak CYP2C9 / CYP3A inducers:** increase dose up to 9 mg
- **CYP3A substrates:** avoid use with sensitive CYP3A substrates with narrow therapeutic index
- **P-gp substrates:** separate dose by ≥ 6 h before or after administration of P-gp substrates with narrow therapeutic index
- **OCT2 substrates:** consider alternative agents or reducing the dose of OCT2 substrates based on tolerability
- **Serum phosphate level-altering agents:** avoid use with agents that can alter serum phosphate levels before the initial dose increase period based on serum phosphate levels (Days 14 to 21)

Food-Drug Interaction

Study EDI1006 was a randomized, open-label, 2-way, cross-over study to evaluate the effect of food on the PK of erdafitinib in healthy subjects (n=16). Subjects were randomized 1:1 into 1 of 2 dosing sequences (fasted/fed or fed/fasted). Subjects were administered a single-dose of 9 mg erdafitinib with or without a high-fat, high-calorie breakfast (washout period = 28 d). Following erdafitinib administration, PK samples for erdafitinib were collected for over 336 h. As seen in **Table 60**, erdafitinib AUC and C_{max} were similar when administered with or without a high-fat, high-calorie meal. Median T_{max} slightly increased from 2.5 to 4.0 h with the meal.

Since no clinically relevant changes in erdafitinib PK were observed, erdafitinib may be taken without regard to food.

Table 60: Summary of Erdafitinib PK Results from Food Effect Study (EDI1006)

	Erdafitinib Geometric Mean		Erdafitinib Geometric Mean Ratio (90% CI)	
	AUC _{0-∞} (ng·h/mL)	C _{max} (ng/mL)	AUC _{0-∞}	C _{max}
Fed (n=16)	19540	294	0.94 (0.89, 0.99)	0.86 (0.81, 0.92)
Fasted (n=16)	20871	341		

Source: Adapted from Table 4 in Applicant's EDI1006 CSR

Note that in pivotal Study BLC2001, erdafitinib was initially administered as fasted. Once the results of Study EDI1006 became available, an amendment was made to the Protocol BLC2001 to administer erdafitinib without regard to food (Amendment 5).

Drug-Drug Interaction (in vivo and model-based approaches)

Effects of fluconazole (moderate CYP2C9/moderate CYP3A inhibitor) and itraconazole (strong CYP3A/P-gp inhibitor) on erdafitinib PK

Erdafitinib is metabolized by CYP2C9 and CYP3A. It is a substrate for P-gp. Study EDI1007 was a randomized, open-label, parallel-group, single-center study to evaluate the effects of concomitant fluconazole and itraconazole on single-dose erdafitinib in healthy subjects (n=54). The study used a parallel-group design to avoid a long washout period between dosing. Subjects were randomized (1:1:1) by CYP2C9 genotype into 1 of the following 3 dosing groups:

Dosing Group (n)	CYP2C9 Polymorphism (n)			Dosing	
	*1/*1	*1/*2	*1/*3	Victim (Erdafitinib)	Perpetrator
A (n=19)	12	5	2	Day 1: 4 mg erdafitinib SD	none
B (n=18)	12	4	2	Day 5: 4 mg erdafitinib SD	Days 1-11: 400 mg fluconazole QD
C (n=17)	13	4	0	Day 5: 4 mg erdafitinib SD	Days 1-11: 200 mg itraconazole QD

SD = single-dose, QD = once daily

Following erdafitinib administration under fasted condition, PK samples were collected from pre-dose to post-dose 28 day. An exploratory objective of this study was to explore the effect of CYP2C9 genotype on erdafitinib PK. However, the protocol excluded subjects with CYP2C9 poor metabolizer genotypes (CYP2C9*2/*2, *2/*3, *3/*3). Additionally, the protocol did not enroll subjects with CYP2C9*1/*3 genotypes in Dosing Group C due to potential safety concerns regarding inhibition of erdafitinib metabolic pathways. As seen in **Table 61**, for the primary analysis, concomitant fluconazole increased erdafitinib AUC by 48% and C_{max} by 21%, while concomitant itraconazole increased erdafitinib AUC by 34% but did not significantly change C_{max}. Based on the observed erdafitinib exposure increases, for concomitant strong CYP2C9 / CYP3A inhibitors, patients should consider alternative agents or monitor closely for adverse reactions.

Table 61: Summary of Erdafitinib PK Results from DDI Study (EDI1007)

Dosing Group	Erdafitinib Geometric Mean		Erdafitinib Geometric Mean Ratio (90% CI)	
	AUC _{0-∞} (ng·h/mL)	C _{max} (ng/mL)	AUC _{0-∞}	C _{max}
<i>CYP2C9*1/*1 + *1/*2 (primary)</i>				
A (erdafitinib alone) (n=17)	8655	136	N/A	N/A
B (erdafitinib + fluconazole) (n=15-16)	12796	164	1.48 (1.20, 1.82)	1.21 (1.00, 1.47)
C (erdafitinib + itraconazole) (n=17)	11585	142	1.34 (1.09, 1.64)	1.05 (0.87, 1.27)
<i>CYP2C9*1/*1 + *1/*2 + *1/*3 (exploratory)</i>				
A (erdafitinib alone) (n=19)	8935	135	N/A	N/A
B (erdafitinib + fluconazole) (n=17-18)	12850	163	1.44 (1.17, 1.77)	1.21 (0.99, 1.47)

Source: Adapted from Tables 5 and 6 in Applicant's EDI1007 CSR

Note that out of 210 patients in pivotal Study BLC2001 (all three dosing regimens), only 3 patients had a concomitant strong CYP2C9 and none had a concomitant strong CYP3A inhibitor. No apparent safety difference was observed between patients with or without CYP2C9 / CYP3A inhibitors (including weak, moderate, strong inhibitors)—although there were slightly higher rates of adverse events leading to dose interruption, reductions, treatment discontinuations in patients with concomitant CYP2C9 / CYP3A inhibitors.

Effect of rifampin (strong CYP3A/moderate CYP3A inducer) on erdafitinib PK

The Applicant used PBPK modeling to evaluate the effect of concomitant rifampin on the exposure of erdafitinib. Co-administration of rifampin (600 mg QD for 15 d) and erdafitinib (9 mg QD) was predicted to decrease erdafitinib steady-state AUC by 62% and C_{max} by 51% (Table 62). Refer to the PBPK review in the Appendix for details.

Table 62: Predicted Effect of Concomitant Rifampin on Erdafitinib Exposure

Strong CYP3A/Moderate CYP3A Inducer	Erdafitinib Dosing	Erdafitinib Geometric Mean Ratio (+rifampin/-rifampin)	
		AUC	C _{max}
600 mg rifampin QD	9 mg QD (steady-state)	0.38	0.49

Source: Adapted from Tables 33 in Applicant's AG120-C-001-PBPK Report

Although the PBPK modeling was found to be adequate in predicting the effect of rifampin on erdafitinib PK, the inherent variability of prediction tools should be considered. In this case, it is important to have clinical DDI data to pinpoint the magnitude change in erdafitinib exposure with concomitant strong CYP2C9 / CYP3A inducers to match exposure, given the possible loss of efficacy based on exposure-response for efficacy. Therefore, based on inherent variability and uncertainty regarding the predicted decrease in erdafitinib steady-state AUC with rifampin,

concomitant strong CYP3A inducers should be avoided. A PMR will be issued for the Applicant to conduct a clinical DDI study to evaluate the effect of a strong CYP2C9 / CYP3A inducer (e.g., rifampin) on erdafitinib exposure.

Co-administration of BALVERSA with moderate inducers of CYP2C9 or CYP3A4 may decrease erdafitinib plasma concentrations. Decreased erdafitinib plasma concentrations may lead to decreased activity. If a moderate CYP2C9 or CYP3A4 inducer must be co-administered at the start of erdafitinib treatment, administer BALVERSA dose as recommended (8 mg once daily with potential to increase to 9 mg once daily based on serum phosphate levels on Days 14 to 21 and tolerability). If a moderate CYP2C9 or CYP3A4 inducer must be co-administered after the initial dose increase period based on serum phosphate levels and tolerability, increase BALVERSA dose up to 9 mg. When a moderate inducer of CYP2C9 or CYP3A4 is discontinued, continue BALVERSA at the same dose, in the absence of drug-related toxicity.

This recommendation is based on anticipated decrease in erdafitinib exposure with concomitant moderate or weak CYP2C9 / CYP3A inducers, with recommendation to increase dose up to 9 mg based on tolerability. This recommendation will be revisited after the results of PMC study with a strong inducer of CYP2C9 and CYP3A4 is available.

Effect of erdafitinib on a P-gp substrate PK

The Applicant used PBPK modeling to evaluate the effect of erdafitinib on the PK of concomitant digoxin (P-gp substrate), however the modeling was considered qualitative, and not quantitative, due to uncertainty in translating in vitro K_i to in vivo K_i . Based on the qualitative analysis using an absorption model simulation (refer to PBPK review in the Appendix for details), erdafitinib dose should be separated by ≥ 6 h before or after administration of P-gp substrates with narrow therapeutic index.

Drug-Drug Interaction (in vitro)

Effect of erdafitinib on a CYP3A substrate PK

Based on vitro studies, erdafitinib is a time-dependent inhibitor of CYP3A and an inducer of CYP3A, however the results were inconclusive to rule out a net inhibition or induction effect of erdafitinib on CYP3A substrates in vivo. The Applicant used PBPK modeling to evaluate the effect of erdafitinib on the PK of concomitant midazolam (sensitive CYP3A substrate), however the modeling was found to be inadequate to support Applicant's proposed labeling that PBPK predicted a lack of clinically relevant DDI between erdafitinib and CYP3A substrates (refer to PBPK review in the Appendix for details). Therefore, concomitant CYP3A substrates with narrow therapeutic index should be avoided. A PMR will be issued for the Applicant to conduct a clinical DDI study to evaluate the effect of erdafitinib on the exposure of a CYP3A sensitive substrate.

Effect of erdafitinib on an OCT2 substrate PK

Based on in vitro study, an in vivo interaction between erdafitinib and a OCT2 substrate cannot be ruled out ($C_{max,u}/IC_{50} = 0.33$ but increases to 1.0 when $f_{u,p}$ is capped at 1%, per FDA Draft Guidance for DDI, for drugs that are >99% bound to human plasma proteins). The Applicant used PBPK modeling to evaluate the effect of erdafitinib on the PK of concomitant metformin (OCT2 substrate), however the metformin model found to be inadequate to support Applicant's proposed labeling that PBPK predicted a lack of clinically relevant DDI between erdafitinib and metformin (refer to PBPK review in the Appendix for details). Therefore, for concomitant OCT2 substrates, alternative agents should be considered or the dose of OCT2 substrates should be reduced as tolerated. A PMR will be issued for the Applicant to conduct a clinical DDI study to evaluate the effect of erdafitinib on the exposure of a probe OCT2 substrate.

Effect of gastric pH modulators on erdafitinib PK

Erdafitinib has adequate solubility across the pH range of 1 to 7.4. Acid-lowering agents (e.g., antacids, H₂-antagonists, proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib. Therefore, no dose adjustment is needed in patients taking concomitant gastric pH modulators.

Effect of phosphate level-altering agents on patient serum phosphate levels

In Applicant's pivotal Study BLC2001, the use of drugs which can increase serum phosphate levels, such as potassium phosphate supplements, vitamin D supplements, antacids, phosphate-containing enemas or laxatives, and medications known to have phosphate as an excipient (unless no alternatives exist) were prohibited. To manage hyperphosphatemia, phosphate binders were permitted. To ensure that the serum phosphate level signal for dose increase is attributed to erdafitinib only, agents that can alter serum phosphate levels before the initial dose increase period based on serum phosphate level (Days 14-21) should be avoided.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant has submitted three clinical studies to support NDA 212018 (Study BLC2001, Study EDI1001, and Study GAC1001). This NDA is primarily based on findings from 87 patients with relapsed/refractory advanced or metastatic urothelial cancer and susceptible FGFR genomic alterations enrolled in Cohort 3 of study BLC2001. These patients all received erdafitinib at the proposed dose of 8 mg, with PD-guided up-titration to 9 mg in patients. Our efficacy review primarily focused on data from these 87 patients who received the dose under review in the proposed indication population.

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Table 63: Listing of Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Primary Study to Support Efficacy and Safety</i>								
4275649 3BLC200 1, Regimen 3 ^a	NCT 023 655 97	Phase 2 Two-arm, open-label, efficacy study	Regimen 3: erdafitinib 8 mg, once every day, orally with PD-guided dose increase to 9 mg	Objective Response Rate, per RECIST 1.1 by investigator and BICR. If ORR was above 25%, the response assessed by IRRC was to be used for the primary and final analyses.	Treated until disease progression, unacceptable toxicity, or any other protocol-defined reason for treatment discontinuation. Follow-up period from until death, withdrawal, lost to follow-up	N = 100 Relapsed/refractory = 87 Cisplatin ineligible = 12 Enrolled but never dosed = 1 ^b	Metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations.	58 centers, 13 countries
<i>Additional supportive safety and efficacy data obtained from these additional dosing cohorts</i>								
Regimen 1	NCT 023 655 97	Phase 2 Two-arm, open-label, efficacy study	Regimen 1: erdafitinib 10 mg, once every day, orally with PD-guided dose increase to 12mg, 7 days on / 7 days off	Objective Response Rate, per RECIST 1.1 by investigator.	Treated until disease progression, unacceptable toxicity, or any other protocol-defined reason for treatment discontinuation. Follow-up period from until death, withdrawal, lost to follow-up	N = 33	Metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations.	58 centers, 13 countries

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Regimen 2	NCT 023 655 97	Phase 2 Two-arm, open-label, efficacy study	Regimen 2: erdafitinib 6 mg, once every day, orally with PD-guided dose increase to 8mg	Objective Response Rate, per RECIST 1.1 by investigator.	Treated until disease progression, unacceptable toxicity, or any other protocol-defined reason for treatment discontinuation. Follow-up period from until death, withdrawal, lost to follow-up	N = 78	Metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations.	58 centers, 13 countries
Additional Studies to Support Safety								
Study EDI1001	NCT 017 034 81	Phase 1, First-in-Human, open-label study	Part 1: 0.5 mg –12 mg once daily Part 2: 9 mg once daily Part 3: 9 mg once daily Part 4: 10 mg intermittent (7 days on-drug, 7 days off) dosing	To determine safe and biologically active Phase 2 doses (recommended Phase 2 doses [RP2D]) for erdafitinib in the Part 1 Dose Escalation Phase	Treated until disease progression (radiographic or clinical), unacceptable toxicity, , concurrent medical conditions, or unmanageable disease-related events.	N = 187 Part 1: 66 Part 2: 11 Part 3: 46 Part 4: 64	Advanced or refractory solid malignancies or lymphoma	32 centers, 3 countries
Study GAC100 1	n/a	Phase 1, dose-escalation/expansion, PK/PD	Continuous: 2 mg, 4 mg, and 6 mg once daily dose	To determine a safe and biologically active	Treated until disease progression,	N = 19 Continuous: 9	Advanced or refractory solid malignancies or	3 centers, 1 country (Japan)

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
 BALVERSA™ (erdafitinib)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			regimen Intermittent: 10 mg and 12 mg 7 d on/7 d off regimen	Phase 2 dose in Japanese and Asian subjects	unacceptable toxicity, concurrent medical conditions, or unmanageable disease-related events.	Intermittent : 10	lymphoma	
^a As of Data Cut-off date 03/15/2018. ^b For a single arm study, the efficacy analysis population is all treated patients. As that patient did not receive any study treatment, the patient is not included in the denominator for efficacy evaluations:								

7.2. Review Strategy

The clinical and statistical review included the following:

1. Review of the current literature on urothelial carcinoma epidemiology, and treatment, including preclinical and clinical data on therapies targeting the FGFR pathway and of the natural history of FGFR-altered urothelial cancer
2. Review of Applicant-submitted clinical study BLC2001, including CSR, protocols, protocol amendments, and SDTM and ADaM datasets
3. Review of Applicant-submitted real-world data from the Flatiron-FMI Database, including white papers, protocols, and datasets
4. Review of Applicant-submitted real-world data from the BRIDGE Consortium study including white papers, protocols, and datasets
5. Review and assessment of Applicant analysis of erdafitinib efficacy and safety for evaluation of Applicant's claims
6. Review of datasets and SAS programming algorithm submitted by the Applicant
7. Use of the datasets to determine the baseline patient characteristics, verify reported response rate, and adverse event profile.
8. Review of patient narratives of serious adverse events, deaths, and immune-mediated AEs
9. Review of meeting minutes conducted during drug development
10. Assessment of the Module 2 summaries, including the Summary of Clinical Efficacy and Summary of Clinical Safety
11. Evaluation of reviews conducted by other FDA disciplines
12. Review of consultation reports from the Office of Scientific Investigations
13. Requests for additional information from the Applicant and review of Applicant responses
14. Formulation of the benefit-risk analysis and recommendations
15. Review and evaluation of proposed labeling
16. EDR link for the electronic data sources is:
\\CDSESUB1\evsprod\NDA212028\212018.enx

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 42756493BLC2001 (BLC2001)

Trial Design

BLC2001 was a multi-center, open-label, Phase 2 clinical study of erdafitinib in patients with metastatic or surgically unresectable urothelial cancer harboring select FGFR genetic alterations.

Key Eligibility Criteria

1. Metastatic or surgically unresectable urothelial cancer (cT4b, N+, M+). A minor component of patients (<50% overall) with variant histologies (glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change) were eligible for enrolment
2. Disease progression following:
 - a. Chemotherapy for metastatic disease
 - b. Progression within 12 months of receiving chemotherapy in the neoadjuvant or adjuvant setting
 - c. Patients who were ineligible for cisplatin-based chemotherapy were also eligible for enrolment. Platinum ineligibility was based upon:
 - i. Impaired renal function defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m² by 24-hour urine measurement or calculated by Cockcroft-Gault
 - ii. Grade 2 or higher peripheral neuropathy by CTCAE version 4.0
3. All patients must have had FGFR mutation or fusion:
 - a. FGFR3 gene mutations: R248C, S249C, G370C, and Y373C,
 - b. FGFR fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, and FGFR3-BAIAP2L1.
4. ECOG performance status score 0, 1, or 2
5. Adequate bone marrow, liver, and renal function
6. Absence or persistent phosphate level > upper limit of normal during screening

Reviewer Comments: *Although cisplatin-ineligible patients were enrolled on BLC2001, they were not ultimately included in the indication population for this approval due to insufficient numbers enrolled in the indicated dosing regimen (Regimen 3, see section below on Study Treatment) to adequately assess the efficacy of erdafitinib in these patients (n=12).*

Study Treatment

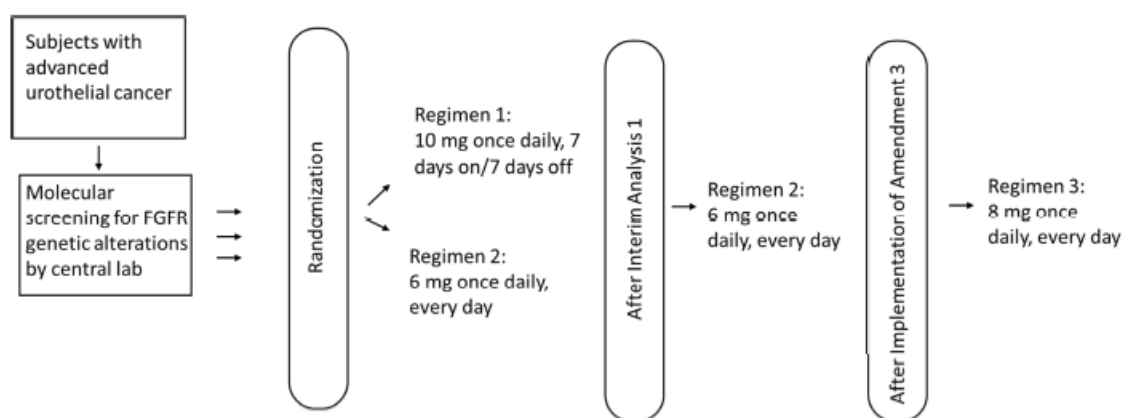
There were 3 dosing regimens evaluated in patients on BLC2001;

- Regimen 1: 10 mg once daily, 7 days on/ 7 days off
- Regimen 2: 6 mg once daily, every day

- Regimen 3: 8 mg once daily, with pharmacologic-guided dose increase to 9 mg based on tolerance and serum phosphate levels

At the initiation of the study, patients were randomized to Regimen 1 or Regimen 2. At Interim Analysis 1 (IA1), the Data Review Committee (DRC) recommended the selection of Regimen 2 for continued development and also recommended additional safety and efficacy analyses. Based on these additional analyses and PK/PD modeling, the DRC recommended that BLC2001 use Regimen 3 for continued development. These changes were implemented in Amendment 3 (August 9, 2016).

Figure 5: Study Schema (BLC2001)



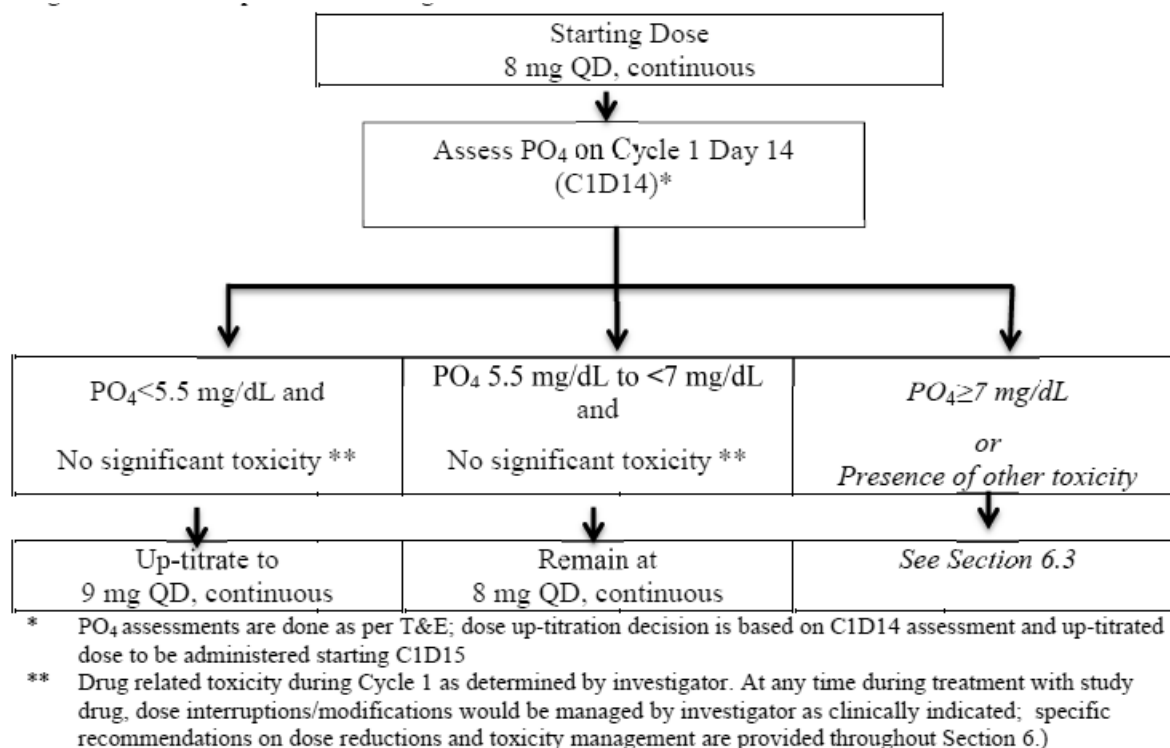
Source: Clinical Study Report for 42756493BLC2001

Dose Increase Schema

For patients treated with Regimen 3, erdafitinib dosing was increased or maintained based on phosphate level measured on Cycle 1 Day 14, with observed toxicity to that point also considered

Figure 6). The increased dose was given starting on Cycle 1 Day 15 .

Figure 6: Dose increase based on phosphate levels, Regimen 3 (BLC2001)



Source: Clinical Study Report for 42756493BLC2001

Study Monitoring

The study was conducted in an outpatient setting. Subjects were seen at the study center on pre-specified days for safety monitoring, pharmacokinetic and biomarker sample collection, and provision of clinical supplies. Safety was monitored routinely throughout the study by the sponsor's study responsible physician and scientist as well as the sponsor's safety management team. Safety review was based on reported adverse events, clinical laboratory tests, vital sign measurements, physical examinations, ophthalmologic examinations, and electrocardiogram (ECG) findings. In addition, plasma concentrations were measured for pharmacokinetic and pharmacokinetic/pharmacodynamic evaluations. Subjects were assessed for disease response every 6 weeks during the first 3 months. Thereafter, scans were performed every 12 weeks for the next 9 months, then every 4 to 6 months until disease progression.

Radiology Charter

Radiographic scans for patients enrolled to Regimen 3 were independently reviewed by PAREXEL Informatics, Medical Imaging and Patient Technology Solutions. Each imaging timepoint for a patient was assessed by one (single read) independent radiologist who determined an overall tumor assessment at each post-baseline timepoint according to RECIST (version 1.1). After the timepoint by timepoint radiology review, the same independent radiologist(s) globally assessed the reviewed timepoints and confirmed or updated their previous overall tumor assessments.

Study Endpoints

The primary study endpoint was the confirmed best objective response (BOR), defined as the best (overall) objective response a patient achieved during the study in the order of Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), where CR and PR are confirmed as per RECIST 1.1. Patients without measurable disease at baseline or without post-baseline tumor assessment are considered non-responders. Responders are patients with best response of CR or PR.

Response was evaluated using RECIST version 1.1. Response was assessed by investigators for all patients in the study as well as by a Blinded Independent Review Committee (BIRC) for patients in the 8-mg daily regimen (Regimen 3). The confirmed objective response rate (ORR) is the proportion of patients with a confirmed BOR of CR or PR. Per protocol, if the lower bound of 95% 2-sided confidence interval for the response rate assessed by the investigator was above 25%, the response assessed by BIRC was to be used for the primary and final analyses, and the response assessed by the investigators was to be used for supportive analyses.

The Applicant submitted an Independent Review Charter with [REDACTED] (b) (4) [REDACTED] Refer to subsection “Radiology Charter” for additional details.

Secondary efficacy endpoints included the following:

- Duration of Response (DOR), calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (or relapse for patients who experience CR during the study) or death.
- Progression-free survival (PFS), defined as the duration from the date of the first dose of study drug until the date of first documented evidence of progressive disease (or relapse for patients who experience CR during the study) or death, whichever comes first.
- Overall Survival (OS), measured from the date of first dose of study drug to the date of patient’s death.

Reviewer Comments: *In single arm trials, FDA does not use inferential procedures to evaluate trial results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response. Additionally, we note that time-to-event endpoints are uninterpretable without a comparator arm.*

Patient reported outcome (PRO) endpoints

PROs were assessed using the Symptom Measurement Questionnaire (SMQ). SMQ is a self-administered PRO instrument that measures symptoms experienced by patients with urothelial

cancer. It consists of five items covering five different symptoms including pain, fatigue, cough, shortness of breath, and blood in urine. The change from baseline to each time point for the overall symptom score and each item were to be summarized.

Analysis Population

The Applicant defined the primary analysis population as all patients who were treated with at least 1 dose of study drug in Regimen 3 (n=99).

Reviewer Comments: *The Applicant and FDA agreed that the patients with chemo-relapsed/refractory disease would be the primary efficacy population in Regimen 3 (n=87) and would form the basis for the labeled indication population. Patients ineligible for cisplatin-based therapy (n=12) were excluded from the FDA primary efficacy analysis.*

In addition, FDA review of efficacy included evaluating patients based on type of FGFR genetic alteration (point mutation versus gene fusion; FGFR2 versus FGFR3). The FGFR2 test kit was not validated by FDA. The following 6 patients were detected with FGFR2 gene fusions in the primary analysis population of 87 patients.

FGFR2: BICC1 – [REDACTED] (b) (6)
FGFR2: CASP7 – [REDACTED]

Of the 6 patients, patient [REDACTED] (b) (6) also had a detected fusion involving FGFR3, and was positive for fusions of both FGFR2: CASP7 and FGFR3-TACC3-V3.

Subgroup Analyses

The Applicant submitted pre-specified subgroup analyses:

1. Response by FGFR Alterations
2. Response by Prior Lines of Therapy
3. Response by Tumor Location
4. Response by Demographic and Baseline Disease Characteristics

Reviewer Comments: *Additional subgroup analyses were performed during the FDA analysis of this NDA:*

- *FGFR genetic alteration*
- *FGFR genetic alteration subtype (point mutation versus gene fusion)*
- *FGFR genetic alteration location (FGFR2 versus FGFR3)*
- *Risk prognostic scoring systems:*
 - *MSKCC score*
 - *Bellmunt score*
- *Presence or absence of liver metastases*

Statistical Analysis Plan

The primary hypothesis was that the selected dose regimen had an objective response rate > 25% in patients with metastatic or surgically unresectable urothelial cancer harboring select FGFR alterations.

Sample Size Consideration: Regimen 3 planned to enroll approximately 100 patients, with at least 80 chemo-relapsed/refractory patients. If the true response rate is 42%, 88 patients would provide at least 85% power to obtain the lower bound of 95% 2-sided confidence interval above 25%.

Reviewer Comments: *The CSR submitted for this NDA was based on the FGFR-positive patients with the number of treated chemo-relapsed/refractory patients consisting of N=87 patients and a database cutoff of March 15, 2018.*

For the analysis of the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by BIRC, the ORR was summarized by the percentage of confirmed responses (CR or PR), and its 95% 2-sided confidence interval (CI) were calculated using normal approximation to the binomial distribution. The secondary endpoints of DOR, PFS, and OS were analyzed using Kaplan-Meier methods. DOR was only assessed in responders.

Protocol Amendments

The study protocol was proposed on January 19, 2015. Before its initiation on March 25, 2015 and during the study, the protocol was amended with feedback from the Agency. There were 5 amendments, the third of which added Regimen 3.

Table 64: Protocol Milestones and Amendments (BLC2001)

Milestone	Date	Major Changes or Comments
Original Protocol	01/19/2015	
Amendment 1	04/02/2015	- Change in both Regimen 1 (10 mg once daily, 7 days on/ 7 days off) and Regimen 2 (6 mg once daily, every day) to allow for a dose increase - Change in Regimen 2 from an interrupted schedule to a continuous dosing schedule
Protocol Initiation	05/25/2015	
Amendment 2	06/25/2015	Addition of analysis of circulating tumor DNA from blood to biomarker study

Milestone	Date	Major Changes or Comments
Amendment 3	08/09/2016	- Addition of Regimen 3 (8 mg once daily, with pharmacologic-guided dose increase to 9 mg based on tolerance and serum phosphate levels) - Addition of warnings about CYP2C9 interactions - Addition of pre-treatment, on-treatment, and end-of-treatment biopsy collection
Amendment 4	05/03/2017	Clarification of the post treatment follow-up period and timing between enrollment and Cycle 1 Day 1 for Regimen 3 patients
Amendment 5	10/11/2017	- Addition of precautionary language regarding concomitant use of P-gp substrates - Allowance for erdafitinib to be taken with or without food.
Last patient enrolled	12/21/2017	
Database Lock Date	03/15/2018	

Source: Clinical Study Report 42756493BLC2001, adsl.xpt.

The original statistical analysis plan (SAP) was approved on 04 June 2015. The SAP amendment 1 (based on Protocol Amendment 3, dated 09 August 2016) was finalized on 29 September 2016. Dosing Regimen 3 (8 mg once daily (with provision for up-titration to 9 mg once daily) was added following the recommendation of the DRC at Interim Analysis 1. The primary efficacy analysis population was changed to the patients treated at Regimen 3 in the SAP amendment 1. Additionally, the original planned Interim Analysis 2 for Regimen 1 and 2 were removed, and analysis of Symptom Measurement Questionnaire was added.

Reviewer Comment: Overall, the protocol amendments do not appear to have affected the integrity of the study. Additionally, we note that the SAP considered all enrolled patients as the primary efficacy population, including cisplatin-ineligible patients. SAP amendment 1 was finalized at the time of adding regimen 3. In Amendment 1, the chemo-relapsed/refractory population was considered as a secondary objective only.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that clinical study 42756493BLC2001 was conducted in compliance with

Good Clinical Practice, including the archival of essential Documents. It was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study.

DOP1 consulted the OSI on 10/24/2018 to perform an audit of select clinical sites. Sites were selected based on the high number of patients enrolled, the high proportion of responders, and the low overall reporting of safety data such as adverse events and serious adverse events. Two domestic sites were chosen for inspection: Sites US00011 and US00014. One international site was chosen: Site FR00005 in France. Additionally, Janssen Biotech, Inc. was selected for inspection.

Three clinical sites, Dr. Arlene Siefker Radtke (Site US00011), Dr. Scott Tagawa, (US00014), and Dr. Yohann Lorient (Site FR00005), were selected for audit. The inspections conducted by OSI identified the following items:

1. Dr. Arlene Siefker Radtke (Site US00011): The site screened 53 patients and enrolled 5 patients, including 4 in Regimen 3). The inspection revealed no objectionable observations in the conduct at this site.
2. Dr. Scott Tagawa, (US00014). The site screened 31 patients and enrolled 6 patients, including 5 in Regimen 3. There was a verbal observation regarding out of window scans regarding subject (b) (6). It was also noted that the subject was an inclusion/exclusion criteria failure reported in the background materials. SAEs were reviewed with no observations and the study had proper approval and communication with the IRB.
3. Dr. Yohann Lorient (Site FR00005): The site screened 104 patients and enrolled 10 patients, including 5 in Regimen 3. The inspection revealed no significant deficiencies. For one subject (b) (6) on Regimen 2) who had a partial response at the first on-study assessment, there was a difference in reporting of the second assessment between the data listing (progressive disease as assessed by Investigator) and the source radiology report (stable disease). The Investigator explained that based on his review with another radiologist and to his assessment, the second assessment showed disease progression, consistent with the reported data listing by the applicant.

Financial Disclosure

Refer to Section 19.2 for details.

Patient Disposition

Overall, 2214 patients with tissue samples were screened for molecular eligibility for enrollment, of which 417 patients had tissue specimens that were adequate for molecular screening and that were found to carry an FGFR genetic alteration. Of the 417 patients, 224

patients met the molecular eligibility criteria (FGFR+) but did not meet the other study eligibility criteria. Twenty of these FGFR+ patients were treated with erdafitinib despite not meeting eligibility criteria that would have otherwise made them screen failures. Of these patients, 6 had received prior chemotherapy and received Regimen 3 (Table 65).

Table 65: Patient Listing of Screen Failures who Received Study Treatment. Regimen 3, Relapsed/Refractory Population (BLC2001)

Patient ID	Unmet Eligibility Criteria	BOR by BIRC
(b) (6)	Must have adequate bone marrow, liver, and renal function as described below: Bone marrow function (without the support of cytokines and/or erythropoiesis-stimulating agent [ESA] in preceding 2 weeks)	Partial Response
	Must have adequate bone marrow, liver, and renal function as described below: Bone marrow function (without the support of cytokines and/or erythropoiesis-stimulating agent [ESA] in preceding 2 weeks)	Stable Disease
	Has a history of or current uncontrolled cardiovascular disease including: unstable angina, myocardial infarction, or known congestive heart failure Class II-IV within the preceding 12 months	Stable Disease
	Has a history of or current uncontrolled cardiovascular disease including: unstable angina, myocardial infarction, or known congestive heart failure Class II-IV within the preceding 12 months	Stable Disease
	Has persistent phosphate level >ULN during screening (within 14 days of treatment and prior to Cycle 1 Day 1) and despite medical management	Stable Disease
	Must have adequate bone	Progressive Disease

Patient ID	Unmet Eligibility Criteria	BOR by BIRC
	marrow, liver, and renal function as described below: Bone marrow function (without the support of cytokines and/or erythropoiesis-stimulating agent [ESA] in preceding 2 weeks)	
Source: adsl.xpt, adefx.xpt, ie.xpt		

Overall, 16 of the 87 patients (18%) in Regimen 3 who received prior chemotherapy continued to receive study treatment as of the clinical cut-off date of 03/15/2018. The most common ($\geq 10\%$) reason for treatment discontinuation was progressive disease (67%) and adverse events (13%) (Table 66). Among the 58 patients with who discontinued due to disease progression, 33 patients died, 3 patients withdrew from the study, and 1 patient was lost to follow-up.

Table 66: Patient Disposition. Regimen 3, Relapsed/Refractory Population (BLC2001)

Disposition	Regimen 3 (N=87)
Patients on Treatment (as of clinical cut-off date, 03/15/2018)	16 (18.4)
<u>Reason for Treatment Discontinuation</u>	
Progressive disease	58 (66.7)
Adverse event	11 (12.6)
Withdrawal by subject	1 (1.1)
Other	1 (1.1)
<u>Reason for Study Discontinuation</u>	
Death	37 (42.5)
Withdrawal by subject	4 (4.6)
Lost to follow-up	1 (1.1)

[Source: Reviewer analysis using adds.xpt and adsl.xpt dataset (BLC2001)]

Reviewer Comments:

Review of the results of patient screening process for BLC2001 identified 6 patients enrolled and treated with Regimen 3, but who did not meet all eligibility criteria. These events were recorded as major protocol deviations. There was one partial response achieved by these 6 patients. These deviations do not have a significant impact on the efficacy results.

Protocol Violations/Deviations

Major protocol deviations were categorized in the SAP for Study BLC2001 (Section 4.4) as the following:

1. Patient safety
2. Eligibility criteria
3. Efficacy assessment deviation
4. Treatment compliance

Sixteen of the 87 patients (18%) in Regimen 3 who received prior chemotherapy experienced 25 protocol violations. The most frequent type of protocol deviation is related to safety assessments (13 deviations) that were not performed within the allowed window of time provided by the protocol. Eligibility Criteria Unmet was the second most frequent type of protocol deviation.

Table 67: Major Protocol Deviations. Regimen 3, Relapsed/Refractory Population (BLC2001)

Protocol Deviation	Regimen 3 (N=87), n(%)
Safety Assessments	
Ophthalmology exam	10 (11)
End of treatment visit	2 (2.3)
Follow up visit	1 (1.1)
Eligibility Criteria	
Inclusion 7 (adequate bone marrow, liver, and renal function)	4 (4.6)
Inclusion 3 (measurable disease per RECIST v1.1 at baseline)	2 (2.3)
Exclusion 2 (persistently elevated phosphate level >ULN at baseline despite medical management)	1 (1.1)
Efficacy Assessments	
Confirmatory scan	1 (1.1)
Week 6 scan	1 (1.1)
Incorrect dose	
Dose not held for abnormal ophthalmology exam	2 (2.3)
Wrong dose taken by patient	1 (1.1)

[Source: Reviewer analysis using advv.xpt and adsl.xpt dataset (BLC2001)]

Table of Demographic Characteristics

The baseline demographics for 87 patients who received prior chemotherapy and Regimen 3 are shown in Table 68.

Table 68: Baseline Demographics. Regimen 3, Relapsed/Refractory Population (BLC2001)

Demographic Parameters	Regimen 3, Relapsed/Refractory (N=87) n (%)
Sex	
Female	18 (20.7)
Male	69 (79.3)
Age	
Mean years (SD)	65.4 (10.1)
Median (years)	67
Min, max (years)	36-87
Age Group	
< 65 years	34 (39.1)
65-< 75 years	43 (49.4)
>75 years	10 (11.5)
Race	
White	64 (73.6)
Asian	4 (4.6)
Black or African American	2 (2.3)
Not Reported	11 (12.6)
Unknown	5 (5.7)
Other ¹	1 (1.1)
Ethnicity	
Hispanic or Latino	2 (2.3)
Not Hispanic or Latino	64 (73.6)
Not reported	16 (18.4)
Unknown	5 (5.7)
Region	
United States	19 (21.8)
Rest of the World	
Europe	61 (70.1)
Asia	7 (8.0)

¹ Data on race and/or ethnicity were not collected in Belgium, France, and Italy country because of local regulations.

[Source: Reviewer analysis using adsl.xpt dataset (BLC2001)]

Reviewer Comment: Overall, 22% of patients were enrolled in the United States, and additional 60% were enrolled in Western Europe, where the practices of medicine and standards of care are similar (Table 69). The remainder of patients (18%) were enrolled in Eastern Europe and Asia, where the practice of medicine and patient population may differ.

Table 69: Enrollment by Country. Regimen 3, Relapsed/Refractory Population (BLC2001)

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Geographic Region	Regimen 3, Relapsed/Refractory (N=87) n (%)
United States	19 (22)
Western Europe	52 (60)
France	18 (21)
Italy	16 (18)
Germany	6 (7)
Belgium	4 (4.6)
Spain	4 (4.6)
Great Britain	4 (4.6)
Eastern Europe	9 (10)
Russia	7 (8)
Austria	1 (1.1)
Romania	1 (1.1)
Asia	7 (8)
Israel	3 (3.4)
Korea	3 (3.4)
Taiwan	1 (1.1)

[Source: Reviewer analysis using adsl.xpt dataset (BLC2001)]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 70: Other Baseline Patient Characteristics. Regimen 3, Relapsed/Refractory Population (BLC2001)

Baseline Characteristics	Regimen 3, Relapsed-Refractory (N=87) n (%)
ECOG	
0-1	80 (92.0)
2	7 (8.0)
Smoking Status	
Never	26 (29.9)
Ex-smoker	45 (51.7)
Current smoker	11 (12.6)
Missing	5 (5.7)

Baseline Characteristics	Regimen 3, Relapsed-Refractory (N=87) n (%)
Prior Chemotherapy¹	
Platinum-based	
Yes	84 (96.6)
Best response to prior platinum-based chemo	29 (34.5)
No ¹	3 (3.4)
Cisplatin-based	
Yes	57 (65.5)
Best response to prior cisplatin-based chemo	20 (35.1)
No	30 (34.5)
Carboplatin-based	
Yes	35 (40.2)
Best response to prior carboplatin-based chemo	11 (31.4)
No	52 (59.8)
Prior Immunotherapy	
Yes	21 (24.1)
Best response to prior immunotherapy	1 (4.8)
No	66 (75.9)
Lines of Therapy	
1	44 (50.6)
2	29 (33.3)
>= 3	14 (16.1)
Prior Treatment Setting	
Locally advanced only	8 (9.2)
Metastatic only	66 (75.8)
Both	13 (14.9)

¹Three patients received non-platinum -based therapy. These included paclitaxel, docetaxel, and gemcitabine. All three patients achieved a BOR of stable disease with erdafitinib by BIRC and investigator.

[Source: Reviewer analysis using adsl.xpt and adcm.xpt datasets (BLC2001)]

Reviewer's comment: In these molecularly-defined patients, reported response rate to prior platinum-based chemotherapy was approximately 35%, which is in line with expected response rates. This is in contrast to the 1 patient of 21 who responded to treatment with prior immunotherapy, which is an especially low response rate compared to expected responses to immunotherapy (see Table 1). The review team took this submitted information into account when considering whether patients whose tumors harbor FGFR genetic alterations represent a subset of urothelial cancer to which the OS advantage demonstrated by pembrolizumab in the second-line setting might not apply, as these patients may be expected to do less well on immunotherapy.

Table 71 provides information on the extent of disease at baseline in the enrolled patients. Two

scoring systems have been used in the literature to assess prognostic factors in patients with urothelial cancer, the Bellmunt and MSKCC scoring systems. These have been used in urothelial cancer and have prognostic value in determination of OS. The Bellmunt scoring system uses performance status, hemoglobin, and the presence of liver metastases. The MSKCC system uses performance status and the presence of visceral (bone, liver, and lung) metastases.

Table 71: Other Baseline Disease Characteristics. Regimen 3, Relapsed/Refractory Population (BLC2001)

Baseline Disease Characteristics	Regimen 3, Relapsed-Refractory (N=87) n (%)
TNM Staging at time of enrolment	
Locally advanced	2 (2.3)
Metastatic	85 (98)
Location of metastases – by INV	
Visceral metastases	57 (66.7)
Liver	18 (20.7)
Lung	49 (56.3)
Bone	19 (21.8)
Primary Tumor Location – by INV	
Upper tract (renal pelvis, ureter)	22 (25.3)
Renal Pelvis	17 (19.5)
Ureter	5 (5.7)
Lower tract (bladder, urethra)	65 (74.7)
Bladder	64 (73.6)
Urethra	1 (1.1)
FGFR genetic alteration	
Mutations	64 (74)
FGFR3-G370C	4 (4.6)
FGFR3-R248C	9 (10)
FGFR3-S249C	40 (46)
FGFR3-Y373C	11 (13)
Fusions	23 (26)
FGFR2-BICC1	2 (2.3)
FGFR2-CASP7	3 (3.4)
FGFR2-CASP7/FGFR3-TACC3_V3	1 (1.1)
FGFR3-BAIAP2L1	1 (1.1)
FGFR3-TACC3_V1	10 (11)
FGFR3-TACC3_V3	6 (7)
Median Sum of Diameter ¹ (range) – at	5.5 (1.2, 24.6)

Baseline Disease Characteristics	Regimen 3, Relapsed-Refractory (N=87) n (%)
screening by BIRC	
≤ 2 cm [n(%)]	1.6 (1.2, 1.8) [7(8.6)]
≤ 5 cm [n(%)]	3.4 (1.2, 4.9) [36(44.4)]
Number of Target Lesions (BIRC)	
0	3 (3.4)
1-2	59 (68)
≥ 3	24 (28)
Number of Non-Target Lesions (BIRC)	
0	24 (28)
1-2	41 (47)
≥ 3	21 (24)
Bellmunt Score ²	
0	36 (41)
1	31 (36)
2	16 (18)
3	4 (4.6)
MSKCC Score	
0	18 (21)
1	62 (71)
2	7 (8)
¹ The BIRC did not identify measurable disease at baseline for 6 patients. The median sum of diameter was based on 81 patients. ² Bellmunt Scores for patients were calculated using Investigator-assessed liver lesions based on Investigator read of baseline scans.	

[Source: Reviewer analysis using adsl.xpt, adbio.xpt, adtr.xpt and adcm.xpt datasets (BLC2001)]

Efficacy Results – Primary Endpoint

The analysis of the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by Independent Radiologic Review Committee was based upon the efficacy population (N=87) and a database cutoff of March 15, 2018; the results are shown in

Table 72. The confirmed ORR assessed by BIRC was 32.2% (n=28; 95% CI: 22.4%, 43.1%) consisting of 2 complete responses (CRs, 2.3%) and 26 partial responses (PRs, 29.9%). The confirmed ORR assessed by investigator was 39.1% (n=34; 95% CI: 28.8%, 43.3%) consisting of 3 complete responses (CRs, 3.4%) and 31 partial responses (PRs, 35.6%). The duration of response among these responders is also shown in

Table 72.

Table 72: Best overall response, by BIRC versus Investigator. Regimen 3, Relapsed/Refractory Population (BLC2001)

	By BIRC N=87, n(%)	By Investigator N=87, n(%)
Objective Response Rate (CR+PR)	28 (32.2)	34 (39.1)
95% CI	(22.4, 42.0)	(28.8, 43.3)
Best Overall Response		
Complete Response, n(%)	2 (2.3)	3 (3.4)
Partial Response, n(%)	26 (29.9)	31 (35.6)
Stable Disease, n(%)	40 (46.0)	35 (40.2)
Progressive Disease, n(%)	16 (18.4)	16 (18.4)
Inevaluable, n(%)	3 (3.4)	2 (2.3)
Duration of response (months) DCO: March 15, 2018		
Median	5.42	5.58
95% CI	(4.21, 6.93)	(4.24, 7.00)
[Source: Reviewer analysis using adsl.xpt and adefx.xpt datasets (BLC2001)]		

Reviewer Comments: FDA review identified patient (b) (6) who was inappropriately assessed as having a PR by investigator. This patient was reassigned as having SD as the BOR (

Table 72). The discrepancy was due to a rounding error by the Applicant. We noted that BIRC assessment was based on a single read model. Thirteen scans were found by the independent radiologist to have no measurable disease per RECIST 1.1 at baseline, and these scans were re-read as provided for in the Independent Review Charter. After the double read, 6 scans still did not have measurable disease per independent radiologist.

Table 73 shows the concordance between confirmed responses determined by BIRC assessment compared to by investigator. As explained above, BIRC did not identify measurable disease at baseline for 6 of patients who were chemo-relapsed/refractory. Patients without measurable disease at baseline or without post-baseline tumor assessment are considered non-responders. Of 87 patients, there were 62 patients (71.3%) whose overall responses were agreed upon completely by both BIRC and investigator.

Of the 28 patients with confirmed response (CR or PR) by BIRC, 23 (82.1%) also had confirmed response (CR or PR) by investigator, and the remaining 5 were considered to have SD (4 patients) and PD (1 patient). Of the 34 patients with confirmed response (CR or PR) by investigator, 23 (67.6%) also had confirmed response (CR or PR) by investigator, and the remaining 11 were considered to have SD (11 patients), PD (1 patient) and NE (1 patient).

Table 73: Concordance between BIRC and Investigator Assessment. Regimen 3, Relapsed/Refractory Population (BLC2001)

	By Investigator					
By BIRC	CR	PR	SD	PD	NE	Total
CR	1	1	0	0	0	2
PR	2	19	4	1	0	26
SD	0	9	28	3	0	40
PD	0	1	3	12	0	16
NE	0	1	0	0	2	3
Total	3	31	35	16	2	87

[Source: Reviewer analysis using adsl.xpt and adefx.xpt datasets (BLC2001)]

Table 74: Discordance rate of response assessment between BIRC and Investigator. Regimen 3, Relapsed/Refractory Population (BLC2001)

		Investigator Assessment		Discordance Rate
		Responder	Non-Responder	
Independent Radiographic Review	Responder	23	5	18.4%
	Non-Responder	11	48	

[Source: Reviewer analysis using adsl.xpt and adefx.xpt datasets (BLC2001)]

Reviewer Comments: The discordance rate was 18.4% (Table 74) and is acceptable for ORR assessment in a single arm study.

Subgroup analyses – baseline characteristics of patient, prior therapy, and disease characteristics

Exploratory subgroup analyses of confirmed ORR by BIRC and investigator were assessed by ECOG score, smoking status (self-reported by patients), prior chemotherapy, lines of therapy, FGFR genetic alteration, tumor stage and Bellmunt and MSKCC risk factors. Results are shown in Table 75.

Table 75: Response Rate by Baseline Characteristics. Regimen 3, Relapsed/Refractory Population (BLC2001)

Baseline Characteristics	N (%)	Regimen 3, Relapsed/Refractory BIRC Assessed (N=87) n (%) 95% CI	Regimen 3, Relapsed/Refractory Investigator-Assessed (N=87) n (%) 95% CI
Sex			

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BALVERSA™ (erdafitinib)

Baseline Characteristics	N (%)	Regimen 3, Relapsed/Refractory BIRC Assessed (N=87) n (%) 95% CI	Regimen 3, Relapsed/Refractory Investigator-Assessed (N=87) n (%) 95% CI
M	69 (79)	22 (32)	28 (40.6)
F	18 (21)	6 (33)	6 (33.3)
Age			
< 65	34 (39)	12 (35)	12 (35.3)
>= 65	53 (61)	16 (30)	22 (41.5)
Race			
White	64 (74)	22 (34)	26 (40.6)
Asian	4 (4.6)	0 (0)	1 (25.0)
Black or African American	2 (2.3)	0 (0)	2 (100)
Not Reported	11 (13)	4 (36)	0 (0)
Unknown	5 (6)	2 (40)	4 (36.4)
Other	1 (1.1)	0 (0)	1 (100)
ECOG			
0-1	80 (92.0)	26 (32.5) (22.2, 42.8)	33 (41.3) (30.5, 52.0)
0	44 (50.6)	15 (34.1) (20.1, 48.1)	18 (40.9) (26.4, 55.4)
1	36 (41.4)	11 (30.6) (15.5, 45.6)	15 (41.7) (25.6, 57.8)
2	7 (8.0)	2 (28.6) (0, 62.0)	1 (14.3) (0, 40.2)
Smoking Status			
Never	26 (29.9)	11 (42.3) (23.3, 61.3)	13 (50.0) (30.8, 69.2)
Ex-smoker	45 (51.7)	14 (31.1) (17.6, 44.6)	20 (44.4) (30.0, 59.0)
Current smoker	11 (12.6)	2 (18.2) (0, 41.0)	0 (0)
Missing	5 (5.7)	1 (20.0) (0, 55.1)	1 (20.0) (0, 55.1)
Prior Chemotherapy			
Platinum-based			
Yes	84 (96.6)	28 (33.3) (23.3, 43.4)	34 (40.5) (30.0, 51.0)
No	3 (3.4)	0 (0)	0 (0)
Cisplatin-based			
Yes	57 (65.5)	22 (38.6) (26.0, 51.2)	27 (47.4) (34.4, 60.3)
No	30 (34.5)	6 (20.0) (5.7, 34.3)	7 (23.3) (8.2, 38.5)

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Baseline Characteristics	N (%)	Regimen 3, Relapsed/Refractory BIRC Assessed (N=87) n (%) 95% CI	Regimen 3, Relapsed/Refractory Investigator-Assessed (N=87) n (%) 95% CI
Carboplatin-based			
Yes	35 (40.2)	11 (31.4) (16.1, 46.8)	13 (37.1) (21.1, 53.2)
No	52 (59.8)	17 (32.7) (19.9, 45.5)	21 (40.4) (27.1, 53.7)
Prior Therapy - Immunotherapy			
Yes	21 (24.1)	14 (66.7) (46.5, 86.8)	12 (57.1) (36.0, 78.3)
No	66 (75.9)	14 (21.2) (11.4, 31.1)	22 (33.3) (22.0, 44.7)
Lines of Therapy			
1	44 (50.6)	11 (25.0) (12.2, 37.8)	15 (34.1) (20.1, 48.1)
2	29 (33.3)	9 (31.0) (14.2, 47.9)	11 (37.9) (20.2, 55.6)
≥3	14 (16.1)	8 (57.1) (31.2, 83.1)	8 (57.1) (31.2, 83.1)
FGFR genetic alteration			
Mutations	64 (73.4)	26 (40.6) (28.6, 52.7)	30 (46.9) (34.7, 59.1)
Fusions	23 (26.4)	2 (8.7) (0, 20.2)	4 (17.4) (1.9, 32.9)
TNM Staging			
Locally advanced	2 (2.3)	2 (100)	2 (100)
Metastatic	85 (97.7)	26 (30.6) (20.8, 40.4)	32 (37.7) (27.4, 48.0)
Bellmunt Risk Factor ¹			
0	36 (41.4)	11 (30.6) (15.5, 45.6)	13 (36.1) (20.4, 51.8)
1	31 (35.6)	10 (32.3) (15.8, 48.7)	14 (45.2) (27.6, 62.7)
2	16 (18.4)	6 (37.5) (13.8, 61.2)	6 (37.5) (13.8, 61.2)
3	4 (4.6)	1 (25.0) (0, 67.4)	1 (25.0) (0, 67.4)
MSKCC Score			
0	18 (20.7)	4 (22.2) (3.0, 41.4)	8 (44.4) (21.5, 67.4)
1	62 (71.3)	22 (35.5) (23.6, 47.4)	25 (40.3) (28.1, 52.5)

Baseline Characteristics	N (%)	Regimen 3, Relapsed/Refractory BIRC Assessed (N=87) n (%) 95% CI	Regimen 3, Relapsed/Refractory Investigator-Assessed (N=87) n (%) 95% CI
2	7 (8.0)	2 (28.6) (0, 62.0)	1 (14.3) (0,40.2)
Baseline Hemoglobin Level			
<10 g/dL	73 (83.9)	23 (31.5) (20.9, 42.2)	27 (37.0) (25.9, 48.1)
>=10 g/dL	14 (16.1)	5 (35.7) (10.6, 60.8)	7 (50.0) (23.8, 76.2)
Liver Metastases			
Yes	18 (20.7)	7 (38.9) (16.4, 61.4)	6 (33.3) (11.6, 55.1)
No	69 (79.3)	21 (30.4) (19.6, 41.3)	28 (40.6) (29.0, 52.2)
¹ Bellmunt Scores for patients were calculated using Investigator-assessed liver lesions based on Investigator read of baseline scans.			

[Source: Reviewer analysis using adsl.xpt and adefl.xpt datasets (BLC2001)]

Reviewer Comments: Higher response rates are seen in patients who never smoked (42.3%) and who had prior immunotherapy (66.7%), although we note the confidence intervals are wide and those subgroups had small sample sizes. There were only two patients whose tumor diagnosis at study entry was locally advanced; both were responders. No outlier subgroups were otherwise observed. Responses were seen among patients with liver metastases, and responses were seen among patients in all Bellmunt and MSKCC risk groups.

All subgroup analyses presented are considered exploratory or hypothesis generating, and no formal inference can be drawn.

Subgroup analyses – FGFR genetic alterations

Exploratory subgroup analyses of confirmed ORR by BIRC and investigator were assessed by genetic alteration subtype. Results are shown in Table 76.

Additional subgroup analyses by specific FGFR genetic alterations were performed on response rates per BIRC and investigator.

Table 76: Response Rate by FGFR Alteration. Regimen 3, Relapsed/Refractory Population (BLC2001)

	N (%)	Responses- BIRC n (%) 95% CI	Responses-INV n (%) 95% CI
Any Alterations	87 (100)	28 (32.2) (22.4, 42.0)	34 (39.1) (28.8, 43.3)
Mutations	64 (73.6)	26 (40.6) (28.6, 52.7)	30 (46.9) (34.7, 59.1)
FGFR3 G370C	4 (4.6)	2 (50.0) (1.0, 99.0)	2 (50.0) (1.0, 99.0)
FGFR3 R248C	9 (10.3)	3 (33.3) (2.5, 64.1)	5 (55.6) (23.1, 88.0)
FGFR3 S249C	40 (46.0)	16 (40.0) (24.8, 55.2)	17 (42.5) (27.2, 57.8)
FGFR3 Y373C	11 (12.6)	5 (45.5) (16.0, 74.9)	6 (54.6) (25.1, 84.0)
Fusions	23 (26.4)	2 (8.7%) (0, 20.2)	4 (17.4%) (1.9, 32.9)
FGFR2 BICC1	2 (2.3)	0	0
FGFR2 CASP7	3 (3.4)	0	0
FGFR3 BAIAP2L1	1 (1.1)	0	0
FGFR3 TACC3_V1	10 (11.5)	2 (20.0) (0, 44.8)	4 (40.0) (9.6, 70.4)
FGFR3 TACC3_V3	6 (6.9)	0	0
FGFR2 CASP7/FGFR3 TACC3_V3	1 (1.1)	0	0

[Source: Reviewer analysis using adsl.xpt, adbio.xpt and adefeff.xpt datasets (BLC2001)]

Reviewer Comments: No responses were observed in the 6 patients with FGFR2 fusions. We note that 1 patient with an FGFR2 alteration who was treated in the cohort of BLC2001 evaluating the 6 mg regimen was reported to have had a partial response per investigator but this was classified as PD when reviewed by BIRC. See the Integrated Assessment of Effectiveness for further discussion.

All subgroup analyses presented are considered exploratory or hypothesis-generating and no formal inference can be drawn.

Subgroup Analysis: Dose Increase and Phosphate Levels.

Table 77: Response Rate by Maximum Phosphorus Levels and Dose Increase to 9 mg. Regimen 3, Relapsed/Refractory Population (BLC2001)

Baseline Characteristics	N (%)	Regimen 3, Relapsed/Refractory BIRC Assessed (N=87) n (%) 95% CI		Regimen 3, Relapsed/Refractory Investigator-Assessed (N=87) n (%) 95% CI	
		Dose Increase to 9 mg			
Yes	36	15 (42)		17 (47)	
No	51	13 (25)		18 (35)	
Maximum Phosphate Level (30 days)					
<5.5 mg/dL	24	7 (29)		8 (33)	
5.5 - <7 mg/dL	43	13 (30)		17 (40)	
7 - <9 mg/dL	18	8 (44)		9 (50)	
>=9 mg/dL	1	0 (0)		1 (100)	
Maximum Phosphate					
<5.5 mg/dL	21	6 (29)		7 (33)	
5.5 - <7 mg/dL	45	14 (31)		17 (38)	
7 - <9 mg/dL	19	8 (42)		10 (53)	
>=9 mg/dL	1	0 (0)		1 (100)	
		Increased to 9 mg		Increased to 9 mg	
Maximum Phosphate	N, Y	N	Y	N	Y
<5.5 mg/dL	8, 13	2 (25)	4 (31)	2 (25)	5 (38)
5.5 - <7 mg/dL	30, 15	6 (20)	8 (53)	9 (30)	8 (53)
7 - <9 mg/dL	11, 8	5 (45)	3 (38)	6 (55)	4 (50)
>=9 mg/dL	1, n/a	0 (0)	n/a	1 (100)	n/a
		Uptitrated to 9 mg		Uptitrated to 9 mg	
Maximum Phosphate Level (30 days)		N	Y	N	Y
<5.5 mg/dL	8, 13	2 (22)	5 (33)	2 (22)	6 (40)
5.5 - <7 mg/dL	30, 15	6 (20)	7 (54)	10 (33)	7 (54)
7 - <9 mg/dL	11, 8	5 (50)	3 (38)	5 (50)	4 (50)
>=9 mg/dL	1, n/a	0 (0)	n/a	1 (100)	n/a
Source: adsl.xpt, adeff.xpt					

Data Quality and Integrity

The original NDA submission included efficacy and safety results for Regimen 3 of Study 42756493BLC2001, based upon a database cutoff of March 15, 2018. Imaging SDTM datasets (tr.xpt, tu.xpt, supptr.xpt, and supptu.xpt) were reviewed to verify responses.

Efficacy Results – Secondary and other relevant endpoints

Progression-free survival, time to response and overall survival results are summarized below for the 87 relapsed/refractory patients in Table 78 and Table 79.

Table 78: Progression-free Survival and Time to Response. Regimen 3, Relapsed/Refractory Population (BLC2001)

	By BIRC	By Investigator
Progression-free Survival		
Events: n (%)	71 (81.6)	71 (81.6)
Censoring: n (%)	16 (18.4)	16 (18.4)
Median (95% CI), in months	5.45 (3.98, 5.62)	5.48 (3.98, 5.68)
Time to Response		
Number of responders	28	34
Median (min, max), in months	1.41 (1.22, 4.04)	1.41 (1.31, 5.52)

[Source: Reviewer analysis using adsl.xpt and adtt.xpt datasets (BLC2001)]

Table 79: Overall Survival. Regimen 3, Relapsed/Refractory Population (BLC2001)

Overall Survival	Erdafitinib, Regimen 3
Total number of patients	87
Death: n (%)	38 (43.7)
Censored: n (%)	49 (56.3)
Median (95% CI), in months	12.02 (8.64, NE)

NE=Not Estimable

[Source: Reviewer analysis using adsl.xpt and adtte.xpt datasets (BLC2001)]

Reviewer Comments: Responding patients generally had evidence of tumor shrinkage by their first scans in most cases, with median time to response both per investigator and per BIRC corresponding with the pre-planned scan intervals. In single arm trials, we note that time-to-event endpoints are uninterpretable without a comparator arm.

Dose/Dose Response

Refer to Section 6.2 for analysis of dose-response data. Also refer to Table 77: Response Rate by Maximum Phosphorus Levels and Dose Increase to 9 mg. Regimen 3, Relapsed/Refractory Population (BLC2001).

Durability of Response

Duration of response is discussed with the assessment of the primary endpoint, ORR. Results of duration of response analyses are shown in

Table 72.

Persistence of Effect

Duration of response is discussed with the assessment of the primary endpoint, ORR. Results of duration of response analyses are shown in

Table 72.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant collected patient reported outcome (PRO) using the Symptom Measurement Questionnaire (SMQ). The SMQ was a self-administered instrument measuring symptoms experienced by patients with urothelial cancer. It consists of five items covering five different symptoms including pain, fatigue, cough, shortness of breath, and blood in urine. Responses to each of the five items are from 1 to 7 on a Likert scale, with higher scores indicating a more severe degree of symptomatology. An overall symptom score is generated by summing the score of the five items and dividing the total by five. If there were missing items, the total score was calculated by the sum of all completed items and dividing it by the number of completed items. A higher score indicates higher degree of symptoms severity.

The Global Impression of Change (Symptoms) is a single-item self-administered PRO to rate the change in health since the start of the trial. A 7-point response scale is used, with a lower score indicating greater improvement in patient's self-reported health.

The Global Impression of Change (Quality of Life) is a single-item self-administered PRO to rate the change in health-related quality of life (HRQoL) since the start of the trial. A 7-point response scale is used, with a lower score indicating greater improvement in patient's self-reported HRQoL.

The questionnaire was implemented with Amendment 3 to the protocol. The questionnaire was administered only to patients in the 8-mg regimen who could read English. The questionnaire time recall period for this instrument was 1 week (the past week) and was completed by the patient at baseline, Cycle 1 Day 14, Cycle 2 Day 1, Cycle 3 Day 1, and at the end of treatment.

Shifts from baseline to worst values post-baseline were analyzed for each specific symptom, including pain, fatigue, cough, shortness of breath, and blood in the urine. Only 22 of the 87 patients had values at both baseline and post-baseline and were included in the analyses. Worsening in scores from ≤ 3 at baseline to >3 during treatment were most common for fatigue, reported for 8 patients (36%). Other shifts from ≤ 3 at baseline to >3 during treatment were as

follows: 3 patients for shortness of breath (14%), 2 patients (9.1%) each for pain and cough, and 1 patient (4.5%) for blood in the urine.

Reviewer Comments: *The SMQ is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by patients. This instrument is a generic preference-based measure intended to determine if response to therapy and side effects of therapy are accompanied by measurable changes in symptoms reported. This questionnaire is limited in its ability to ascertain the cause of any decreased level of functioning or quality of life for an individual patient. Moreover, there were only 22 patients who had values at both baseline and post-baseline. Due to the small number and limitations, no conclusion can be made based on PRO data generated from the SMQ.*

8.1.3. Assessment of Efficacy Across Trials (including Real-World Evidence)

As discussed with the FDA in the pre-NDA meeting of July 2018, the Applicant conducted a Real-World Evidence (RWE) retrospective study using the Flatiron-FMI and the Bladder Cancer Research Initiative for Drug Targeting in Germany (BRIDGE) databases to provide natural history and prognostic information on patients with metastatic urothelial cancers with FGFR alterations. This study was performed with the intention of demonstrating that patients with FGFR alterations have lower rates of response to anti PD-L1/PD-1 therapy including pembrolizumab, which has regular approval for the treatment of platinum-refractory advanced urothelial cancer.

Flatiron-FMI Database

Study Design

Flatiron Health (Flatiron) collected real-world, longitudinal, de-identified patient-level clinical data from electronic health records (EHRs) from US community-based cancer clinics. In partnership with Foundation Medicine, Inc. (FMI), Flatiron patient EHRs were linked with FoundationOne next-generation sequencing (NGS) results to generate a database termed the Flatiron-FMI clinico-genomic (CG) database. The Flatiron-FMI CG database thus included patients with both a confirmed diagnosis of advanced bladder cancer and with FoundationOne testing results for FGFR status available.

FGFR Population Definitions

The primary analysis population focused on FGFR-positive and FGFR-negative patients as per the specific mutations used in the Janssen diagnostic panel used for patient selection in the BLC2001 Phase 2 study of erdafitinib. In addition, a sensitivity analysis assessed all-FGFR-altered patients detected to have any FGFR alterations.

The specific definitions of these populations include:

- Janssen-FGFR-positive: patients positive for 1 or more of the 9 FGFR mutations and gene fusions in the Janssen diagnostic panel (FGFR3 gene mutation: S249C, Y373C, 248C, G370C; FGFR gene fusion: FGFR3-TACC3v1, FGFR3-TACC3v3, FGFR3-BAIAP2L1, FGFR2-CASP7, FGFR2-BICC1)
- Janssen-FGFR-negative: patients negative for 9 FGFR mutations and gene fusions in the Janssen diagnostic panel
- All-FGFR-positive: patients with all observed alterations in FGFR, including mutations, fusions, rearrangements, deletions and truncations
- All-FGFR-negative: patients for whom FGFR mutations, fusions, rearrangements, deletions, or truncations were not detected

Reviewer Comments: *To be consistent with Study BLC2001, the review team only focused on the FGFR-positive and FGFR-negative patients relative to the Janssen-FGFR diagnostic panel.*

Inclusion Criteria

1. Patient had at least 1 documented clinical visit in the Flatiron network on or after January 01, 2011
2. Patient had an ICD code consistent with bladder cancer in their EHR
3. Patient had a confirmed diagnosis of advanced bladder cancer (any histology)
4. Patient had NGS testing by FMI on a tumor sample with pathologist-confirmed histology consistent with bladder cancer
5. Patient had 1 of the following confirmed primary sites of disease: bladder, renal pelvis, ureter, or urethra

Diagnosis Criteria

Confirmation of these diagnoses were based upon review of Flatiron unstructured data and confirmation of histology from the patient's tumor sample received by FMI.

Study Objectives

Part 1. To assess the association between FGFR mutations or fusions and anti PD-L1/PD-1 therapy outcome in locally advanced or metastatic bladder cancer, and to assess the prognostic value of FGFR alterations in the advanced disease setting

Part 2. To compare OS among FGFR-positive patients treated with erdafitinib (from Study BLC2001) vs. those treated with currently available treatment options (i.e., anti PD-L1/PD-1 therapy and/or chemotherapy) in the real-world setting (from Flatiron-FMI database)

Analysis Sets

Part 1

- The treated patients with any (1st or 2nd) line of therapy analysis set included all patients who had any treatment with a 1st or 2nd line of therapy after the diagnosis date of

advanced disease. This analysis was used to assess the prognostic value of FGFR mutations and gene fusions.

- The treated patients with any (or 1st, or 2nd) line of anti PD-L1/PD-1 therapy analysis set included all patients who had 1 of the 5 approved anti PD-L1/PD-1 therapy (pembrolizumab, nivolumab, durvalumab, atezolizumab, or avelumab) used at any (or 1st, or 2nd) line of therapy after the advanced diagnosis date. This analysis set was used to assess the value of FGFR mutations and gene fusions for predicting anti PD-L1/PD-1 therapy outcomes.
- The treated patients with any (or 1st, or 2nd) line of chemotherapy analysis set included all patients who had any chemotherapy at any (or 1st, or 2nd) line of therapy after the advanced diagnosis date. This analysis set was used to assess the value of FGFR mutations and gene fusions for predicting outcomes of chemotherapy treatment.

Part 2

- Patients from BLC2001 Regimen 3
FGFR-positive patients treated with the proposed registration dose regimen of erdafitinib 8 mg QD (Regimen 3) in BLC2001
- Patients in Flatiron-FMI database
 - a. FGFR-positive patients treated with anti PD-L1/PD-1 therapy
 - b. FGFR-positive patients treated with chemotherapy

Study Endpoints

Overall survival (OS), defined as the index date to the date of death from any cause. The index date was the starting date of any or one specific treatment line.

Real world tumor response (rwTR) was defined qualitatively as

- Complete Response (CR): Complete resolution of all visible disease.
- Partial Response (PR): Partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease.
- Stable Disease (SD): No change in overall size of visible disease.
- Progressive Disease (PD): Increase in visible disease and/or presence of any new lesions
- Pseudoprogression: Increase in tumor size, which the clinician states as possibly being an effect of immunotherapy.
- Indeterminate response: Situations in which the clinician explicitly states that he/she is not able to make a determination of the assessment.
- Not documented: There is a record of radiology scan but no record of a clinician assessment of the scan.

Reviewer Comments: *Real-world tumor response assessment is limited by the lack of utilization of a standardized approach (such as RECIST v.1.1) in the real-world setting to objectively assess and compare clinical response among patient cohorts. RECIST utilizes a numerically quantifiable change in pre-defined target lesions selected at baseline to determine clinical response status. In addition to sum of diameters, clinical protocols require confirmation of response, accounting for*

response duration in RECIST response assignment. These quantifiable and time-dependent assessments are not typically captured in EHR data. Real-world tumor response is defined as a qualitative change in burden of disease over the course of treatment of a given therapy. The goal of rwTR data is to identify and document the point in time at which a patient's tumor shrinks or disappears. However, tumor response is assessed and described in a variety of ways in the real-world, and therefore the data usually carries large variability.

Statistical Analysis Plan

This is a retrospective study, and the sample size was not based on statistical consideration.

Part 1

Flatiron Health and FMI datasets were linked together and included patients who had at least 1 documented clinical visit in the Flatiron network on or after 01 January 2011, and those who underwent NGS testing by FMI on a tumor sample in the database. That meant patients who died before having FoundationOne testing, and/or who did not have a visit in the Flatiron network in or after 2011 were not included in the CG dataset. Thus, the dataset is subject to left truncation, which occurs when a dataset does not include patients with events that occur before a pre-specified time. To adjust for left truncation, a delayed entry model was used in a Cox proportional hazards model. Patients who received therapies under analyses prior to the FMI specimen report date were not considered as being in the risk set until the FMI specimen report date, i.e., their entry in the risk set was “delayed”. The entry date was the FMI specimen report date. The follow-up time for each patient extended from the entry date to the event date (or censor date).

Multivariate analyses were performed using a selected set of potential prognostic variables (obtained at baseline, e.g., sex, age, tumor stage, tumor mutation burden, primary tumor location, transitional cell carcinoma, and smoking history) as covariates in Cox regression model for OS. Each factor was assessed individually in addition to the main factor of FGFR status in a bivariate model as well as including all covariates in a multivariate model to assess the impact of these factors on the effect of FGFR alterations.

Real-world best tumor response rate (rwBTRR) and real-world disease control rate (rwDCR) were compared between FGFR-positive and FGFR-negative groups. Two-sided 95% confidence intervals (CIs) for the relative risks were calculated based on Wald chi-square statistics.

Reviewer Comments: *The reviewer considers the delayed entry model reasonable in this analysis given the fact that the data from the Flatiron-FMI CG database was left truncated.*

Part 2

Propensity score weighting approaches were used in the analysis to compare OS between patients in BCL2001 Regimen 3 and FGFR-positive patients from the Flatiron-FMI database. Variables used for propensity score estimation were age, sex, line of treatment, smoking history, primary tumor location, hemoglobin level, and time since most recent therapy. The

stabilized inverse probability treatment weighting (sIPTW) approach was used with propensity score estimate as the weight to assess treatment effect on OS in the proportional hazards regression model. Hazard ratios with 95% Wald-type confidence interval were estimated from weighted Cox proportional hazards models. Weighted Kaplan-Meier curves were applied to describe OS, where median survival with 95% CI was reported for each treatment group. Summary statistics of the baseline covariates for both cohorts were provided before and after adjustment. Other weighting schemes, e.g., average treatment effect for overlap population (ATO), average treatment effects on the treated (ATT) and average treatment effects on the control (ATC) were also presented for the propensity score method. Multivariate proportional hazards regression model including treatment and baseline covariates were also performed.

SAP Amendments

Table 80: SAP and data analysis milestones (Flatiron-FMI)

Date	Event
March 2018	First Draft of SAP
16 April 2018	Draft of SAP sent to Flatiron for review from Janssen. 1 st Data transfer from Flatiron to Janssen
25 April 2018	Face to face analysis kickoff meeting Flatiron-FMI and Janssen. Flatiron highlighted that the data was left truncated and discussed the need for adjustment
All analysis of the predictive and prognostic value of FGFR alterations were adjusted for left truncation	
After 25 April 2018	Analysis of Flatiron data initiated
22 June 2018	Flatiron data analysis using delayed entry model shared with FDA in pre-NDA briefing book, and discussed with FDA on 24 July 2018
29 August 2018	SAP finalized
18 September 2018	SAP submitted in NDA

Reviewer Comments: *The delayed entry model was not in the original SAP. FDA sent an Information Request asking when the amendment adding this model/approach was made. According to the Applicant's response, the decision to use this model was made before any analysis was done or results revealed, as shown in **Table 80** detailing chronology of events leading to the finalization of the SAP.*

Results/Discussion

Part 1

There were 426 patients with advanced bladder cancer represented in the Flatiron-FMI clinico-genomic database as of January 31, 2018 (data cutoff). Of 426 patients in the database, 103 patients did not have specific treatment information available. Among the remaining 323

patients who received any treatment, 141 patients received anti PD-L1/PD-1 therapy. Of the 141 patients, 17 patients were treated in the context of a clinical study and did not have specific treatment information available. Therefore, 124 patients were included in the analyses for anti PD-L1/PD-1 therapy. Table 81 presents the demographics and baseline characteristics and **Table 83** presents the baseline disease characteristics of patients who received any treatment (N=323) and patients who received any line of anti PD-L1/PD-1 therapy (N=124). None of the patients had fusions involving FGFR2.

Table 81: Baseline Demographics, Patients Treated with Any Treatment; and Patients Treated with Anti PD-L1/PD-1 Therapy (Flatiron-FMI)

	Any Therapy (N=323)		Any Anti PD-L1/PD-1 (N=124)	
	FGFR-pos ¹ (N=62)	FGFR-neg ² (N=261)	FGFR-pos ¹ (N=27)	FGFR-neg ² (N=97)
	n (%)	n (%)	n (%)	n (%)
Age (years)				
Mean (SD)	67.2 (8.2)	65.3 (10.3)	66.8 (8.8)	66.4 (10.6)
Median	68	66	69	66
Range	(45.0, 82.0)	(25.0, 84.0)	(45.0, 82.0)	(25.0, 84.0)
Age Group				
<65	22 (35.5)	117 (44.8)	9 (33.3)	42 (43.3)
>=65	40 (64.5)	144 (55.2)	18 (66.7)	55 (56.7)
65-74	28 (45.2)	91 (34.9)	13 (48.1)	32 (33.0)
>=75	12 (19.4)	53 (20.3)	5 (18.5)	23 (23.7)
Sex				
Female	18 (29.0)	82 (31.4)	3 (11.1)	32 (33.0)
Male	44 (71.0)	179 (68.6)	24 (88.9)	65 (67.0)
Race				
White	52 (83.9)	195 (74.7)	21 (77.8)	69 (71.1)
Black or African American	2 (3.2)	10 (3.8)	0	7 (7.2)
Asian	2 (3.2)	7 (2.7)	2 (7.4)	4 (4.1)
Other	2 (3.2)	18 (6.9)	2 (7.4)	6 (6.2)
Unknown/Not Reported	4 (6.5)	31 (11.9)	2 (7.4)	11 (11.3)
Smoking History				
Yes	42 (68.9)	169 (64.8)	18 (66.7)	70 (72.2)
No	19 (31.1)	89 (34.1)	8 (29.6)	27 (27.8)
Missing	1 (1.6)	3 (1.1)	1 (3.7)	0
Baseline Hemoglobin				
< 10 g/dL	3 (4.9)	10 (3.8)	1 (3.7)	7 (7.2)
≥ 10 g/dL	22 (36.1)	60 (23.0)	10 (37.0)	22 (22.7)
Missing	37 (60.7)	191 (73.2)	16 (59.3)	68 (70.1)
Baseline ECOG				
0	3 (4.8)	17 (6.5)	2 (7.4)	7 (7.2)

	Any Therapy (N=323)		Any Anti PD-L1/PD-1 (N=124)	
	FGFR-pos ¹ (N=62)	FGFR-neg ² (N=261)	FGFR-pos ¹ (N=27)	FGFR-neg ² (N=97)
	n (%)	n (%)	n (%)	n (%)
1	8 (12.9)	12 (4.6)	5 (18.5)	7 (7.2)
2	0	1 (0.4)	0	1 (1.0)
3	0	1 (0.4)	0	0
Unknown	51 (82.3)	230 (88.1)	20 (74.1)	82 (84.5)
Practice Type				
Academic	11 (17.7)	44 (16.9)	3 (11.1)	16 (16.5)
Community	51 (82.3)	217 (83.1)	24 (88.9)	81 (83.5)
FGFR alterations				
Mutations	48 (77.4)	-	22 (81.5)	-
FGFR3 G370C	1 (1.6)	-	0	-
FGFR3 R248C	6 (9.7)	-	2 (7.4)	-
FGFR3 S249C	31 (50.0)	-	13 (48.1)	-
FGFR3 Y373C	9 (14.5)	-	7 (25.9)	-
FGFR3 S249C/Y373C	1 (1.6)	-	0	-
Fusions	14 (22.6)	-	5 (18.5)	-
FGFR3 TACC3	14 (22.6)	-	5 (18.5)	-
FGFR3 BAIAP2L1	0	-	0	-
FGFR2 CASP7	0	-	0	-
FGFR2 BICC1	0	-	0	-

¹FGFR-pos: FGFR-positive

²FGFR-neg: FGFR-negative

[Source: Reviewer analysis using adsl.xpt and adbio.xpt datasets (Flatiron-FMI)]

Table 82: Baseline Disease Characteristics, Patients Treated with Any Treatment; and Patients Treated with Anti PD-L1/PD-1 Therapy (Flatiron-FMI)

	Any Therapy (N=323)		Any Anti-PD-L1/PD-1 (N=124)	
	FGFR-pos ¹ (N=62)	FGFR-neg ² (N=261)	FGFR-pos ¹ (N=27)	FGFR-neg ² (N=97)
	n (%)	n (%)	n (%)	n (%)
Primary Tumor Location				
Bladder	41 (66.1)	183 (70.1)	16 (59.3)	65 (67.0)
Urethra	1 (1.6)	7 (2.7)	1 (3.7)	2 (2.1)
Ureter/renal pelvis	20 (32.3)	71 (27.2)	10 (37.0)	30 (30.9)
Histology Type				
Transitional cell (urothelial) carcinoma	60 (96.8)	235 (90.0)	25 (92.6)	87 (89.7)
Adenocarcinoma	0	7 (2.7)	0	3 (3.1)
Small cell carcinoma	0	7 (2.7)	0	3 (3.1)
Squamous cell carcinoma	2 (3.2)	4 (1.5)	2 (7.4)	1 (1.0)
Other	0	7 (2.7)	0	2 (2.1)

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

	Any Therapy (N=323)		Any Anti-PD-L1/PD-1 (N=124)	
	FGFR-pos ¹ (N=62)	FGFR-neg ² (N=261)	FGFR-pos ¹ (N=27)	FGFR-neg ² (N=97)
	n (%)	n (%)	n (%)	n (%)
Unknown/not documented	0	1 (0.4)	0	1 (1.0)
Tumor Stage				
Stage 0	0	1 (0.4)	0	0
Stage I	0	2 (0.8)	0	1 (1.0)
Stage II	3 (4.8)	8 (3.1)	2 (7.4)	5 (5.2)
Stage III	5 (8.1)	11 (4.2)	2 (7.4)	6 (6.2)
Stage IV	19 (30.6)	121 (46.4)	11 (40.7)	48 (49.5)
Unknown/not documented	35 (56.5)	118 (45.2)	12 (44.4)	37 (38.1)
Tumor Mutation Burden				
Low	29 (46.8)	94 (36.0)	13 (48.1)	33 (34.0)
Medium	28 (45.2)	135 (51.7)	13 (48.1)	51 (52.6)
High	5 (8.1)	32 (12.3)	1 (3.7)	13 (13.4)
Prior Chemotherapy				
Yes	16 (25.8)	31 (11.9)	8 (29.6)	14 (14.4)
No	46 (74.2)	230 (88.1)	19 (70.4)	83 (85.6)
Prior I/O Treatment				
Yes	2 (3.2)	0	0	0
No	60 (96.8)	261 (100.0)	27 (100.0)	97 (100.0)
PD-L1 Status IHC Testing ³				
Positive	4 (6.5)	11 (4.2)	2 (7.4)	7 (7.2)
Negative	6 (8.1)	35 (13.4)	2 (7.4)	13 (13.4)
Unknown	0	5 (1.9)	0	3 (3.1)
Missing	52 (83.9)	210 (80.5)	23 (85.2)	74 (76.3)

¹FGFR-pos: FGFR-positive

²FGFR-neg: FGFR-negative

³PD-L1 status was determined via IHC testing with antibodies SP142, 22C3, 28-8, or other Lab developed test
[Source: Reviewer analysis using adsl.xpt dataset (Flatiron-FMI)]

Reviewer Comments: Baseline demographic characteristics for the treated population of 323 patients who received any therapy and for the anti PD-L1/PD-1 population of 124 patients who received anti PD-L1/PD-1 therapy in any line of therapy were balanced between FGFR-positive and FGFR-negative patients regarding age, sex, race and smoking history. However, due to substantial missing data, conclusions summarizing tumor stage, ECOG performance status, hemoglobin level, and PD-L1 expression are difficult to make. We note that no patients with FGFR2 alterations were included in this database.

There are, therefore, multiple limitations with the data on which the analyses presented are based. First, the size of the cohort is small, with only 27 patients with FGFR-positive tumors who received anti PD-L1/PD-1 therapy. Second, there are several inherent limitations of real-world

data that present challenges even with something as basic as accurately recording baseline characteristics.

EHRs often contain incomplete data. Determining the timing of a diagnosis from clinical data alone is challenging. Not every diagnosis is recorded at every visit. First diagnosis in a database is not necessarily an incident case of disease. Flatiron's database may not capture all therapies received by individual patients, as patients may seek care from providers that do not contribute to the Flatiron database. Thus, defining the number of lines of therapy that patients have previously received is problematic.

PD-L1 expression status, ECOG performance score, clinical stage, histology, chemotherapy regimen (dose and schedule), and other clinical factors cannot always be determined from the available data. Because of these issues and the resultant missing data, these important factors could not be incorporated into a multivariate model. This is especially important in survival analysis, as causality in survival is complicated, and death is affected by many socioeconomic factors that are not captured in EHR data. It is difficult to interpret OS results in a non-randomized setting as a retrospective study cannot measure all known or unknown prognostic factors.

Prognostic effect analysis results

Of 323 patients treated with any treatment, 17 patients had last known alive date before FMI reporting date and did not contribute to the OS analysis. The prognostic value of FGFR alterations was assessed in patients treated with any line (N=306; 59 FGFR-positive, 247 FGFR-negative) or 2nd line (N=199; 37 FGFR-positive, 162 FGFR-negative) of therapy. Results of the OS comparison between FGFR-positive and FGFR-negative cohorts by line of therapies are summarized in

Table 83. Kaplan-Meier curves of OS by FGFR status are shown in Figure 7.

Table 83: Overall Survival among Patients Treated with Any Therapy (Flatiron-FMI)

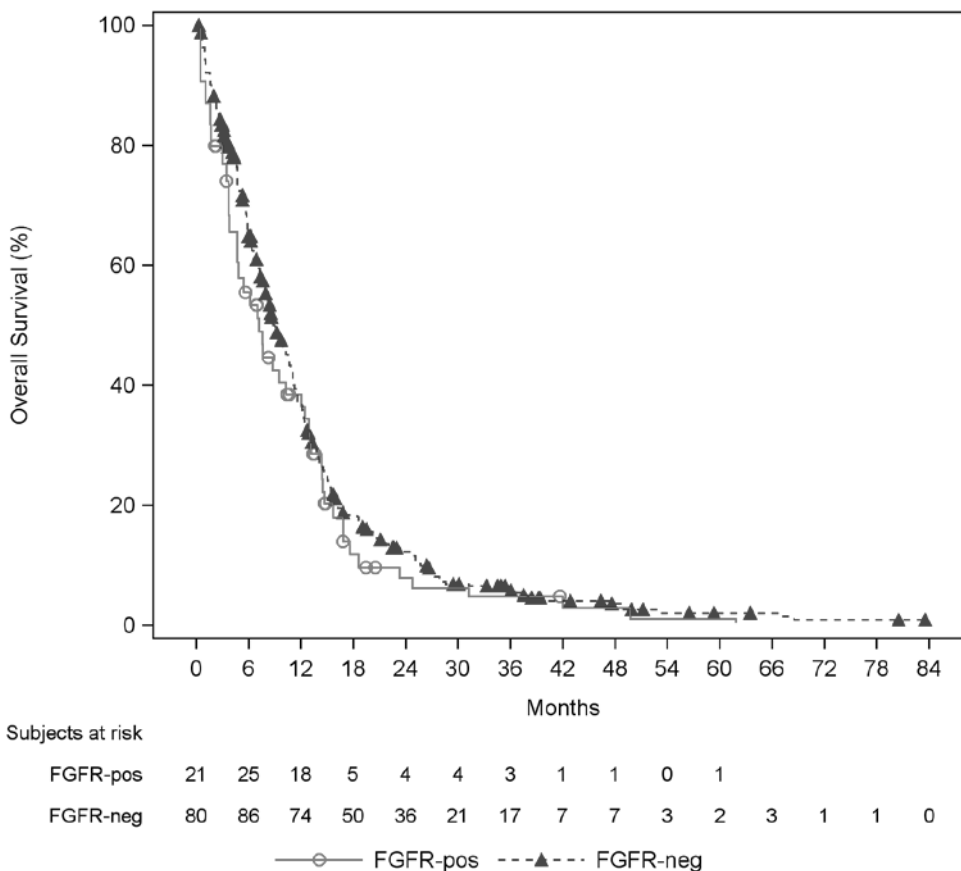
	FGFR-positive	FGFR-negative	Total
Given ≥1 Line of Therapy (N)	59	247	306
Deaths: n (%)	42 (71.2)	172 (69.6)	214 (69.9)
Median (95% CI), months	7.2 (4.7, 12.9)	9.0 (7.3, 11.1)	8.6 (7.2, 10.8)
Hazard ratio (95% CI)	1.18 (0.84, 1.66)		
Hazard ratio* (95% CI)	1.18 (0.83, 1.67)		
Given ≥2 Lines of Therapy (N)	37	162	199
Deaths: n (%)	27 (73.0)	117 (72.2)	144 (72.4)
Median (95% CI), months	5.4 (3.1, 10.8)	5.8 (4.8, 7.2)	5.6 (4.8, 6.9)
Hazard ratio (95% CI)	1.20 (0.79, 1.82)		
Hazard ratio* (95% CI)	1.16 (0.74, 1.81)		

*Multivariate Cox regression models adjusting for baseline covariates including sex, age, Stage IV diagnosis, tumor mutation burden, primary tumor location, transitional cell carcinoma, and smoking history.

Note: A hazard ratio above 1 indicates higher hazard of death among FGFR-positive cohort.

Figure 7: Overall Survival Among Patients Treated with Any Therapy by FGFR Status (Flatiron-FMI)

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[Source: Reviewer analysis using adsl.xpt and adtte.xpt datasets (Flatiron-FMI)]

Reviewer Comments:

As the OS comparison between FGFR-positive and FGFR-negative is not based on randomization, potential confounders would affect the comparison results from univariate Cox models. The applicant conducted multivariate analyses using a selected set of potential prognostic variables as covariates in Cox regression models. However, with small number of events in the FGFR-positive cohort, results from the multivariate Cox regression model adjusted by 7 covariates are problematic and the confidence interval estimates are not reliable. As shown in Figure 7, the Kaplan-Meier curves of FGFR-positive and FGFR-negative cohorts are close to each other. Though the point estimate of hazard ratio between FGFR-positive and FGFR-negative was higher than 1 favoring the FGFR-negative cohort, the confidence intervals were wide and covered 1. No definitive conclusion can be made from the Flatiron data about the prognostic impact of FGFR alterations in mUC patients who have received any line of therapy or 2nd line therapy.

FGFR Alterations as Predictive Factor

- OS with Anti PD-L1/PD-1 Therapy

Of 124 patients treated with any anti PD-L1/PD-1 therapy, 6 patients had last known alive date before FMI reporting date and did not contribute to the OS analysis. The predictive value of FGFR alterations was assessed in patients who received anti PD-L1/PD-1 therapy in any line (N=118; 26 FGFR-positive, 92 FGFR-negative), in 1st line (N=40; 12 FGFR-positive, 28 FGFR-negative), and/or in 2nd line (N=59; 12 FGFR-positive, 47 FGFR-negative). The hazard ratio of the OS comparison between FGFR-positive and FGFR-negative cohorts in patients receiving any line of anti PD-L1/PD-1 therapy is 1.33 with a 95% CI from 0.78 to 2.26. The hazard ratio adjusted by the pre-specified baseline covariates using the multivariate Cox regression model is 1.25 (95% CI: 0.71, 2.21). The hazard ratios of the OS comparison in patients receiving anti PD-L1/PD-1 therapy at 1st and 2nd line are 1.94 (95% CI: 0.78, 4.82) and 1.17 (95% CI: 0.53, 2.59), respectively.

- **OS with Chemotherapy**

Of 274 patients who treated with chemotherapy, 36 patients did not have specific treatment information available and 12 patients had last known alive date before FMI reporting date and did not contribute to the OS analysis. The predictive value of FGFR alterations was assessed in patients treated with chemotherapy in any line (N=224; 34 FGFR-positive, 190 FGFR-negative), in 1st line (N=209; 28 FGFR-positive, 181 FGFR-negative), and/or in 2nd line (N=97; 13 FGFR-positive, 84 FGFR-negative). The hazard ratio of the OS comparison between FGFR-positive and FGFR-negative cohorts in patients receiving any line of chemotherapy is 1.07 with a 95% CI from 0.69 to 1.66. The hazard ratios of the OS comparison in patients receiving chemotherapy at 1st and 2nd line are 0.96 (95% CI: 0.60, 1.54) and 2.08 (95% CI: 1.05, 4.13), respectively.

Reviewer Comments: *As the OS comparison between FGFR-positive and FGFR-negative is not based on randomization, potential confounders would affect the comparison results from the Cox regression models. With small number of events in the FGFR-positive cohort and the lack of randomization in the study design, results from the multivariate Cox regression model adjusted by 7 covariates are problematic and the confidence interval estimates are not reliable.*

Among patients treated with anti PD-L1/PD-1 therapy, the point estimate for the hazard of death numerically favored patients without FGFR alterations, but the confidence interval was wide and included 1.0. Given the small sample size in the FGFR-positive cohort, imbalance between the two groups with respect to number of patients, and wide confidence interval observed for hazard ratio, no conclusion on the predictive value of FGFR alterations could be made in patients who received anti PD-L1/PD-1 therapy or chemotherapy.

- **Real-world tumor response**

Anti PD-L1/PD-1 in any line of therapy

Of 141 patients treated with anti PD-L1/PD-1 therapy in any line of therapy, 17 patients were treated in the context of a clinical study and did not have data available for rwTR assessment. Flatiron retrospectively abstracted response information for the remaining 124 anti PD-L1/PD-1 treated patients (27 FGFR-positive, 97-FGFR-negative) in the Flatiron-FMI database. The real world best tumor response data are summarized in Table 84.

Table 84: Real World Best Tumor Response (rwBTR) to anti PD-L1/PD-1 Therapy (Flatiron-FMI)

	FGFR-pos ¹	FGFR-neg ²	Total
Anti PD-L1/PD-1 in any line of therapy (N)	27	97	124
CR or PR, n (%)	6 (22)	19 (20)	25 (20)
95% CI (%)	(7-38)	(12-28)	(13-27)
rw disease control rate (CR+PR+SD), n (%)	8 (30)	31 (32)	41 (33)
95% CI (%)	(12-47)	(23-41)	(25-41)
Anti PD-L1/PD-1 in 1st line (N)	12	30	42
CR or PR, n (%)	3 (25)	9 (30)	12 (29)
95% CI (%)	(1-50)	(14-46)	(15-42)
rw disease control rate (CR+PR+SD), n (%)	4 (33)	12 (40)	16 (38)
95% CI (%)	(7-60)	(23-58)	(23-53)
Anti PD-L1/PD-1 in 2nd line (N)	13	49	62
CR or PR, n (%)	2 (15)	10 (20)	12 (19)
95% CI (%)	(0-35)	(9-32)	(10-29)
rw disease control rate (CR+PR+SD), n (%)	2 (15)	16 (33)	20 (32)
95% CI (%)	(0-35)	(20-46)	(21-44)

CR = complete response; PR = partial response; SD = stable disease

¹FGFR-pos: FGFR-positive

²FGFR-neg: FGFR-negative

[Source: Reviewer analysis using adsl.xpt and adtte.xpt datasets (Flatiron-FMI)]

Reviewer Comments: The response rates were comparable (approximately 20-22% of patients met rwBTR criteria for CR or PR) irrespective of FGFR status in patients who received anti PD-L1/PD-1 treatment in any line, with wide, overlapping confidence intervals (Table 84). The real world disease control rate were also comparable (30-31%, irrespective of FGFR status, based on our assessment of radiology and clinical reports). The Applicant acknowledged that interpretation of these response rates must be approached cautiously because rwBTR criteria are less stringent than RECIST criteria.

The original Flatiron-assessed rwDCR was 31/97 (34%) in the anti PD-L1/PD-1 treated, FGFR-negative patients. However, given the inherent subjectivity and variable application of real world radiologic assessment, FDA sent an IR to obtain patient-level clinical and radiologic

response narratives. FDA review of data submitted in response revealed that two of the SD patients originally classified as having a rwBTR of SD had incomplete restaging to support an assessment of SD at any point. These two patients were re-categorized as PD in the analysis presented in Table 84.

FDA's overall conclusion on prognostic/predictive value of FGFR alterations (Part 1):

In summary, with the analysis results observed and limitation of the dataset we cannot make any definitive conclusion on the prognostic or predictive impact of FGFR alterations in patients with advanced urothelial cancer.

Part 2

The Applicant compared overall survival among the FGFR-positive patients with advanced or metastatic urothelial cancer from the Phase 2 clinical study (BLC2001) who received erdafitinib, versus the FGFR-positive patients identified from the Flatiron-FMI database who received anti PD-L1/PD-1 therapy or chemotherapy. Per the Applicant's analysis, the results suggested an improvement in overall survival in patients treated with erdafitinib in Regimen 3 (8 mg once daily) of BLC2001 when compared to those treated with anti PD-L1/PD-1 or chemotherapy in the real-world setting from Flatiron-FMI database. The point estimate of hazard ratios for the OS analysis based on propensity score weighting methodologies and multivariate regression were approximately 0.3 for different comparisons. The Applicant concluded that patients treated with erdafitinib in the BLC2001 Study had a survival benefit compared to FGFR-positive patients in the Flatiron-FMI dataset treated with anti PD-L1/PD-1 therapies or chemotherapy.

Reviewer Comments: *Several important methodological issues impact interpretability of these findings. These include 1) unmeasured confounding and substantial missingness of key confounding factors, e.g., ECOG was missing in approximately 30% of control patients; 2) more stringent exclusion criteria for trial patients such that these were more likely to be healthier than controls; 3) differential selection of comparison groups, specifically, that trial patients were enrolled from academic medical centers primarily from Europe, while controls were enrolled from community oncology centers in the US; 4) potential differential treatment misclassification; 5) incomplete capture of death information in controls, and 6) very small sample size (n=16~26) in the real-world control cohorts. Refer to the review conducted by Office of Surveillance and Epidemiology for additional details.*

FDA's conclusion on indirect comparison of erdafitinib versus standard of care (Part 2):

Because both internal and external validity are significantly impacted by these methodological issues, we do not consider these analyses sufficient for use as evidence supporting the effectiveness of the drug.

Bladder Cancer Research Initiative for Drug Targeting in Germany (BRIDGE) Database

Study Design

Clinical data were obtained from 5 BRIDGE consortium clinical sites (Universities of: Erlangen, Mannheim; Ulm, Regensburg, and Herne), and FGFR alteration screening was performed jointly by the Universities of Erlangen (mutations) and Mannheim (fusions). Study-eligible patients were those who:

- had sufficient tissue available for FGFR alteration testing
- were not treated in the context of a clinical study

Study Objectives

The primary objective was to determine the value of FGFR alterations in predicting anti PD-L1/PD-1 treatment outcome. PD-L1 expression and correlation with OS were also assessed.

Study Endpoints

Overall survival (OS) was defined as the start date of anti PD-L1/PD-1 therapy to the date of death.

Statistical Analysis Plan

Kaplan-Meier survival function estimation and Cox proportional hazard models were implemented in the analysis.

Results/discussion

Across clinical sites, 109 advanced or mUC patients (i.e., bladder and upper urinary tract) were identified who received anti PD-L1/PD-1 treatment on or after February 2016. Of those patients, 16 were excluded due to treatment in the context of a clinical study, and 30 had no tissue available or insufficient tissue for testing (n=28) or missing treatment start dates in the transferred data (n=2), who were also excluded. A total of 63 patients who had both clinical data and FGFR alteration status were included in the analysis. Results of the OS comparison between FGFR-positive and FGFR-negative cohorts are summarized in Table 85.

Table 85: Overall Survival Among Patients Treated with Anti PD-L1/PD-1 Therapy (BRIDGE)

	FGFR-positive (N=11)	FGFR-negative (N=52)	Total (N=63)
Deaths: n (%)	6 (55%)	24 (46%)	30 (48%)
Median, months (95% CI)	13.3 (1.8, NE)	10.6 (5.5, NE)	13.3 (5.5, NE)
Hazard ratio (95% CI)	1.28 (0.52,3.13)		

[Source: Reviewer analysis using adsl.xpt and adtte.xpt datasets (BRIDGE)]

Reviewer Comments: While the overall survival hazard ratio was worse in patients with FGFR alterations, given the limited number (11) of patients in the FGFR positive cohort, no conclusion can be drawn.

FDA requested the tumor response data since the BRIDGE dataset was more recent than the Flatiron-FMI dataset, and data were likely to be obtained in a more uniform and complete manner. The Applicant submitted the available response data for 57/63 patients in the BRIDGE dataset on December 27, 2018. RECIST-based response data were not available for the BRIDGE dataset. Response was determined from review of clinical records by investigators at each of 5 participating centers. Investigators were not given pre-defined criteria by which to assess response and were not required to provide an overall response determination. No guidelines were used to assess responses consistently across all 5 sites.

In the 57 patients with response data available, the real world tumor response rate (CR or PR) was reported as 38% (3/8) for FGFR-positive patients and 25% (12/49) for FGFR-negative patients, with large and overlapping confidence intervals (Table 86).

Table 86: Real World Best Tumor Response (rwBTR) to Anti PD-L1/PD-1 Therapy (BRIDGE)

	FGFR-positive (N=8)	FGFR-negative (N=49)	Total (N=57)
CR or PR, n (%)	3 (37.5)	12 (24.5)	15 (26.3)
95% CI (%)	(4.0-71.0)	(12.4-36.5)	(14.9-37.7)
Disease control rate, n (%)	3 (37.5)	17 (34.7)	20 (35.1)
95% CI (%)	(4.0-71.0)	(21.4-48.0)	(22.7-47.5)

[Source: Reviewer analysis using adsl.xpt and adtte.xpt datasets (BRIDGE)]

Reviewer Comments: Due to the small sample size, these data carried large variability and were inconclusive. The Applicant acknowledged that interpretation of these response rates must be approached cautiously because rwBTR criteria are less stringent than RECIST criteria. The disease control rates were comparable between FGFR-positive vs. FGFR-negative patients. The higher response rate seen in the FGFR-positive patients is likely attributed to the small sample size (N=8) and we note that the confidence interval is very wide.

Overall conclusion of RWE from the review team

Given the analysis results observed and data limitations, no definitive conclusion can be made about the prognostic or predictive impact of FGFR alterations in patients with metastatic urothelial cancer.

8.1.4. Integrated Assessment of Effectiveness

In NDA 212018, the Applicant has submitted substantial evidence of effectiveness in support of the approval of erdafitinib. This approval is primarily based on efficacy results of BLC2001, a single-arm, open-label, multi-center clinical study of erdafitinib, in which 87 patients were enrolled with locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 and FGFR2 genetic alterations and who progressed during or following at least one line of prior

chemotherapy, including within 12 months of neoadjuvant adjuvant platinum-containing chemotherapy. These 87 patients all received erdafitinib at the proposed dose, which is 8mg daily with pharmacodynamically-guided dose increase to 9 mg based on serum phosphate and tolerability. The conduct of this non-randomized, single-arm clinical study is adequate to generate sufficient data to support the effectiveness of erdafitinib. The efficacy results of these 87 patients enrolled at the proposed dose and proposed disease setting in BLC2001 support the claim of clinical benefit through the surrogate endpoint of ORR, and this supports the decision to grant accelerated approval of erdafitinib for the treatment of adult patients with urothelial carcinoma which has susceptible FGFR3 or FGFR2 genetic alterations, and which has progressed during or following at least one line of prior platinum -containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, under the provisions in 21 CFR Part 601 Subpart E (accelerated approval).

A confirmed ORR as assessed by BIRC per RECIST v1.1 of 32.2% (95%CI: 22.4, 42.0) was observed in patients receiving erdafitinib 8 mg once daily. The detected responses appeared durable with a duration of response of 5.4 months (95%CI: 41.2, 6.9 months). Subgroup analyses support the overall substantial evidence of effectiveness. Patients in all risk categories based on Bellmunt and MSKCC scores demonstrated responses on erdafitinib, as did patients with liver metastases. These results indicate a clinically meaningful benefit for patients in the indicated population in this setting.

In the second-line treatment of urothelial cancer, pembrolizumab is the standard of care with a demonstrated overall survival advantage over chemotherapy. Patients with FGFR-altered cancers are considered a genetically-defined subset of patients who may not respond as other patients would to available therapy. The ORR per BIRC reported by pembrolizumab in Keynote 361 is 21% (95% CI:16,27). While the confidence intervals for the ORRs for pembrolizumab and erdafitinib overlap, the review team believes that there is sufficient evidence to demonstrate clinical benefit. This molecularly-defined subgroup of patients with urothelial cancer that harbor FGFR genetic alterations also appears to have a very low reported response rate to anti PD-L1/PD-1 therapy, as reported in BLC2001 with a reported response rate of 4.8%, in comparison to a reported response rate of 34.5% to prior chemotherapy. These patients who had for the most part not demonstrated a previous response to anti PD-L1/PD-1 therapy had a 59% response rate to erdafitinib when treated on BLC2001. In contrast, attempts by the applicant to use real-world evidence from the Flatiron-FMI and BRIDGE consortium data to demonstrate that patients with urothelial cancer and FGFR alterations did less well than those without FGFR alterations in terms of response rate and overall survival to anti PD-L1/PD-1 directed therapies were hampered by methodologic flaws that made these analyses uninterpretable.

A review issue faced by the review team when considering the erdafitinib indication statement was whether to include all enrolled FGFR genetic alterations in the approved and labeled population. Generally, while FGFR genetic alterations occur in about 20% of patients with metastatic bladder cancer, the majority of alterations in this setting are FGFR point mutations,

specifically point mutations in FGFR3. FGFR fusions (of FGFR3 and FGFR2) are far less common in this setting. FGFR2 fusions specifically appear to be very rare in bladder cancer and it is unclear if they represent molecular “drivers” in this setting, although they appear to be of clinical importance in other settings such as hepatobiliary cancers.

The review team thus undertook several analyses of submitted data for this NDA to characterize the expected frequency of various FGFR molecular alterations in a metastatic urothelial cancer population. The first analysis was based on screened patients on BLC2001. Overall, 2214 patients were screened for molecular eligibility for enrollment for BLC2001, of which 417 patients had tissue specimens that were adequate for molecular screening and were found to carry an FGFR genetic alteration. This points to an approximately 18.8% overall incidence rate in this screened population. Data on the specific type of FGFR alteration present in each of the screened patients was not provided by the sponsor, but data was available for all 210 of those patients who were treated on BLC2001.

Table 87: FGFR Genetic Alteration Status. All Patients (BLC2001)

FGFR alterations*	n (%) n=210
FGFR3 Point Mutations Only	163 (78)
G370C	22 (10)
R248C	32 (15)
S249C	73 (35)
Y373C	31 (15)
G370C/S249C	2 (<1)
R248C/Y373C	2 (<1)
S249C/Y373C	1 (<1)
FGFR Fusions Only	40 (19)
FGFR2-BICC1	3 (1)
FGFR2-CAPS7	4 (2)
FGFR3-BAIAP2L1	3 (1)
FGFR3-TACC3_V1	20 (10)
FGFR3-TACC3_V3	6 (3)
FGFR2-CASP7/FGFR3-BAIAP2L1	1 (<1)
FGFR2-CASP7/FGFR3-TACC3_V1	1 (<1)
FGFR2-CASP7/FGFR3-TACC3_V3	1 (<1)
FGFR2-CASP7/FGFR2-BICC1	1 (<1)
Point Mutations and Fusions	7 (3)
G370C/FGFR2-BICC1	1 (<1)
G370C/FGFR3-TACC3_V1	1 (<1)
R248C/FGFR3-TACC3_V1	2 (<1)
S249C/FGFR3-BAIAP2L1	1 (<1)
R248C/S249C/FGFR3-TACC3_V1	1 (<1)
S249C/Y373C/FGFR2-CASP7/FGFR3-BAIAP2L1/FGFR3-TACC3_V1/FGFR3-TACC3_V3	1 (<1)

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FGFR alterations*	n (%) n=210
* FGFR genetic alterations were detected using an investigational clinical trial assay (CTA) performed at a central laboratory, designed to detect the specific FGFR alterations.	

The team also reviewed real world evidence submitted with NDA 212018 from the Flatiron-FMI database to characterize the frequency of various FGFR alterations in these patients. In a cohort of 426 patients with advanced urothelial cancer and available Janssen genetic diagnostic results, FGFR3 alterations (FGFR3 point mutation or FGFR3 fusions) were identified in 79 (18.5%) patients. None of the patients had FGFR2 fusions. The table below summarizes the number of enrolled patients by FGFR alterations.

Table 88: FGFR Genetic Alteration Status among FGFR-altered Urothelial Patients (Flatiron-FMI)

FGFR alterations*	n (%) n=79
FGFR3 Point Mutations	65 (82)
S249C	40 (51)
Y373C	10 (13)
R248C	12 (15)
G370C	1 (1)
S249C/Y373C**	2 (3)
FGFR3 Fusions	14 (18)
FGFR3-TACC3	14 (18)
FGFR3-BAIAP2L1	0 (0)
FGFR2 Fusions	0 (0)
FGFR2-CASP7	0 (0)
FGFR2-BICC1	0 (0)
* FGFR genetic alterations were detected using an investigational clinical trial assay (CTA) performed at a central laboratory, designed to detect the specific FGFR alterations.	
** Two patients had more than one FGFR3 point mutation detected.	

Based on review of the above data from BLC2001 and the Flatiron-FMI data, the majority of the ~20% of the patients with advanced FGFR-altered urothelial cancers have FGFR3 mutations (~80%). FGFR fusions appear to be much rarer, occurring in approximately 20% of these FGFR-altered patients, with most of these patients harboring FGFR3 fusions.

Molecular eligibility for BLC2001 included the presence of several prespecified FGFR genetic alterations, including several FGFR fusions (FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3 [V1, V3], FGFR3-BAIAP2L1) as detected by a PCR-based clinical trial assay (CTA). These FGFR alterations were selected based on presumed frequency in bladder and/or other types of cancers and on

available nonclinical and clinical data at the time. On 12/04/2014, a pre-Phase 2 Meeting with the Sponsor was held to discuss the trial design of BLC2001, based on data from an ongoing Phase 1 study, 42756493EDI1001. The Sponsor cited preclinical studies as well as preliminary clinical findings from EDI1001 as the rationale for the FGFR genetic alterations to be used as an eligibility criterion for enrollment in BLC2001. Specifically, the FGFR fusions identified from the four patients in EDI1001 who achieved either a PR or SD (no patients achieved CR) and had urothelial carcinoma that had a FGFR fusion, responses of either PR or SD were observed in four patients with fusions: FGFR3-TACC3, FGFR2-BICC1/FGFR2-CASP7, FGFR3-BIAP2L1/ FGFR2-BICC1/FGFR2- CASP7/ FGFR2-OFD1, and FGFR3-TACC3/FGFR3 amp. These preliminary efficacy findings provided the primary clinical rationale for the selected FGFR genetic alterations included in BLC2001. In addition, the Sponsor also discussed the rationale for excluding other FGFR genetic alterations, such as FGFR gene amplifications and FGFR2-CCDC6 fusions, because of lack of sufficient clinical activity observed in the EDI1001. FDA agreed with these rationales, and thus patients with these prespecified FGFR fusions were enrolled on BLC2001.

Table 89 below compares investigator-assessed objective response rate by FGFR alteration type in all 189 chemotherapy relapsed/refractory patients with urothelial cancer enrolled in BLC2001. The 8 mg dosing cohort is highlighted (n=87). Investigator-assessed response rates are presented for uniformity, as efficacy results of the 6 mg and 10 mg dosing cohorts were not independently reviewed.

Table 89: Investigator-assessed ORR by FGFR Alteration. All Regimens, Relapsed/Refractory Population (BLC2001)

FGFR POINT MUTATIONS / FUSIONS N=189	8 mg QD Efficacy Dataset		6 mg QD		10 mg 7on/7off	
	Patients (N)	Responses (N)	Patients (N)	Responses (N)	Patients (N)	Responses (N)
Chemo Relapsed/Refractory	87	34	73	27	29	6
INV-ORR (%)	39.1		37.0		20.7	
FGFR3 Point Mutations Only *	64	30	59	22	24	5
INV-ORR (%)	46.9^s		37.3		20.8	
G370C	4	2	11	3	5	0
R248C	9	5	14	6	5	0
S249C	40	17 ^s	19	7	8	2
Y373C	11	6	13	5	3	1
G370C/S249C	0	0	1	0	1	1
R248C/Y373C	0	0	1	1	1	1
S249C/Y373C	0	0	0	0	1	0
FGFR Fusions Only *	23	4	10	2	2	0
INV-ORR (%)	17.4		20.0		0	
FGFR2-BICC1	2	0	1	1	0	0
FGFR2-CASP7	3	0	0	0	0	0
FGFR3-BAIAP2L1	1	0	1	0	1	0

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FGFR3-TACC3_V1	10	4	7	1	1	0
FGFR3-TACC3_V3	6	0	0	0	0	0
FGFR2-CASP7/FGFR3-BAIAP2L1	0	0	1	0	0	0
FGFR2-CASP7/FGFR3-TACC3_V3	1	0	0	0	0	0
Point Mutations and Fusions						
	0	0	4	3	3	1
INV-ORR (%)	NA		75.0		33.3	
G370C/FGFR2-BICC1	0	0	1	1	0	0
G370C/FGFR3-TACC3_V1	0	0	1	1	0	0
R248C/FGFR3-TACC3_V1	0	0	1	0	1	1
S249C/FGFR3-BAIAP2L1	0	0	0	0	1	0
R248C/S249C/FGFR3-TACC3_V1	0	0	1	1	0	0
S249C/Y373C/FGFR2-CASP7/FGFR3-BAIAP2L1/FGFR3-TACC3_V1/FGFR3-TACC3_V3	0	0	0	0	1	0

*§The investigator-assessed response for one patient (8mg; S249C) was changed from PR to SD by FDA review resulting in an INV-ORR of 46.9% for the subset of FGFR3 Point Mutations Only. *Only refers to the only FGFR alteration(s) detected in the tumor sample as assessed by the CTA assay. INV-ORR: Investigator-assessed objective response rate= (CR+PR).*

Based on the above table, it is apparent that several types of FGFR fusions had no patients with responses observed on BLC2001 in any dosing cohort. One question faced by the review team was therefore whether to extend erdafitinib's indication to all patients with FGFR3 fusions, as responses were only observed in the most common type of FGFR3 fusion (FGFR3-TACC3_V1). A second question faced by the review team was whether to extend erdafitinib's indication to patients with FGFR2 fusions.

In terms of nonclinical data on FGFR fusions in bladder cancer, there is evidence of FGFR2 (and FGFR3 fusions) transforming in vitro, but not in urothelial cell lines. In bladder cancer models, 2 cell lines with FGFR3-TACC3 fusions demonstrated response to erdafitinib. No analogous data was submitted for FGFR2 fusions in bladder cancer models. Both FGFR2 and FGFR3 fusions were inhibited by erdafitinib in transfected cell-line models and in some xenograft models.

As can be seen in Table 89, the applicant reported one PR by investigator-assessed response that was observed in an FGFR2-BICC1 fusion positive patient in a different dosing cohort of erdafitinib (6mg, i.e. not part of the 87 patient primary efficacy population). This patient had nodal disease and a reported duration of response of 4.2 months. However, once the images of this patient were reviewed by an independent review committee (by request of FDA review team), the patient was found to have had a best overall response of PD, as a new lesion was seen at the first follow-up assessment by the independent reviewer. The applicant also provided data from the Phase 1 EDI1001 Study in which a patient with urothelial cancer and with an FGFR2-BICC1 fusion had an investigator-assessed PR with response duration of 7.2 months. However, review of this response revealed that the PR involved a single target lesion in the lung that decreased from a baseline value of 19 mm to a follow-up value of 4 mm. Central review of these images was not done on this phase 1 protocol and is no longer possible per the

applicant due to absence of patient consent. There were also investigator-assessed PRs seen in patients with other tumor types with FGFR2 fusions- all PRs- in NSCLC, cervical cancer, and cholangiocarcinoma.

An additional consideration faced by the review team is that the companion diagnostic approved with erdafitinib has the following as a warning and precaution: FGFR2 fusions (FGFR2:BICC1 and FGFR2:CASP7) and FGFR3 fusion FGFR3:BAIAP2L1 not included in the intended use are also designed to be identified by the theascreen FGFR RGQ RT-PCR kit but have not been analytically and clinically validated using clinical specimens.

The overall summary of evidence for the inclusion of FGFR3 and FGFR2 fusions in the indication statement is presented below-

Table 90: Overall Summary of Evidence for FGFR Fusions Included in the Indication Statement

EVIDENCE	FGFR3 fusions	FGFR2 fusions
PUBLISHED LITERATURE		
Literature support potential role as a oncogenic driver in UC?	Yes	No
NONCLINICAL		
Activity shown in bladder models?	Yes, tested 2 cell lines with FGFR3-TACC3	No data
Inhibited by erdafitinib in transfected cell-line models?	Yes	Yes
Inhibited by erdafitinib in xenograft models?	Some ¹	Some ¹
CLINICAL		
Estimated frequency, overall advanced urothelial cancer population	~5%	0-3%
Responders (BIRC)	Yes (only FGFR3-TACC3_V1)	No
CDx DEVICE		
Unresolved issues?	Yes ²	Yes ²

¹Signaling context and/or expression level may impact response

²FGFR2 fusions (FGFR2:BICC1 and FGFR2:CASP7) and FGFR3 fusion FGFR3:BAIAP2L1 not included in the intended use are also designed to be identified by the theascreen FGFR RGQ RT-PCR kit but have not been analytically and clinically validated using clinical specimens.

Ultimately, the review team concluded that per the recommendations in the Guidance for Industry- Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease previously published by the FDA, mechanism-based evidence, non-clinical studies and clinical studies can be used as rationale to support an accelerated approval. Additionally, per the guidance, if the clinical trials are successful and other conditions for approval are met, the FDA

will, in most circumstances, approve the drug for all patients who meet the inclusion criteria for the trial based on the prespecified criteria, irrespective of the extent to which patients with various molecular alterations were represented in the clinical trial. Due to the rarity of FGFR fusions in this population, the subsets with no demonstrated responses on BLC2001 may be due to underrepresentation and low numbers of enrolled patients. The number of patients with FGFR fusions may be too small to exclude drug activity. The inclusion of these patients was agreed to in a pre-phase 2 meeting with the applicant. Additionally, the molecular eligibility criteria for the ongoing confirmatory clinical study BLC3001 include the same FGFR genetic alterations as were enrolled in BLC2001. The confirmation of clinical benefit in this small subgroup of patients in enrolled patients with FGFR fusions is part of the PMR related to submitting the BLC3001 results. Continued inclusion of these FGFR fusions in the erdafitinib indication statement at the time of BLC3001 submission will be a review issue.

8.2. Review of Safety

8.2.1. Safety Review Approach

The erdafitinib clinical safety database contains pooled data from a total of 416 patients in two phase 1 dose escalation trials in subjects with advanced solid tumors (EDI1001, and GAC1001) and one phase 2 trial (BLC2001) in patients with advanced or metastatic urothelial cancers. The proposed dose and regimen for approval is 8 mg daily with pharmacodynamically guided up-titration to 9 mg daily. A total of 99 subjects were treated with this dosing regimen in BLC2001. This includes the 87 patients who form the primary efficacy population for this NDA, as well as 12 patients who were treated in the first-line metastatic setting due to their cisplatin-ineligible status. Additionally, to expand the safety database of this dosing regimen, data from subjects in EDI1001 treated with 9-mg daily (no up-titration; n = 65) was also reviewed, for a total of 164 subjects treated with what is referred to as the 8/9 mg daily regimen. The Applicant coded verbatim adverse event (AE) terms for all three trials using MedDRA version 20.0.

Reviewer's comment: *Because the intended patient population in this submission was relatively small (N = 87) the clinical review team examined the 8/9 mg daily population (N = 164) for a more in-depth review. The strategy of pooling of safety data for the 8/9 mg daily regimen from EDI1001 and BLC2001 is considered scientifically sound because the safety profile of erdafitinib is not thought to be markedly indication-dependent. This population forms the basis of the analyses for much of this safety review. For labeling purposes, the 87 patients with advanced urothelial cancer who form the primary efficacy (i.e. the indication) population for erdafitinib were used to inform safety analyses for section 6. The 87 patients were chosen for labeling purposes for clarity, to align with the efficacy population, and because the safety profile of erdafitinib in these patients was generally representative of the overall safety profile of the pooled analyses in the pooled 8/9 mg dosing cohort (n=164).*

Table 91: Pooling of Dose Regimens in the Safety Database

Dose Regimen	BLC2001	EDI1001	GAC1001	Pooled Safety Group*
0.5 mg daily	0	3	0	< 6 mg daily (n = 20)
2 mg daily	0	4	3	
4 mg daily	0	7	3	
6 mg daily	78	10	3	6 mg daily (n = 91)
8 mg daily	99[§]	0	0	8 or 9 mg daily (n = 164)
9 mg daily	0	65	0	
12 mg daily	0	7	0	12 mg daily (n = 7)
10 mg weekly	33	78	3	Weekly (n = 134)
12 mg weekly	0	13	7	
Total	210	187	19	416

* pooling is based on starting dose

[§] includes 87 patients with advanced urothelial cancer and progression on prior chemotherapy.

The safety data presented this review were submitted to the New Drug Application on September 18, 2018. The Applicant submitted a 90-Day Safety Update on December 18, 2018. The findings presented in the 90-Day Safety Update did not significantly change the overall safety conclusions.

8.2.2. Review of the Safety Database

Overall Exposure

One hundred sixty-four subjects were treated with erdafitinib on the 8/9 mg daily regimen. At the time of clinical cut-off, 21 subjects (13%) were still receiving erdafitinib and 143 (87%) had discontinued treatment. The most common reason for treatment discontinuation was progressive disease, reported for 82 of subjects who discontinued treatment. Adverse events led to treatment discontinuation for 11.2% of subjects who discontinued treatment.

Of the 416 patients who received erdafitinib across all doses, 25 (6%) were still on treatment as of the clinical cut-off, and 391 (94%) had discontinued treatment. Median time on study (including follow-up after treatment discontinuation) was 8.2 months. Progressive disease led to treatment discontinuation for 83.9% of subjects who discontinued treatment, and adverse events led to treatment discontinuation for 9.2% of subjects. Death was the reason for discontinuation for 4 subjects: 3 subjects in Study EDI1001 (Subject (b) (6), sepsis; Subject (b) (6), pulmonary edema; and Subject (b) (6), pneumonia aspiration) and 1 subject in BLC2001 (Subject (b) (6), sepsis).

Table 92: Subject Disposition (Safety Population)

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Treatment Ongoing	16 (18.4%)	21 (12.8%)	25 (6.0%)
Discontinued Treatment	71 (81.6%)	143 (87.2%)	391 (94.0%)
Reason for Discontinuation			
Adverse Event	11 (12.6%)	16 (11.2%)	36 (9.2%)
Death	0	1 (0.7%)	4 (1.0%)
Progressive Disease	58 (66.7%)	117 (81.8%)	328 (83.9%)
Physician Decision	0	1 (0.7%)	7 (1.8%)
Withdrawal by Subject	1 (1.1%)	6 (4.2%)	14 (3.6%)
Other	1 (1.1%)	2 (1.4%)	2 (5.1%)

Dataset ADSL; Variables: EOTSTT, TR01AG1, EOTREAS

The median duration of treatment on the 8/9 mg regimen was 3.3 months, with 49 subjects (30%) treated for ≥ 6 months and 13 subjects (7.9%) treated for ≥ 12 months. The median number of cycles was 4. The median treatment duration was shorter in the Phase 1 Study EDI1001 (1.5 months) than for the Phase 2 Study BLC2001 (5.3 months).

For all doses combined, the median treatment duration was 2.8 months, with 93 (22%) subjects treated for ≥ 6 months and 30 (7.2%) treated for ≥ 12 months.

Table 93: Extent of Exposure

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Treatment Duration (months)			
0 to < 3	29 (33.3%)	79 (48.2%)	228 (54.8%)
3 to < 6	25 (28.7%)	36 (22.2%)	95 (22.8%)
6 to < 9	16 (18.4%)	23 (14.0%)	44 (10.6%)
9 to < 12	11 (12.6%)	13 (7.9%)	19 (4.6%)
≥ 12	6 (6.9%)	13 (7.9%)	30 (7.2%)
Mean (SD)	5.7	4.9 (4.4)	4.6 (4.4)
Median	5.3	3.3	2.9
Range	0.5 – 17.4	0.2 – 23.4	0.2 – 23.4
Cumulative Dose (mg)			
Mean (SD)	1083.0	890.2 (729)	745.7 (737)
Median	854	718.5	488
Range	88 – 3010	63 – 3789	20 – 4632
Dose Intensity (mg/day)			
Mean (SD)	6.6 (1.6)	6.7 (1.8)	6.0 (1.8)
Median	7.1	7.1	5.8
Range	3.0 – 8.9	2.1 – 9.7	0.5 – 12.0

Source; Dataset ADEXS; variables PARAM, TR01AG1, AVAL

Reviewer's comment: Although median treatment durations overall were relatively short, the availability of safety information for patients treated >6 months, and in particular, data from 30 patients in the pooled safety population treated for ≥ 12 months, was considered adequate to

inform the safety analysis for the accelerated approval of erdafitinib. It is for this reason that safety data was analyzed in detail for patients at all dose levels (n=416) in this review.

Relevant characteristics of the safety population:

For the 8/9-mg daily regimen, the median age was 63.5 years. Seventy-five subjects (45.7%) were 65 years or older. Females were 37.2% of the population and males were 62.8%. Most subjects were white (78.7%), 31.1% were from the United States, 66.9% were from Europe, and 3.0% were from Asia. Common primary tumor sites were urothelial (67.1%), breast (11.0%), and reproductive system (6.7%). Baseline Eastern Cooperative Oncology Group (ECOG) scores were mostly 0 (45.1%) or 1 (50.0%). These subject characteristics were similar for all doses combined and for the 87 patients in the indication population.

Table 94: Baseline Demographic Characteristics (Safety Population)

	Erdafitinib Dose					
	< 6 mg QD (n = 20)	6 mg QD (n = 91)	8 or 9 mg QD (n = 164)	≥ 10 mg QD (n = 7)	Intermittent (n = 134)	Total (n = 416)
Age (years)						
Mean (SD)	58.7 (11.4)	63.8 (10.3)	62.4 (12.16)	51.7 (13.1)	61.6 (11.7)	61.6 (11.7)
Median	61.5	64.0	63.5	48.0	63.5	63.0
Range	32-79	41-88)	23-87	38-75	21-88	21-88
≥ 65	5 (25.0%)	44 (48.4%)	75 (45.7%)	1 (14.3%)	63 (47.0%)	188 (45.2%)
≥ 75	1 (5.0%)	14 (15.4%)	20 (12.2%)	1 (14.3%)	14 (10.4%)	50 (12.0%)
Sex						
Female	12 (60.0%)	32 (35.2%)	61 (37.2%)	5 (71.4%)	63 (47.0%)	173 (41.6%)
Male	8 (40.0%)	59 (64.8%)	103 (62.8%)	2 (28.6%)	71 (53.0%)	173 (41.6%)
Race						
Asian	6 (30.0%)	14 (15.4%)	8 (4.9%)	0	14 (10.4%)	42 (10.1%)
Black/African American	0	2 (2.2%)	3 (1.8%)	0	3 (2.2%)	8 (1.9%)
White	14 (70.0%)	66 (72.5%)	129 (78.7%)	7 (100.0%)	108 (80.6%)	324 (77.9%)
Other	0	2 (2.2%)	1 (0.6%)	0	0	3 (0.7%)
Not reported	0	7 (7.7%)	17 (10.4%)	0	8 (6.0%)	32 (7.7%)
Unknown	0	0	6 (3.7%)	0	1 (0.7%)	7 (1.7%)
Region						
US	0	14 (15.4%)	51 (31.1%)	0	36 (26.9%)	101 (24.3%)
EU	14 (70.0%)	63 (69.2%)	108 (65.9%)	7 (100.0%)	86 (64.2%)	278 (66.8%)
Asia	6 (30.0%)	14 (15.4%)	5 (3.0%)	0	12 (9.0%)	37 (8.9%)

Dataset ADL; variables TR01AG1, AGE, SEX, RACE, GEOGR1

Table 95: Baseline Disease Characteristics (Safety Population)

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Primary tumor location			
Urothelial	87 (100%)	110 (67.1%)	243 (58.4%)
Breast	0	18 (11.0%)	37 (8.9%)
Gastrointestinal	0	6 (3.7%)	34 (8.2%)
Lung	0	6 (3.7%)	27 (6.5%)
Reproductive system	0	11 (6.7%)	24 (5.8%)
Other	0	14 (8.5%)	51 (12.2%)
Creatinine clearance (mL/min)			
≥ 60	46 (52.9%)	104 (63.4%)	285 (68.5%)
< 60 to ≥ 30	41 (47.1%)	59 (36.0%)	128 (30.8%)
< 30	0	1 (0.6%)	3 (0.7%)
ECOG performance status			
0	44 (50.6%)	74 (45.1%)	159 (38.2%)
1	36 (41.4%)	82 (50.0%)	227 (54.6%)
2	7 (8.0%)	8 (4.9%)	30 (7.2%)
Pretreatment status			
Chemo-naïve	0	13 (7.9%)	27 (6.5%)
Chemo-refractory	87 (100%)	151 (92.1%)	389 (93.5%)

Dataset ADSL; variables: TR01AG1, PCANLOC, CREAGR1, ECOGBL, PRCHEMFL

One hundred and twenty-eight subjects (30.8%) in the total safety database had mild renal insufficiency (creatinine clearance < 60 to ≥ 30 mL/min), including 15 patients (11.7%) with urothelial carcinoma who were cisplatin-ineligible.

Reviewer's comment: *This relatively high percentage of patients with decreased baseline renal function likely reflects the advanced cancer population enrolled.*

One hundred fifty-three (93.3%) subjects on the 8/9 mg daily regimen received prior systemic chemotherapy, mostly cisplatin (50.0%), gemcitabine (50.0%), and carboplatin (40.9%; subjects may have received multiple prior therapies), consistent with the high number of primary urothelial cancers. Prior anti PD-L1/PD-1 therapy was reported for 13.4% of subjects, endocrine therapy for 10.4% of subjects, and investigational drugs for 7.3%. Similar prior use of antineoplastic agents was reported across all dose regimens (data not shown).

Adequacy of the safety database:

The size of the safety database and duration of erdafitinib exposure were sufficient to characterize the safety of erdafitinib for this NDA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear acceptable.

Categorization of Adverse Events

Class effects of FGFR inhibitors include eye disorders, nail and skin disorders, and hyperphosphatemia. In addition, arrhythmia-related TEAEs were considered adverse events of interest based on preclinical findings. Specific groupings of PTs included for each of these categories were outlined in the Statistical Analysis Plan for the SCS.

Routine Clinical Tests

Safety testing of patients enrolled in the clinical trials included adverse events, clinical hematology and chemistry tests, urinalysis, vital sign measurements, physical examinations, ECGs, and ophthalmologic examinations. The latter were to include assessment of visual acuity, tonometry, central and peripheral funduscopy, and optical coherence tomography (OCT). Treatment-emergent safety reporting periods were defined as the time from the first dose of study drug through the safety follow-up visit, initiation of cytotoxic chemotherapy or an investigational agent, or 30 days after the last dose of study drug.

Reviewer's comment: *The routine clinical testing of patients enrolled in the clinical trials appears to have been adequate.*

8.2.4. Safety Results

Deaths

Overall, 58 subjects of the 416 erdafitinib-treated patients (13.9%) died within 30 days of their last dose of study drug, 47 (11.3%) due to progressive disease. In the 8/9 mg daily population, 18 subjects (11.0%) died within 30 days of the last dose, 15 (9.1%) due to progressive disease.

Table 96: Deaths within 30 Days of Last Dose (Safety Population)

Attribution	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Adverse event	1 (1.1%)	3 (1.8%)	11 (2.6)
Progressive disease	7 (8.0%)	15 (9.1%)	47 (11.3%)
Total	8 (9.2%)	18 (11.0%)	58 (13.9%)

Source: dataset ADSL; variables: DTHTRFL, DTHCAUS, TR01AG1

Reviewer's comment: *The fatal adverse event in the indication population was a myocardial infarction (see below). The narratives for all patients with deaths within 30 days of last dose were reviewed and the reviewer agreed with the investigator's attribution of death in these cases. One patient (Subject (b) (6)) in the indication population experienced a fatal adverse event (myocardial infarction) one day after the last dose of study drug. Several narratives for these patients are presented in greater detail below:*

The following narratives provide further detail on three patients in the 8/9 mg daily group who had fatal adverse events within 30 days of the last dose of study drug.

- Subject (b) (6) (Study EDI1001) was a 52-year-old female who entered the study with urothelial cancer and a history of anemia. On Study Day 270, one day after the last dose of study drug, she had a headache, which quickly progressed to a coma. A CT scan showed brain metastasis with hemorrhage. The following day, she died due to cerebral hemorrhage.
- Subject (b) (6) (Study EDI1001) was a 52-year-old male who entered the study with head and neck neuroendocrine carcinoma metastatic to cervical and retropharyngeal nodes, parotid gland, anterior nasal passage, and ethmoid sinus. On Study Day 17, the subject presented to the emergency room with Grade 3 tumor hemorrhage and Grade 4 sepsis. On Study Day 21, he was unstable with hypotension, hypoxia, and fever. The surgical oncologist stated that there was no surgical option. On Study Day 25, the subject died due to sepsis.
- Subject (b) (6) (Study BLC2001) was a 77-year-old male with a history of hyperlipidemia, diabetes mellitus, pulmonary embolism and myocardial infarction. On Day 100 he was hospitalized with Grade 3 urinary tract infection. While hospitalized, on Day 102, a Grade 3 acute myocardial infarction was reported. Treatment included acetylsalicylic acid and furosemide. Study drug was interrupted that day and was restarted at the same dose (9 mg/day) on Day 108. The subject received the last dose of the study drug on Day 120. On Day 121, the events of urinary tract infection and acute myocardial infarction resolved, and the subject was discharged. On the day of discharge, after arriving at home, he felt dizzy and was shortly pulseless and apneic. Resuscitation attempts were unsuccessful. It was suspected that he had a Grade 5 acute myocardial infarction.

The following narratives provide additional detail regarding two patients treated with other dosing regimens who had fatal adverse events which investigators considered to be at least possibly related to erdafitinib:

- Subject (b) (6) (10 mg intermittent regimen; Study EDI1001) was a 66-year-old female who entered the study with glioblastoma multiforme. On Study Day 15, the subject, who was on enoxaparin, was diagnosed with an SAE of Grade 2 intracranial hemorrhage, as well as Grade 3 hemiparesis, Grade 3 dehydration, Grade 3 muscle twitching, Grade 2 increased intracranial pressure, and Grade 2 seizures. The subject was transferred to the hospital for neurological intervention, and the following day, was placed in hospice care. On Study Day 20, the subject died from intracranial hemorrhage, which the investigator considered possibly related to study drug.

- Subject (b) (6) (10 mg intermittent regimen; Study EDI1001) was a 52-year old male who entered the study with head and neck cancer. Medical history included hypomagnesemia, hypothyroidism controlled, anemia, and tumor pain. On Study Day 40, 19 days after the last dose of study drug, he experienced Grade 4 tumor hemorrhage, was admitted to the hospital, and died from tumor bleeding that same day. Although the hemorrhage was listed as the probable cause of death, the investigator suspected the underlying tumor rather than erdafitinib to be the cause of the hemorrhage.

Reviewer's comment: Four of these deaths were attributed to tumor bleeding. Tumor bleeding is discussed further in Section 8.5.6 of this review.

Serious Adverse Events

Serious TEAEs occurred in 67 subjects (40.9%) on the 8/9 mg daily regimen, with dyspnea and general physical health deterioration being most common. For all doses combined, serious TEAEs occurred in 180 subjects (43.3%) with general physical health deterioration the most common (4.6%).

Table 97: Treatment-Emergent Serious Adverse Events Occurring in ≥ 2% of Safety Population

	Indication Population (n = 87)	8/9 mg AD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any	36 (41.4%)	67 (40.9%)	180 (43.3%)
General physical health det.	3 (3.4%)	4 (2.4%)	19 (4.6%)
Dyspnea	2 (2.3%)	6 (3.7%)	12 (2.9%)
Asthenia ^a	2 (2.3%)	4 (2.4%)	10 (2.4%)
Urinary tract infection	3 (3.4%)	3 (1.8%)	10 (2.4%)
Abdominal pain ^b	2 (2.3%)	3 (1.8%)	9 (2.2%)
Urosepsis	2 (2.3%)	3 (1.8%)	9 (2.2%)
Acute kidney injury	2 (2.3%)	2 (1.2%)	8 (1.9%)
Keratitis ^c	2 (2.3%)	3 (1.8%)	6 (1.4%)
Hematuria	2 (2.3%)	2 (1.2%)	5 (1.2%)
Cataract	2 (2.3%)	2 (1.2%)	4 (0.9%)
Colitis	2 (2.3%)	4 (2.4%)	4 (0.9%)

^a Includes asthenia and fatigue

^b Includes abdominal pain, abdominal pain lower, and abdominal pain upper

^c includes dry eye, keratitis, foreign body sensation, and corneal erosion

Source: Dataset ADAE; variables USUBJID, AEDECOD, TR01AG1, AETOXGR

Dropouts and/or Discontinuations Due to Adverse Effects

Thirty subjects (18%) on the 8/9 mg daily regimen experienced at least one TEAE leading to treatment discontinuation, most commonly general physical health deterioration (4 subjects; 2.4%). For all doses combined, 69 subjects (16.6%) experienced at least one TEAE leading to treatment discontinuation.

Table 98: Treatment-Emergent Adverse Events Leading to Discontinuation in ≥ 2 Subjects

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any	18 (20.7%)	30 (18.3%)	69 (16.6%)
General disorders and administration site condit.	5 (5.7%)	6 (3.7%)	17 (4.1%)
General physical health deterioration	3 (3.4%)	4 (2.4%)	9 (2.2%)
Fatigue ^a	0	3 (1.8%)	7 (1.7%)
Eye disorders	8 (9.2%)	6 (3.7%)	12 (2.9%)
Detachment of retinal pigment epithelium	2 (2.3%)	2 (1.2%)	3 (0.7%)
Keratitis	2 (2.3%)	2 (1.2%)	3 (0.7%)
Visual acuity reduced	1 (1.1%)	1 (0.6%)	2 (0.5%)
Gastrointestinal disorders	3 (3.4%)	6 (3.7%)	11 (2.6%)
Dry mouth	1 (1.1%)	2 (1.2%)	4 (1.0%)
Abdominal pain	0	1 (0.6%)	2 (0.5%)
Dysphagia	1 (1.1%)	1 (0.6%)	2 (0.5%)
Small intestinal obstruction	1 (1.1%)	2 (1.2%)	2 (0.5%)
Skin and subcutaneous disorders	4 (4.6%)	6 (3.7%)	8 (1.9%)
Palmar-plantar erythro-dysaesthesia syndrome	2 (2.3%)	3 (1.8%)	3 (0.7%)
Onycholysis ^b	1 (1.1%)	2 (1.2%)	4 (1.0%)
Metabolism and nutrition disorders	1 (1.1%)	3 (1.8%)	7 (1.7%)
Decreased appetite	0	2 (1.2%)	4 (1.0%)
Infections and infestations	1 (1.1%)	3 (1.8%)	6 (1.4%)
Sepsis	0	1 (0.6%)	2 (0.5%)
Urosepsis	1 (1.1%)	1 (0.6%)	2 (0.5%)
Renal and urinary disorders	2 (2.3%)	2 (1.2%)	5 (1.2%)
Acute kidney injury	2 (2.3%)	2 (1.2%)	3 (0.7%)
Hematuria	0	0	2 (0.5%)
Investigations	1 (1.1%)	3 (1.8%)	4 (1.0%)
AST increased	0	2 (1.2%)	2 (0.5%)
Respiratory, thoracic, and mediastinal dis.	0	0	4 (1.0%)
Dyspnea	0	0	3 (0.7%)
Musculoskeletal and connective tissue dis.	0	0	3 (0.7%)
Bone pain	0	0	2 (0.5%)

^a Includes fatigue and asthenia

^b Includes onycholysis and nail dystrophy

Source: dataset ADAE; variables USUBJID, TR01AG1, TRTEMFL, AEDECOD, AETOXGR, AEACN

Reviewer's comment: The value of 20.7% cited in Table 96 includes some patients who experienced AEs which investigators considered manifestations of disease progression rather than true adverse drug reactions. Overall, 11 patients (12.6%) discontinued therapy primarily due to adverse reactions independent of disease progression; see also Table 66: Patient Disposition (BLC2001) for overall reasons for patient's discontinuation of study drug.

TEAEs led to dose reduction in 53% of patients and TEAEs led to dose interruption in 68% of the indication population.

Table 99: TEAEs Leading to Dose Reduction and Interruption in ≥ 2 Subjects in Indication Population

	TEAEs Leading to Dose Reduction	TEAEs Leading to Dose Interruption
Any	46 (52.9%)	59 (67.8%)
General disorders and administration site conditions	7 (8.0%)	10 (11.5%)
Fatigue ^a	5 (5.7%)	7 (8.0%)
Pyrexia	0	4 (4.6%)
Eye disorders	20 (23.0%)	15 (17.2%)
Vision blurred ^b	6 (6.9%)	3 (3.4%)
Dry eye ^c	2 (2.3%)	2 (2.3%)
Keratitis ^d	2 (2.3%)	2 (2.3%)
Astigmatism	2 (2.3%)	0
Detachment of retinal pigment epithelium ^d	12 (13.8%)	8 (9.2%)
Gastrointestinal disorders	15 (17.2%)	27 (31.0%)
Stomatitis ^e	13 (14.9%)	15 (17.2%)
Dry mouth	2 (2.3%)	1 (1.1%)
Diarrhea	0	3 (3.4%)
Abdominal pain upper ^e	0	4 (4.6%)
Nausea	0	2 (2.3%)
Vomiting	1 (1.1%)	2 (2.3%)
Skin and subcutaneous disorders	19 (21.8%)	17 (19.5%)
Palmar-plantar erythro-dysaesthesia syndrome	6 (6.9%)	7 (8.0%)
Onycholysis ^f	13 (14.9%)	7 (8.0%)
Metabolism and nutrition disorders	7 (8.0%)	27 (31.0%)
Hyperphosphatemia	6 (6.9%)	21 (24.1%)
Decreased appetite	0	4 (4.5%)
Hyponatremia	0	4 (4.5%)
Infections and infestations	7 (8.0%)	10 (11.5%)
Paronychia	6 (6.9%)	5 (5.7%)
Renal and urinary disorders	2 (2.3%)	3 (3.4%)
Renal impairment	2 (2.3%)	0
Investigations	2 (2.3%)	3 (3.4%)
Weight decreased	1 (1.1%)	2 (2.3%)
Nervous system disorders	0	3 (3.4%)
Dysgeusia	3 (3.4%)	2 (2.3%)
Paresthesia	0	2 (2.3%)

^a Includes fatigue and asthenia

^b Includes vision blurred and visual impairment

^c Includes dry eye and xerophthalmia

^d Includes keratitis and keratopathy

^e Includes stomatitis and cheilitis

^f Includes chorioretinopathy, retinopathy, retinal edema, and detachment of retinal pigment epithelium

^g Includes abdominal pain, abdominal pain upper, and abdominal discomfort

^h Includes onycholysis, nail dystrophy, onychomadesis, nail ridging, nail discoloration, and nail disorder

Source: dataset ADAE; variables USUBJID, TR01AG1, TRTEMFL, AEDECOD, AETOXGR, AEACN

Significant Adverse Events

One hundred nine (66.5%) subjects on the 8/9-mg daily regimen reported Grade 3 or 4 TEAEs, with 10 (6.1%) reporting Grade 4 events. The most common Grade 3 or 4 TEAEs were stomatitis, hyponatremia, asthenia, PPES and anemia.

Table 100: Grade 3-4 Treatment-Emergent Adverse Events Occurring in ≥ 2% of Safety Population

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any Grade 3-4 TEAE	51 (58.6%)	109 (66.5%)	253 (60.8%)
Anemia	4 (4.6%)	9 (5.5%)	32 (7.7%)
Stomatitis	8 (9.2%)	17 (10.4%)	30 (7.2%)
Hyponatremia	9 (10.3%)	16 (9.8%)	29 (7.0%)
Urinary tract infection	5 (5.7%)	5 (3.0%)	15 (3.6%)
Dyspnea	2 (2.3%)	6 (3.7%)	14 (3.4%)
Decreased appetite	0	4 (2.4%)	13 (3.1%)
Fatigue ^a	7 (8.0%)	17 (10.4%)	39 (9.4%)
General physical health deterioration	1 (1.1%)	3 (1.8%)	12 (2.9%)
Onycholysis ^b	9 (10.3%)	13 (7.9%)	24 (5.8%)
Abdominal pain ^c	2 (2.3%)	3 (1.8%)	11 (2.6%)
Palmar-plantar erythrodysesthesia syndrome	5 (5.7%)	9 (5.5%)	11 (2.0%)
AST increased	0	5 (3.0%)	10 (2.4%)
Musculoskeletal pain ^d	0	5 (3.0%)	16 (3.8%)
Sepsis	1 (1.1%)	3 (1.8%)	10 (2.4%)
ALT increased	1 (1.1%)	3 (1.8%)	9 (2.2%)

^a Includes asthenia, fatigue, lethargy, and malaise

^b Includes onycholysis, onychoclasia, nail disorder, nail dystrophy, and nail ridging

^c Includes abdominal pain, abdominal discomfort, abdominal pain upper, and abdominal pain lower

^d Includes back pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal chest pain, neck pain, pain in extremity Source: dataset ADAE; variables USUBJID, TRTEMFL, TR01AG1, AEDECOD,

Treatment Emergent Adverse Events and Adverse Reactions

All 164 subjects treated on the 8/9-mg daily regimen experienced at least one treatment emergent adverse event (TEAE). Grade 3 or 4 TEAEs were experienced by 109 subjects (66.5%), with 10 (6.1%) reporting Grade 4 events. Across all doses, 415 subjects (99.8%) experienced at least one TEAE, and 253 (60.8%) experienced Grade 3 or 4 TEAEs.

For the 8/9-mg daily regimen, hyperphosphatemia was the most frequent TEAE (81.7%), followed by stomatitis (56.1%), dry mouth (45.7%), diarrhea (41.5%), decreased appetite (37.8%), constipation (35.4%), dysgeusia (35.4%), and dry skin (31.7%). The results were similar for all doses combined.

Table 101. All-Grade Treatment-Emergent Adverse Events Occurring in ≥ 10% of Safety Population

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any TEAE	87 (100%)	164 (100%)	415 (99.8%)
Gastrointestinal disorders	80 (92.0%)	150 (91.5%)	366 (88.0%)
Stomatitis	49 (56.3%)	92 (56.1%)	183 (44.0%)
Dry mouth	39 (44.8%)	75 (45.7%)	182 (43.8%)
Diarrhea	41 (47.1%)	68 (41.5%)	162 (38.9%)
Constipation	24 (27.6%)	58 (35.4%)	132 (31.7%)
Nausea	18 (20.7%)	45 (27.4%)	99 23.8 (%)
Vomiting	11 (12.6%)	35 (21.3%)	86 (20.7%)
Abdominal pain ^a	20 (23.0%)	46 (28.0%)	110 (26.4%)
Metabolism and nutrition disorders	78 (89.7%)	151 (92.1%)	350 (84.1%)
Hyperphosphatemia	66 (75.9%)	134 (81.7%)	280 (67.3%)
Decreased appetite	33 (37.9%)	62 (37.8%)	143 (34.4%)
General disorders and administration site condit.	60 (69.0%)	113 (68.9%)	272 (65.4%)
Fatigue ^b	47 (54.0%)	91 (55.5%)	221 (53.1%)
Pyrexia	12 (13.8%)	23 (14.0%)	56 (13.5%)
Skin and subcutaneous disorders	65 (74.7%)	114 (69.5%)	257 (61.8%)
Dry skin ^c	30 (34.5%)	52 (31.7%)	119 28.6%)
Alopecia	23 (26.4%)	45 (27.4%)	80 (19.2%)
Onycholysis ^d	36 (41.4%)	59 (36.0%)	122 (29.3%)
Palmar-plantar erythrodysesthesia	23 (26.4%)	32 (19.5%)	58 (13.9%)
Infections and infestations	49 (56.3%)	82 (50.0%)	200 (48.1%)
Urinary tract infection	15 (17.2%)	22 (13.4%)	58 (13.9%)
Paronychia	15 (17.2%)	58 (35.4%)	42 (10.0%)
Nervous system disorders	50 (57.5%)	67 (40.9%)	196 (47.1%)
Dysgeusia	32 (36.8%)	58 (35.4%)	114 (27.4%)
Musculoskeletal and connective tissue disorders	27 (31.0%)	14 (8.5%)	177 (42.5%)
Musculoskeletal pain ^e	17 (19.5%)	41 (25.0%)	116 (27.9%)
Arthralgia	6 (6.9%)	17 (10.4%)	50 (12.0%)
Eye disorders	54 (62.1%)	81 (49.9%)	170 (40.9%)
Dry eye ^f	21 (24.1%)	37 (22.6%)	66 (15.9%)
Respiratory, thoracic and mediastinal disorders	35 (40.2%)	64 (39.0%)	167 (40.1%)
Dyspnea ^g	9 (10.3%)	19 (11.6%)	55 (13.2%)
Investigations	38 (43.7%)	64 (39.0%)	148 (35.6%)
ALT increased	15 (17.2%)	24 (14.6%)	56 (13.5%)
Weight decreased ^h	14 (16.1%)	26 (15.9%)	53 (12.7%)
AST increased	8 (9.2%)	19 (11.6%)	49 (11.8%)
Blood and lymphatic system disorders	21 (24.1%)	40 (24.4%)	110 (26.4%)
Anemia	17 (19.5%)	34 (20.7%)	95 (22.8%)

^a Includes abdominal pain, abdominal discomfort, abdominal pain upper, and abdominal pain lower

^b Includes asthenia, fatigue, lethargy, and malaise

^c Includes dry skin and xerostomia

^d Includes onycholysis, onychoclasia, nail disorder, nail dystrophy, and nail ridging

^e Includes back pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal pain, neck pain, pain in extremity

^f Includes dry eye, xerophthalmia, keratitis, foreign body sensation, and corneal erosion

^g Includes dyspnea and dyspnea exertional

^h Includes weight loss and cachexia

Source: dataset ADAE; variables USUBJID, TRTEMFL, TR01AG1, AEDECOD, AETOXGR

Laboratory Findings

On the 8/9-mg daily regimen, the only Grade 3 abnormality reported for more than 2% of subjects was decreased hemoglobin (8 subjects; 4.9%). Two subjects (1.2%) reported Grade 4 neutrophil decrease, and 1 subject (0.6%) reported Grade 4 platelets decrease.

Table 102: Select Hematological Abnormalities

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Neutropenia	86	163	406
All grades	9 (10.5%)	23 (14.1%)	54 (13.3%)
Grades 3-4	2 (2.3%)	2 (1.2%)	5 (1.2%)
Anemia	86	163	407
All Grades	30 (34.9%)	68 (41.7%)	189 (46.4%)
Grade 3-4	3 (3.5%)	8 (4.9%)	33 (8.1%)
Thrombocytopenia	86	163	407
All grades	16 (18.6%)	23 (14.1%)	70 (17.2%)
Grade 3-4	1 (1.2%)	1 (0.6%)	2 (0.5%)

Source: dataset ADLB; variables: SUBJID, PARAM, TR01AG1, LBBFL, AVISIT, ATOXGR

The Applicant provided a narrative summary of Subject (b) (6), who experienced Grade 4 neutropenia on study. Subject (b) (6) was a 63-year-old male assigned to erdafitinib 6 mg once daily. On Study Day 7, Grade 2 abdominal pain was reported, and on Day 8, Grade 1 pyrexia was reported. No action was taken with erdafitinib due to these events. Treatment included activated charcoal. On Day 10, the subject was hospitalized for Grade 3 enterocutaneous fistula, and erdafitinib was interrupted. No treatment was reported for this event. Erdafitinib was restarted at the same dose on Day 16. On Day 21, Grade 2 PICC infection was reported. No action was taken with erdafitinib, and treatment included amikacin, piperacillin/tazobactam, cefotaxime, and vancomycin. On Day 22, the abdominal pain and pyrexia resolved. On Day 67, the PICC infection resolved, and the enterocutaneous fistula improved to Grade 1. No action was taken with erdafitinib, and no treatment was reported for this event. On Day 53, Grade 4 neutropenia was reported, but this resolved to Grade 0 on Day 54 and did not recur. On an unspecified date between Days 93 and 124, a non-serious TEAE of proctalgia was reported. No action was taken with erdafitinib due to this event, and treatment included aloplastine, amphotericin B, ceftrimide, amikacin, and piperacillin/tazobactam. Erdafitinib was discontinued on Day 168 due to disease progression. On Day 181, the subject was hospitalized due to Grade 4 septic shock, and on Day 187, he died of septic shock.

Reviewer's comment: Grade 4 neutropenia in Subject (b) (6) resolved to Grade 0 the following day, suggesting a spurious laboratory value. This neutropenia resolved 124 days before the patient developed Grade 4 sepsis, and therefore did not appear to be causally related.

Grade 3-4 clinical chemistry abnormalities reported for > 2% of subjects on the 8-9 mg daily regimen were Grade 3 AST increase (5 subjects; 3.1%) and Grade 3 decreased sodium (27 subjects; 16.6%). Grade 4 events were decreased sodium was reported (3 subjects; 1.8%),

decreased corrected calcium, increased corrected calcium, increased creatinine, and decreased magnesium (1 subject each; 0.6%).

Table 103: Select Clinical Chemistry Abnormalities

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
ALT	N = 86	N = 162	N = 407
All grades	35 (%)	67 (41.4%)	165 (40.5%)
Grade 3-4	1 (1.2%)	3 (1.9%)	10 (2.5)
Alkaline phosphatase	N = 86	N = 163	N = 408
All grades	35 (40.7%)	71 (43.6%)	193 (47.3%)
Grade 3-4	1 (1.2%)	3 (1.8%)	23 (5.6%)
AST	N = 86	N = 163	N = 409
All Grades	26 (30.2%)	65 (39.8%)	163 (39.9)
Grade 3-4	0	5 (3.1%)	11 (2.7%)
Bilirubin	N = 86	N = 162	N = 407
All grades	7 (8.1%)	15 (9.3%)	39 (9.6%)
Grade 3-4	0	0	2 (0.5%)
Creatinine	N = 86	N = 163	N = 406
All Grades	44 (51.2%)	80 (49.1%)	185 (45.6%)
Grade 3-4	4 (4.7%)	4 (2.5%)	12 (29.6%)

Source: dataset ADLB; variables: SUBJID, PARAM, TR01AG1, LBLFL, AVISIT, ATOXGR

No Hy's law cases were reported in any dosing cohort. Most of the Grade 3-4 clinical chemistry abnormalities listed in Table 104 above began more than 30 days after erdafitinib was discontinued. The Applicant submitted the following narratives which provide further detail on subjects who experienced Grade 3-4 clinical chemistry abnormalities on Study BLC2001 within 30 days of last dose of erdafitinib:

- Subject (b) (6) was a 79-year-old male assigned to erdafitinib 6 mg once daily. Medications at study entry included pantoprazole, aspirin, calcium, rivaroxaban, amlodipine/losartan, magnesium hydroxide, sucralfate, megestrol, and hydromorphone. Erdafitinib was discontinued on Day 28, as the subject refused further treatment. On Day 45, Grade 3 sialadenitis, Grade 2 gingival bleeding, and Grade 2 pain in jaw were reported. The subject was hospitalized on Day 47 and treated with cefazolin for sialadenitis, which resolved on Day 51. Concurrent events included Grade 1 oral candidiasis, Grade 2 constipation, Grade 3 anemia, and Grade 3 hyponatremia. The subject died on Study Day 60.

Reviewer's comment: Advanced cancer, infectious sialadenitis, and/or concomitant medication seem more likely than erdafitinib to have caused Grade 3 hyponatremia in Subject (b) (6)

- Subject (b) (6) was a 56-year-old male assigned to erdafitinib 6 mg once daily. Medical history included stage 3 chronic kidney disease, acute pyelonephritis, gout, and hydronephrosis. Medications at study entry included colchicine and febuxostat. On Study Day 28, erdafitinib was increased to 8 mg once daily. On Day 34 Grade 1

hyperphosphatemia was reported. No action was taken with the study drug due to this event and no treatment was reported. On Day 56, the hyperphosphatemia resolved. On Day 76, recurrent Grade 1 hyperphosphatemia was reported. No action was taken with erdafitinib due to this event and no treatment was reported. On Day 82, the hyperphosphatemia resolved. On Day 112, erdafitinib was reduced to 6 mg once daily due to Grade 2 nail disorder. On Day 165, Grade 2 flank pain was reported. On Day 167 Grade 1 nausea and abdominal pain upper were reported. On Day 168, erdafitinib was discontinued due to progressive disease. On Day 175, Grade 1 hypomagnesemia, Grade 1 hyponatremia, and Grade 3 acute kidney injury were reported. Treatment included ceftriaxone, ertapenem, magnesium, metoclopramide, propacetamol, sodium bicarbonate, tetracosactide, and morphine. The hyponatremia worsened to Grade 4 on Day 176 and resolved on Day 178 with sodium bicarbonate. On Day 181, the hypomagnesemia was reported. On Day 181, Grade 2 hyperkalemia was reported, and resolved on Day 187 with calcium polystyrene sulfonate. On Day 195, the events of acute kidney injury and flank pain resolved. Concurrent events included Grade 1 vision blurred, onychomadesis, nail bed bleeding, abdominal pain, and nausea; Grade 2 stomatitis, constipation, nail disorder, and decreased appetite; and Grade 3 anemia. The subject died on Day 362.

Reviewer's comment: *Acute on chronic kidney disease, abdominal infection, and/or concomitant medication seem more likely than erdafitinib to have caused Grade 4 hyponatremia in Subject (b) (6).*

- Subject (b) (6) was an 83-year-old female assigned to erdafitinib 10 mg once daily (7 days on/7 days off). Medical history included hypertension, diabetes, and bilateral lower extremity edema. Medications at study entry included insulin, ramipril, aspirin, and iron. On Study Day 1, Grade 1 abdominal edema was reported, for which no action was taken with erdafitinib, and no treatment was reported. Concurrent events included Grade 2 muscular weakness and Grade 1 epistaxis. On Day 11, Grade 2 peripheral edema and Grade 3 cellulitis were reported. No action was taken with erdafitinib due to these events. On Day 16, the cellulitis resolved with ceftriaxone, cefuroxime, cefalexin, furosemide, and spironolactone. On Day 26, Grade 3 cellulitis was treated with furosemide, ceftriaxone, famotidine, heparin, insulin, and spironolactone. Erdafitinib was increased to 12 mg daily on Day 29. On Day 32, the cellulitis improved to Grade 2. On Day 62, the subject was hospitalized with Grade 3 pneumonia, Grade 4 sepsis, Grade 2 acute kidney injury, Grade 2 constipation, Grade 3 hyperkalemia, and Grade 2 pleural effusion. Erdafitinib was discontinued due to sepsis, and the subject died of sepsis on Day 71.

Reviewer's comment: *Sepsis seems more likely than erdafitinib to have led to Grade 3 hyperkalemia in Subject (b) (6).*

- Subject (b) (6) was an 82-year-old male with significant underlying cardiac and pulmonary disease. He had Grade 3 hyponatremia at baseline, and this worsened to Grade 4 two days after the onset of Grade 1 diarrhea.

Reviewer's comment: Subject (b) (6) is discussed in detail in Section 8.5.3 of this review. His Grade 4 hyponatremia seems more likely due to underlying cardiopulmonary disease and fluid shifts than to erdafitinib.

- Subject (b) (6) was a 68-year-old male assigned to erdafitinib 8 mg once daily. His medical history included anorexia and general pain. Medications at study entry included glimepiride, linagliptin, tramadol, and acetaminophen. At screening, the subject was hospitalized with Grade 3 arthralgia from bone metastasis. On Day 18, the subject was hospitalized with Grade 3 mental impairment due to hypoglycemia. The subject had nausea and could not eat, yet continued glimepiride and linagliptin. Glimepiride was discontinued, and on Day 19, the hypoglycemia and mental impairment resolved. Erdafitinib was discontinued due to stomatitis and progressive disease and stomatitis on Day 44. On Day 50, the subject was hospitalized due to Grade 3 asthenia. Concurrent events included Grade 2 hypoalbuminemia and Grade 4 hyponatremia. Treatment included amino acids, sodium chloride, and albumin. The hyponatremia improved to Grade 3 on Day 51 and to Grade 1 severity on Day 64. The subject developed Grade 3 acute respiratory distress syndrome on Day 53 and died of asthenia and disease progression on Day 66.

Reviewer's comment: Acute respiratory distress syndrome and nutritional problems seem more likely than erdafitinib to have led to Grade 4 hyponatremia in Subject (b) (6)

- Subject (b) (6) was a 74-year-old male assigned to erdafitinib 8 mg once daily. Medications at study entry included, aspirin, apixaban, and atorvastatin. On Day 15, Grade 1 blurred vision was reported, and on Day 22, erdafitinib was interrupted due to this event. On Day 43, the blurred vision resolved without treatment, and erdafitinib was resumed at 6 mg daily. Erdafitinib was interrupted on Day 66 for non-serious Grade 3 hyponatremia and was resumed on Day 67. On Day 99, erdafitinib was interrupted for non-serious Grade 2 blurred vision which resolved without treatment. Erdafitinib was resumed on Day 120. On Day 148, erdafitinib was reduced to 5 mg daily due to non-serious Grade 2 blurred vision, which resolved on Day 161. On Day 216, erdafitinib was interrupted for Grade 2 stomatitis. Treatment was ongoing as of Day 223.

Reviewer's comment: Grade 3 hyponatremia in Subject (b) (6) seems to have been an isolated event which resolved rapidly without sequelae.

Vital Signs

No clinically meaningful changes in vital signs were reported during the two phase 1 trials. In BLC2001, for the 8-mg daily regimen, median increases from baseline to the highest point on

treatment were 3.1% for diastolic blood pressure and 2.1% for systolic blood pressure. Median decreases from baseline to the lowest point on treatment were 16% and 14%, respectively. For subject weight, the median maximum decrease during the study was 5.3%, and the median maximum increase was 0.8%.

Electrocardiograms (ECGs)

ECGs, echocardiographic and MUGA findings, and arrhythmia-related adverse events are discussed in Section 8.2.5 of this review.

QT

The Applicant performed an exposure-response analysis of time-matched QTc and Holter data from patients on part 1 of Study EDI1001. The highest dose evaluated was 12 mg once daily, which covered steady state exposure at the maximum therapeutic dose of 9 mg daily. No placebo or positive control was used. The CDER Interdisciplinary Review Team for QT Studies reviewed these data and concluded that erdafitinib had no large effect (i.e., >20 ms) on QTc. See Section 8.5.3 of this review for details.

Immunogenicity

The review of clinical safety raised no concerns of immunogenicity with this small molecule. No formal immunogenicity studies were required or were done.

8.2.5. Analysis of Submission-Specific Safety Issues

Eye disorders, nail and skin disorders, and hyperphosphatemia are class effects of FGFR inhibitors and were therefore considered adverse events of special interest (AESI). In addition, arrhythmia-related TEAEs were considered AESIs based on preclinical findings.

Retinal pigment epithelium detachment/central serous retinopathy

Background

Retinal pigment epithelial detachment (RPED) is defined as separation between the RPE and the inner aspect of Bruch's membrane. The space created by this separation is occupied by blood, serous exudate, drusenoid material, and/or fibrovascular tissue.

RPED in the general population may be inflammatory, ischemic, degenerative, or idiopathic, and most commonly occurs a part of age-related macular degeneration. The prototype idiopathic RPED is central serous retinopathy (CSR). RPED typically presents clinically as painless blurred vision and/or visual field defect, and its fundoscopic and fluorescein angiographic features vary according to the etiology.

The mitogen activated protein kinase (MEK) inhibitors (e.g., trametinib, cobimetinib, binimetinib) are a class of small molecule drugs associated with retinopathy. In the trials supporting approval of the MEK inhibitors, subjects underwent ophthalmological examination, including funduscopy and OCT, pretreatment and at regular intervals during treatment. Symptomatic or asymptomatic CSR was identified in up to 26% of subjects. Most patients were asymptomatic. Symptoms when present included reduced visual acuity, dyschromatopsia, photophobia, shadows, and glare. This reviewer is not aware of any reports of permanent ocular sequelae in patients who experienced RPED due to MEK inhibitors. The prescribing information for MEK inhibitors recommends that patients undergo ophthalmological evaluation at regular intervals and for new or worsening visual disturbances, and that treatment be withheld, dose reduced, or discontinued based on severity of retinopathy.

The CTCAE criteria, widely used for AE reporting in oncology trials, include a 4-category grading schema for retinopathy according to symptom severity (Table 105).

Table 104: Common Terminology Criteria for Adverse Events. CTCAE, v5.0 – Retinopathy Classification

Grade	Findings
1	Asymptomatic
2	Moderate decrease in visual acuity (20/40 or better or ≤ 3 lines from baseline)
3	Marked decrease in visual acuity (worse than 20/40 or > 3 lines from baseline)
4	Blindness (20/200 or worse in the affected eye)

Incidence of CSR Events in the Safety Database

The GAC1001, EDI1001, and BLC2001 clinical protocols required Amsler grid testing (a grid of horizontal and vertical lines used to evaluate central visual fields) for all subjects at screening, at the beginning of each treatment cycle, and at the end of treatment. A full ophthalmic examination was to be performed at screening and in the event of newly positive Amsler grid test results or new clinical symptoms.

Reviewer's Comment: *The FDA ophthalmology consultant noted that the case report form for BLC2001 was not optimal and did not capture all information needed to adequately evaluate RPED events. For example:*

- 1. The case report form should record visual acuity as numeric values for each eye.*
- 2. Routine tonometry is not necessary.*
- 3. The case report form should ideally have included fundoscopic findings, findings from the slit lamp examination, and results of OCT. RPED events should ideally be monitored at approximately 2-3 week intervals (the BLC2001 protocol specified no monitoring frequency).*
- 4. Amsler grid testing provides an evaluation of central macular distortion. It is a poor screening test for RPED.*

The Applicant considered the following MedDRA Preferred terms under the category of RPED/CSR: retinal detachment, vitreous detachment, retinal edema, retinopathy,

chorioretinopathy, detachment of RPE, and detachment of macular RPE. For the 8/9-mg daily regimen, 26 (15.9%) of subjects experienced one or more treatment-emergent RPED/CSR events, most commonly chorioretinopathy, retinal detachment, and detachment of RPE.

Table 105: Central Serous Retinopathy Events by Preferred Term

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any	22 (25.3%)	26 (15.9%)	45 (10.8%)
Retinal detachment*	18 (20.7%)	20 (12.2%)	39 (9.4%)
Retinal edema	4 (4.6%)	4 (2.4%)	5 (1.2%)
Vitreous detachment	2 (2.3%)	2 (1.2%)	2 (0.5%)

* Includes retinal detachment, chorioretinopathy, detachment of RPE, retinopathy, and detachment of macular RPE

Source: Dataset ADAE; variables: CQ06NAM USUBJID, TRTEMFL, TR01AG1, AEDECOD, AETOXGR

Reviewer's comment: *Retinal detachment, chorioretinopathy, detachment of RPE, retinopathy, and detachment of macular RPE likely represent the same or similar events. Vitreous detachment and retinal edema are likely separate events from each other and separate from the RPED events described by the other terms.*

Relationship between Prior Retinal Disease and Treatment-Emergent CSR Events

In BLC2001, 14 (6.7%) subjects had a history of macular or retinal problems. During the study, 2 (13.3%) of these subjects experienced retinal AEs (1 RPED and 1 retinal tear; Table 107). The grade of the retinal problem at baseline was not reported in these two subjects, so it is unclear whether their CSR events were treatment-emergent. In contrast 196 (93.3%) subjects had no prior history of retinal disease, and of them, 37 (18.9%) experienced treatment-emergent CSR events (data not shown).

Table 106: BLC2001 Ocular TEAEs in Subjects with History of Retinal Problems

Patient No.	History	Retinal TEAE(s)
(b) (6)	Grade 1 macular edema Grade 1 macular fibrosis	None
	Grade 1 vitreous opacity	None
	Grade 1 left CSR	None
	Grade 1 vitreous detachment	None
	Retinal dystrophy, grade missing	Grade 2 RPED Grade 2 visual acuity decreased
	Grade 1 maculopathy	None
	Grade 1 macular fibrosis	None
	Grade 1 retinal angiopathy bilateral	None
	Retinal detachment, grade missing	Grade 2 retinal detachment Grade 2 retinal tear
	Grade 1 hypertensive retinopathy	None
	Grade 1 macular edema	None
	Grade 2 age-related macular degeneration	None
	Grade 1 macular edema right	None
	Grade 1 retinal angiopathy	None

Source: dataset MH; variable USUBJID, MHDECOD, MHTOXGR

Time Course and Outcome of Treatment-Emergent CSR Events

The median time to first onset of any Grade CSR event was 55 days in the 8-9 mg group and 57 days for all dose regimens combined. Dosing was reduced, interrupted, or discontinued for all subjects with CSR events, per protocol. In 7 of 26 subjects whose doses were interrupted or reduced, the CSR event resolved but later recurred; all recurrences were Grade 1 or 2. Three subjects in the 8/9 mg daily group and 6 subjects across all regimens discontinued erdafitinib due to CSR events.

Table 107: Central Serous Retinopathy Event Severity, Timing, and Outcome

	Efficacy Population (n = 87)	8-9 mg Daily (n = 164)	All Regimens Combined (n = 416)
Incidence	22 (25.3%)	26 (15.9%)	45 (10.8%)
Median time to first onset	50 days (range 22-207)	55 days (range 22-210)	57 days (range 18-221)
Maximum severity	Grade 1-2: 19 (86.4%) Grade 3: 3 (13.6%) Grade 4: None	Grade 1-2: 23 (88.5%) Grade 3: 3 (11.5%) Grade 4: None	Grade 1-2: 42 (93.3%) Grade 3: 3 (6.7%) Grade 4: None
Action taken	Dose reduction: 12 (13.8%) Dose interruption 8 (9.2%) Discontinuation: 3 (11.5%)	Dose reduction: 14 (53.8%) Dose interruption 10 (38.5%) Discontinuation: 3 (11.5%)	Dose reduction: 23 (51.1%) Dose interruption: 17 (37.8%) Discontinuation: 6 (13.3%)

Source: dataset ADAE; variables: USUBJID, TRTEMFL, ASTDY, TR01AG1, CQ06NAM, AEDECOD, AETOXGR

By the clinical cutoff date, 25 (55.6%) CSR events across all dose regimens resolved, 5 (11.1%) improved in severity, and 15 (33.3%) continued at maximum severity. All CSR events had resolved to Grade 2 by the time of data cut-off. No grade 4 CSR events occurred.

Table 108: Outcome of Central Serous Retinopathy Events

Maximum Severity of Event		Last Recorded Severity			
		0	1	2	3-4
Efficacy Population (n = 22)	1 (n = 9)	4 (44.4%)	5 (55.6%)	—	—
	2 (n = 10)	4 (40.0%)	3 (30.0%)	3 (30.0%)	—
	3 (n = 3)	2 (66.7%)	1 (33.3%)	—	—
	4 (n = 0)	—	—	—	—
8-9 mg Daily (n = 26)	1 (n = 9)	4 (44.4%)	5 (55.6%)	—	—
	2 (n = 14)	7 (50.0%) ^a	4 (28.6%) ^b	3 (21.4%)	—
	3 (n = 3)	2 (66.7%)	1 (33.3%)	0	0
	4 (n = 0)	—	—	—	—
All Regimens (n = 45)	1 (n = 20)	13 (65.0%)	7 (35.0%)	—	—
	2 (n = 22)	10 (45.5%) ^a	4 (18.2%) ^b	8 (36.4%)	—
	3 (n = 3)	2 (66.7%)	0	1 (33.3%)	0
	4 (n = 0)	—	—	—	—

Source: dataset ADAE; variables: USUBJID, TR01AG1, CQ06NAM, AEDECOD, AETOXGR

^a Subjects (b) (6) had Grade 2 events reported as resolved to Grade 0 with sequelae

^b Subject (b) (6) had Grade 2 retinopathy reported as Recovering/Resolving

The following narratives provide further detail on the three Grade 3 CSR events reported in patients on the 8/9 mg daily regimen:

- Subject (b) (6) was a 73-year-old male with no relevant medical history, who on Study Day 207 experienced a SAE of Grade 3 retinopathy. Ocular events reported prior to retinopathy were increased lacrimation, dry eye, eye pain, and blepharitis, all Grade 1, treated with clotrimazole and other ophthalmologicals. Upon occurrence of retinopathy, the subject was also discovered to have progressive disease, because of which, erdafitinib was discontinued. The event of retinopathy resolved on Study Day 316. At the time of clinical cutoff, the event of blepharitis was reported as not resolved.
- Subject (b) (6) was a 65-year-old male with no relevant medical history, who on Study Day 57 experienced a serious TEAE of Grade 3 detachment of retinal pigment epithelium and a non-serious TEAE of Grade 2 vision blurred. No concomitant medications were reported for these events. Treatment with erdafitinib was interrupted due to the detachment of retinal pigment epithelium. On Study Day 139, the detachment of retinal pigment epithelium and vision blurred were reported. On Study Day 165, detachment of retinal pigment epithelium (Grade 2) recurred. Erdafitinib was interrupted on Study Day 166 and was subsequently discontinued due to the detachment of retinal pigment epithelium.
- Subject (b) (6) was a 63-year-old male with no relevant medical history, who on Study Day 87 experienced a serious TEAE of Grade 3 retinal edema, treated with hyaluronate sodium and retinol. Erdafitinib had been interrupted on Study Day 81 due to non-serious Grade 1 renal impairment and Grade 2 onycholysis. Other ocular events reported prior to retinal edema were Grade 1 vision blurred and Grade 2 conjunctivitis. On Study Day 115, the retinal edema improved to Grade 1. Erdafitinib was resumed on Study Day 130 at 5 mg daily. On 165, erdafitinib was discontinued due to disease progression. On Study Day 199, the retinal edema resolved.

Reviewer's comments:

1. Approximately 16% of subjects treated with erdafitinib at 8-9 mg daily experienced one or more RPED/CSR events, with a median time to first onset of 55 days. All three Grade 3 RPED/CSR events improved to Grade 2 (n = 1) or Grade 0 (n = 2) by the clinical cutoff date.
2. No subject developed tearing of the RPE (RPE tears, usually at the junction between the detached and attached portions of the RPE, with a marked decrease in visual acuity, have been reported in other types or RPED) or retinal vein occlusion (reported in some patients receiving MEK inhibitors).
3. A prior history of retinal disease was not associated with an increased risk of treatment-emergent CSR events. Therefore, exclusion criteria pertaining to history of CSR, RVO, AMD, diabetic retinopathy, uncontrolled glaucoma, or corneal pathology need not be retained as contraindications for use of erdafitinib.

Other Eye Disorders

Eye disorders other than CSR events were reported for 44.5% of subjects at the 8-9 mg dose level and for 35.5% across all doses combined. The most common non-CSR ocular events were dry eye and vision blurred.

Table 109: Other Eye Disorders in ≥ 2 Subjects by Preferred Term

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any	44 (50.6%)	73 (44.5%)	156 (37.5%)
Dry eye ^a	24 (27.6%)	34 (20.1%)	70 (16.8%)
Visual acuity reduced ^c	23 (2.6%)	33 (20.1%)	54 (13.0%)
Conjunctivitis ^b	12 (13.8%)	19 (11.6%)	40 (9.6%)
Lacrimation increased	9 (10.3%)	13 (7.9%)	34 (8.2%)
Cataract	6 (6.9%)	6 (3.7%)	12 (2.9%)
Blepharitis	5 (5.7%)	5 (3.0%)	10 (2.4%)
Eye pain	3 (3.4%)	4 (2.4%)	8 (1.9%)
Photophobia	1 (1.1%)	2 (1.2%)	6 (1.4%)

^a includes dry eye, xerophthalmia, keratitis, foreign body sensation, and corneal erosion

^b includes conjunctivitis, eye irritation, ocular hyperemia, and conjunctival hyperemia

^c includes vision blurred, visual impairment, and visual acuity reduced

Source: dataset ADAE; variables USUBJID, TRTEMFL, TR01AG1, CQ05NAM, AEDECOD, AETOXGR

Reviewer's comment: Although listed separately, lacrimation is often a response to the dry eye events listed above.

Five subjects on the 8/9 mg daily regimen had ≥ Grade 3 non-CSR ocular events of keratitis (n = 3), dry eye, visual acuity reduced, corneal erosion, and cataract (n = 1 each). One subject on the 8-9 mg daily regimen experienced a Grade 4 non-CSR ocular event (cataract).

- Subject (b) (6) was a 65-year-old male who on Day 57 experienced non-serious Grade 2 vision blurred and Grade 3 SAE of detachment of retinal pigment epithelium. Treatment was interrupted. On Study Day 60, he complained of decreased visual acuity and dry syndrome. Visual acuity was 4/10. Fundoscopy and OCT showed bilateral pigmentary epithelial detachment. No treatment was reported for these events. Repeat OCT on Day 81 revealed right eye 288 μm and left eye 282 μm . On an unspecified date, ophthalmological examination was normal. On Day 139, the detachment of retinal pigment epithelium and vision blurred resolved. On Day 144, erdafitinib was resumed at 6 mg once daily. On Day 165, a non-serious AE of Grade 2 detachment of retinal pigment epithelium was reported. No treatment was reported for this event. Erdafitinib was discontinued.
- Subject (b) (6) was a 63-year-old male who on Day 22 experienced non-serious Grade 1 vision blurred. No action was taken with the study drug. On Day 28, visual acuity, tonometry, and funduscopy, and OCT were normal in both eyes. On Day 43, the event of vision blurred resolved. On an unspecified date during Month 2 of treatment, Grade 2 conjunctivitis was reported. Treatment included carmellose and cethexonium, and no action was taken with the study drug. On Day 81, erdafitinib was interrupted due to non-ocular AEs. On Day 85, the conjunctivitis improved to Grade 1. On Day 87, Grade 3 retinal edema was reported. OCT was abnormal (thickness 180 μm in the right eye and 331 μm in the left eye). Erdafitinib continued to be held, and the subject was treated with hyaluronate and retinol. On Day 98, the conjunctivitis resolved, a Grade 2 cataract was reported, OCT showed thickness of 247 μm in the right eye (normal) and 276 μm in the left eye (abnormal), no action was taken with erdafitinib, and treatment included hyaluronate, retinol, carmellose, and cethexonium. On Day 115, the retinal edema improved to Grade 1. On Day 130, erdafitinib was resumed at 5 mg daily, Grade 1 dry eye was reported, no action was taken with the study drug, and no treatment was reported. On Day 166, erdafitinib was interrupted due to non-ocular AEs. On Day 168, the dry eye resolved. On Day 169, erdafitinib was discontinued due to progressive disease. On Day 199, the event of retinal edema resolved. At the data cutoff date, the events of cataract and pneumothorax had not resolved.

Approximately two thirds of subjects on the 8-9 mg regimen who had non-CSR ocular events continued erdafitinib treatment without dose modification. At the time of data cutoff, 31 subjects (42.5%) had ongoing non-CSR ocular events.

Table 110. Severity, Timing, and Outcome of Non-CSR Ocular Adverse Events

	8-9 mg Daily (n = 164)	All Regimens Combined (n = 416)
Incidence	73 (44.5%)	156 (37.5%)
Median time to first onset	49 days (range 1-345)	49 days (range 1-489)
Maximum severity	Grade 1-2: 67 (91.8%) Grade 3: 5 (6.8%) Grade 4: 1 (1.4%)	Grade 1-2: 144 (92.3%) Grade 3: 10 (6.4%) Grade 4: 2 (1.3%)
Action taken	Dose reduction: 12 (16.4%) Dose interruption 10 (13.6%) Discontinuation: 3 (4.1%)	Dose reduction: 21 (13.5%) Dose interruption: 21 (13.5%) Discontinuation: 7 (4.5%)
Outcome	Resolved: 42 (57.5%) Unresolved: 31 (42.5%) Grade 1: 22 (71.0%) Grade 2: 7 (22.6%) Grade 3: 1 (3.2%) Grade 4: 1 (3.2%)	Resolved: 90 (57.7%) Unresolved: 66 (42.3%) Grade 1: 43 (65.2%) Grade 2: 19 (28.8%) Grade 3: 2 (3.0%) Grade 4: 2 (3.0%)

Source: dataset ADAE; variables USUBJID, TR01AG1, CQ05NAM, AEDECOD, AETOXGR, AEACN, AEOUT

Reviewer's comment: Events of dry eye syndrome are frequent during treatment with erdafitinib. Dry eye is also frequently associated with aging. The Applicant recommends the use of artificial tear substitutes, hydrating or lubricating eye gels or ointments as routine prophylaxis for dry eye syndrome during the entire treatment period at least every 2 hours while the patient is awake. The FDA ophthalmology consultant concurred that all patients should receive prophylaxis with ocular demulcents as needed; however, recommendations to use lubricating eye gels are discouraged since there are no FDA-approved dry eye therapy gels.

Nail and Skin Disorders

Nail disorder TEAEs were reported for 53.0% of subjects on the 8/9-mg daily regimen, most commonly onycholysis, paronychia, nail dystrophy, and nail discoloration. The incidence of nail disorders across all dose regimens combined was 41.3%.

Table 111: Nail Toxicities in ≥ 2 Subjects by Preferred Term

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any	49 (56.3%)	87 (53.0%)	172 (41.3%)
Onycholysis	17 (19.5%)	23 (14.0%)	58 (13.9%)
Paronychia	15 (17.2%)	22 (13.4%)	42 (10.1%)
Nail dystrophy	12 (13.8%)	21 (12.9%)	41 (9.9%)
Nail discoloration	10 (11.5%)	19 (11.6%)	32 (7.7%)
Nail disorder	8 (9.2%)	14 (8.5%)	23 (5.5%)
Onychalgia	3 (3.4%)	10 (6.1%)	16 (3.8%)
Onycholysis	2 (2.3%)	5 (3.0%)	10 (2.4%)
Nail ridging	3 (3.4%)	5 (3.0%)	9 (2.2%)
Nail bed bleeding	0	1 (0.6%)	4 (1.0%)

Source: dataset ADAE; variables: USUBJID, TR01AG1, CQ08NAM, AEDECOD, AETOXGR

In both the 8-9 mg daily group and in all doses combined, approximately half of nail disorders were managed by dose interruptions or reductions, and approximately two thirds resolved.

Table 112: Severity, Timing, and Outcome of Nail Adverse Events

	Indication Population (n = 87)	8-9 mg Daily (n = 164)	All Regimens Combined (n = 416)
Incidence	49 (56.3%)	87 (53.0%)	172 (41.3%)
Time to 1st onset	Median 66 days (range 16 - 196)	Median 63 days (range 15-281)	Median 64 days (range 1-308)
Maximum severity	Grade 1-2: 37 (75.5%) Grade 3: 12 (24.5%) Grade 4: None	Grade 1-2: 70 (80.5%) Grade 3: 17 (19.5%) Grade 4: None	Grade 1-2: 142 (82.6%) Grade 3: 30 (17.4%) Grade 4: None
Action taken	Dose reduction: 17 (34.7%) Dose interrupt.: 13 (26.5%) Discontinuation: 1 (2.0%)	Dose reduction: 23 (26.4%) Dose interrupt.: 23 (26.4%) Discontinuation: 2 (2.3%)	Dose reduction: 38 (22.1%) Dose interrupt.: 41 (23.8%) Discontinuation: 4 (2.3%)
Outcome	Resolved: 17 (34.7%) Unresolved: 32 (65.3%) Grade 1: 18 (36.7%) Grade 2: 10 (20.4%) Grade 3: 4 (8.2%) Grade 4: None	Resolved: 30 (34.5%) Unresolved: 57 (65.5%) Grade 1: 30 (52.6%) Grade 2: 23 (40.4%) Grade 3: 4 (7.0%) Grade 4: None	Resolved: 59 (34.3%) Unresolved: 113 (65.7%) Grade 1: 63 (55.8%) Grade 2: 44 (38.9%) Grade 3: 6 (5.3%) Grade 4: None

Source: dataset ADAE; variables: USUBJID, TR01AG1, CQ08NAM, AEDECOD, AETOXGR, ADSTDY, AEACN,

Cutaneous TEAEs were reported for 47.6% of subjects on the 8/9-mg daily regimen, most commonly dry skin and PPES. The incidence of skin disorder for all dose regimens combined was 42.8%.

Table 113: Skin Toxicities in ≥ 2 Subjects by Preferred Term

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
Any	45 (51.7%)	78 (47.6%)	178 (42.8%)
Dry skin ^a	30 (34.5%)	52 (31.7%)	119 (28.6%)
Palmar-plantar erythro-dysaesthesia syndrome	23 (26.4%)	32 (19.5%)	58 (13.9%)
Skin fissures	3 (3.4%)	7 (4.3%)	15 (3.6%)
Rash ^b	5 (5.7%)	8 (4.9%)	23 (5.5%)
Hyperkeratosis	1 (1.1%)	4 (2.4%)	10 (2.4%)
Erythema	2 (2.2%)	5 (3.0%)	8 (1.9%)
Skin exfoliation	0	3 (1.8%)	4 (1.0%)
Skin ulcer	1 (1.1%)	3 (1.8%)	4 (1.0%)
Blister	0	1 (0.6%)	2 (0.5%)
Palmar erythema	0	0	2 (0.5%)
Skin atrophy	0	1 (0.6%)	2 (0.5%)
Skin lesion	1 (1.1%)	1 (0.6%)	2 (0.5%)

^a includes dry skin and xeroderma

^b includes rash, rash erythematous, rash generalized, and rash maculopapular

Source: dataset ADSL; variables: USUBJID, TR01AG1, CQ02NAM, AEDECOD, AETOXGR

Of 78 subjects on the 8/9-mg daily regimen with skin disorder events, 67 (85.9%) had Grade 1 or 2 events and 11 (14.1%) had Grade 3 events; no Grade 4 events were reported. PPES was the only event reported as Grade 3 for more than 1 subject (9 subjects). Approximately two thirds of skin toxicities led to dose reduction or interruption or to discontinuation of treatment, and over half were ongoing at the time of data cutoff.

Table 114: Severity, Timing, and Outcome of Skin Adverse Events

	Indication Population (n = 87)	8-9 mg Daily (n = 164)	All Regimens Combined (n = 416)
Incidence	46 (52.9%)	78 (50.0%)	178 (42.8%)
Time to first onset	Median 48.5 days (range 5-268)	Median 43 days (range 15-281)	Median 42 days (range 1-308)
Maximum severity	Grade 1-2: 46 (100%) Grade 3: None Grade 4: None	Grade 1-2: 67 (40.9%) Grade 3: 11 (6.8%) Grade 4: None	Grade 1-2: 164 (39.4%) Grade 3: 14 (3.4%) Grade 4: None
Action taken	Dose reduction: 1 (2.2%) Dose interrupt.: 3 (6.5%) Discontinuation: None	Dose reduction: 10 (12.8%) Dose interrupt.: 14 (17.9%) Discontinuation: 4 (5.1%)	Dose reduction: 15 (8.4%) Dose interrupt.: 21 (11.8%) Discontinuation: 4 (2.2%)
Outcome	Resolved: 13 (28.3%) Unresolved: 33 (71.7%) Grade 1: 24 (72.7%) Grade 2: 9 (27.3%) Grade 3: None Grade 4: None	Resolved: 29 (37.2%) Unresolved: 49 (62.8%) Grade 1: 31 (63.3%) Grade 2: 16 (32.7%) Grade 3: 2 (4.1%) Grade 4: None	Resolved: 74 (41.6%) Unresolved: 104 (58.4%) Grade 1: 77 (74.0%) Grade 2: 24 (23.1%) Grade 3: 3 (2.9%) Grade 4: None

Source: dataset ADAE; variables: USUBJID, TR01AG1, CQ09NAM, TRTEMFL, AEDECOD, AETOXGR, AEACT, AEOU

Arrhythmias

Erdafitinib is a human ether-a-go-go-related gene (hERG) blocker, and erdafitinib prolonged repolarization in guinea pigs and dogs. Because of this preclinical signal, arrhythmias were identified as of potential clinical importance.

Electrocardiography

In the phase 1 trials GAC1001 and EDI1001, all subjects had electrocardiography at screening; predose and 2, 4, and 8 hours postdose on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycle 2; and postdose on Day 1 of subsequent cycles.

In GAC1001, no subject had a QTc value > 500 msec or a Δ QTc > 60 msec from baseline.

In EDI1001, 19 subjects (10.1%) had average maximum Δ QTcF values 30 to 60 msec, and 27 subjects (14.4%) had maximum average Δ QTcB values 30 to 60 msec. Average QTc values exceeded 500 msec on treatment in 2 subjects (Subjects (b) (6)), both of whom has screening values above 500 msec. Four subjects had electrocardiogram QT prolonged reported as a TEAE (Table 112). None of these events was considered serious, and none of these four subjects had other arrhythmia-related adverse events.

Table 115: TEAEs of Electrocardiogram QT Prolonged

Subject	Max Grade	Erdafitinib Dose	Onset of Max Grade	Action Taken
(b) (6)	1	9 mg daily	Day 1	Dose not changed
(b) (6)	1	10 mg 7d on/7d off	Day 127	Dose not changed
(b) (6)	1	9 mg daily	Day 44	Dose not changed
(b) (6)	3	10 mg 7d on/7d off	Day 43	Erdafitinib discontinued

Source: Dataset ADAE; variables USUBJID, ASTDY, TR01AG1, AEOU, AETOXGR, AEACN

Based on these findings, the phase 2 trial BLC2001 collected ECGs at screening only in subjects on the 8 mg daily regimen. In this group, no QTcF values > 500 msec, Δ QTcF > 60 msec or arrhythmia-related TEAEs were reported.

Echocardiography

In the dose-escalation part of the phase 1 trial EDI1001, echocardiography or multigated acquisition (MUGA) was performed at screening and in Cycle 3, Week 1. The left ventricular ejection fraction (LVEF) was > 50% at screening in all subjects. Of thirty-five subjects who had one or more post-baseline assessments, three had a maximum decrease in LVEF of 5-6%. No subject experienced a post-baseline decrease in LVEF > 6% or a post-baseline LVEF value below 55%.

In the phase 2 trial BLC2001, all subjects underwent echocardiography or MUGA at screening. Two subjects on the 8-mg regimen were enrolled despite not meeting the LVEF eligibility criterion of $\geq$ 50%. Subsequent echocardiogram or MUGA assessments were to be done at the discretion of the investigator, and no subject required either study for suspected cardiac issues.

Adverse Events

The Applicant considered the following MedDRA Preferred terms arrhythmia related: ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, ventricular tachycardia, electrocardiogram QT prolonged, bradycardia, atrial fibrillation, atrial flutter, loss of consciousness, syncope, and ventricular arrhythmia. Five subjects (3.0%) on the 8/9 mg daily regimen experienced arrhythmia-related TEAEs, two of which were Grade 3 (both syncope); no Grade 4 events were reported. No arrhythmia-related event was serious or resulted in dose reduction, interruption, or discontinuation.

Across all dose regimens, 15 subjects (3.6%) had arrhythmia-related TEAEs, with a median time to first onset of 20.0 days. Two subjects had dosing interrupted as a result, and 1 subject discontinued erdafitinib.

Table 116: Treatment-Emergent Arrhythmia-Related Events

		Total Events	Serious	≥ Gr 3	Action Taken		
					Dose Reduced	Dose Interrupted	Discontinued
8-9 mg Daily (n = 164)	All	6 (3.7%)	0	2	0	0	0
	Bradycardia	1 (0.6%)	0	0	0	0	0
	Ventricular arrhythmia	1 (0.6%)	0	0	0	0	0
	Syncope	2 (1.2%)	0	2 (1.2%)	0	0	0
	QT prolonged	2 (1.2%)	0	0	0	0	0
	Atrial fibrillation	1 (0.6%)	0	0	0	0	0
All Regimens (n = 416)	All	15 (3.6%)	3 (0.7%)	5 (1.2%)	0	2 (0.5%)	1 (0.2%)
	QT prolonged	4 (1.0%)	0	1 (0.2%)	0	0	1 (0.2%)
	Syncope	4 (1.0%)	1 (0.2%)	3 (0.7%)	0	1 (0.2%)	0
	Loss of consciousness	3 (0.7%)	1 (0.2%)	0	0	0	0
	Bradycardia	2 (0.5%)	0	0	0	0	0
	Atrial fibrillation	1 (0.2%)	0	0	0	0	0
	Atrial flutter	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)	1 (0.2%)
	Ventricular arrhythmia	1 (0.2%)	0	0	0	0	0

Source: dataset ADAE; variables: USUBJID, TR01AG1, CQ01NAM, TRTEMFL, AEDECOD, AETOXGR

The following narratives provide further detail on select subjects with arrhythmia-related events:

- Subject (b) (6), a 63-year-old male on the 8-9 mg daily regimen, had Grade 1 ventricular arrhythmia that was reported on Study Day 1 and persisted throughout his study participation. The subject had a history of hypertension, and his screening ECG showed intraventricular conduction delay, ventricular premature complexes, and a QTc of 412 msec. His Day 1 ECG showed first degree atrioventricular block and a QTcB of 450 msec. The subject continued study treatment without further cardiac events until Day 163, when he discontinued treatment due to disease progression (his event of syncope on Day 141 occurred with groin pain and urinary retention).
- Subject (b) (6) a 71-year-old male with a history of anemia and hypertension on the 6-mg daily regimen, had a fatal event of loss of consciousness at home 3 days after erdafitinib was discontinued because of progressive disease. No autopsy was performed.
- Subject (b) (6) was an 82-year-old male assigned to erdafitinib 8 mg daily. Medical history included angina pectoris, atrial fibrillation, hypertension, myocardial infarction, and ventricular ectopy. Concomitant medications included aspirin, amiodarone, atenolol, ramipril, simvastatin, salbutamol, tiotropium, levothyroxine, and furosemide. On Study Day -1, non-serious Grade 3 hyponatremia was reported. No treatment was reported for this event. On Day 24, non-serious Grade 1 diarrhea was reported and was treated with loperamide. No action was taken with the study drug. On Day 26, the diarrhea resolved. On Day 28, the hyponatremia worsened to Grade 4. On Day 35 the subject was hospitalized. On Day 36, erdafitinib was interrupted due to hyponatremia and was never resumed. On Day 38, non-serious Grade 3 syncope was reported. The subject received oxygen. The event of syncope resolved the same day. On Day 77, the

hyponatremia improved to Grade 3 and was considered non-serious. On Day 168, the hyponatremia resolved. Concurrent AEs included eye pain, hyperphosphatemia, insomnia, conjunctivitis, and stomatitis (all Grade 1).

- Subject (b) (6) was a 65-year-old Asian male with metastatic lung cancer previously treated with pemetrexed, carboplatin, bevacizumab. His medical history included hyponatremia, elevated alkaline phosphate, and exertional dyspnea. Grade 1 ALT was present at screening. The subject was assigned to erdafitinib 12 mg 7 days on/7 days off. On Study Day 1, he had SAEs of Grade 4 hyponatremia, Grade 3 tachycardia, and Grade 3 atrial flutter. Two hours after his first dose of erdafitinib, he felt nauseous and vomited. He received ondansetron without recurrence. His 8 hour post-dose EKG showed a heart rate of 161. This was treated with diltiazem, digoxin, acetylsalicylic acid, and adenosine, and erdafitinib was interrupted. Concomitant medications included magnesium sulfate, sodium chloride, enoxaparin, and tolvaptan. On Day 3, the subject was in sinus rhythm. On Day 6, he was discharged from the hospital. On Day 8, erdafitinib was resumed at 12 mg. On Day 11, the subject experienced SAEs of atrial flutter and tachycardia and Grade 3 anemia, treated with oxygen, diltiazem, sodium chloride, and whole blood. Erdafitinib was interrupted, and the heart rhythm converted to normal sinus. On Day 14, Grade 3 ALT and Grade 3 AST were reported. Erdafitinib continued to be held. On Day 29, AST and ALT resolved to Grade 1, and erdafitinib was resumed at 8 mg intermittent. On Day 35, ALT increased to Grade 2, and erdafitinib was interrupted. On Day 43, these resolved to Grade 1. On Day 45, erdafitinib was resumed at 8 mg. On Day 50, per protocol, a drug holiday of 7 days ended the cycle. On Day 55, the subject was hospitalized because of Grade 3 acute kidney injury and Grade 4 hyponatremia, and concomitant AEs included Grade 2 renal tubular necrosis, Grade 2 atrial flutter, Grade 3 congestive heart failure, Grade 2 hypervolemia, Grade 2 restrictive cardiomyopathy, and Grade 2 malnutrition. Chest radiography showed worsening left pleural effusion and opacity. Broad spectrum antibiotics were administered. Echocardiography showed a decrease in LVEF to 35%, with tumor infiltrating the heart. He had been off rate controlling agents for his atrial flutter and went into rapid atrial flutter on Day 65. He was treated with amiodarone. On Day 69, the subject was transferred to hospice care, and on Day 71, he died of disease progression. No autopsy was performed.

Reviewer's comment: *The patients described in these narratives all had alternative causes for their arrhythmia-related events, and some of those causes seemed more likely than erdafitinib. This will need to be further assessed in the ongoing randomized trial.*

Exposure-Response Analysis of Cardiovascular Safety

Holter recordings were obtained in Part 1 of Study EDI1001 at screening, on Cycle 1 Day 1, and at steady state on Cycle 2 Day 1, and Cycle 3 Day 1. ECGs were obtained at the same times as total and free erdafitinib plasma concentrations. The dataset includes 62 subjects Holter/ECGs

paired with 704 total erdafitinib concentrations, and 60 subjects with Holter/ECGs paired with 685 free erdafitinib concentrations. The QT interval corrected individually for heart rate (QTcI) was selected as the dependent variable.

The Applicant's exposure-response analysis estimated the slopes for total and free erdafitinib plasma concentrations as -0.00269 ms/(ng/mL) and -1.138 ms/(ng/mL), respectively, indicating that increases in erdafitinib plasma concentrations result in decreased QTcI. The model-predicted mean Δ QTcI at the observed geometric mean of the C_{max} for total (1911 ng/mL) and free (4.51 ng/mL) plasma concentration at steady state following a 9 mg dose of erdafitinib was -5.1 msec (90% CI: -8.8, -1.5) and -5.1 msec (90% CI: -8.3, -2.0), respectively.

Hyperphosphatemia

Laboratory Values

Because hyperphosphatemia is a pharmacodynamic effect of FGFR inhibitors, protocols EDI1001 and BLC2001 directed that erdafitinib be up-titrated from 8 to 9 mg in some cohorts for phosphate levels below 5.5 mg/dL, in the absence of drug-related toxicity. The dose was to be reduced in all cohorts if serum phosphate levels exceeded prespecified values.

Hyperphosphatemia was also managed by dose modification and treatment with phosphate binders (although the protocols provided no guidance regarding the use of phosphate binders). Treatment with phosphate binders used included sevelamer (26 subjects), sevelamer carbonate (5 subjects), and lanthanum carbonate, calcium carbonate, and calcium acetate (1 subject each). Phosphate binders were used prophylactically for 5 subjects and for 29 subjects following phosphate assessment during the study. The median total duration of phosphate binder treatment was 81 days. The median phosphate value prompting phosphate binder treatment was 6.10 mg/dL

In the 8-9 mg daily group and in all groups combined, mean phosphate values increased starting at Week 2, peaked by Week 6, and decreased from that point forward. During treatment, 132 (81.0%) subjects on the 8/9-mg daily regimen had phosphate increases of Grade 1 or 2, and 2 subjects (1.2%) had increases to Grade 3. Across all regimens, 282 (68.5%) subjects had phosphate increases to Grade 1 or 121 values, and 3 subjects (0.7%) had shifts to Grade 3 post-baseline. No Grade 4 values were reported.

Table 117: Worst Serum Phosphate Toxicity Grade

Dose regimen	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
8-9 mg daily (n = 164)	30 (18.3%)	78 (47.6%)	54 (32.9%)	2 (1.2%)	0
All (n = 412)	132 (32.0%)	189 (45.9%)	88 (21.4%)	3 (0.67%)	0

Source: dataset AD5L; variables: USUBJID, TR01AG1, TEMFL, AEDECOD, AETOXGR

Adverse Events

Treatment-emergent hyperphosphatemia was reported for 134 subjects (81.7%) in the 8/9 mg daily regimen, with a median time to onset of 15 days (range 2 to 116). The maximum severity

was Grade 1 or 2 for all but 2 subjects with Grade 3 events. Of 134 subjects in the 8/9-mg daily regimen with treatment-emergent hyperphosphatemia, 53 had dose interruptions, 16 had dose reductions, and 1 discontinued erdafitinib due to the event. Both Grade 3 events resolved with dose reductions, one in 8 days and the other in 22 days.

For all dose regimens combined, 280 subjects (67.9%) experienced TEAEs of hyperphosphatemia: 277 (67.2%) Grade 1-2, and 3 (0.7%) Grade 3. At the time of data cutoff, 253 (90.3%) hyperphosphatemia TEAEs had resolved.

Table 118: Severity, Timing, and Outcome of Hyperphosphatemia TEAEs

	Indication Population (n = 87)	8-9 mg Daily (n = 164)	All Regimens Combined (n = 416)
Incidence	66/87 (75.9%)	134 (81.7%)	280 (67.3%)
Time to 1st onset	Median 20 days (range 8-116)	Median 15 days (range 2-116)	Median 15 days (range 2-363)
Max. severity	Grade 1-2: 65/66 (98.5%) Grade 3: 1/66 (1.5%) Grade 4: None	Grade 1-2: 132/134 (80.5%) Grade 3: 2/134 (1.2%) Grade 4: None	Grade 1-2: 277/280 (66.6%) Grade 3: 3/280 (0.7%) Grade 4: None
Action taken	Dose reduction: 6/66 (9.1%) Dose interrupt.: 21/66 (31.8%) Discontinuation: 1/66 (1.5%)	Dose reduction: 16/164 (9.8%) Dose interrupt.: 53/164 (32.3%) Discontinuation: 1/164 (0.6%)	Dose reduction: 22/280 (5.3%) Dose interrupt.: 78/280 (18.8%) Discontinuation: 1/280 (0.2%)
Outcome	Resolved: 62/66 (93.9%) Unresolved: 4/66 (6.1%) Grade 1: 4/4 (100%) Grade 2: None Grade 3: None Grade 4: None	Resolved: 120/134 (89.6%) Unresolved: 14/134 (10.4%) Grade 1: 13/14 (92.9%) Grade 2: 1/14 (7.1%) Grade 3: None Grade 4: None	Resolved: 253/280 (90.3%) Unresolved: 27/280 (9.6%) Grade 1: 26/27 (96.3%) Grade 2: 1/27 (3.7%) Grade 3: None Grade 4: None

Source: dataset ADAE; variables: USUBJID, TR01AG1, CQ07NAM, TRTEMFL, AEDECOD, ASTDY, AETOXGR, AEACTION, AEOU

Sequelae

Clinical consequences of acute, severe hyperphosphatemia are due to the formation of calcium phosphate precipitates and to the resulting hypocalcemia. These can include, tetany, seizures, renal failure due to nephrocalcinosis, and heart block due to cardiac calcifications. Prolonged hyperphosphatemia can also lead to anemia, hypotension, hypercalcemia, renal impairment, hypocalcemia, hyperparathyroidism. The overall incidence of these TEAEs in patients with prolonged hyperphosphatemia (≥ 5.5 mg/dL for > 1 month) was similar to that in the overall safety database (32.1% vs. 33.5% for the 8-9 mg regimen, and 34.0% vs. 32.9% for all doses combined).

Table 119: Potential Sequelae of Prolonged Hyperphosphatemia

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Pop. (n = 164)	Total (n = 416)
All Subjects	N = 87	N = 164	N = 416
Any	30 (34.5%)	55 (33.5%)	137 (32.9%)
Anemia	17 (19.5%)	34 (20.7%)	95 (22.8%)
Hypotension	7 (8.0%)	10 (6.1%)	26 (6.3%)
Hypercalcemia	6 (6.9%)	11 (6.7%)	25 (6.0%)
Renal impairment	7 (8.0%)	10 (6.1%)	19 (4.6%)
Hypocalcemia	4 (4.6%)	5 (3.0%)	13 (3.1%)
Renal failure	2 (2.3%)	4 (2.4%)	5 (1.2%)
Hyperparathyroidism	2 (2.3%)	2 (1.2%)	3 (0.7%)
Normochromic/normocytic anemia	0	0	1 (0.2%)
Subjects with phosphate > 5.5 mg/dL for ≥ 1 month	N = 16	N = 28	N = 50
Any	6 (37.5%)	10 (35.7%)	18 (36.0%)
Anemia	5 (31.2%)	9 (32.1%)	15 (30.0%)
Renal impairment	3 (18.7%)	5 (17.9%)	6 (12.0%)
Hypercalcemia	0	0	3 (6.0%)
Hypotension	1 (6.2%)	1 (3.6%)	2 (4.0%)

Source: FDA/OCE Safety Analytic Team

Reviewer's comment: *It is difficult to assign causality to these relatively common adverse reactions in this single arm study. Hyperphosphatemia was added to section 5 of the package insert because of the frequency and expectedness of this laboratory abnormality in patients being treated with erdafitinib.*

Bleeding

Because four deaths were attributed to tumor bleeding (Section 8.2.4 of this review), this reviewer further explored the potential safety signal of tumor bleeding. Fifty-two subjects in the safety database were identified with one or more of 14 MedDRA Preferred Terms potentially representing tumor bleeding.

Table 120: Adverse Events Potentially Signaling Tumor Bleeding

	Indication Population (n = 87)	8/9 mg QD plus 9 mg QD Safety Population (n = 164)	Total (n = 416)
Any	13 (14.9%)	24 (14.7%)	52 (12.5%)
Gastrointestinal hemorrhage	0	0	1 (0.2%)
Hematuria	10 (11.5%)	13 (7.9%)	27 (6.5%)
Hemoptysis	0	1 (0.6%)	6 (1.4%)
Rectal hemorrhage	1 (1.2%)	2 (1.2%)	4 (1.0%)
Urethral hemorrhage	0	0	1 (0.2%)
Vaginal hemorrhage	0	1 (0.6%)	3 (0.7%)
Anal hemorrhage	2 (2.3%)	2 (1.2%)	2 (0.5%)
Cerebral hemorrhage	0	1 (0.6%)	1 (0.2%)
Hematochezia	0	2 (1.2%)	3 (0.7%)
Hemorrhage	0	1 (0.6%)	1 (0.2%)
Tumor hemorrhage	0	1 (0.6%)	1 (0.2%)
Hematemesis	0	0	1 (0.2%)
Hemorrhage intracranial	0	0	2 (0.5%)
Renal hemorrhage	0	0	1 (0.2%)

The following narratives provide further detail on subjects who experienced potential tumor bleeding events that were Grade 3-4, serious, or led to erdafitinib discontinuation:

Subj. No.	Abbreviated Subject Narrative	Reviewer's Comment
(b) (6)	79-year-old male with urothelial carcinoma assigned to erdafitinib 6 mg daily. On Day 74, the subject was hospitalized due to a SAE of Grade 3 hematuria (without significant fall in hematocrit), and erdafitinib was discontinued. On Day 137, the hematuria and catheter site hemorrhage resolved.	Hematuria at the site of a urethral catheter is unlikely to be drug-induced tumor bleeding.
(b) (6)	67-year-old female with urothelial carcinoma assigned to erdafitinib 6 mg daily. Medical history included nausea, cough, vomiting, hemoptysis, and lung resections. Medications at study entry included hydrochlorothiazide, lisinopril, codeine, guaifenesin, cetirizine, lorazepam, metoclopramide, ondansetron, pantoprazole, coloxyl, senna, escitalopram, fluticasone, and travoprost. Erdafitinib was interrupted for non-serious Grade 1-2 hyperphosphatemia between Days 9 and 18, Days 23 and 38 (resumed at 5 mg daily), Days 46 and 53, Days 60 and 71, Days 79 and 92 (resumed at 4 mg daily), and Days 120 and 129. On Day 148, erdafitinib was interrupted due to non-serious Grade 1 hyperphosphatemia. On Day 154, the subject was hospitalized due to Grade 3 hemoptysis. On Day 155, non-serious Grade 1 cough was reported. No action was taken with the study drug. On Day 157, the hemoptysis resolved, and erdafitinib was discontinued due to progressive disease.	Although this subject had a prior history of hemoptysis, prior lung resections, and had no known thoracic metastases, hemoptysis near the time of disease progression could represent tumor bleeding, and a role for erdafitinib cannot be excluded.
(b) (6)	66-year-old male with urothelial carcinoma assigned to erdafitinib 6 mg daily. Medical history included heartburn and lower gastrointestinal bleeding. Medications at study entry included esomeprazole, aspirin, amlodipine, simvastatin, bisoprolol, enalapril, metamizole, oxycodone, cannabis, gabapentin, methadone, enoxaparin, and brotizolam. At screening non-serious Grade 2 anemia was reported. No	Subject had prior gastrointestinal bleeding, and colonoscopy showed abdominal metastases eroding into the colon. Thus, this report represents an instance of tumor bleeding.

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	treatment was reported for this event. On Day 3, the subject was hospitalized due to a SAE of Grade 3 gastrointestinal hemorrhage. Colonoscopy showed abdominal metastases eroding into the colon. Erdafitinib was interrupted on Day 4, the gastrointestinal hemorrhage resolved on Day 9, and erdafitinib was resumed at 5 mg daily on Day 10. On Day 27, the subject was hospitalized due to a SAE of Grade 3 gastrointestinal hemorrhage. CT angiography suggested that the origin of bleeding was “intra-abdominal venous bleeding of abdominal metastases”. Erdafitinib was discontinued due to progressive disease on Day 42.	
(b) (6)	77-year-old male with urothelial carcinoma assigned to erdafitinib 8 mg once daily. Medical history included diabetes mellitus, pulmonary embolism, hyperlipidemia and myocardial infarction. Medications at study entry included atorvastatin, ezetimibe, famotidine, metformin, metoprolol tartrate, omeprazole, pravastatin, valsartan, and enoxaparin. On Day 16, erdafitinib was increased to 9 mg daily. On Day 89, a SAE of Grade 3 hematuria was reported. Radiation to the bladder was advised, and no action was taken with erdafitinib. On Day 91, the hematuria resolved. On Day 100, the subject was hospitalized due to Grade 3 Pseudomonas urinary tract infection, thought to be due to nephrostomy obstruction, with Grade 2 pyrexia and Grade 2 blood creatinine increased. No action was taken with the study drug. On Day 101, the pyrexia improved to Grade 1.	Nephrostomy obstruction and urinary tract infections are more likely than tumor bleeding as causes of this subject’s hematuria.
(b) (6)	57-year-old male with urothelial carcinoma assigned to erdafitinib 8 mg once daily. On Day 278, Grade 2 orchitis and Grade 3 microhematuria were reported, and erdafitinib was interrupted due to reason reported as “other”. On Day 291, the subject underwent cystostomy with surgical hemostasis.	Bleeding at the primary urothelial tumor site is a common presentation and complication of bladder cancer. A role for erdafitinib cannot be excluded.
(b) (6)	66-year-old female with glioblastoma multiforme on Study Day 15, while on enoxaparin, experienced a Grade 2 intracranial hemorrhage, Grade 3 hemiparesis, Grade 3 dehydration, Grade 3 muscle twitching, Grade 2 increased intracranial pressure, and Grade 2 seizures. On Study Day 20, the subject died from intracranial hemorrhage.	While drug-induced tumor bleeding cannot be excluded, enoxaparin is a confounding factor. Also, glioblastoma is not the indication being sought for erdafitinib.
(b) (6)	52-year-old male with head and neck neuroendocrine carcinoma with metastases to cervical nodes, parotid gland, anterior nasal passage, post ethmoid sinus, and retropharyngeal nodes. On Day 17, Grade 3 hemorrhage of a large ulcerating head and neck tumor mass and Grade 4 sepsis were reported. The surgical oncologist stated that there was no surgical option. On Day 25, 9 days after last dose, the subject died due to Grade 5 sepsis.	The large size and progressive nature of this subject’s tumor likely predisposed to local bleeding.
(b) (6)	52-year-old female with urothelial carcinoma assigned to erdafitinib 9 mg once daily. Her early course on study was complicated by an acetabular fracture treated by osteoplasty, and anemia requiring blood transfusion. On Study Day 270, the subject experienced Grade 4 cerebral hemorrhage. CT showed brain metastasis with hemorrhage.	A causal relationship between erdafitinib and bleeding into a cerebral metastasis seems unlikely but cannot be excluded.
(b) (6)	52-year-old male with head and neck cancer previously treated with radiotherapy, right pharyngolaryngectomy and lymphadenectomy, and systemic chemotherapy, assigned to	A causal relationship between erdafitinib and bleeding from an oral

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	erdafitinib 10 mg daily (7 days on/7 days off). Medical history included hypomagnesemia, hypothyroidism, anemia, and tumor pain. Erdafitinib was discontinued on Study Day 21, after a total of 14 doses. On Day 39, the subject experienced Grade 5 tumor hemorrhage, which the investigator suspected was caused by fistula bleeding from oral squamous cell carcinoma.	squamous carcinoma seems unlikely but cannot be excluded.
(b) (6)	35-year-old female with breast cancer assigned to erdafitinib 9 mg once daily. On Study Day 29, after a post-treatment liver metastasis biopsy, the subject developed hypotension. CT angiography showed acute bleeding at the biopsy site. Erdafitinib was interrupted. The subject received vessel embolization and blood transfusion.	Bleeding into a liver biopsy site is unlikely due to study drug.
(b) (6)	56-year-old female with urothelial carcinoma assigned to erdafitinib 10 mg daily (7 days on/7 days off) on Day -26 (screening) was hospitalized with Grade 4 kidney infection, Grade 3 renal failure and hemorrhage, and Grade 2 hematuria. On Day 7, the subject was hospitalized with Grade 3 hematuria due to tumor infiltration of kidney. Erdafitinib was permanently discontinued. On Day 9, acute kidney injury worsened to Grade 4 and the subject developed Grade 5 renal hemorrhage.	Tumor bleeding began before erdafitinib was started and was therefore unlikely drug-related.
(b) (6)	72-year-old male with urothelial carcinoma assigned to erdafitinib 6 mg daily. Medical history included lymphedema. Medications at study entry included ferrous sulfate, Ginkgo biloba, magnesium oxide, benzydamine, tamsulosin, prucalopride, fentanyl, finasteride, megestrol acetate, bisacodyl, and calcium. On Study Day 31, erdafitinib was increased to 8 mg daily. On Day 58, erdafitinib was interrupted due to Grade 3 lymphedema which was treated with furosemide. On Day 65, erdafitinib was resumed at 8 mg daily. Erdafitinib was interrupted on Day 85 due to Grade 1 AST, Grade 1 ALT, and Grade 2 creatinine increased, and was restarted on Day 91 at 6 mg daily. On Day 169, a tumor assessment revealed disease progression. On Day 170, the subject was hospitalized with Grade 3 lymphedema, and underwent invasive lymphatic drainage. On Day 175, Grade 2 cough was reported, which was considered not related to the study drug. No action was taken with the study drug due to the cough. Erdafitinib was interrupted on Day 180 due to reason reported as 'other'. The subject was hospitalized on Day 195 for Grade 3 dyspnea treated with furosemide and invasive lymphatic drainage and was discharged on Day 202. On Day 187, Grade 1 hemoptysis was reported, and no action was taken with erdafitinib. Erdafitinib was interrupted on Day 242 due to Grade 3 dyspnea. On Day 244, the subject was hospitalized with hypotension, tachypnea, elevated serum troponin, and hypoxia, and increasing lung metastases on CT. On Day 247, a sputum acid-fast bacillus fluorescent smear was positive, consistent with pulmonary tuberculosis.	Although hemoptysis in this subject occurred in the setting of chronic cough, pulmonary edema, and progressing lung metastases, and pulmonary tuberculosis, the possibility that it was exacerbated by erdafitinib cannot be excluded.

Reviewer's comment: Several instances of bleeding at a tumor site were reported. Many of these reports of possible tumor bleeding above had alternative causes for tumor bleeding, and some of those causes seemed more likely than erdafitinib. Therefore, tumor bleeding was not

included in the warnings and precautions section of the package insert. However, this signal will need to be assessed in the ongoing randomized trial.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The symptomatic measurement questionnaire was an abbreviated set of self-reported questions rating the subject's experience of pain, fatigue, cough, and dyspnea. The questionnaire was implemented with Amendment 3 to the protocol and was developed by reviewing clinical reports from the subjects in BLC2001 treated prior to Amendment 3. The questionnaire was administered only to subjects in the 8-mg regimen who could read English.

Subjects were to rate their symptoms on a scale ranging from 0 to 7, with higher scores indicating more severe symptoms. The questionnaire time recall period was 1 week (the past week) and was to be completed at screening, Day 14 of Cycle 1 and Day 1 of Cycles 2 and 3.

Reviewer's comment: *The collection of patient-reported outcomes for this NDA was too rudimentary to allow an in-depth analysis*

8.2.7. Safety Analyses by Demographic Subgroups

In the 8-9 mg daily regimen and in all regimens combined, approximately 83% of subjects were ≥ 65 years of age and approximately 14% were age ≥ 75 years. For both patient pools and age cutoffs, overall incidences were within 5% for all TEAEs, serious TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death. Grade 3-4 TEAEs were reported more frequently for subjects ≥ 75 years of age than for those age < 75 .

Approximately 60% of subjects in the 8-9 mg daily regimen and in all regimens combined were male. Overall incidences of TEAEs, serious TEAEs, Grade 3-4 TEAEs, and TEAEs leading to discontinuation were slightly higher among males compared to females.

Reviewer's comment: *Of the 416 patients treated with BALVERSA in clinical studies, 45% were 65 years of age or older, and 12% were 75 years of age or older. No overall significant differences in safety or effectiveness were observed between these patients and younger patients.*

Table 121: Treatment-Emergent Adverse Events by Demographic Subgroup

		N	Treatment-Emergent Adverse Event					
			All	Serious	Grade 3-4	Leading to Discontin.	Leading to Death	
Efficacy Population (n = 87)	Age	< 65	34	34 (100%)	13 (38.2%)	3 (8.8%)	0	2 (5.9%)
		≥ 65	53	53 (100%)	23 (43.4%)	6 (11.3%)	0	5 (9.4%)
		< 75	76	76 (100%)	31 (40.8%)	6 (7.9%)	0	5 (6.6%)
		≥ 75	11	11 (100%)	5 (45.5%)	3 (27.3%)	1 (9.1%)	2 (18.2%)
	Sex	M	69	69 (100%)	31 (44.9%)	6 (8.7%)	1 (1.4%)	7 (10.1%)
		F	18	18 (100%)	5 (27.8%)	3 (16.7%)	0	0
	Region	N. Amer	19	19 (100%)	7 (36.8%)	1 (5.3%)	1 (5.3%)	1 (5.3%)
	Europe	61	61 (100%)	25 (41.0%)	6 (9.8%)	0	3 (4.9%)	
	Asia	7	7 (100%)	4 (57.1%)	2 (28.6%)	0	3 (42.9%)	
8-9 mg Daily (n = 164)	Age	< 65	89	89 (100%)	36 (40.4%)	59 (66.3%)	16 (18.3%)	6 (6.7%)
		≥ 65	75	75 (100%)	31 (41.3%)	50 (66.7%)	14 (18.7%)	5 (6.7%)
		< 75	144	144 (100%)	58 (40.3%)	94 (65.3%)	27 (18.8%)	9 (6.3%)
		≥ 75	20	20 (100%)	9 (45.0%)	15 (75.0%)	3 (15.0%)	2 (10.0%)
	Sex	M	103	103 (100%)	48 (46.6%)	73 (70.9%)	22 (21.4%)	9 (8.7%)
		F	61	61 (100%)	19 (31.1%)	36 (59.0%)	8 (13.1%)	2 (3.3%)
	Region	N. Amer	51	51 (100%)	19 (37.3%)	35 (68.6%)	8 (15.7%)	2 (3.9%)
Europe		108	108 (100%)	45 (41.7%)	71 (65.7%)	22 (20.4%)	8 (7.4%)	
Asia		5	5 (100%)	3 (60.0%)	3 (60.0%)	0	1 (20.0%)	
All Regimens (n = 416)	Age	< 65	228	227 (99.6%)	98 (43.0%)	131 (57.5%)	32 (14.0%)	24 (10.5%)
		≥ 65	188	188 (100%)	82 (43.6%)	122 (64.9%)	27 (19.7%)	19 (10.2%)
		< 75	366	365 (99.7%)	158 (43.2%)	220 (60.1%)	59 (16.1%)	37 (10.1%)
		≥ 75	50	50 (100%)	22 (44.0%)	33 (66.0%)	10 (20.0%)	6 (12.0%)
	Sex	M	243	242 (99.6%)	116 (47.7%)	158 (65.0%)	46 (18.9%)	31 (12.8%)
		F	173	173 (100.0%)	64 (37.0%)	95 (54.9%)	23 (13.3%)	12 (6.9%)
	Region	N. Amer.	101	101 (100.0%)	45 (44.6%)	65 (64.4%)	15 (14.9%)	6 (5.9%)
Europe		278	277 (99.6%)	122 (43.9%)	175 (62.9%)	49 (17.6%)	33 (11.9%)	
Asia		37	37 (100.0%)	13 (35.1%)	13 (35.1%)	5 (13.5%)	4 (10.8%)	

Source: datasets ADAE and ADSL; variables: USUBJID, TR01AG1, AGE, SEX, GEOGR1, TRTEMFL, AESER, AETOXGR, AEACT, AEOUT

8.2.8. Specific Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Given the intended clinical use in patients with advanced cancer, no stand-alone fertility or carcinogenicity studies were conducted.

Human Reproduction and Pregnancy

There are no data on the use of erdafitinib in pregnant women. Based on findings in animal reproduction studies, erdafitinib can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic at exposures less than human exposures at all doses studied.

Women of childbearing potential are advised to use highly effective contraception prior to and during treatment, and for 3 months after the last dose of erdafitinib. Men are advised to use a condom and not to donate or store semen during treatment and for 3 months after the last dose of erdafitinib.

There are no data on the presence of erdafitinib in human milk, or the effects of erdafitinib on the breastfed infant, or on milk production. Women are advised not to breastfeed during treatment with erdafitinib and for 3 months following the last dose of erdafitinib.

Pediatrics and Assessment of Effects on Growth

Given the intended clinical use in patients with advanced cancer, no stand-alone toxicology studies were conducted in juvenile animals.

On May 8, 2018, the FDA issued an agreement to the Applicant's initial Pediatric Study Plan, where a full waiver was requested for the indication of urothelial cancer, because studies would be impossible or highly impracticable, and erdafitinib is not likely to be used in a substantial number of pediatric patients.

On December 12, 2018, the Oncology Subcommittee of the Pediatric Review Committee concurred with the Division's recommendation to grant a full waiver for pediatric studies of erdafitinib for patients with urothelial cancer due to the rarity of this indication in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no information on overdose of erdafitinib and no known specific antidote for erdafitinib overdose. In the event of an overdose, erdafitinib should be stopped and general supportive measures undertaken until clinical toxicity has diminished or resolved.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Erdafitinib is not marketed in any country.

Expectations on Safety in the Postmarket Setting

Erdafitinib is being approved under the provisions in 21 CFR Part 601 Subpart E (accelerated approval). A confirmatory trial(s) is therefore required to verify and describe the clinical benefit of erdafitinib in patients with urothelial carcinoma. The confirmatory randomized trial BLC3001 is ongoing (see Section 13 of this review).

8.2.11. Integrated Assessment of Safety

The erdafitinib clinical safety database contains pooled data from a total of 416 patients in two phase 1 dose escalation trials in subjects with advanced solid tumors (EDI1001, and GAC1001) and one phase 2 trial (BLC2001) in patients with advanced or metastatic urothelial cancers. The proposed dose is 8 mg daily with pharmacodynamically guided up-titration to 9 mg daily. A total of 99 subjects with urothelial cancer were treated with this dosing regimen in BLC2001. This includes the 87 patients who form the primary efficacy population for this NDA, as well as 12 patients who were treated in the first-line metastatic setting due to their cisplatin-ineligible status. Additionally, to expand the safety database of this dosing regimen, data from subjects in EDI1001 treated with 9-mg daily (no up-titration; n = 65) was also reviewed, for a total of 164 subjects treated with what is referred to as the 8/9 mg daily regimen.

Key safety results for this pooled analysis from these 87 patients, 164 patients, and from all 416 patients across the erdafitinib safety database (all doses) are as follows:

- Commonly reported TEAEs with the 8-9 mg daily regimen, irrespective of attribution, were hyperphosphatemia (81.7%), stomatitis (56.1%), dry mouth (45.7%), diarrhea (41.5%), decreased appetite (37.8%), constipation and paronychia (35.4% each), and dry skin (31.7%). Labeled TEAEs, including laboratory abnormalities, for the 87-patient efficacy population included hyperphosphatemia (75.9%), stomatitis (56.3%), fatigue (54.0%), diarrhea (47.1%), dry mouth (44.8%), and onycholysis (41.4%).
- Grade 3 or 4 TEAEs were reported for 66.5% of subjects receiving the 8-9 mg daily regimen, with 10 subjects (6.1%) reporting Grade 4 events. Commonly reported Grade 3 or 4 TEAEs were stomatitis (10.4%), hyponatremia (9.8%), asthenia (6.1%), palmar-plantar erythrodysesthesia syndrome (PPES), and anemia (5.5% each). In the 87-patient efficacy population, Grade 3 or 4 TEAEs were reported for 58.6% of subjects, including stomatitis (10.3%), onycholysis (10.3%), stomatitis (9.2%), and fatigue (8.0%).

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- Serious TEAEs occurred in 41.4% of subjects in the 87-patient efficacy population, 40.9% of subjects on the 8-9 mg daily regimen and 43.3% of subjects on all doses combined. Serious TEAEs reported by 2% or more subjects were general physical health deterioration, dyspnea, urinary tract infection, and abdominal pain.
- Eleven subjects (12.6%) in the 87-patient efficacy population had TEAEs leading to treatment discontinuation. Sixteen (11.2%) on the 8-9 mg daily regimen and 36 subjects (9.2%) across all doses had TEAEs leading to treatment discontinuation, the most common being general physical health deterioration.
- TEAEs leading to death were reported for 11 subjects (2.6%) across all doses. Except for myocardial infarction in one subject with a prior cardiac history, intracranial hemorrhage in one subject with brain metastases, and sepsis in one subject with head and neck carcinoma, all TEAEs leading to death occurred in the context of progressive disease.

Expected toxicities of FGFR inhibitors as a class include eye disorders, nail and skin disorders, and hyperphosphatemia. In addition, arrhythmia-related TEAEs were considered adverse events of interest because of preclinical findings. These toxicities are presented in the pooled 8/9 mg daily regimen and overall safety database.

- Eye disorders

TEAEs consistent with central serous retinopathy (CSR) were reported in 26 (15.9%) of subjects on the 8/9-mg daily regimen. Grade 3 events consistent with CSR were retinopathy, detachment of retinal pigment epithelium, and retinal edema in one subject each. Three subjects permanently discontinued treatment due to such events (detachment of retinal pigment epithelium [n = 2], and chorioretinopathy [n=1]). At the time of data cutoff, 14 central serous retinopathy events had resolved, while 12 events were ongoing, all Grade 1-2.

Other eye toxicities such as dry eye or keratitis were observed for 44.5% of subjects on the 8/9 mg daily regimen and 37.5% of subjects across all dose levels. Approximately 4% of these events led to discontinuation of study treatment.

- Nail and skin disorders

Nail disorders, most commonly onycholysis, paronychia, and nail dystrophy, were reported in 53.0% of subjects on the 8-9 mg daily regimen and in 41.3% of subjects across all doses. Skin disorders, most commonly dry skin and PPES, were reported in 47.6% of subjects on the 8-9 mg daily regimen and 42.8% of subjects across all doses. Two subjects discontinued treatment due to nail disorders and 4 subjects discontinued due to skin disorders.

- Hyperphosphatemia

Treatment-emergent hyperphosphatemia, thought to result from inhibition by erdafitinib of renal FGF23 signaling, was reported in 81.7% of subjects on the 8-9 mg daily regimen and in 67.3% across all dose regimens. Mean phosphate values peaked at approximately 6 mg/dL approximately 6 weeks after the start of treatment and subsequently decreased to less than 4.5 mg/dL by Cycle 6 (due to dose reduction of erdafitinib, the use of phosphate binders, or other unidentified mechanisms). Hyperphosphatemia was added to section 5 of the package insert because of the frequency and expectedness of this laboratory abnormality in patients being treated with erdafitinib.

- Arrhythmias

Because preclinical studies identified arrhythmia as a potentially important adverse event, electrocardiography and echocardiography were monitored in the phase 1 trials (predose, and 2, 4, and 8 hours postdose on Days 1, 8 and 15 of Cycles 1 and on Day 1 of Cycle 2; and postdose on subsequent cycles). No adverse effect of erdafitinib on QT interval or cardiac function were observed, and the incidence of arrhythmia-related TEAEs across all dosing regimens was low (3.6%). In addition, an analysis of time-matched QTc and Holter data from the phase 1 trial EDI1001 detected no effect of erdafitinib on cardiac repolarization. However, in one patient (Subject (b) (6)) with no stated history of cardiac disease experienced an arrhythmia soon after starting erdafitinib. Arrhythmias should therefore be assessed in the ongoing randomized controlled trial.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

In general, there were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for the BLC2001 study. The study showed a confirmed ORR of 32.2% (95% CI: 22.4, 42.0) in the target chemotherapy-relapsed/refractory population (N=87) with an estimated median duration of response of 5.42 months (95% CI: 4.21, 6.93) per BIRC assessment. The study showed a confirmed ORR of 32.2% (95% CI: 22.4, 42.0) in the target chemotherapy-relapsed/refractory population at the proposed dose (N=87) with an estimated median duration of response of 5.42 months (95% CI: 4.21, 6.93) per BIRC assessment. Efficacy results based on investigator were consistent with BIRC assessment. We reiterate that no inferential procedures can be used to evaluate results from this single arm study. Instead, the efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although progression-free survival, time to response and overall survival results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm. The real world data submitted in the application to augment the clinical trial data did not provide additional supportive evidence.

8.4. Conclusions and Recommendations

The review team recommends accelerated approval for erdafitinib 8 mg (two 4 mg tablets) orally once daily, with dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate levels and tolerability at 14 to 21 days. Erdafitinib is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has:

- susceptible FGFR3 or FGFR2 genetic alterations, and
- progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Patients should be selected for therapy based on an FDA-approved companion diagnostic.

Primary Statistical Reviewer

Statistical Team Leader

Primary Clinical Reviewer

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This NDA was not presented to an advisory committee because the benefit-risk profile demonstrated for erdafitinib is clearly favorable for its proposed use. No controversial issues were identified that would necessitate an advisory committee meeting.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

Given the intended clinical use in patients with advanced cancer, no stand-alone toxicology studies were conducted in juvenile animals.

On May 8, 2018, the FDA issued an agreement to the Applicant's initial Pediatric Study Plan, where a full waiver was requested for the indication of urothelial cancer, because studies would be impossible or highly impracticable, and erdafitinib is not likely to be used in a substantial number of pediatric patients.

APPEARS THIS WAY ON ORIGINAL

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Highlights of Prescribing Information	Contraception recommendation was not included.	"Embryo-fetal toxicity: Can cause fetal harm. Advise patients of the potential risk to the fetus and to use effective contraception (5.3, 8.1, 8.3)."
Warnings and Precautions - Section 5.3	Terminology was used incorrectly.	FDA added to the highlights section: "Based on the mechanism of action and findings in animal reproduction studies, BALVERSA can cause fetal harm when administered to a pregnant woman. In an embryo-fetal toxicity study, oral administration of erdafitinib to pregnant rats during the period of organogenesis caused malformations and embryo-fetal death at maternal exposures that were less than the human exposures at the maximum human recommended dose based on area under the curve (AUC)."
Use in Specific Populations (Pregnancy 8.1 – Animal Data)	(b) (4)	FDA revised and added additional detail to clarify the nonclinical findings in the embryo-fetal study: Doses ≥4mg/kg/day produced embryo-fetal death, major blood vessel malformations and other vascular anomalies, limb malformations (ectrodactyly, absent or misshapen long bones), an increased incidence of skeletal anomalies in multiple bones (vertebrae, sternbrae, ribs), and decreased fetal weight."
Use in Specific Populations (Lactation 8.2, Risk Summary)	(b) (4)	FDA revised this section to reflect data from section 12.3 <i>Pharmacokinetics, Elimination</i> . No milk data is available in humans or animals. Effect on rat mammary gland (atrophy) was reported in one month and 13-week repeat dose toxicology studies, however recovery was

		reported in the one month study (not measured in 13-week study). The duration of time a patient should wait to breastfeed following last dose was calculated using the higher limit of erdafitinib half life ($T_{1/2}$) from clinical studies which was 120.5 hours. Five half lives is considered sufficient to allow full clearance of drug, which amounts to approximately~30 days. P/T provides the following recommendation: <i>“....., advise lactating women not to breastfeed during treatment with BALVERSA and for one month following the last dose”</i>
Section 8.3 - Females and Males of Reproductive Potential; Contraception, Females	(b) (4)	FDA revised this section to (b) (4) <i>“BALVERSA can cause fetal harm when administered to pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the last dose”</i>
	Section 8.3 - Females and Males of Reproductive Potential; Contraception, male	(b) (4) (b) (4) <i>“Advise male patients with female partners of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the</i>

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		last dose.”
Section 8.3 - Fertility	(b) (4)	FDA revised this section to reflect data from the 13-week study in rats: <i>“Based on animal studies, BALVERSA may impair fertility in females of reproductive potential”</i>
Section 8.4 - Pediatric Use	Safety and effectiveness of BALVERSA in pediatric patients have not been established.	FDA revised this section to reflect data from the 13-week studies in rats and dogs: <i>“Safety and effectiveness of BALVERSA in pediatric patients have not been established. In 13-week repeat-dose toxicology studies in rats and dogs, toxicities in bone and teeth were observed at an exposure less than the human exposure (AUC) at the maximum recommended human dose. Chondroid dysplasia/metaplasia were reported in multiple bones in both species, and tooth abnormalities (including discoloration/malocclusion and degeneration of odontoblasts) were reported in rats.”</i>
Section 12 - Clinical Pharmacology (Mechanism of Action 12.1)	(b) (4)	(b) (4) FDA revised this section to reflect data from the pharmacology in vitro and in vivo studies: <i>“Erdafitinib is a kinase inhibitor that binds to FGFR1, FGFR2, FGFR3 and FGFR4 and inhibits enzymatic activity based on in vitro data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including mutations, amplifications, and fusions. Erdafitinib demonstrated antitumor activity in FGFR-expressing cell lines and xenograft models, derived from tumor types, including bladder cancer.”</i>

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	(b) (4)	
Nonclinical Toxicology (Carcinogenesis, Mutagenesis, and Impairment of Fertility 13.1)		FDA revised this section to clarify the effects of erdafitinib on female reproductive organs in animals and the exposure levels at which these toxicities were observed, respective to the human recommended dose of 8 mg (which are supported by data listed in section 12.3). “erdafitinib showed effects on female reproductive organs (necrosis of the ovarian corpora lutea) in rats at an exposure less than the human exposure (AUC) at maximum recommended human dose.”
Pateint Counseling Information - Section 17		Updated to reflect changes made to label sections above.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS was required based on review of the safety results of this application

12.1. Central Serous Retinopathy (CSR)

The clinical trials that generated the safety population for this application excluded from enrollment patients with the following corneal or retinal conditions thought to increase the risk of eye toxicity (the ongoing randomized trial BLC3001 has these exclusion criteria as well):

- History of CSR or retinal vascular occlusion
- Active wet, age-related macular degeneration
- Nonproliferative diabetic retinopathy with macular edema
- Uncontrolled glaucoma
- Corneal pathology such as keratitis, keratoconjunctivitis, keratopathy, corneal abrasion, inflammation or ulceration.

The Applicant proposed the following risk mitigation measures for ocular toxicity:

- Baseline ophthalmologic examination to include evaluation of visual acuity, tonometry, slit lamp examination including screening for dry eye, fundoscopy, Amsler grid test, and OCT if indicated by findings on fundoscopy. Should signs of active, $\geq$ Grade 2 CSR be found, treatment should be delayed until resolution.
- Monthly Amsler Grid testing and holding erdafitinib if evidence of early CSR is detected. When CSR is suspected, OCT should be performed.
- Use of hydrating and lubricating eye gels or ointments every two hours while awake, beginning the start of treatment and continue during the entire treatment period.

Reviewer's Recommendation:

- *A history of prior macular or retinal disease (e.g., CSR, RVO, age related macular degeneration, diabetic neuropathy) without active RPED/CSR did not predict the occurrence of CSR on ED1001 or BLC2001. Therefore, this need not be retained as a contraindication for erdafitinib use.*
- *Sections 2.4 and 5.1 of the Prescribing Information should recommend an ophthalmological examination at baseline and monthly during treatment, and provide dose modification guidelines for patients developing eye disorders.*
- *Section 17 of the Prescribing Information should provide advice to patients developing eye problems.*
- *Ophthalmological examinations should include fundoscopy, slit lamp observation, and OCT. Amsler grid testing is insensitive for CSR, and should not be recommended. Routine tonometry should not be recommended.*
- *Dry eye symptoms are frequent during treatment with erdafitinib. All patients should receive prophylaxis with ocular demulcents as needed; however, recommendations to*

use lubricating eye gels are discouraged since there are no FDA-approved dry eye therapy gels.

- *A REMS is not required to address ocular toxicity*

12.2. Teratogenicity

Based on findings in animal reproduction studies, erdafitinib can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic at exposures less than the human exposures at all doses studied. Fetal toxicity was characterized by hand/foot defects and malformations of major blood vessels. No teratogenicity events with the use of erdafitinib have been reported from the available clinical trials. There are no clinical trials of erdafitinib in pregnant women.

Sections 5.2, 8.1, and 17 of the Prescribing Information will contain advice for pregnant women, females of reproductive potential, and male patients.

12.3. Drug-Drug Interaction (P-glycoprotein inhibition)

Erdafitinib inhibited human P-gp in vitro. Physiologically-based PK simulation predicted a C_{max}-ratio of 1.45 and an AUC-ratio of 1.18 for digoxin when erdafitinib was coadministered with digoxin at the same time, whereas dose staggering by 6 hours could avoid this interaction.

Sections 7.2 and 12.3 of the Prescribing Information will contain recommendations regarding the use of erdafitinib with narrow therapeutic index P-gp substrates, and Section 17 will contain information for patients using concomitant medications.

12.4. Use During Pregnancy and Lactation

Sections 8.1, 8.2, and 17 will provide advice for pregnant women, female patients of reproductive potential, and women who are breastfeeding or plan to breastfeed.

12.5. Use in Patients with Moderate to Severe Hepatic Failure

In the safety database, 25 patients with mild hepatic impairment (total bilirubin $\leq$ ULN and AST $>$ ULN, or ULN $<$ total bilirubin $\leq 1.5 \times$ ULN) at baseline were exposed to erdafitinib for 142.5 person-months. Based on population PK analysis, there were no clinically meaningful differences in exposure between subjects with mild hepatic impairment and subjects of normal hepatic function. No data are available in UC subjects with moderate ($1.5 \times$ ULN $<$ total bilirubin $\leq 3 \times$ ULN) or severe (total bilirubin $>$ $3 \times$ ULN) hepatic impairment at baseline. A Phase 1 trial (EDI1008) to evaluate the effect of hepatic impairment on the PK of erdafitinib is planned.

13 Postmarketing Requirements and Commitment

1. PMR 3561-1. Submit the final report and datasets demonstrating clinical benefit of erdafitinib in patients with locally advanced and metastatic urothelial carcinoma with susceptible FGFR3 or 2 genetic alterations from clinical trial BLC3001: “A Phase 3 Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations.” PMR 3561-1. Submit the final report and datasets demonstrating clinical benefit of erdafitinib in patients with locally advanced and metastatic urothelial carcinoma with susceptible FGFR 3 or 2 genetic alterations from clinical trial BLC3001: “A Phase 3 Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations.”
2. PMR 3561-2. Complete and submit the results of your ongoing hepatic impairment study EDI1008 titled “A Phase 1, Open-Label, Single-Dose Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Erdafitinib”.
3. PMR 3561-3. Submit the datasets with the final report of a clinical pharmacokinetic trial that evaluates the effect of repeated doses of erdafitinib on the single dose pharmacokinetics of a sensitive CYP3A substrate (e.g., midazolam), to address the potential for excessive drug toxicity or decreased drug exposure, and to determine appropriate dosing recommendations when coadministering erdafitinib with a sensitive CYP3A substrate. This trial should be designed and conducted in accordance with FDA Draft Guidance for Industry: Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications.
4. PMC 3561-4. Submit the datasets with the final report from a clinical pharmacokinetic trial that evaluates the effect of repeated doses of a strong inducer (e.g., rifampin) of CYP2C9 and CYP3A on the single dose pharmacokinetics of erdafitinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations when erdafitinib is coadministered with CYP2C9 and CYP3A inducers. This trial should be designed and conducted in accordance with the FDA Draft Guidance for Industry: “Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications.”
5. PMC 3561-5. Submit the datasets with the final report from a clinical pharmacokinetic study that evaluates the effect of repeated doses of erdafitinib (at steady-state) on the single dose pharmacokinetics of a probe substrate of OCT2 to determine appropriate dosing recommendations for OCT2 substrate when it is coadministered with erdafintib. This trial should be designed and conducted in accordance with the FDA Draft Guidance for Industry: “Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications.”

14 Division Director (DHOT)

15 Division Director (OCP)

16 Division Director (OB)

17 Division Director (Clinical)

18 Office Director (or designated signatory authority)

The risk-benefit profile was assessed by Drs. Ibrahim, Weinstock, Chi and Brave and I agree with their assessment. This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature also represents approval of this application under CDER.

19 Appendices

19.1. References

References cited throughout text.

19.2. Financial Disclosure

In accordance with 21 CFR 54, the Applicant has submitted Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators (Module 1.3.4). Form 3454 includes a table listing all investigators who participated in clinical study 42756493BLC2001 supporting NDA 212018 and identifies 99 Principal Investigators and 201 Sub-Investigators for Clinical Study BLC2001. The Applicant has certified that the Sponsor and Investigators of Clinical Study BLC20001 had no financial arrangements with the clinical investigators to disclose.

Reviewer Comment

The covered clinical study for this NDA is Cohort 3 of the Phase 2 Study BLC2001. Since this study relied on independent-review determined objective responses, financial issues are less likely to affect the analyses of the effectiveness of atezolizumab in the intended patient population.

Covered Clinical Study (Name and/or Number): 42756493BLC2001, BLC2001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>630</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages].

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Erdafitinib concentrations in human plasma or urine were assayed in clinical trials. Two LC-MS/MS methods were validated to measure erdafitinib in human plasma (**Table 122 and Table 123**) and a LC-MS/MS method was qualified to measure erdafitinib in human urine (**Table 124**). Additionally, methods to measure total radiolabeled erdafitinib in plasma, feces, and urine were also developed.

Table 122. Summary method performance of a bioanalytical method to measure erdafitinib in human plasma (method validated at Janssen R&D)

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an LC-MS/MS method for the determination of JNJ-42756493 in human EDTA plasma. BA10240 (Mod5.3.1.4/BA10240) Final report +amendments 1, 2 and 3		
Method description	LC-MS/MS method for the determination of JNJ-42756493 in human EDTA plasma after protein precipitation		
Materials used for calibration curve & concentration	Human EDTA plasma 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200, 500 ng/mL		
Validated assay range	0.500 to 500 ng/ml		
Material used for QCs & concentration	Human EDTA plasma; 0.500, 1.30, 15.0, 380 ng/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Non-weighted Linear regression with logarithmically transformed x- and y-axes		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	MVR BA10240 (Mod5.3.1.4/ BA10240)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.5 to 5.8%	MVR BA10240 (Mod5.3.1.4/ BA10240)

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	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 5.8%	MVR BA10240 (Mod5.3.1.4/B A10240)
QCs performance during accuracy & precision	<u>Cumulative accuracy (%inter run bias) in 6 QCs</u> QCs:	-6.7 to -3.9%	MVR BA10240 (Mod5.3.1.4/B A10240)
	Inter-batch %CV QCs:	≤ 5.5%	MVR BA10240 (Mod5.3.1.4/B A10240)
	<u>Total error</u> QCs:	Not applicable	
Selectivity & matrix effect	6 lots of blank human EDTA plasma, spiked at LLOQ level, were tested. The % bias observed ranged from -2.2 to 5.6%. No significant contribution was observed in blanks at the retention time of the compound or the internal standard. No significant matrix effects were observed in 6 different matrix lots.		MVR BA10240 (Mod5.3.1.4/B A10240)
Interference & specificity	Not applicable		
Hemolysis effect	Not evaluated in this validation		
Lipemic effect	Not evaluated in this validation		
Dilution linearity & hook effect	Not applicable		
Bench-top/process stability	Stability of JNJ-42756493 in human EDTA plasma was proven for 72 hours at room temperature (protected from light) and for 4 hours at room temperature (exposed to light). Stability in processed samples was proven for 139 hours at 4 °C		MVR BA10240 (Mod5.3.1.4/B A10240)
Freeze-Thaw stability	Stability of JNJ-42756493 in human EDTA plasma was proven after 6 freeze/thaw cycles.		MVR BA10240 (Mod5.3.1.4/B A10240)
Long-term storage	Stability of JNJ-42756493 in human EDTA plasma was proven after storage in a freezer for 831 days		MVR BA10240 (Mod5.3.1.4/B A10240)
Parallelism	Not applicable		
Carry over	Assessed in each validation run		

Source: Table 1 from Applicant's Response to Clinical Pharmacology Information Request (dated 01-25-2019)

Table 123. Summary method performance of a bioanalytical method to measure erdafitinib in human plasma (method validated at PRA after transfer from Janssen R&D)

NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a method for the determination of JNJ-42756493 in human EDTA plasma samples by LC-MS/MS BA10843 (Mod5.3.1.4/BA10843) Final report + Amendment 1		
Method description	LC-MS/MS method for the determination of JNJ-42756493 in human EDTA plasma after protein precipitation		
Materials used for calibration curve & concentration	Human EDTA plasma 1.00, 2.00, 5.00, 20.0, 50.0, 200, 400, 1000, 1600, 2000 ng/mL		
Validated assay range	1.00 to 2000 ng/ml		
Material used for QCs & concentration	Human EDTA plasma; 1.00, 3.00, 125, 1600 ng/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Non-weighted Linear regression with logarithmically transformed x- and y-axes (Power)		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	MVR BA10843 (Mod5.3.1.4/BA10843)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.8 to 2.5%	MVR BA10843 (Mod5.3.1.4/BA10843)
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 5.2%	MVR BA10843 (Mod5.3.1.4/BA10843)
QCs performance during accuracy & precision	<u>Cumulative accuracy (%inter run bias) in 6 QCs</u> QCs:	-8.1 to 2.5%	MVR BA10843 (Mod5.3.1.4/BA10843)
	<u>Inter-batch %CV</u> QCs:	≤ 1.0%	MVR BA10843 (Mod5.3.1.4/BA10843)
	<u>Total error (Total % CV)</u> QCs:	≤ 3.9%	MVR BA10843 (Mod5.3.1.4/BA10843)
Selectivity & matrix effect	6 lots of blank human EDTA plasma, spiked at LLOQ level, were tested. The mean % bias was -4.5%. No significant contribution was observed in blanks at the retention time of the compound or the internal standard. No significant matrix effects were observed.		MVR BA10843 (Mod5.3.1.4/BA10843)
Interference & specificity	Selectivity was demonstrated in spiked samples in the presence of fluconazole and itraconazole in 1 lot of plasma		BSS 42756493EDI1007 (Mod5.3.3.1/EDI1007/16.2.5)
Hemolysis effect	1 lot tested. The % bias observed ranged from -9.8 to -4.4%.		MVR BA10843 (Mod5.3.1.4/BA10843)
Lipemic effect	Not evaluated in this validation		

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Dilution linearity & hook effect	Not applicable	
Bench-top/process stability	Stability of JNJ-42756493 in human EDTA plasma was proven for 26 hours at room temperature (protected from light) and for 4 hours at room temperature (exposed to light). Stability in processed samples was proven for 120 hours at 4 °C	MVR BA10843 (Mod5.3.1.4/B A10843)
Freeze-Thaw stability	Stability of JNJ-42756493 in human EDTA plasma was proven after 5 freeze/thaw cycles.	MVR BA10843 (Mod5.3.1.4/B A10843)
Long-term storage	Stability of JNJ-42756493 in human EDTA plasma was proven after storage in a freezer for 449 days	MVR BA10843 (Mod5.3.1.4/B A10843)
Parallelism	Not applicable	
Carry over	In some runs the acceptance criteria were not met for the first carry-over sample following the ULOQ standard and high QC sample. This was evaluated and was found to have no impact on method performance.	MVR BA10843 (Mod5.3.1.4/B A10843)

Source: Table 2 from Applicant's Response to Clinical Pharmacology Information Request (dated 01-25-2019)

Table 124. Summary method performance of a bioanalytical method to measure erdafitinib in human urine

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Bioanalytical method validation report name, amendments, and hyperlinks	BA10074 qualified assay for JNJ-42756493 in human urine; Method summary located in BSS-SV-42756493EDI1005-urine Addendum 1 (Mod5.3.1.2/EDI1005/Study Report)		
Method description	LC-MS/MS assay for quantification of JNJ-42756493 in human urine containing 0.2% Tween 80 after protein precipitation		
Materials used for calibration curve & concentration	human urine containing 0.2% Tween 80 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200, 500 ng/mL		
Validated assay range	0.500-500 ng/ml		
Material used for QCs & concentration	human urine containing 0.2% Tween 80; 2.00, 20.0, 200 ng/mL		
Minimum required dilutions (MRDs)	Not Applicable		
Source & lot of reagents (LBA)	Not Applicable		
Regression model & weighting	Non-weighted Linear regression with logarithmically transformed x- and y-axes		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	Raw data on study file
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-5.2 to +4.0%	Raw data on study file
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	Not applicable (one qualification run)
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs:	-7.5 to -5.0%	Raw data on study file
	Inter-batch %CV QCs:	Intra-batch: ≤ 3.1%	Raw data on study file
	Total error QCs:	Not applicable	
Selectivity & matrix effect	Selectivity tested for 1 urine lot Matrix effect not evaluated		Addendum 1 of BSS-SV-42756493EDI1005 (Mod5.3.3.1/EDI1005/16.2.5)
Interference & specificity	Not evaluated		
Hemolysis effect	Not Applicable (urine)		
Lipemic effect	Not Applicable (urine)		

Dilution linearity & hook effect	Not Applicable	
Bench-top/process stability	24h at room temperature	Addendum 1 of BSS-SV 42756493EDI1005 (Mod5.3.3.1/E DI1005/16.2.5)
Freeze-Thaw stability	1xF/T	Addendum 1 of BSS-SV 42756493EDI1005 (Mod5.3.3.1/E DI1005/16.2.5)
Long-term storage	1384 days in a freezer	Addendum 1 of BSS-SV 42756493EDI1005 (Mod5.3.3.1/E DI1005)
Parallelism	Not Applicable	
Carry over	Assessed in each study run	

Source: Table 3 from Applicant's Response to Clinical Pharmacology Information Request (dated 01-25-2019)

19.4.2. Relative Bioavailability of Erdafitinib Formulations

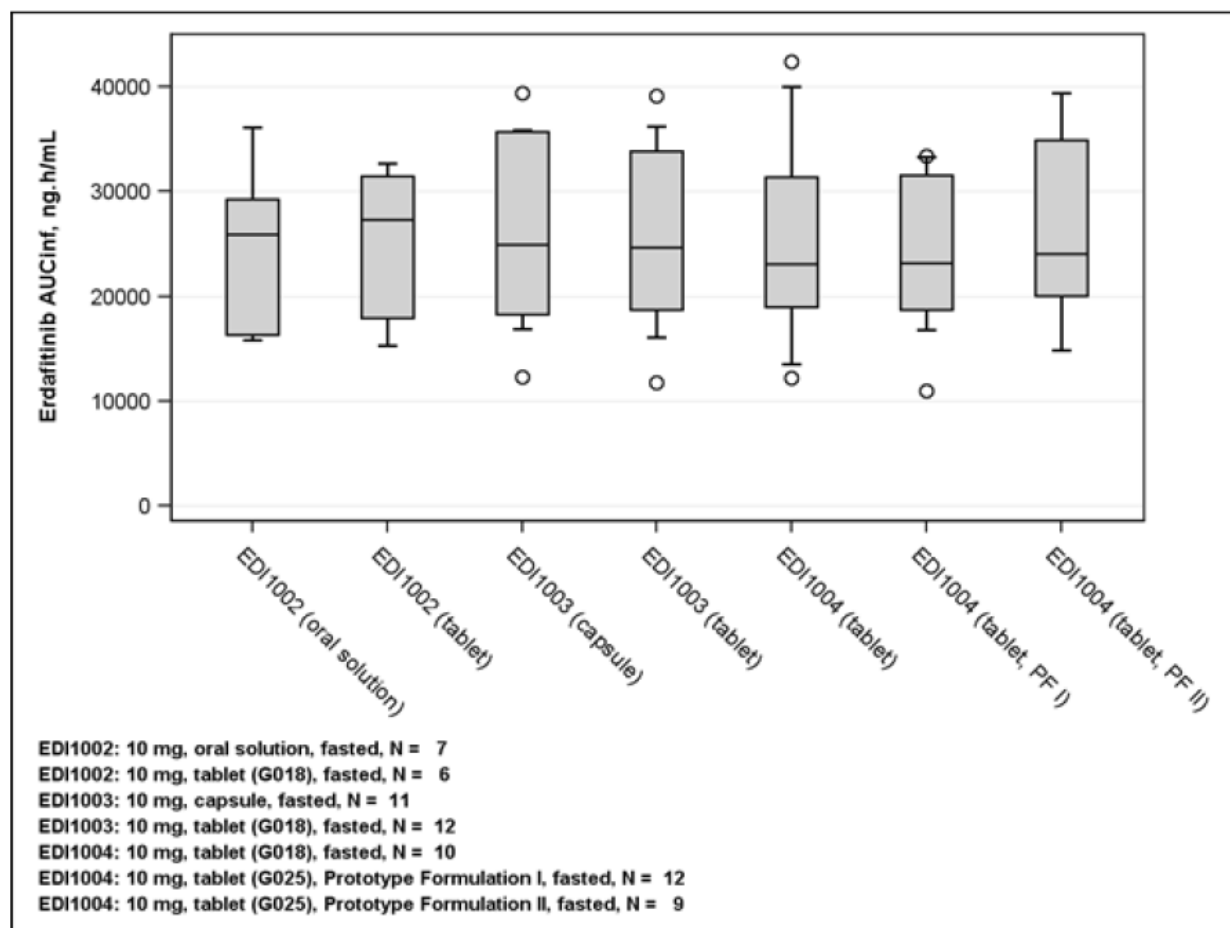
PK parameters of erdafitinib from Applicant's relative bioavailability studies (EDI1002, EDI1003, EDI1004) are provided in **Table 125** and shown as boxplots in **Figure 8**. These studies evaluated 10 mg erdafitinib single-dose in healthy subjects under fasted conditions. The data indicate that erdafitinib PK is comparable between the formulations used in clinical studies (solution, capsule, initial film-coated tablet) compared to the to-be-marketed formulation (final film-coated tablet (5 mg) = G025).

Table 125. Erdafitinib PK parameters from relative bioavailability studies

Study ID	Dose (mg)	Formulation	N	Median (Range)		Mean (SD)		
				t _{max} (h)	C _{max} (ng/mL)	AUC _{last} (ng.h/mL)	AUC _∞ (ng.h/mL)	t _{1/2} (h)
Single-dose studies assessing the impact of formulation changes								
EDI1002	10	Tablet; G018; fasted	8	3.50 (1.00-4.01)	357 (107)	19900 (6251)	25300 (7474)	53.8 (7.02)
	10	Solution; G004; fasted	8	2.10 (1.01-2.75)	373 (141)	20100 (6537)	24700 (7124)	52.2 (3.46)
EDI1003	10	Tablet; G018; fasted	12	3.00 (2.00-8.00)	357 (113)	21900 (7680)	25400 (8890)	49.1 (5.29)
	10	Capsule; G014; fasted	12	3.00 (2.00-6.00)	372 (110)	23000 (7620)	26400 (8850)	49.7 (6.76)
EDI1004	10	Tablet; G018 (17 micron); fasted	11	2.00 (1.50-4.00)	433 (143)	21845 (7780)	25206 (9717)	50.7 (8.1)
	10	Tablet; G025 (78 micron); fasted	12	2.51 (1.50-8.00)	389 (93.7)	20788 (6089)	23788 (7285)	46.0 (4.9)
	10	Tablet; G025 (119 micron); fasted	11	2.99 (1.00-8.00)	411 (109)	22227 (6707)	26171 (8460)	50.2 (3.3)

Source: Table 13 from Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods

Figure 8: Boxplot of erdafitinib AUC from relative bioavailability studies



The bottom and top edges of the box indicate the intraquartile range (the 25th and 75th percentiles). The line inside the box indicates the median value.

The whiskers indicate the 10th and 90th percentiles. Points indicate values outside the 10th and 90th percentiles.

Source: Figure 7 from Applicant's Summary of Biopharmaceutics Studies and Associated Analytical Methods

19.4.3. Population PK Analyses

The Applicant submitted a population PKPD report entitled "Population Pharmacokinetic Pharmacodynamic Report for Erdafitinib (b) (4)" to characterize the PK of erdafitinib in health subjects and patients with cancer and the time course of serum phosphate concentrations in patients

Objectives: The general aim of the population PK and PK-PD analyses was to characterize the PK of total and free erdafitinib plasma concentrations after various oral dose levels and dosing regimens of erdafitinib, and to subsequently link erdafitinib drug concentrations to the time course of serum phosphate concentrations.

The specific objectives of these analyses were:

- To characterize the population PK of erdafitinib including typical PK parameters and quantify inter- and intra-individual variability.

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- To provide a quantitative assessment of the effect of intrinsic and extrinsic factors on erdafitinib exposure.
- To characterize the PK-PD parameters characterizing the effect of erdafitinib total and free plasma concentrations on serum phosphate concentrations and quantify their inter- and intra-individual variability.
- To provide a quantitative assessment of the potential effect of the intrinsic and extrinsic factors on erdafitinib-related phosphate changes

Data: Two datasets, a PK dataset and a PK-PD dataset, were used for the PK and PK-PD analyses, respectively. A total of 6 clinical studies (EDI1001, EDI1002, EDI1003, EDI1005, BLC2001, and GAC1001) were included in the pooled dataset for population PK analysis, while 3 clinical studies conducted in subjects with cancer (EDI1001, BLC2001, and GAC1001) were selected for PK-PD analysis.

The final PK analysis included data from 373 subjects receiving oral single doses (range: 10 to 12 mg), continuous once daily doses (range: 0.5 to 12 mg), or intermittent once daily doses (range: 10 to 12 mg) of erdafitinib, and included 5060 total erdafitinib plasma concentrations and 650 free erdafitinib plasma concentrations. Summary statistics of the continuous and categorical subject covariates most relevant for the PK analysis are presented in **Table 126**.

Table 126: Summary of Key Demographic and Laboratory Covariates for Population PK Analysis

Subject characteristics	PK dataset (N = 373)	Missing data in PK dataset
Age (years)	60.1 (12.3) [21-88]	0 (0.00%)
Body weight (kg)	71.6 (16.6) [36.2-132]	0 (0.00%)
AGP (g/L)	1.20 (0.604) [0.249-3.15]	6 (1.61%)
Free fraction (%)	0.356 (0.221) [0.070-1.50]	13 (3.49%)
eGFR-MDRD ^a (mL/min/1.73 m ²)	80.9 (28.4) [30.8-150]	1 (0.268%)
eGFR ^b (mL/min)	84.0 (27.1) [30.1-150]	3 (0.804%) ^c
Sex		0 (0.00%)
Male	211 (56.6%)	
Female	162 (43.4%)	
Race		0 (0.00%)
White	296 (79.4%)	
Caucasian	259 (69.4%)	
Hispanic	37 (9.92%)	
Black	7 (1.88%)	
Asian	38 (10.2%)	
Other ^d	32 (8.58%)	

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Hepatic impairment ^e		3 (0.804%)
Normal	300 (80.4%)	
Mild	69 (18.5%)	
Moderate	1 (0.268%)	
Renal impairment ^f		1 (0.268%)
Normal	121 (32.4%)	
Mild	156 (41.8%)	
Moderate	95 (25.5%)	
Health status		0 (0.00%)
Healthy	28 (7.51%)	
Cancer subjects	345 (92.5%)	
Number of subjects		0 (0.00%)
EDI1001	187 (50.1%)	
EDI1002	8 (2.14%)	
EDI1003	12 (3.22%)	
EDI1005	8 (2.14%)	
BLC2001	139 (37.3%)	
GAC1001	19 (5.09%)	

Continuous variables are expressed as mean (standard deviation) [range]. Values are rounded to 3 significant digits. Ranges can have less than 3 significant digits if data had less than 3 digits.

Categorical variables are expressed as counts (%).

a eGFR-MDRD was truncated at a value of 150 mL/min.

b eGFR=eGFR-MDRD x body surface area/1.73, eGFR was truncated at a value of 150 mL/min.

c 1 subject had missing non-normalized eGFR (mL/min/1.73 m²) and 2 subjects had missing body surface area.

d Native Hawaiian, Pacific Islander, American Indian or Alaskan native, other, multiple and Race=White but without known ethnicity (Caucasian or Hispanic).

e Classification for hepatic impairment based on NCI.

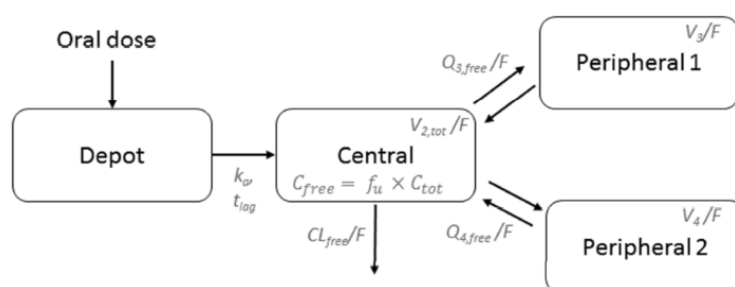
f Classification for renal impairment based on eGFR-MDRD.

g 1 subject had missing non-normalized eGFR (mL/min/1.73 m²) and 2 subjects had missing body surface area, leading to 3 subjects with missing body surface area-normalized eGFR but only 1 subject with missing renal impairment.

Population PK Model Development

Final Model: The final population PK model describing the time profiles of erdafitinib total and free plasma concentrations was an open, linear, 3-compartment disposition model with first-order absorption and elimination. A lag-time (t_{lag}) was used to describe the plasma PK profile of total and free erdafitinib. The binding of erdafitinib to plasma proteins was linear with respect to erdafitinib concentration. Free erdafitinib plasma concentrations were derived from total concentrations using measured FU. The model was parameterized in terms of the apparent central volume of distribution of total drug ($V_{2,tot/F}$), 2 apparent peripheral volumes of distribution ($V_{3/F}$ and $V_{4/F}$), the apparent clearance of free erdafitinib ($CL_{free/F}$), and the apparent inter-compartmental clearances of free ($Q_{3,free/F}$ and $Q_{4,free/F}$). Inter-individual variability (IIV) in model parameters was quantified using an exponential model for $CL_{free/F}$, $V_{2,tot/F}$, $V_{3/F}$, and apparent first-order absorption rate constant (k_a). Residual unexplained variability (RUV) was additive on natural logarithmic-transformed plasma concentrations and was estimated separately for total and free erdafitinib concentrations. A schematic representation of the final population PK model for erdafitinib is demonstrated in **Figure 9**. The parameter estimates for the final model including covariate effects are summarized in **Table 127**.

Figure 9: Schematic of the Final Population PK Model for Erdafitinib



Source: Figure 1 on page 179 of Applicant's population PKPD report

Table 127: Population PK Parameter Estimates, RSE, and 95% CI for the Final Population PK Model for Erdafitinib Using the Covariance Matrix and SIR

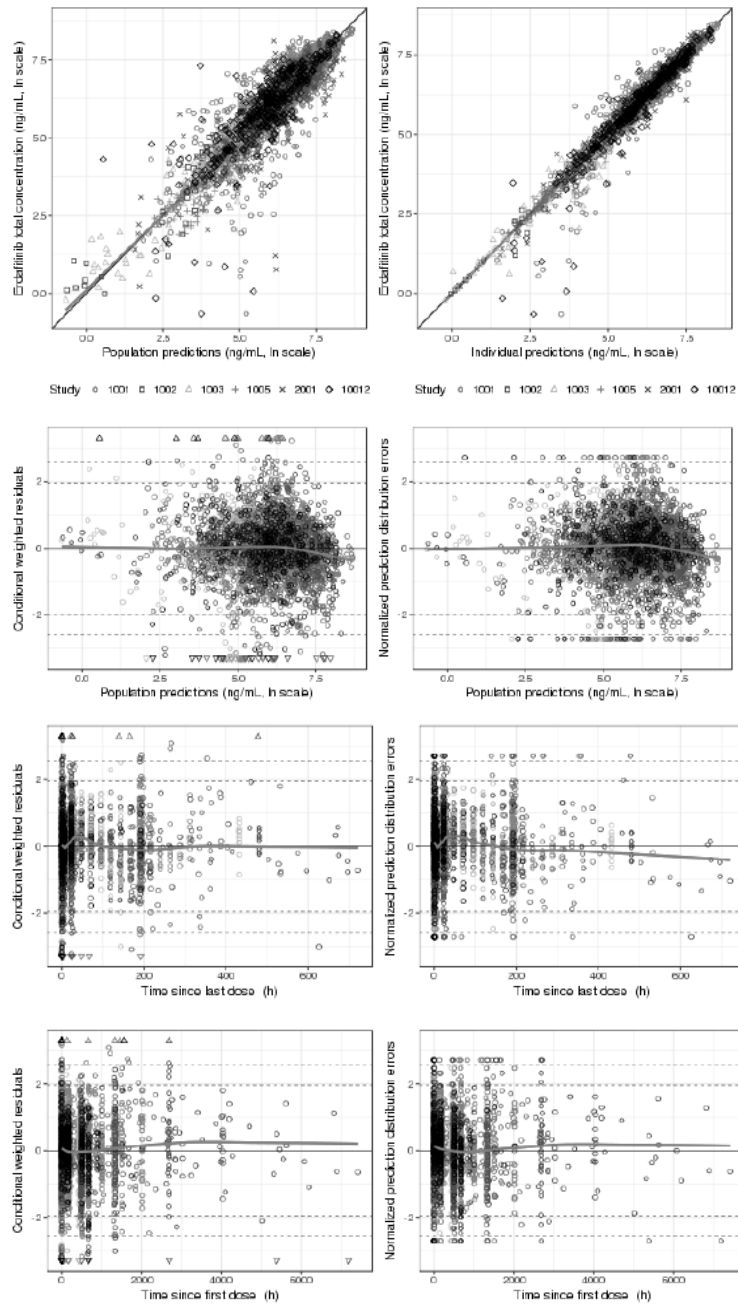
Pharmacokinetic Parameters ^a	Covariance matrix Estimate (RSE%) [95%CI]	SIR Median (RSE%) [95%CI]
CL _{free} /F (L/h)	83.2 (5.6%) [74.1 - 92.3]	83.2 (5.2%) [75.6 - 92.1]
V _{2,tot} /F (L)	18.9 (2.8%) [17.9 - 19.9]	18.9 (2.6%) [17.9 - 19.9]
V ₃ /F (L)	2480 (8.8%) [2053 - 2907]	2476 (8.5%) [2219 - 2948]
Q ₃ /F (L/h)	129 (26.0%) [63.3 - 195]	130 (12.8%) [101 - 166]
V ₄ /F (L)	767 (11.1%) [600 - 934]	771 (11.5%) [588 - 929]
Q ₄ /F (L/h)	2.72 (22.2%) [1.54 - 3.90]	2.73 (17.5%) [1.90 - 3.76]
k _a solution (h ⁻¹)	2.71 (17.1%) [1.80 - 3.62]	2.71 (17.7%) [1.83 - 3.72]
k _a capsules (h ⁻¹)	1.49 (13.1%) [1.11 - 1.87]	1.50 (9.76%) [1.25 - 1.80]
k _a tablets (h ⁻¹)	2.34 (10.0%) [1.88 - 2.80]	2.36 (11.1%) [1.90 - 2.92]
t _{lag} solution (h)	0.198 (6.1%) [0.174 - 0.222]	0.198 (5.5%) [0.175 - 0.216]
t _{lag} capsules (h)	0.244 (0.4%) [0.242 - 0.246]	0.244 (0.2%) [0.243 - 0.245]
t _{lag} tablets (h)	0.232 (1.6%) [0.225 - 0.239]	0.232 (0.8%) [0.229 - 0.236]
t _{lag} GAC1001 (h)	0.415 (0.4%) [0.411 - 0.419]	0.415 (0.2%) [0.413 - 0.416]
Power AGP on V _{2,tot} (-)	-0.473 (9.3%) [-0.559 - -0.387]	-0.474 (5.9%) [-0.528 - -0.416]
SEX-CL (%)	-18.8 (29.0%) [-29.5 - -8.1]	-19.3 (25.5%) [-29.1 - -9.7]
IMPREN2-CL (%)	21.1 (29.4%) [8.9 - 33.3]	20.9 (26.7%) [9.9 - 32.2]
IMPREN3-CL (%)	21.9 (31.6%) [8.3 - 35.5]	22.3 (30.2%) [8.7 - 35.3]
WT1-V2 (%)	-9.82 (38.4%) [-17.2 - -2.4]	-9.50(36.0%) [-16.4 - -2.7]
WT2-V2 (%)	19.8 (17.2%) [13.1 - 26.5]	20.0 (17.1%) [13.6 - 27.2]
SEX-V2 (%)	-16.4 (19.5%) [-22.7 - -10.1]	-16.5 (18.7%) [-22.6 - -10.1]
IV CL _{free} /F (%CV)	45.7 (6.2%) [40.1 - 51.3]	45.9 (4.2%) [42.3 - 49.8]
IV V _{2,tot} /F (%CV)	23.0 (8.2%) [19.3 - 26.7]	23.1 (5.9%) [20.8 - 25.9]
IV V ₃ /F (%CV)	105 (10.6%) [83.2 - 127]	105 (8.6%) [87.6 - 123]
IV k _a /F (%CV)	115 (10.7%) [90.9 - 139]	115 (6.0%) [103 - 130]
RUV total (%CV)	27.2 (6.4%) [23.8 - 30.6]	27.2 (1.2%) [26.6 - 27.9]
RUV free (%CV)	7.64 (14.1%) [5.53 - 9.75]	7.66 (5.3%) [6.90 - 8.52]

Source: Table 16 on page 89 of Applicant's population PKPD report

Model Evaluation: The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs). The goodness-of-fit plots for the final model are displayed in **Figure 10** and the VPCs plots are demonstrated in **Figure 11**.

Figure 10: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model for Erdafitinib Total Concentrations

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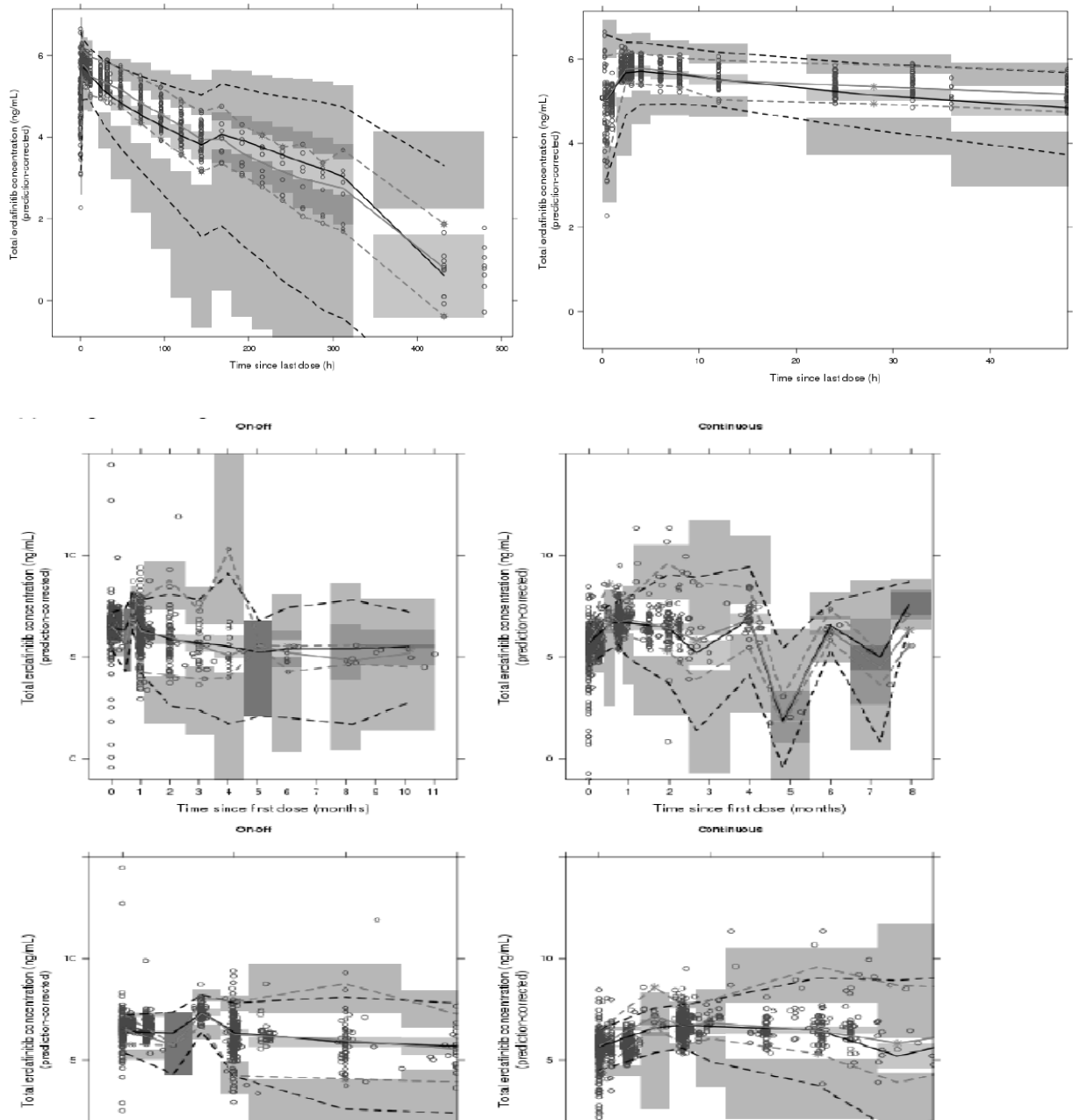


Symbols represent observations/predictions (upper panels), conditional weighted residuals (3 lower left panels) and the normalized prediction distribution errors (3 lower right lower panels) for erdafitinib total concentrations for the studies EDI1001 (red circle), EDI1002 (blue square), EDI1003 (yellow triangle), EDI1005 (green plus symbol), BLC2001 (violet cross) and GAC1001, denoted 10012 (black losange); solid black lines represent the identity lines; solid red lines represent the trend line (lowess, locally weighted scatter plot smoothing).

Source: Figure 39 on page 142 of Applicant's population PKPD report

Figure 11: Prediction-Corrected Visual Predictive Checks for Erdafitinib Total Concentrations (Left Panel: Single Dose; Right Panel: Multiple Dose)

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Prediction-corrected concentrations are on the log scale. Red lines: median (solid line), 5th and 95th (dashed lines) percentiles of the simulated data with its 95% confidence interval (blue and red shaded area); black lines: median (solid line), 5th and 95th (dashed lines) percentiles of the observed data for erdafitinib. Bins were chosen by timepoints (single dose: first day every 6 h or less, then every day; multiple dose: every month) and can be empty (no shaded areas) depending on the stratifica.

Source: Adapted from Figure 41 to 144 on page 53-55 of Applicant's population PKPD report

Posthoc PK Parameter Estimation: A summary of the posthoc PK parameters for erdafitinib by health status using the final model is shown in **Table 128**.

Table 128: Summary of Posthoc Parameters for the Final PK Model by Health Status

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Parameter ^a	Mean	Median	Standard deviation	Minimum	Maximum
Cancer subjects (N=326)					
Dose (mg)	8.3	9.0	2.3	0.5	12
CL _{tot} /F (L/h)	0.29	0.26	0.17	0.036	1.27
V _{2,tot} /F (L)	19.7	18.4	7.4	3.8	63.5
CL _{free} /F ^b (L/h)	99.2	93.4	42.6	7.8	294.2
V _{2,free} /F ^b (L)	7359	6706	3268	1271	22357
AUC _{tot,0-24,SS} ^c (ng.h/mL)	39875	31970	29915	1098	278451
AUC _{free,0-24,SS} ^c (ng.h/mL)	106.0	88.4	88.5	3.4	1280.9
C _{tot,2h,SS} (ng/mL)	1847	1501	1312	52	11805
C _{tot,trough,SS} (ng/mL)	1467	1147	1174	38	11195
C _{free,2h,SS} (ng/mL)	4.9	4.3	3.8	0.2	54.3
C _{free,trough,SS} (ng/mL)	3.9	3.1	3.5	0.1	51.5
DN AUC _{tot,0-24,SS} ^c (ng.h/mL)	38034.14	30577.69	24833.43	6311.18	222760.52
DN AUC _{free,0-24,SS} ^c (ng.h/mL)	99.82	85.70	71.76	27.20	1024.70
DN C _{tot,2h,SS} (ng/mL)	1761	1454	1077	420	9444
DN C _{tot,trough,SS} (ng/mL)	1401	1102	987	164	8956
DN C _{free,2h,SS} (ng/mL)	4.7	4.1	3.1	1.5	43.4
DN C _{free,trough,SS} (ng/mL)	3.6	3.1	2.9	0.80	41.2
Healthy subjects (N=47)					
Dose (mg)	10.6	10	0.9	10	12
CL _{tot} /F (L/h)	0.46	0.41	0.25	0.15	1.40
V _{2,tot} /F (L)	23.9	22.1	8.0	8.2	45.3
CL _{free} /F ^b (L/h)	86.9	86.7	32.3	27.3	168.9
V _{2,free} /F ^b (L)	5000	4406	2322	1616	13616
AUC _{tot,0-24,SS} ^c (ng.h/mL)	25812	25026	14941	5388	74120
AUC _{free,0-24,SS} ^c (ng.h/mL)	119	116	43	16	209
C _{tot,2h,SS} (ng/mL)	1244	1176	711	224	3798
C _{tot,trough,SS} (ng/mL)	908	855	545	180	2503
C _{free,2h,SS} (ng/mL)	5.8	5.9	2.1	0.7	10.6
C _{free,trough,SS} (ng/mL)	4.2	4.2	1.5	0.6	6.9
DN AUC _{tot,0-24,SS} ^c (ng.h/mL)	22578	19332	11479	5729	53568
DN AUC _{free,0-24,SS} ^c (ng.h/mL)	109	92	54	47	293
DN C _{tot,2h,SS} (ng/mL)	1080	917	527	306	2586
DN C _{tot,trough,SS} (ng/mL)	800	700	437	172	1960
DN C _{free,2h,SS} (ng/mL)	5.2	4.6	2.4	2.5	13.3
DN C _{free,trough,SS} (ng/mL)	3.8	3.3	2.1	1.5	11.2

DN: dose-normalized to 8 mg

^a PK parameters were derived using baseline FU. Missing FUs were imputed using AGP if available, else using the study median. Only the first formulation within an individual is reported. Trough concentrations were predicted at 23.99 h postdose.

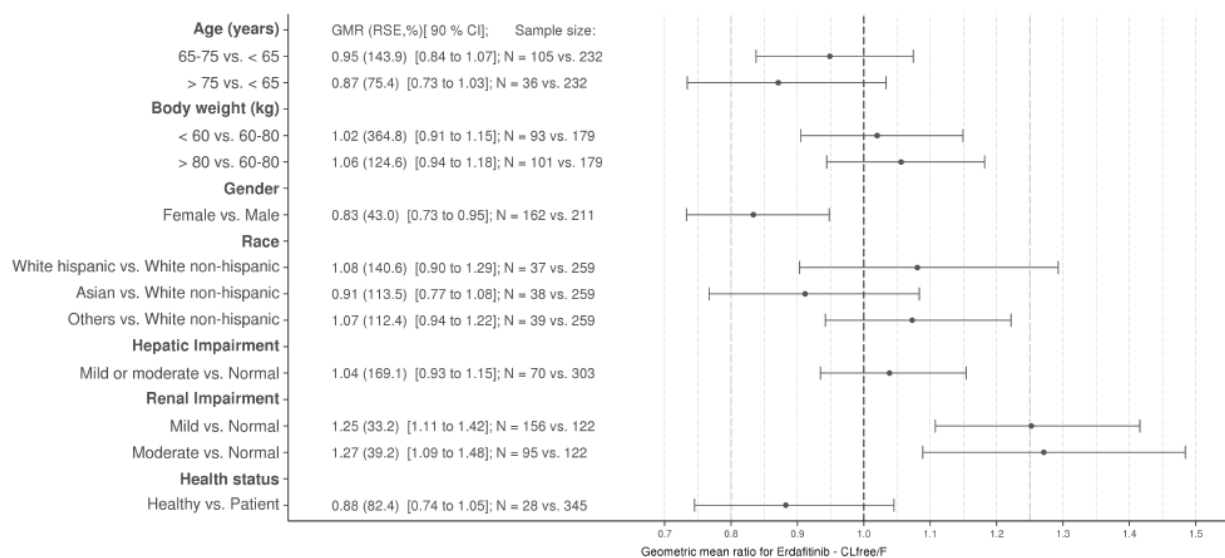
^b $CL_{free}/F = (CL_{tot}/F)/FU$ and $V_{2,free}/F = (V_{2,tot}/F)/FU$.

^c Apparent AUCs were computed for the starting dose and assuming steady-state: $AUC = DOSE/CL$. AUC_{free} was calculated as $AUC_{free} = AUC_{tot} \times FU$.

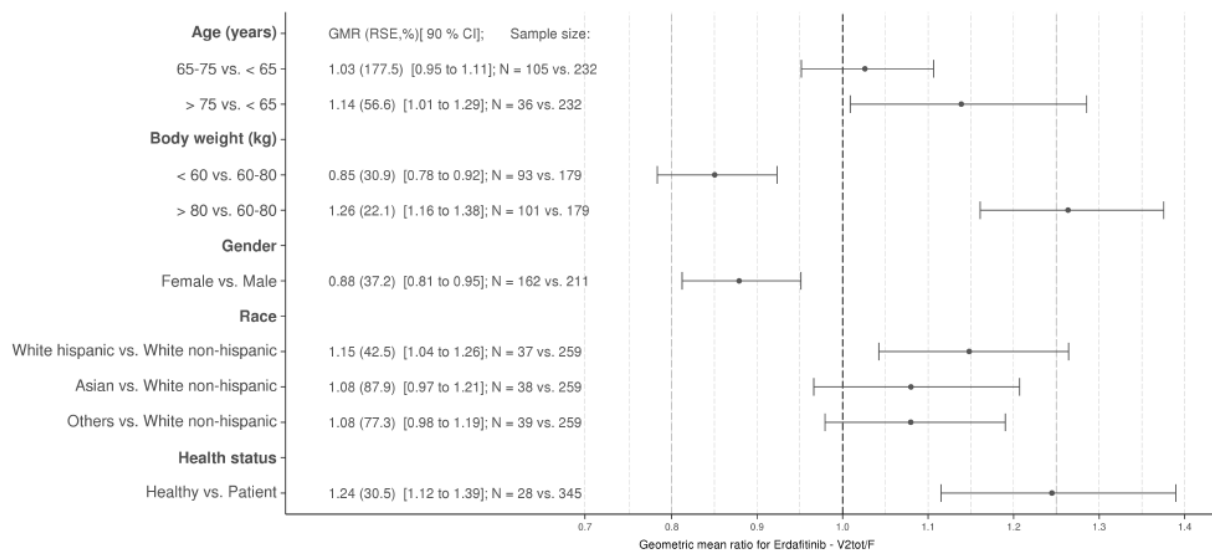
Source: Table 6 on page 60 of Applicant's population PKPD report

Effect of Covariates on Erdafitinib PK: Within the range of covariate values evaluated as part of the full model, the impact of age, race/ethnicity (Hispanic, Asian), and mild hepatic impairment on erdafitinib exposure was not statistically significant (**Figure 12**). In the final model, sex and mild and moderate renal impairment had a statistically significant effect on CL_{free}/F , while weight, sex, and AGP were statistically significant on V_{2tot}/F . Once AGP was incorporated as a covariate on V_{2tot}/F , the effect of health status on V_{2tot}/F was no longer statistically significant. On average, women had 18.8% lower CL_{free}/F relative to men, and subjects with mild and moderate renal impairment had a 21.1% and 21.9% higher CL_{free}/F relative to subjects with normal renal function. On average, subjects with low (<60 kg) and high (>80 kg) body weight had 9.82% lower and 19.8% higher V_{2tot}/F , respectively, relative to median weight (60 to 80 kg). A 50% decrease in AGP (as observed between healthy subjects and subjects with cancer) was estimated to lead to a 38.8% increase in V_{2tot}/F and a 50% increase in CL/F , but no effect on CL_{free}/F .

Figure 12: Forest Plots for CL_{free}/F (Upper Panel) and $V_{2,tot}/F$ (Lower Panel) Using the Full Covariate Model for the Covariate Evaluation for Erdafitinib



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Source: Figure 7 on page 55 of Applicant's population PKPD report

Reviewer's comments: The population PK analysis is acceptable. Overall, the final population PK model was able to characterize the PK profile of erdafitinib as indicated in the applicant's diagnostic plots.

However, the reviewer noticed some difference in key PK parameters (Volume of distribution, effective terminal half-life, and mean clearance) between those calculated by NCA method and those estimated by population PK approach. The label section in 12.3 used values obtained from study EDI1001 and calculated by NCA approach. The difference is summarized in Table 129. The discrepancy in PK parameters could be partially attributed to the difference in number of subjects in study EDI1001 (n=77) and in the population PK dataset (n=345).

Table 129: Summary of difference in key PK parameters of erdafitinib between values Calculated by NCA and Estimated by Population PK

PK parameters	NCA approach by	Population PK Approach
Mean apparent volume of distribution	29 (L)	19.7 (L)*
Mean total apparent clearance (CL/F)	0.36 (L/h)	0.29 (L/h)
Mean effective half-life	59 (hours)	76.4 (hours)

Note: *Apparent central value of distribution.

Population PK-PD Analysis Development

Data: Three clinical studies (EDI1001, BLC2001, and GAC1001) conducted in subjects diagnosed with cancer were included in the pooled dataset for population PK-PD analysis. Data from 345

subjects receiving continuous once daily doses (range: 0.5 to 12 mg) or intermittent once daily doses (range: 10 to 12 mg) of erdafitinib, contributing 4639 total serum phosphate concentrations, were included in the analysis. Subject characteristics were similar to those described above for the PK analysis dataset. The exploration of the prognostic factors in the analysis dataset evidenced that for subjects with fibroblast growth factor receptor (FGFR)-positive tumors, 49.6% (N = 123) had FGFR mutations, 20.6% (N = 51) had FGFR alterations, and 29.8% (N = 74) had FGFR translocations. Urothelial cancer was diagnosed in 44.3% (N = 153) of subjects, whereas 55.7% (N = 192) subjects were diagnosed with other types of cancer. A total of 116 (33.6%), 192 (55.7%), and 18 (5.2%) subjects were classified in the Eastern Cooperative Oncology Group (ECOG) status grade 0, 1, or 2, respectively. Visceral metastases were present in 57.7% (N = 199) of subjects. A phosphate binder was coadministered at least once for 165 (47.8%) subjects. Most of the subjects were chemotherapy-relapsed/refractory (91%, N = 314), whereas 3.5% (N = 12) were chemotherapy-naïve. The mean (range) baseline hemoglobin was 11.8 g/dL (7.90 to 16.7 g/dL).

Population PKPD Model Development

The relationship between the absolute change from baseline in serum phosphate concentrations ($[PO_4]$) and free erdafitinib plasma concentrations in a hypothetical biophase (or effect compartment) was characterized by a slope model, with a coefficient (M) and an exponent (γ). In addition, the equilibration rate constant to predict erdafitinib free concentrations at biophase (effect compartment rate constant $[k_{e0}]$) and the serum phosphate concentrations at pre-treatment baseline ($[PO_4]_{BSL}$) were also estimated from the data according to the following equation:

$$[PO_4]_t = [PO_4]_{BSL} + M \cdot C_e^\gamma, \text{ where } dC_e/dt = k_{e0} \cdot (C_{free} - C_e)$$

Phosphate data pointed toward an attenuation of the drug effect on phosphate over time. This effect was empirically modelled by a time-dependent function of M:

$$M = m \cdot (1 - T), \text{ where } dT/dt = k_{in} \cdot (1 - T)$$

where T was the amount of attenuation over time, k_{in} was the rate constant describing the attenuation of drug effect with time, and m was the coefficient of the slope model describing the relationship between $[PO_4]$ and C_e at time 0. In addition, treatment interruptions longer than approximately 24 days and treatment discontinuation resulted in a new but lower plateau phosphate concentration as compared with pre-treatment baseline. This was accounted for using an empirical time-dependent function of $[PO_4]_{BSL}$:

$$[PO_4]_{BSL} = [PO_4]_0 \quad \text{if } (T_{SLD} \leq t_{lag})$$

$$[PO_4]_{BSL} = [PO_4]_P - ([PO_4]_P - [PO_4]_0) \cdot e^{-(k_{base} \cdot (T_{SLD} - t_{lag}))} \quad \text{if } (T_{SLD} > t_{lag})$$

With $[PO_4]$ as the population estimate of the phosphate baseline value when TSLD was less or

equal to t_{lag} (pre-treatment baseline), TSLD as the time since last dose, $[PO_4]_P$ as the estimate of the phosphate baseline value plateau, k_{base} as the rate of decline of phosphate baseline value with time, and t_{lag} as the time delay after which phosphate baseline value started to decline with time.

IIV in model parameters was quantified using an additive model for $[PO_4]_0$ and $[PO_4]_P$ and an exponential model for m , k_{e0} , and k_{in} . RUV was additive on natural logarithmic-transformed serum phosphate concentrations.

The parameter estimates of the final PK-PD model are presented in **Table 130**. All parameters were estimated with adequate precision, as measured by a RSE below 14.8% for fixed effects and below 15.8% for random effects. The goodness-of-fit plots for the final PKPD model is shown in Figure 13. The VPC plots for the final PKPD model is shown in Figure 14.

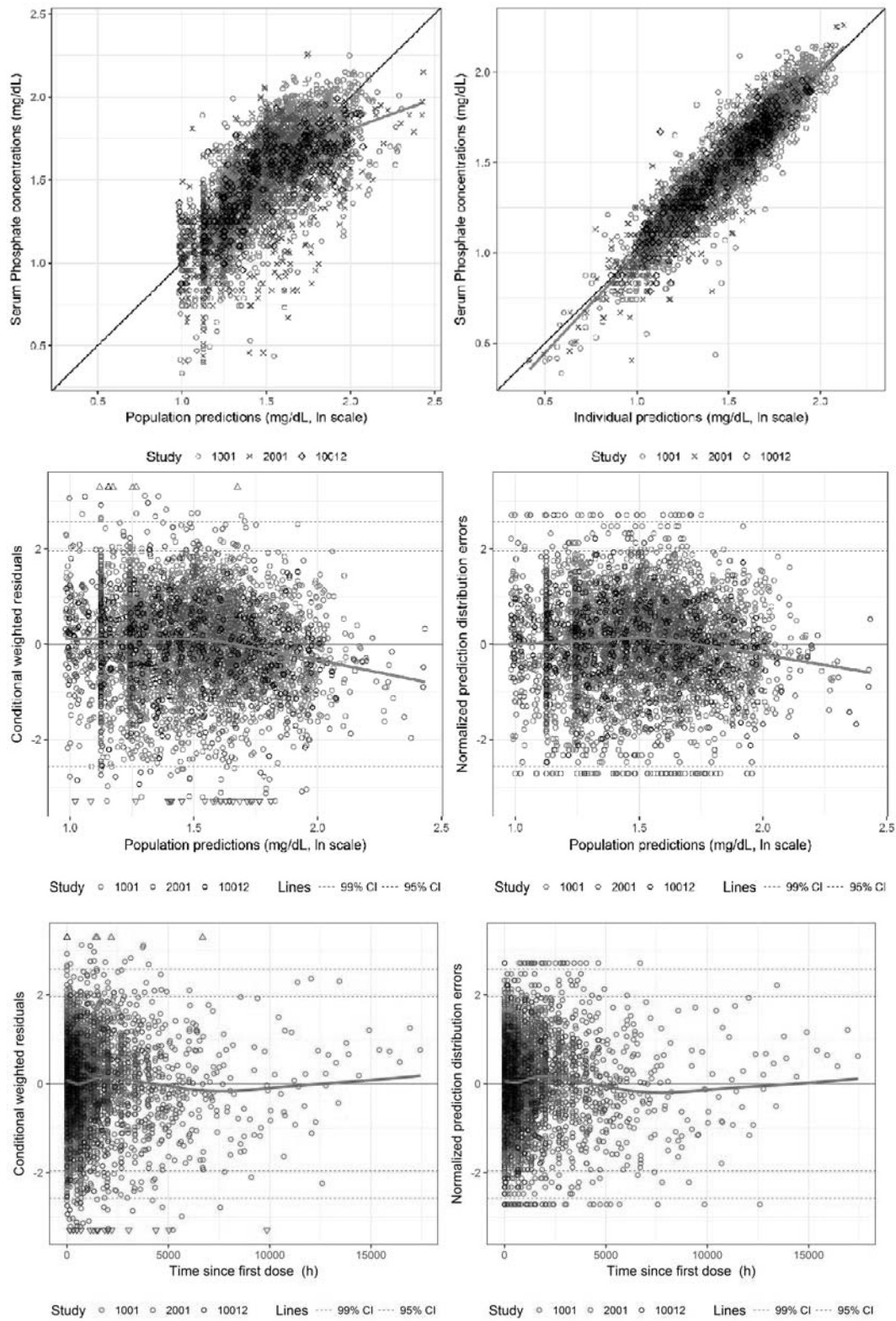
Table 130: Population Parameter Estimates for the Final Population PK-PD Model

Parameters	Description	Final Model Estimate (RSE%)
$[PO_4]_0$ (mg/dL)	Phosphate baseline	3.08 (1.4%)
m (Slope) (mg/dL/(ng/mL))	Slope of drug effect	0.869 (5.5%)
γ (Power exponent)	Exponent of drug effect relationship	0.860 (4.7%)
k_{e0} (h^{-1})	Effect compartment rate constant	0.0199 (2.9%)
k_{in} (h^{-1})	Rate constant describing attenuation of drug effect over time	0.000102 (1.5%)
θ_{SEX} (%)	Gender effect on phosphate baseline (proportional change for females)	12.4 (14.8%)
$[PO_4]_P$ (mg/dL)	Post-treatment interruption phosphate baseline plateau	2.67 (2.1%)
k_{base} (h^{-1})	Post-treatment interruption change of phosphate baseline with time rate constant	0.0101 (13.0%)
t_{lag} (h)	Post-treatment interruption lag-time before phosphate baseline value decline	143 (1.0%)
IIV $[PO_4]_0$ (mg/dL)	Inter-individual variability on phosphate baseline	0.463 (6.0%)
IIV m (%CV)	Inter-individual variability on the slope of drug effect	39.4 (7.4%)
IIV k_{e0} (%CV)	Inter-individual variability on the effect compartment rate constant	90.9 (14.6%)
IIV k_{in} (%CV)	Inter-individual variability on the rate constant describing attenuation of drug effect over time	115 (12.8%)
Correlation IIV k_{e0} - k_{in} (-)	Correlation between inter-individual variabilities of the effect compartment rate constant and the rate constant describing attenuation of drug effect over time	0.577 (15.8%)
IIV $[PO_4]_P$ (mg/dL)	Inter-individual variability on post-treatment interruption phosphate baseline plateau	0.498 (18.0%)
RUV phosphate (%CV)	Residual unexplained variability on serum phosphate concentrations	11.9 (2.7%)

Source: Table A2 on page 18 of Applicant's population PKPD report

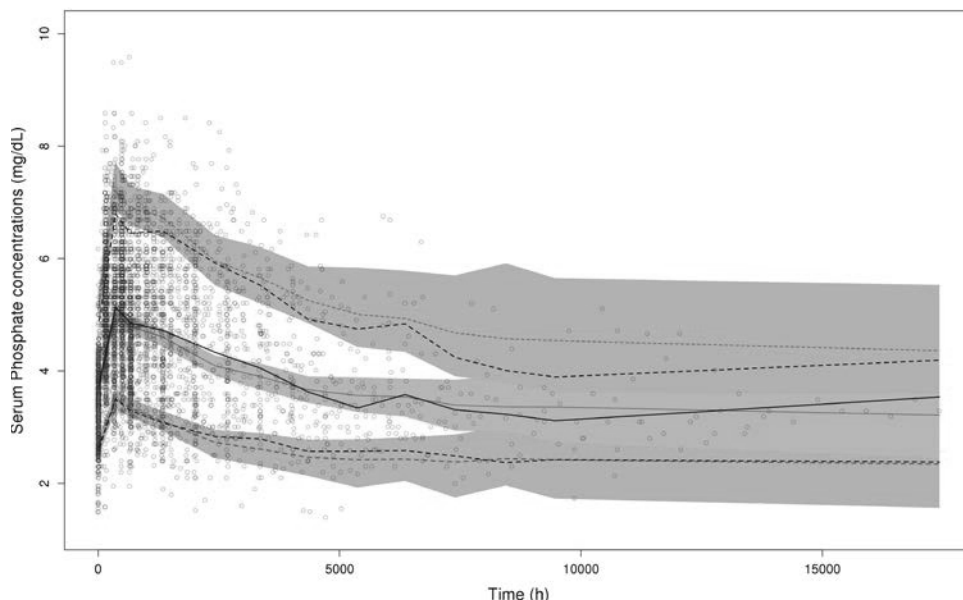
Figure 13: Goodness-of-fit Plots for the Final PK-PD Model

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Source: Figure 50 on page 163 of Applicant's population PKPD report

Figure 14: pcVPC of the Final PK-PD Model for Serum Phosphate Concentrations Versus Time



Red lines: median (solid line), 5th and 95th (dashed lines) percentiles of the simulated data with its 95% confidence interval (blue and red shaded area); black lines: median (solid line), 5th and 95th (dashed lines) percentiles of the observed data for serum phosphate

Source: Figure 52 on page 165 of Applicant's population PKPD report

Summary of Posthoc PD Parameters: A summary of the posthoc PD parameters of all subjects included in the PK-PD dataset is demonstrated in **Table 131**. The peak-to-trough fluctuation within a dosing interval was low for serum phosphate concentrations (5.68 to 5.65 mg/dL on average at Day 14), supporting the monitoring of daily phosphate concentrations for dosage adjustment.

Table 131: Summary of the Posthoc Parameters for the Final PK-PD Model

Parameter	Mean	Median	Standard deviation	Minimum	Maximum	N
$[PO_4]_0$ (mg/dL)	3.21	3.24	0.45	1.52	4.48	345
m (Slope) (mg/dL/(ng/mL))	0.972	0.917	0.348	0.317	2.68	345
$C_{PO_4,12h}$ (mg/dL) ^a	5.68	5.58	1.11	2.33	10.9	345
$C_{PO_4,trough}$ (mg/dL) ^a	5.65	5.56	1.10	2.35	10.9	345

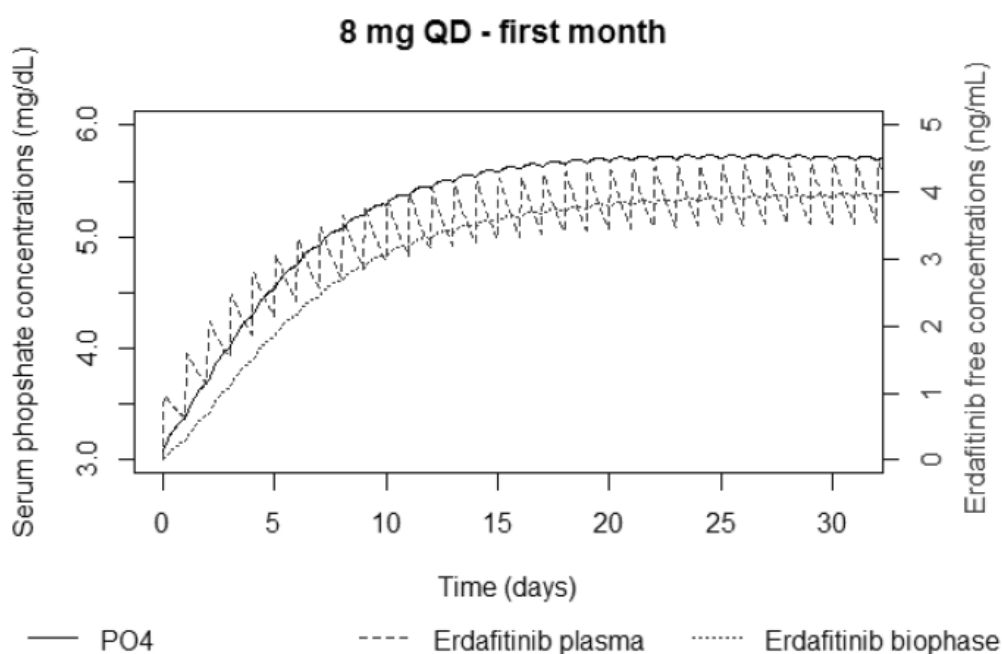
^a At Day 14 for a 8 mg once daily regimen, trough concentrations were predicted at 23.99 h postdose.

Source: Table 8 on page 70 of Applicant's population PKPD report

Serum Phosphate Concentration-Time Course: The relationship between serum phosphate concentrations and erdafitinib free concentrations at biophase was characterized by a slope (M) and an exponent (γ), with the equilibration rate constant accounting for the delay between PK and PD effect. Near steady state for free concentrations in the biophase were reached

around the same time as the steady state for free concentrations in plasma. Figure 15 represents the time course of erdafitinib free concentrations in plasma and in biophase, as well as the increase in phosphate with repeated daily dosing. The relationship between serum phosphate and free erdafitinib concentration in the biophase was almost linear with an exponent of 0.86, with approximately 0.48 mg/dL increase in phosphate concentrations for an increase in erdafitinib free plasma concentration from 0 to 0.5 ng/mL at the first dose. According to this model, doubling the free concentration resulted in a 1.8-fold increase in drug-related phosphate changes. Serum phosphate concentrations increased after administration of the first dose and reached more than 95% maximal level after about 14 days of starting erdafitinib treatment (Figure 15).

Figure 15: Simulated Free Erdafitinib Plasma Concentrations, Free Erdafitinib Concentrations at Biophase and Serum Phosphate Concentrations for a Typical Subject with Urothelial Carcinoma, Based on the Final PK-PD Model (8 mg Once Daily for 1 Month)

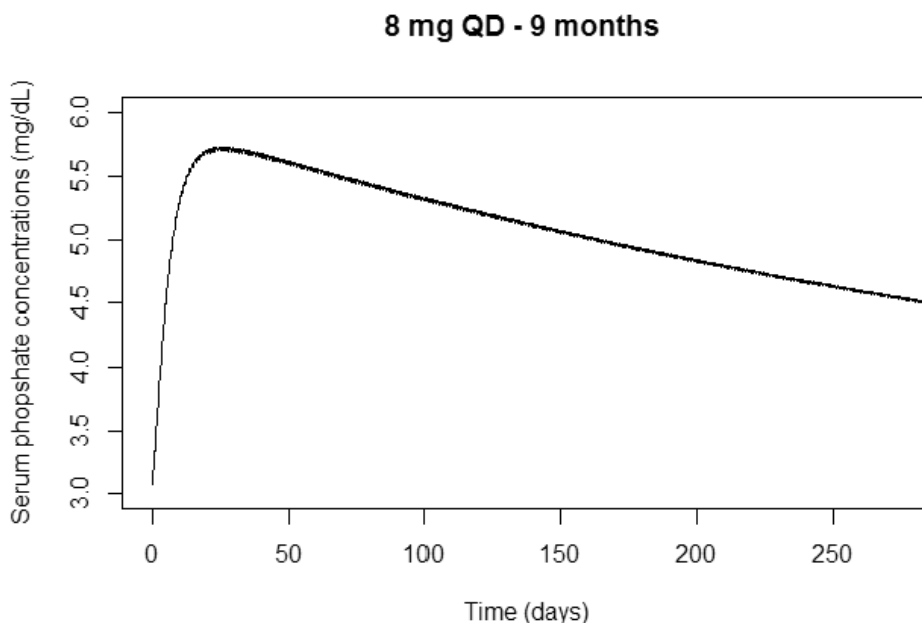


Source: Figure 13 on page 68 of Applicant's population PKPD report

The slope of the drug effect declined with time, with a reduction of 50% in the slope of the drug effect predicted after 9.5 months. This effect was only time-dependent and not concentration related. This translated into a decrease in serum phosphate concentrations with time under a constant dosing regimen and non-stationary serum phosphate concentrations. Based on the typical value of model parameters, serum phosphate concentrations reached a level of about 5.6 mg/dL after 14 days of dosing with erdafitinib 8 mg dose and started declining steadily after 1 month of treatment, resulting in lower phosphate concentration of approximately 1 mg/dL over 9 months (from the 2nd to the 10th months after treatment initiation) despite continuous

dosing (Figure 16). In addition, upon treatment interruption or discontinuation, phosphate concentrations declined with time to reach a level lower than the pre-treatment baseline: approximately 580 hours (24 days) after the last dose of erdafitinib, a post-treatment baseline phosphate concentration was re-established at 2.67 mg/dL, lower than the pre-treatment baseline of 3.08 mg/dL

Figure 16: Simulated Serum Phosphate Concentration-Time Profile for a Typical Subject With Urothelial Carcinoma, Based on the Final PK-PD Model (8 mg Once Daily for 9 Months)



Source: Figure 15 on page 69 of Applicant's population PKPD report

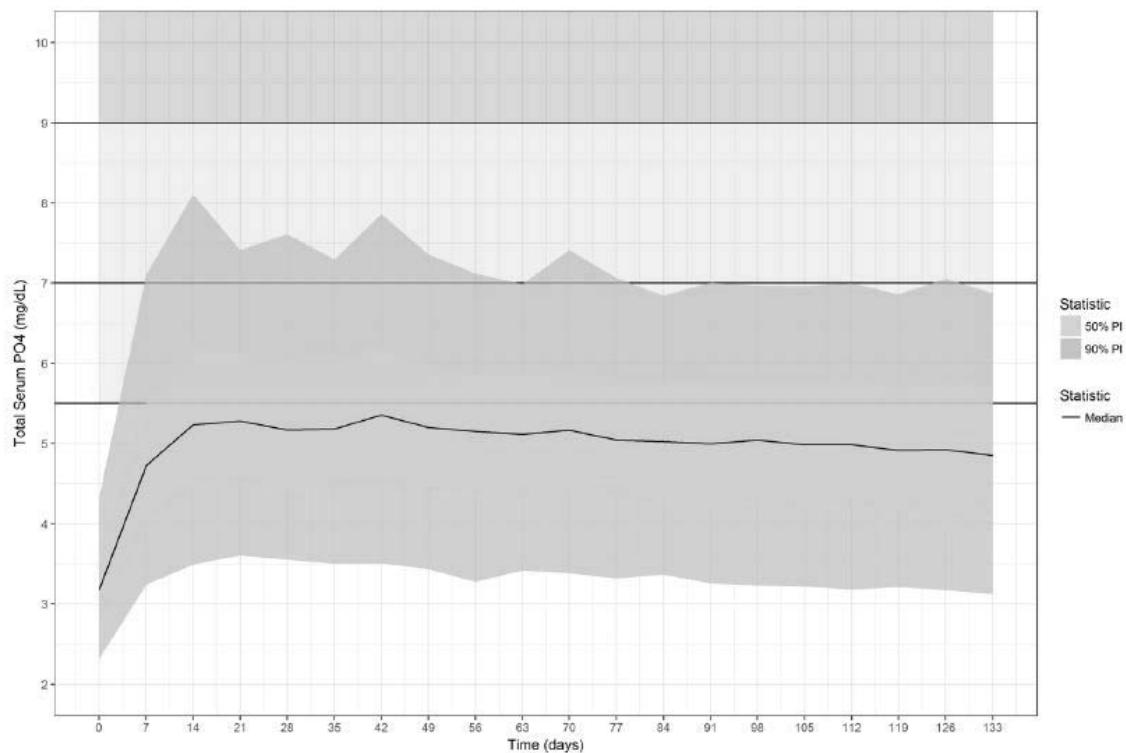
Reviewer's comments: The population PK-PD analysis is acceptable. The final population PKPD model was able to characterize the serum phosphate concentrations as indicated in the applicant's diagnostic plots. The reviewer agrees that the proposed dosing regimen is acceptable based on the PK/PD simulation results,

Simulations of Proposed Dosing Regimen: The population PK (full covariate model) and PK/PD models linking erdafitinib dose to serum phosphate (PO₄) concentrations were used to simulate PK and serum phosphate concentrations in fibroblast growth factor receptor positive (FGFR+) urothelial cancer subjects. A virtual population of 1000 or 10,000 (for the covariate effects scenarios) random virtual subjects were sampled from the final PK/PD model parameter distributions.

For the proposed pharmacodynamically guided dosing algorithm scenario, phosphate concentrations over time are summarized in Figure 17. The proportion of subjects with phosphate concentrations in different concentration ranges is shown in Figure 18. The proportion of subjects given different doses over time is shown in Figure 19.

As shown Figure 17, the proposed pharmacodynamically guided dosing algorithm was predicted to result in 29% of subjects within the phosphate target concentrations range after both 1 and 4 cycles (C1 and C4) of treatment. At the end of cycle 4 (C4), the median treatment duration in the current dataset of BLC2001, 65% of subjects remained below this range (phosphate concentrations <5.5 mg/dL), while only very few subjects were above the range (5% and <1% within 7.0-9.0 mg/dL and above 9.0 mg/dL, respectively). Around 38% of subjects had their treatment interrupted at least once.

Figure 17: Phosphate Concentrations vs Time for the Proposed PD Guided Dosing Regimen

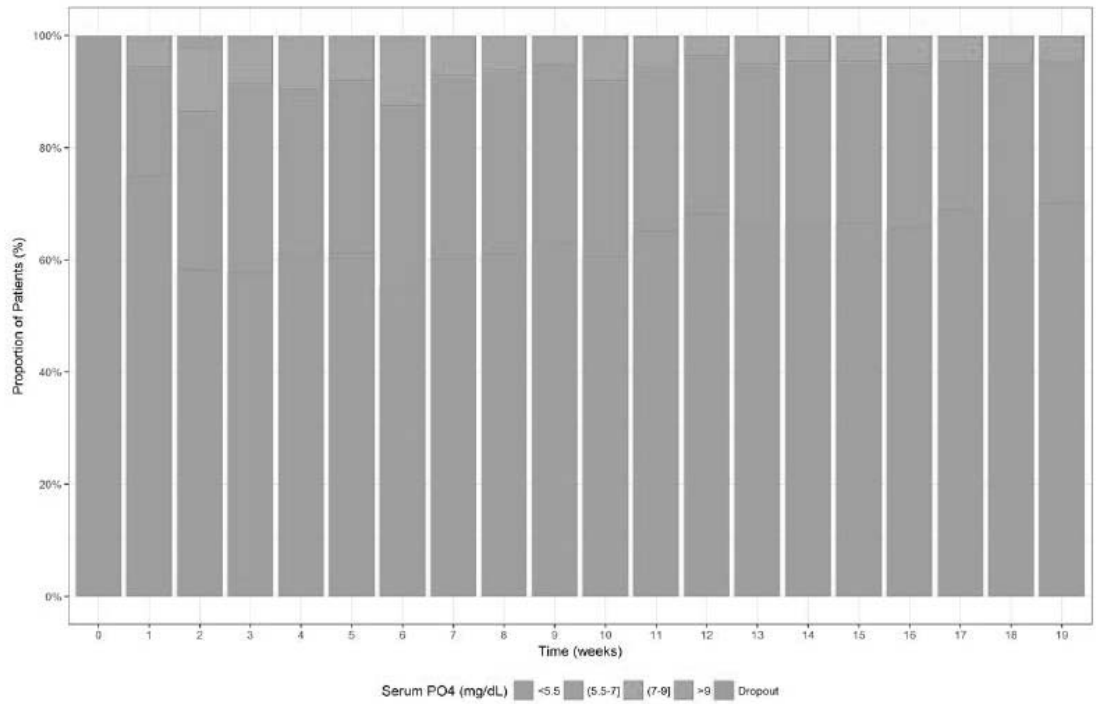


Note: Solid black line represents median serum phosphate concentrations. The blue and grey area are the 50% and 90% prediction intervals, respectively. The green area represents serum phosphate concentrations between 5.5 and 7 mg/dL, the orange area between 7 and 9 mg/dL and the red area >9 mg/dL.

Source: Figure 3 on page 25 of Applicant's Simulation Study Report

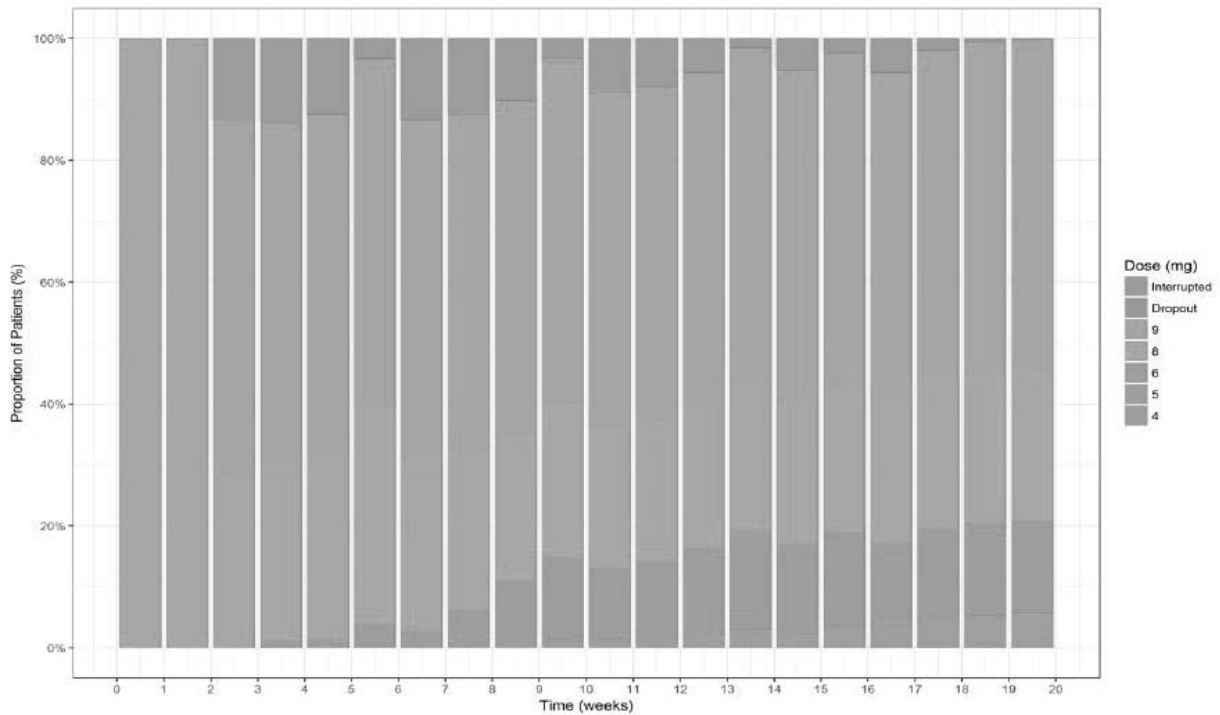
Figure 18: Proportion of Subjects in Different Serum Phosphate Concentration Ranges, vs Time for the Proposed PO4 Guided Dosing Regimen

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Source: Figure 4 on page 25 of Applicant's Simulation Study Report

Figure 19: Proportion of Subjects on Different Dose Levels vs. Time for the Proposed PO4 Guided Dosing Regimen



Source: Figure 5 on page 26 of Applicant's Simulation Study Report

Reviewer's Comments: There were limitations to the above analysis. All simulations and dose adjustments were only based on serum phosphate concentrations, whereas in BLC2001 individualized dose up-titrations, interruptions and reductions were also triggered by other safety endpoints as recommended in the study protocol. No model was available to account for the occurrence of such events. Therefore, predicted proportions may not provide a fully accurate estimation of the different endpoints such as proportions of subjects at different phosphate and dose levels compared to data observed in BLC2001

Despite the limitation, the simulations generally support that the proposed starting dose of 8 mg with individualized up-titration to 9 mg on day 14 if serum phosphate concentration is below 5.5 mg/dL which maximizes the number of subjects with serum phosphate concentrations within the target range defined in BLC2001 while minimizing treatment interruptions and dose reductions.

19.4.4. PD-Clinical Endpoints Analyses

Relationship between PO4 and Efficacy/Safety Endpoints

The applicant submitted a separate exposure-response (ER) analysis report entitled "Exposure Response (Efficacy and Safety) Report Protocol 42756493BLC2001; Phase 2" based on data from study BLC2001. The ER analyses were able to describe the relationship between serum phosphate and objective response rate (ORR) as well as relationship between serum phosphate and selected clinical safety endpoints (eye disorders, nail disorders, CSR, palmar-plantar erythrodysesthesia syndrome (PPES), and skin disorders).

Objective: The objectives of this report were:

- To characterize the relationship between exposure to serum phosphate and objective response rate based on best response (ORR, comprising complete response [CR] and partial response [PR]), the primary efficacy endpoint of Study BLC2001. In addition, secondary objectives were to explore the relationship between exposure to serum phosphate and disease control rate (DCR, comprising CR, PR, and stable disease) and progression-free survival (PFS).
- To characterize the relationship between exposure to erdafitinib and/or serum phosphate and selected clinical safety endpoints: eye disorders (excluding central serous retinopathy [CSR]), CSR, nail disorders, palmar-plantar erythrodysesthesia (PPES), and skin disorders.

Data: The efficacy and safety data were from Phase 2 study BLC2001. Study BLC2001 is a Phase 2, multicenter, open-label study to evaluate the efficacy and safety of single-agent erdafitinib in subjects with locally advanced or metastatic urothelial carcinoma and whose tumors had certain FGFR genetic alterations. Three dosing regimens were involved in the study. At the start of the study, subjects were randomized to either Regimen 1 (10 mg intermittent) or Regimen 2 (6 mg daily). Subjects in Regimen 1 could increase their dose to 12 mg intermittent and subjects in Regimen 2 could increase their dose to 8 mg daily, based on the serum phosphate concentrations on Cycle 1 Day 28 and absence of any drug-related disorder. At interim analysis 1 [IA1], based on efficacy and safety data and supported by preliminary PK-PD modeling, the data review committee decided to terminate further enrollment to the intermittent regimen and selected a higher continuous dose of 8 mg daily (Regimen 3). Subjects in Regimen 3 could increase their dose to 9 mg daily based on the phosphate level on Cycle 1 Day 14 in absence of any drug-related disorder. Overview of data included in the population ER efficacy and safety analysis is demonstrated in Table 132.

Table 132: Overview of Data Included in the Population ER Efficacy and Safety Analyses

Study (n)	Description	Population	Formulation(s) and Dosing	Response Assessment and Safety Assessment ^a
42756493 BLC2001 (Planned n=177 on continuous Regimens 2 and 3)	Multiple dose, open-label, Phase 2, 2-arm multicenter study to determine the efficacy and the safety of two different dose regimens of JNJ-42756493	Male and female subjects with metastatic or unresectable urothelial cancers with FGFR genomic alterations	Tablet Regimen 2: Continuous 6 mg once daily with possible up-titration to 8 mg once daily at Day 28 Regimen 3: Continuous 8 mg once daily with possible up-titration to 9 mg once daily at Day 14 <i>Data from Regimen 1: Intermittent 7on-7off: 10 mg were not used in this analysis (N=33)</i>	Efficacy response assessed every 6 weeks during the first 3 months, then every 12 weeks for the next 9 months, then every 4 to 6 months until disease progression Safety monitored throughout the study

a Details of the PK and phosphate assessments are available in the population PK-PD analysis plan.

Exposure Metrics: The exposure metrics were derived from population PK and PK-PD models. The PK exposure metrics of erdafitinib used to assess their relationship with safety endpoints:

- Predicted area under the concentration curve from 0 to 24 hours (AUC₀₋₂₄)
- Predicted trough concentration at predose (C_{min})
- Predicted C_{max}, if the data allowed.

The metrics were obtained for total and free erdafitinib concentrations. Each metric was derived up to the end of the up-titration period (Day 1 to 14, early exposure metric) and up to the day when the highest severity of the disorder occurred for first time (overall exposure metric).

Serum Phosphate as Exposure Metric: The average daily phosphate concentration was the PD exposure metric obtained for each subject to assess their relationship with efficacy or safety endpoints. This PD metric was derived up to the end of the up-titration period (Day 1 to 14, early exposure metric), up to the day of first response assessment (approximately 6 weeks, overall exposure metric) for the efficacy analysis, or up to the day when the highest severity of the disorder occurred for first time for the safety analysis.

Efficacy Endpoints: The primary endpoint for the study and the ER analysis for efficacy was ORR, which was defined as the proportion of subjects with CR or PR as their best objective response (BOR). Subjects were assessed for disease response every 6 weeks during the first 3 months. Thereafter, scans were performed every 12 weeks for the next 9 months, then every 4 to 6 months until disease progression.

The DCR and PFS were used as secondary exploratory endpoints in the ER analysis for efficacy. The DCR was defined as the rate of subjects having CR, PR, or stable disease. PFS was defined as the duration from the date of the first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever came first, for subjects experiencing progression/death.

Safety Endpoints: The key safety endpoints included in the exposure-safety analyses were selected based on their clinical relevance, occurrence (higher than 10%), or presence of high degree of severity (Grade ≥ 3). Based on the mentioned criteria, the safety endpoints included in the analysis were the following disorders: eye, CSR, nail, PPES, and skin.

Summary of demographic and prognostic data used for ER efficacy and safety analysis is provided in Table 133.

Table 133: Summary of Demographic and Prognostic Factors of the Subjects in the PK-PD Dataset and in the Exposure-Response Analysis Dataset

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	PK-PD Dataset (n=210)	Missing in PK-PD Dataset	Continuous Regimens (n=177)	Missing in Continuous Regimens
Age (years)	65.9±10.0 (36-88)	0 (0.0%)	65.4±10.3 (36-88)	0 (0.0%)
Body weight (kg)	75.0±18.7 (37.5-159.7)	0 (0.0%)	74.7±19.1 (37.5-159.7)	0 (0.0%)
AGP (g/L)	1.33±0.62 (0.25-3.08)	13 (6.2%)	1.33±0.62 (0.25-3.08)	13 (7.3%)
Free fraction (%)	0.28±0.17 (0.06-0.86)	19 (9.0%)	0.28±0.18 (0.06-0.85)	19 (10.7%)
Sex:				
Male	152 (72.4%)	0 (0.0%)	130 (73.4%)	0 (0.0%)
Female	58 (27.6%)		47 (26.6%)	
Race:		0 (0.0%)		0 (0.0%)
White:	149 (71.0%)		125 (70.6%)	
Caucasian	146 (69.5%)		123 (69.5%)	
Latino	3 (1.4%)		2 (1.1%)	
Black	4 (1.9%)		4 (2.3%)	
Asian	18 (8.6%)		16 (9.0%)	
Other	39 (18.6%)		32 (18.1%)	
Renal impairment:		0 (0.0%)		0 (0.0%)
Normal	26 (12.4%)		23 (13.0%)	
Mild	81 (38.6%)		64 (36.2%)	
Moderate	103 (49.0%)		90 (50.8%)	
ECOG ^a :		0 (0.0%)		0 (0.0%)
Grade 0	80 (38.1%)		65 (41.7%)	
Grade 1	109 (51.9%)		79 (50.6%)	
Grade 2	21 (10.0%)		12 (7.7%)	
Disease distribution ^a		0 (0.0%)		0 (0.0%)
Absence of visceral metastases	47 (22.4%)		32 (20.5%)	
Presence of visceral metastasis	163 (77.6%)		124 (79.5%)	
FGFR alteration type ^a :		0 (0.0%)		0 (0.0%)
Mutation	174 (82.9%)		126 (80.8%)	
Fusion	36 (17.1%)		30 (19.2%)	
Hemoglobin ^a (g/dL)	11.8±1.9 (7.6-16.7)	0 (0.0%)	11.8±1.9 (7.6-16.7)	0 (0.0%)

Note: Continuous variables are expressed as mean ± standard deviation (range). Values are rounded to 3 significant digits. Ranges can have less than 3 significant digits if data had less than 3 digits.

Categorical variables are expressed as counts (%).

a For the summary of the continuous regimens, ECOG, disease distribution, FGFR alteration type, and hemoglobin were computed based on the efficacy dataset as these variables are prognostic factors (n=156).

Source: Adapted from Table 2 on page 27 of applicant's population exposure response report

PO₄-Response Analysis for Efficacy: Univariate and multivariate logistic analyses were explored to characterize the relationship between ORR and serum phosphate concentrations. The final model for investigator's response included average daily phosphate concentration up to 6 weeks and FGFR alterations as predictors (Model D in Figure 21). The phosphate effect was statistically significant (OR: 1.38; 95% CI: 1.02, 1.86; Model D, p=0.04). The probability of response as a function of serum phosphate concentration stratified by prognostic factor categories is displayed in Figure 20 and Figure 21. Based on the analysis, higher erdafitinib doses led to higher serum phosphate concentrations and thus increased probability of response. Specifically, given the median average daily phosphate concentration of 4.99 mg/dL for subjects in the 6 mg regimen and 5.34 mg/dL for subjects in the 8 mg regimen predicted after accounting for dose titration, the model-predicted increase in the response odds was 12% (OR: 1.12; 95% CI: 1.01, 1.24 for 0.35 mg/dL serum phosphate). Assuming fixed doses with no titrations, continuous regimens of 6, 8, and 9 mg daily were predicted to result in median average serum phosphate concentrations of 5.05, 5.61, and 5.89 mg/dL, respectively. Under these assumptions, the model-predicted increases in the response odds were 20% (OR: 1.20;

95% CI: 1.01, 1.42 for 0.56 mg/dL serum phosphate) when the dose increased from 6 to 8 mg daily, and a further 13% (OR: 1.13; 95% CI: 1.01, 1.27 for 0.38 mg/dL JNJ-42756493 (Erdafitinib)

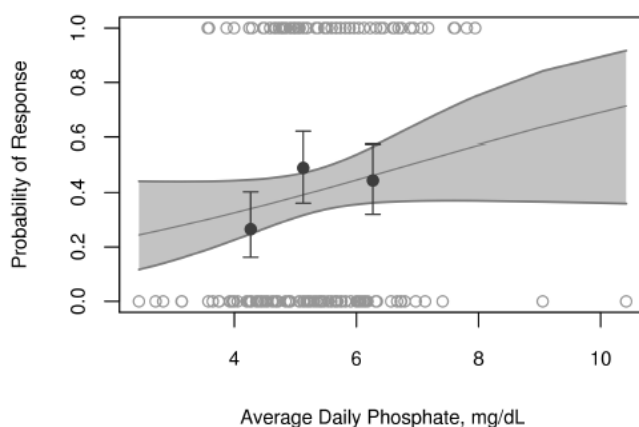
Table 134: Results of the Univariate and Multivariate Logistic Regression Analyses for Investigator’s Response

Subjects	Model	-2LL	AIC	OR (95% CI)	p-value
Chemotherapy-relapsed/refractory subjects (n=156)	Model A: Phosphate up to Day 14 (mg/dL)	209.7	213.7	1.15 (0.84-1.58)	0.39
	Model B Phosphate up to ~6 weeks (mg/dL)	207.3	211.3	1.29 (0.97-1.72)	0.08
	Model C	195.5	207.5		
	Phosphate up to ~6 weeks (mg/dL)			1.31 (0.96-1.78)	0.09
	Hemoglobin (≤ 10 vs > 10 g/L)			0.84 (0.37-1.92)	0.68
	ECOG (> 1 vs ≤ 1)			0.47 (0.12-1.89)	0.29
	Visceral metastases (yes vs no)			0.58 (0.25-1.35)	0.21
	FGFR alteration (fusion vs mutation)			0.24 (0.09-0.67)	0.01
All subjects (n=170)	Model D (final model)	198.9	204.9		
	Phosphate up to ~6 weeks (mg/dL)			1.38 (1.02-1.86)	0.04
	FGFR alteration (fusion vs mutation)			0.26 (0.10-0.70)	0.01
All subjects (n=170)	Model D_all	217.5 ^a	223.5 ^a		
	Phosphate up to ~6 weeks (mg/dL)			1.35 (1.01-1.79)	0.04
	FGFR alteration (fusion vs mutation)			0.28 (0.11-0.75)	0.01

a Likelihood/AIC with all subjects not comparable with chemotherapy-relapsed/refractory subjects as different population.

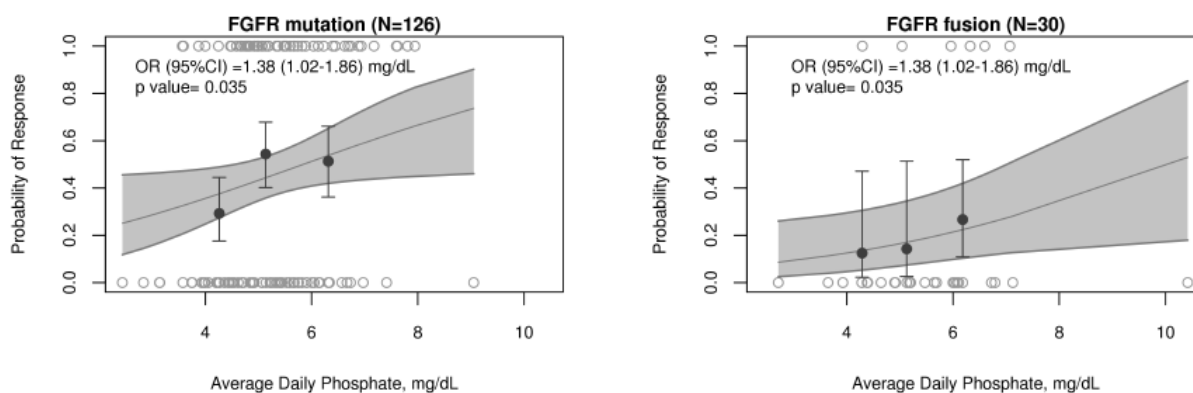
Source: Table 9 on page 36 of applicant’s population exposure response report

Figure 20: Probability of Response (by Investigator) as a Function of Average Daily Phosphate (Model B)



Source: Figure 8 on page 36 of applicant’s population exposure response report

Figure 21: Probability of Response (by Investigator) as a Function of Average Daily Phosphate and Stratified by FGFR Alteration (Prognostic Factor) (Model D, final model)



Source: Figure 9 on page 37 of applicant's population exposure response report

Separately, the Applicant performed phosphate-response for efficacy using BIRC response (ORR). The analysis was performed for chemotherapy-relapsed/refractory subjects (target population, primary analysis) and for all subjects (chemotherapy-relapsed/refractory and chemotherapy-naïve, exploratory analysis). The best response as determined by BIRC was available only for Regimen 3 (8 mg continuous doses). The overall responder rate for BIRC response was 34.5% (n=30/87) in chemotherapy-relapsed/refractory subjects and 35.4% in all subjects (n=34/96). The trend over time was like the one observed for the investigator's response.

As shown in Table 135, There was no statistically significant association between phosphate terciles and IRRC response rate, neither for average phosphate up to Day 14 nor for average phosphate up to 6 weeks. The total number of subjects within each tercile of exposure was small (sample size ranging from 27 to 31).

Table 135: BIRC ORR by Phosphate Exposure Terciles. Regimen 3, Relapsed/Refractory Population (BLC2001)

Parameter	Tercile Range (mg/dL)	ORR N/Ntot (%)	p-value
Average daily phosphate up to Day 14	2.1-4.2	11/29 (37.9%)	p=0.89
	4.2-4.9	9/27 (33.3%)	
	4.9-9.2	10/31 (32.3%)	
Average daily phosphate up to 6 weeks	2.7-4.9	9/27 (33.3%)	p=0.71
	4.9-5.7	9/30 (30.0%)	
	5.8-10.4	12/30 (40.0%)	

Note: p-value corresponds to a Pearson's chi-square test for differences in proportions.

Source: Table 10 on page 37 of applicant's population exposure response report

The univariate logistic regression analysis (Table 136, Model A and Model B) showed that

increases in average daily phosphate in the first 2 weeks or up to 6 weeks did not significantly impact the ORR when response was evaluated by the BIRC. This might be due to the reduced sample size and/or inclusion of only one dose level. The magnitude of the erdafitinib effect was however, similar to that obtained using the investigator’s assessment (point estimates of OR for phosphate up to 6 weeks ranged between 1.13 and 1.44 across univariate and multivariate models, versus 1.29 to 1.38 for investigators’ response). The probability of response as a function of serum phosphate concentration using Model B is displayed in Figure 22.

Table 136: Results of the Univariate and Multivariate Logistic Regression Analyses for BIRC’s Response

Subjects	Model	-2LL	AIC	OR (95% CI)	p-value
Chemotherapy-relapsed/refractory subjects (n=87)	Model A Phosphate up to Day 14	111.3	115.3	0.83 (0.54-1.28)	0.39
	Model B Phosphate up to ~ 6 weeks	111.7	115.7	1.13 (0.77-1.65)	0.54
	Model C Phosphate up to ~ 6 weeks	96.2	108.2	1.44 (0.90-2.32)	0.13
	Hemoglobin (≤10 vs >10 g/L)			1.58 (0.51-4.92)	0.43
	ECOG (>1 vs ≤1)			3.74 (0.30-46.36)	0.30
	Visceral metastases (yes vs no)			1.37 (0.38-5.02)	0.63
	FGFR alteration (fusion vs mutation)			0.05 (0.006-0.49)	0.01
	Model D (final model) Phosphate up to ~ 6 weeks	98.3	104.3	1.30 (0.83-2.06)	0.25
	FGFR alteration (fusion vs mutation)			0.06 (0.007-0.49)	0.01
	All subjects (n=96)	Model D_all Phosphate up to ~ 6 weeks	111.0 ^a	117.0 ^a	1.24 (0.81-1.90)
	FGFR alteration (fusion vs mutation)			0.06 (0.007-0.50)	0.01

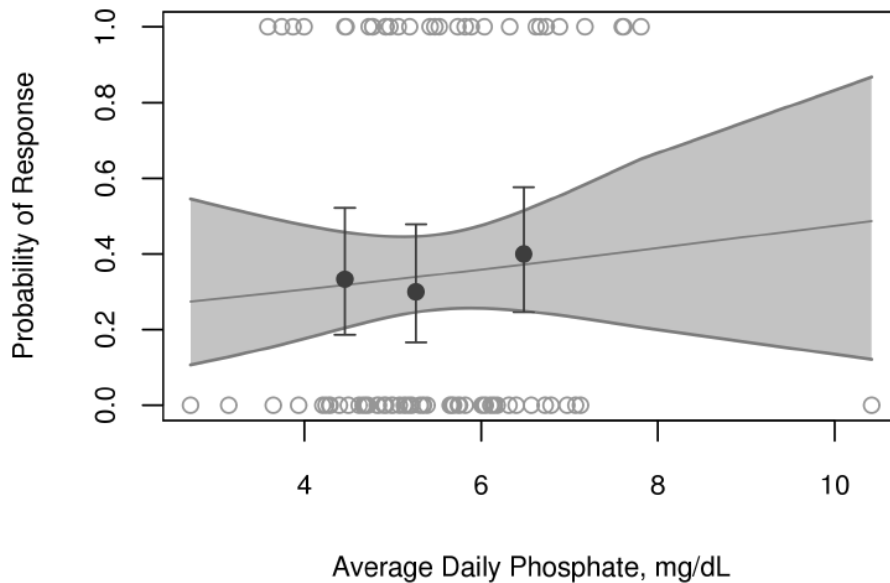
a Likelihood/AIC with all subjects not comparable with chemotherapy-refractory subjects as different population.

Source: Table 20 on page 50 of applicant’s population exposure response report

Similar to the investigator’s response, subjects with tumors displaying FGFR fusions responded less well than those with FGFR mutations (OR: 0.06; 95% CI: 0.007, 0.49, Model D). This effect seemed similar or more marked than for investigator’s response (OR: 0.26; 95% CI: 0.10, 0.70). As stated above (Section 5.4.1.2.2), given the small sample size for each FGFR alteration, analysis was performed combining all mutations compared to all fusions, although clinical response may vary for each FGFR alteration, and thus interpretation of these results may be difficult. Other investigated factors (hemoglobin, ECOG status, and disease distribution) did not significantly impact the response rate (Model C). The magnitude of the drug effect was similar to

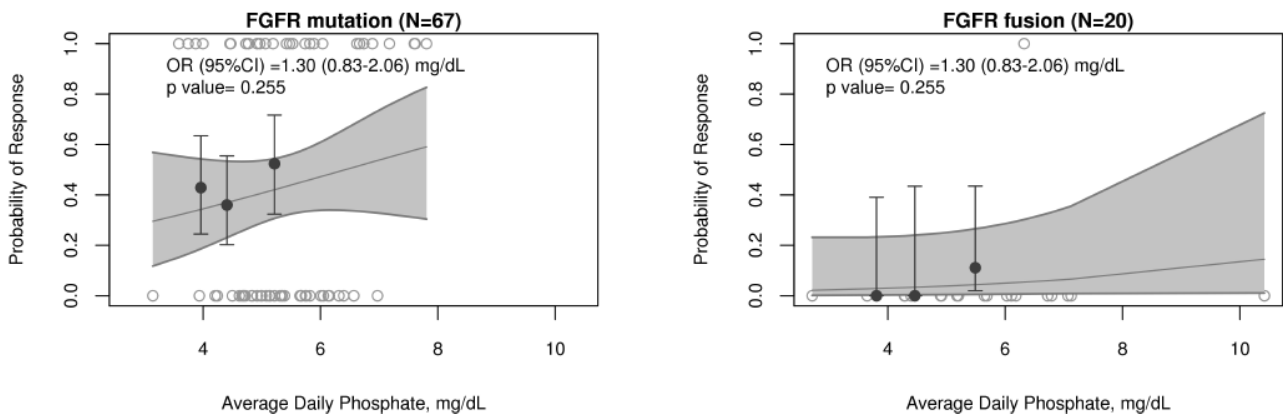
that obtained from the univariate analysis, suggesting limited confounding bias due to the prognostic factor evaluated in the analysis. The probability of response as a function of serum phosphate concentration, stratified by prognostic factor categories is displayed in Figure 23. Results including all subjects did not differ from results including only the chemotherapy-relapsed/refractory subjects (Table 136, Model D_all). These results supported that higher doses lead to higher phosphate concentrations and thus an increased probability of response.

Figure 22: Probability of Response (ORR by BIRC) as a Function of Average Daily Phosphate (Model B)



Source: Figure 10 on page 39 of applicant's population exposure response report

Figure 23: Probability of Response (ORR by BIRC) as a Function of Average Daily Phosphate and Stratified by FGFR Alteration (Prognostic Factor) (Model D, final model)



Source: Figure 11 on page 40 of applicant's population exposure response report

Reviewer's Comments: There was only marginal relationship between serum phosphate and ORR when using response by BIRC. This is not a surprise as the ORR by the BIRC was lower than that by the investigator (32.2% vs. 40.2%). The sample size in response by BIRC was also smaller

than that by the investigator (n=87 vs 126). Overall, both results supported that higher phosphate concentrations were associated with increased probability of response.

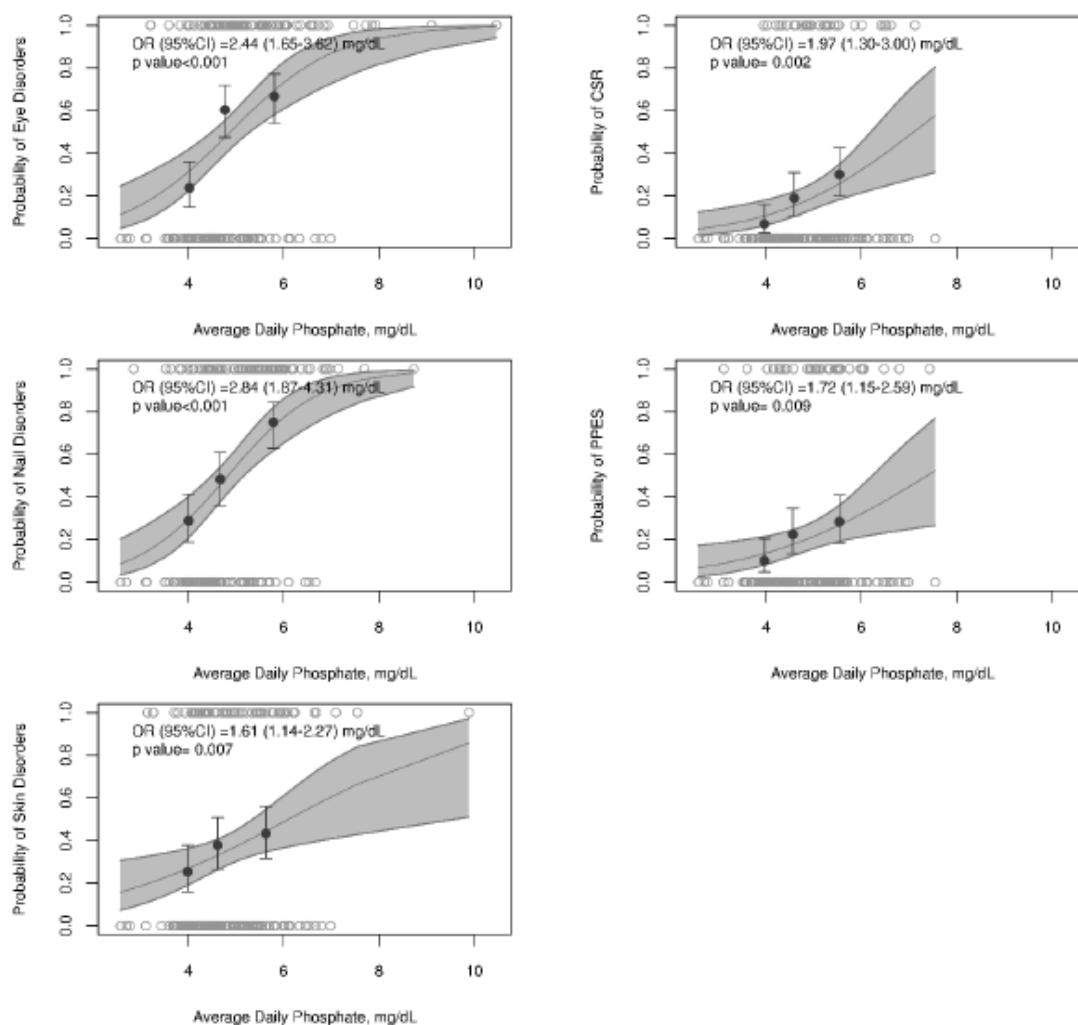
PO₄-Response Analyses for Safety: The relationship between plasma erdafitinib and/or serum phosphate exposure and the incidence of selected disorders were explored using univariate logistic regression analysis. The incidence of eye disorders, central serous retinopathy, nail disorders, palmar-plantar erythrodysesthesia, and skin disorders, at any grade of severity, had a positive and statistically significant relationship with average daily serum phosphate concentrations up to the day the disorder appeared (Table 137). Within the range of average daily serum phosphate concentrations observed in erdafitinib-treated subjects (2.6 to 10.5 mg/dL), the magnitude of the association varied across the different disorders and was strongest (OR>2) with nail and eye disorders.

Table 137: Results of the Univariate Logistic Regression Analyses for Treatment-Emergent Disorder Rates

Disorder	Model	-2LL	AIC	OR (95% CI)	p-value
Eye	Model A Average daily phosphate up to Day 14	216.2	220.2	1.76 (1.23-2.53)	0.002
	Model B (final model) Average daily phosphate up to day of event	217.3	221.3	2.44 (1.65-3.62)	<0.001
CSR	Model A Average daily phosphate up to Day 14	166.4	170.4	1.20 (0.84-1.71)	0.33
	Model B (final model) Average daily phosphate up to day of event	159.7	163.7	1.97 (1.30-3.00)	0.002
Nail	Model A Average daily phosphate up to Day 14	226.6	230.6	1.62 (1.14-2.30)	0.007
	Model B (final model) Average daily phosphate up to day of event	213.3	217.3	2.84 (1.87-4.31)	<0.001
PPES	Model A Average daily phosphate up to Day 14	172.1	176.1	0.89 (0.61-1.31)	0.56
	Model B (final model) Average daily phosphate up to day of event	171.7	175.7	1.72 (1.15-2.59)	0.009
Skin	Model A Average daily phosphate up to Day 14	201.1	205.1	1.27 (0.92-1.74)	0.15
	Model B (final model) Average daily phosphate up to day of event	222.5	226.5	1.61 (1.14-2.27)	0.007

Source: Table 20 on page 50 of applicant's population exposure response report

Figure 24: Probability of Experiencing Eye, CSR, Nail, PPES, and Skin Disorders as a Function of Average Daily Phosphate Concentration up to Day of Event



Source: Figure 17 on page 51 of applicant's population exposure response report

Reviewer's Comments: Reviewers agree that there was a positive relationship between increase in serum phosphate concentrations and efficacy endpoints (ORR, PFS) and selected safety events (eye disorder, nails, skins, etc.). The proposed dosing regimen of 8 mg daily with the potential up-titration to 9 mg daily based on PO4 level is acceptable from pharmacometrics perspective.

19.4.5. Exposure-Response Analyses

Objective: The objectives of the exposure-response analyses were:

- To characterize the relationship between exposure to serum erdafitinib and objective response rate based on best response (ORR, comprising complete response [CR] and partial response [PR]), the primary efficacy endpoint of Study BLC2001.

- To characterize the relationship between exposure to erdafitinib and selected clinical safety endpoints: eye disorders (excluding central serous retinopathy [CSR]), CSR, nail disorders, palmar-plantar erythrodysesthesia (PPES), and skin disorders.

Exposure-Response Analyses for Efficacy (ORR): The primary ER analysis was based on best response as determined by investigator for both Regimen 2 and Regimen 3 (6 and 8 mg continuous doses). The average of the daily area under the free erdafitinib plasma concentration-time curve, AUC_{free} , and investigator's ORR were correlated based on contingency tables and Pearson's chi-square tests (**Table 138**). No major differences in ORR between the terciles of average daily AUC_{free} up to Day 14 or 6 week of treatment were observed.

Table 138: Investigator ORR by AUC_{free} ,0-24 Terciles in Chemotherapy-Relapsed/Refractory Subjects

Parameter	Tercile Range (ng.h/mL)	ORR N/Ntot (%)	p-value
Average daily AUC_{free} up to Day 14	11.8-38.9	17/50 (34.0)	0.536
	39.2-55.3	23/53 (43.4)	
	56.1-162	23/53 (43.4)	
Average daily AUC_{free} up to 6 weeks	10.6-51.2	16/50 (32.0)	0.335
	51.6-74.7	24/53 (45.3)	
	75.5-307	23/53 (43.4)	

Note: p-value corresponds to a Pearson's chi-square test for differences in proportions.

Source: Table 2 on page 7 of Applicant's response to clinical pharmacology information request dated Nov 16, 2018

The univariate logistic regression analysis (

Table 139, Model A and B), as well as the multivariate logistic regression analysis (**Table 139**, Model C and D) were used to explore the relationship between AUC_{free} and ORR and covariate effects. As showed in

Table 139, the average daily AUC_{free} up to 14 days or 6 weeks of treatment were not associated with ORR. Consistent with the results of the multivariate analysis using serum phosphate as exposure variable (Mod5.3.4.2/Exposure-Response-Study-Report/Table 9), the multivariate logistic regression analysis based on average daily AUC_{free} , instead of serum phosphate, (

Table 139, Model C and Model D) showed that subjects with tumors displaying FGFR fusions responded less well than those with FGFR mutations (OR: 0.303; 95% CI: 0.116, 0.791, Model D). Other investigated factors (hemoglobin, ECOG status, and disease distribution) did not significantly impact the response rate (Model C). Removing these variables from the model (Model D) did not substantially modify the magnitude of erdafitinib AUC_{free} effect on ORR. The

magnitude of the erdafitinib AUC_{free} effect on ORR was similar to that obtained from the univariate analysis (Model B), suggesting limited confounding bias due to the prognostic factor being evaluated in the analysis.

Table 139: Results of the Univariate and Multivariate Logistic Regression Analyses for Investigator’s Response in Chemotherapy-Relapsed/Refractory Subjects (n=156)

Model	-2LL	AIC	OR (95% CI)	p-value
Model A	210.42	214.42		
Average daily AUC _{free} up to Day 14 (ng.h/mL)			1.00126 (0.98811-1.01458)	0.852
Model B	210.45	214.45		
Average daily AUC _{free} up to 6 weeks (ng.h/mL)			0.99979 (0.99180-1.00784)	0.958
Model C	198.32	210.32		
Average daily AUC _{free} up to 6 weeks (ng.h/mL)			0.99880 (0.99054-1.00714)	0.778
Hemoglobin (≤10 vs >10 g/L)			0.76881 (0.34063-1.73522)	0.527
ECOG (>1 vs ≤1)			0.42120 (0.10623-1.67008)	0.219
Visceral metastases (yes vs no)			0.52606 (0.23119-1.19702)	0.126
FGFR alteration (fusion vs mutation)			0.27149 (0.10202-0.72247)	0.009
Model D (final)	203.55	209.55		
Average daily AUC _{free} up to 6 weeks (ng.h/mL)			0.99971 (0.99167-1.00781)	0.944
FGFR alteration (fusion vs mutation)			0.30257 (0.11574-0.79096)	0.015

-2LL: -2 log-likelihood; AIC: Akaike information criterion; OR: odds ratio; CI: confidence interval.

Source: Table 4 on page 8 of Applicant’s response to clinical pharmacology information request dated Nov 16, 2018

Exposure-PFS: Median PFS was similar across the AUC_{free} terciles (Table 140). The log-rank test did not show a significant association between PFS and average daily AUC_{free} terciles both up to Day 14 and up to the time of first assessment (6 weeks). However, the hazard ratio (HR) point estimates for the highest versus the lowest terciles show a slight trend, suggesting that higher exposure might be better than lower or middle exposure, although the trend was not statistically significant (**Figure 25**). The association of AUC_{free} up to 6 weeks and PFS was not significant when AUC_{free} was categorized by terciles (log-rank test p=0.095) and when used as a continuous variable (HR: 0.9981 95% CI: 0.9935- 1.003 for 1 ng.h/mL AUC_{free}).

Table 140: Distribution of PFS Evaluated by Investigator Among Terciles of Average Daily AUC_{free}

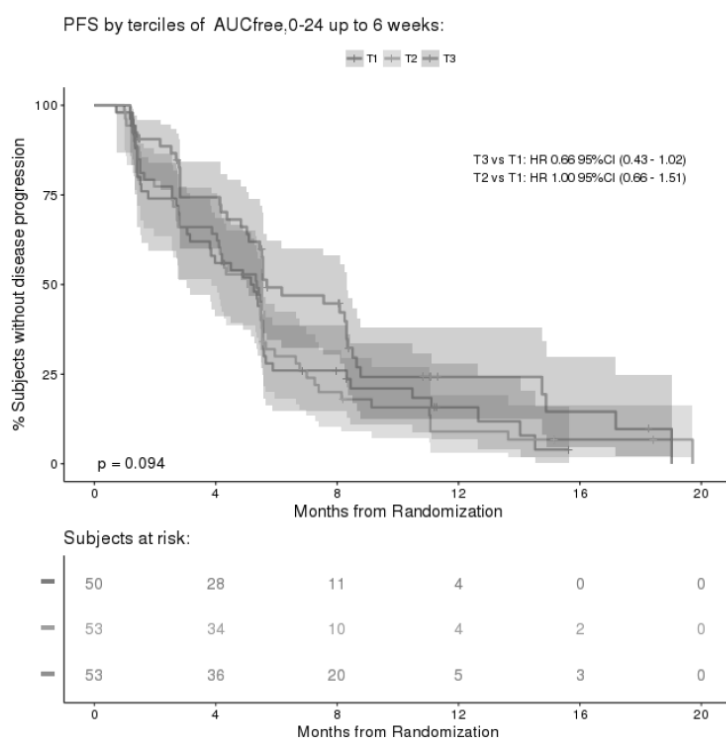
NDA/BLA Multi-disciplinary Review and Evaluation (NDA [NME] 212018)
BALVERSA™ (erdafitinib)

Parameter	Variable	T1	T2	T3	Total
Average daily	N	50	53	53	156
AUC _{free} up to Day 14	AUC _{free} range (ng.h/mL)	11.8-38.9	39.2-55.3	56.1-162	11.8-162
	Median PFS (months)	5.34	5.09	5.55	5.40
Average daily	N	50	53	53	156
AUC _{free} up to 6 weeks	AUC _{free} range (ng.h/mL)	10.6-51.2	51.6-74.7	75.5-307	10.6-307
	Median PFS (months)	5.21	5.36	5.55	5.40

T1, T2 and T3 represent the lowest, middle and highest tertiles of average daily AUC_{free}, expressed in ng.h/mL.

Source: Table 5 on page 8 of Applicant's response to clinical pharmacology information request dated Nov 16, 2018

Figure 25: Kaplan-Meier Plot for Progression-Free Survival Based on the Investigator Assessment as a Function of AUC_{free,0-24} at the First Response Assessment in Chemotherapy-Relapsed/Refractory Subjects.



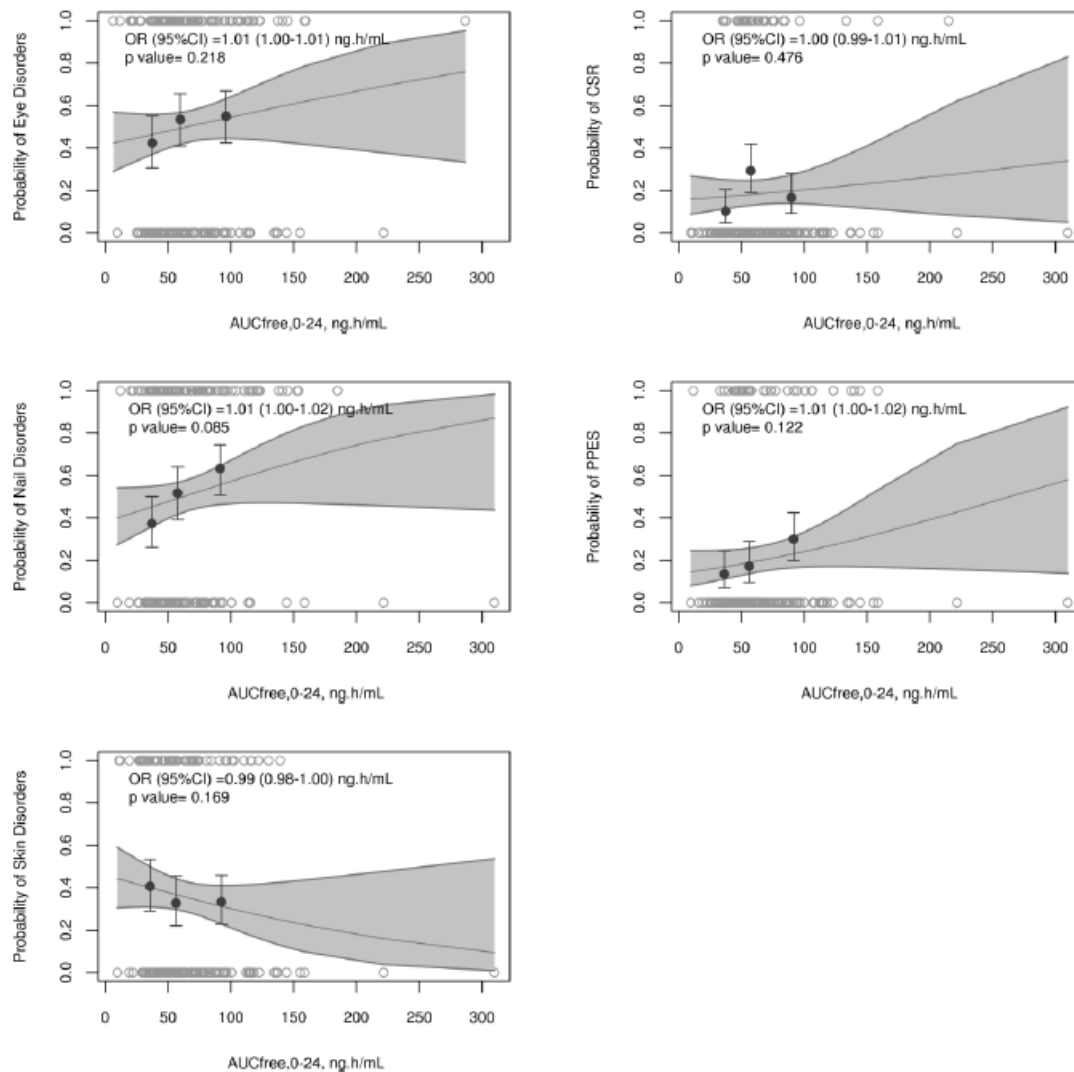
Note: T1, T2, and T3 represent the lowest (10.6-51.2 ng h/mL), middle (51.6-74.7 ng h/mL), and highest (75.5-307 ng.h/mL) tertiles of AUC_{free,0-24} up to 6 weeks.

Source: Figure 1 on page 9 of Applicant's response to clinical pharmacology information request dated Nov 16, 2018

Exposure-Response Analyses for Safety: The relationships between erdafitinib exposure (AUC_{free}) and the incidence of selected adverse events were explored using the univariate

logistic regression analysis. The probability of Experiencing AEs and AUC_{free} up to the time of event is shown in Figure 26.

Figure 26: Probability of Experiencing Adverse Events as a Function of AUC_{free,0-24} up to the Time of Event



Note: The upper and lower open circles represent the presence or absence of the disorder across the range of erdafitinib AUC_{free,0-24}. The dots depict the observed incidence for the terciles of exposure and the corresponding vertical bars represent the 95% CI. The solid blue line and the associated shaded area represent the model-based exposure-efficacy relationship and its 95% CI.

19.4.6. Physiologically Based Pharmacokinetic (PBPK) Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's study report (No. FK12149) entitled "A physiological based pharmacokinetic (PBPK) approach to assess potential drug-drug interactions with erdafitinib as victim and as perpetrator" to support the intended uses. Specifically, the Applicant applied the PBPK modeling approach to (1) predict the pharmacokinetics (PK) of erdafitinib in CYP2C9 poor metabolizers; (2) assess the effects of fluconazole (a moderate CYP2C9 and CYP3A inhibitor), itraconazole (a strong CYP3A inhibitor), and rifampin (a strong CYP3A and moderate CYP2C9 inducer) on erdafitinib PK; and (3) assess the effects of erdafitinib on the PK of midazolam and alprazolam (CYP3A4 substrates), metformin (a OCT2 substrate), and digoxin (a P-gp substrate).

The Division of Pharmacometrics has reviewed the report, supporting modeling files, and the Applicant's responses to our information requests submitted on November 30, 2018, and January 31, 2019 and concluded the following.

- The erdafitinib PBPK model is adequate to predict the PK in CYP2C9 poor metabolizers. The model predicted that erdafitinib exposure (AUC) could be increased approximately by 60% in subjects with CYP2C9 *3/*3 genotype compared to that in subjects with CYP2C9 *1/*1 genotype.
- The PBPK models are adequate to predict the effects of fluconazole (a moderate CYP2C9 and CYP3A inhibitor), itraconazole (a strong CYP3A inhibitor), and rifampin (a strong CYP3A and moderate CYP2C9 inducer) on erdafitinib PK. The model predicted that a dual CYP2C9 and CYP3A4 inhibitor (such as fluconazole) may increase the erdafitinib exposure by approximately 60% to 100%, and a dual CYP2C9 and CYP3A inducer may decrease the erdafitinib exposure by approximately 30%-60% compared to the exposure in subjects with CYP2C9 *1/*1 without comedications.
- The PBPK model suggested that erdafitinib is an inhibitor towards intestinal P-gp. However, the model could not quantitatively predict the magnitude of the effect due to the uncertainty in translating in vitro K_i to in vivo K_i .
- The PBPK models could not quantitatively predict the effects of erdafitinib on a sensitive CYP3A substrate (such as midazolam) because the link between in vitro and in vivo was not appropriately established.
- The PBPK models are not adequate to predict the effects of erdafitinib on metformin (an OCT2 substrate) because the model under-predicted the effects of cimetidine and pyrimethamine on metformin at a dose level of 500 mg.

Background

Erdafitinib has high solubility and moderate to high permeability. The to-be-marketed formulations are 3mg, 4mg, and 5mg tablets. After single dose oral administration, median

T_{max} was 2.5 hours (range: 2 to 6 hours) and oral absorption is near complete. Erdafitinib is highly bound to human plasma proteins due to high affinity binding to alpha-1-acid glycoprotein (AGP). The mean plasma unbound fractions (f_{up}) of erdafitinib were 0.51% (CV 39.4%) and 0.32% (CV 64.0%), in healthy and cancer subjects, respectively (Table 10 of Clinical Pharmacology Summary). The blood-to-plasma (B:P) ratio was 0.60 across the concentration range of 15 to 750 ng/mL, with no concentration dependency. The mean effective half-life of erdafitinib in patients was 58.9 hours. Erdafitinib exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose range of 0.5 to 12 mg following single and multiple once daily administration. Multiple dose erdafitinib PK was time independent.

Erdafitinib is cleared via multiple pathways. Erdafitinib is primarily metabolized by cytochrome P450 (CYP) 2C9 and CYP3A4 to form the O-demethylated metabolite M6 and by CYP3A4 to form the N-dealkylated metabolite M8, a minor pathway. Unchanged erdafitinib was the major drug-related moiety in plasma; there were no major circulating metabolites. About 14.1% to 20.8% of total dose of erdafitinib was excreted in feces in the form of unchanged drug (68.7%) and M6 (approximately 24%). This portion of clearance was later assigned to biliary clearance as erdafitinib is almost completely absorbed and therefore the parent drug found in feces was due to the biliary excretion. About 18.7% of total dose of erdafitinib was excreted in urine with unchanged drug being the major entity.

In vitro, erdafitinib is a P-gp substrate, a time-dependent inhibitor (TDI) and inducer for CYP3A4, a P-gp and OCT2 inhibitor.

Since erdafitinib is a CYP2C9 substrate, CYP2C9 polymorphism is expected to have impact on the PK of erdafitinib in subjects with different CYP2C9 genotypes. Majority of subjects (healthy subjects and cancer patients) enrolled in erdafitinib PK studies carried CYP2C9 *1/*1, *1/*2 genotypes, or unknown. PK in two subjects with CYP2C9 *1/*3 genotype showed large variability with one having 23% increase and one having 45% decrease in clearance compared to the mean clearance in subjects with CYP2C9 *1/*1 genotype (Response to Clinical Pharmacology Information Request submitted on November 30, 2018). A parallel in vivo DDI study was conducted with fluconazole (400 mg QD), and itraconazole (200 mg QD). The study was conducted in healthy subjects with CYP2C9 *1/*1 and *1/*2 genotypes.

It was observed that C_{max} and AUC_{0-24h} were about 48% and 44% higher in cancer patients compared to healthy subjects, respectively, following a single dose administration. The observed mean (CV%) volumes of distribution (V_d/F) of erdafitinib were 28.8 L (51.2%) and 37.4 L (33.1%), respectively, in subjects with cancer and healthy subjects (Clinical Pharmacology Summary). The Applicant stated that the difference in PK was likely due to the differences in α1-AGP levels and the plasma protein binding of erdafitinib in cancer patients and healthy subjects.

Methods

PBPK model structures and development

The erdafitinib PBPK model was developed based on in vitro and in vivo ADME data. Briefly, an Advanced Dissolution, Absorption and Metabolism (ADAM) model and a minimal PBPK model were utilized to describe the erdafitinib PK. The unbound fraction in plasma (fup) values were calculated based on erdafitinib binding to α 1-AGP determined in vitro (Study FK10117) and the observed α 1-AGP concentration in health subjects and cancer patients (Studies EDI1006 and EDI1001). The Applicant calculated a fup value of 0.0044 for healthy subjects and 0.0028 for cancer patients, which were used in the erdafitinib model. The volumes of distribution (Vss) were 0.42 L/kg, and 0.29 L/kg in healthy subjects and cancer patients, respectively. The Vss for healthy subjects was obtained from PK study EDI1003 and adjusted based on fup for cancer patients. Because erdafitinib is almost completely absorbed, the amount of parent drug found in the feces was considered due to the biliary excretion. The renal clearance and the biliary clearance were estimated based on the mass balance study (EDI1005). The in vivo intrinsic clearance (CLint) for each enzymatic pathway (CYP2C9, CYP3A4, and additional hepatic clearance) was derived from the in vitro phenotyping study, in vitro to in vivo scalars for CYP2C9 (tolbutamide) and CYP3A4 (disopyramide), and PK data in EDI1007. The estimated hepatic clearance consisted of CYP2C9 (39%), CYP3A4 (20%), additional hepatic clearance (8%).

To estimate the PK in subjects with various CYP2C9 genotypes, the Applicant incorporated different mean CYP2C9 abundance values in the erdafitinib model which are summarized in Table 141. The relative CYP2C9 activity to *1/*1 was estimated by comparing the mean enzyme abundance to the *1/*1 enzyme abundance. These values agree with the values in the Tables 5 and 6 in the Response to Clinical Pharmacology Information Request submitted on November 30, 2018.

Table 141: Summary of mean enzyme abundance (pmol/mg-protein) in subjects with various CYP2C9 genotypes

CYP2C9 genotype	EM frequency	PM frequency	Mean EM abundance (CV%)	Mean PM abundance (CV%)	Relative CYP2C9 activity to *1/*1
*1/*1	0.94	0.06	73 (18.1%)	29 (73%)	1
*1/*2	0	1	73	65 (24%)	0.92
*1/*3	0	1	73	44 (25%)	0.63
*2/*2	0	1	73	50 (22%)	0.71
*2/*3	0	1	73	32 (13%)	0.45
*3/*3	0	1	73	8 (20%)	0.11

Source: Applicant's submitted workspace files, EM: extensive metabolizer, PM: poor metabolizer

Additional drug models were developed by the Applicant for DDI assessment and Table 142 is a summary of model structures for the compounds involved in the PBPK analyses. The PBPK

analyses were performed in Simcyp v16.1 by the Applicant and repeated by the reviewer in Simcyp v17.1.

Table 142: Summary of model structures and in vivo studies for model development and verification

Drug	A	D	E	Transport (as substrate)	Interaction (as perpetrator)	In vivo studies
Erdafitinib	ADAM	Minimal PBPK	CYP3A4, CYP2C9, CL _{hep} , CL _{bile} , CL _{renal}	None	CYP3A4, P-gp _{intestine} , P-gp _{liver} , OCT1 _{liver} , MATE1 _{liver} , P-gp _{kidney} , OCT2 _{kidney} , MATEs _{kidney}	SD and MD PK studies, mass balance, DDI with itraconazole and fluconazole
Itraconazole	1 st order	Minimal PBPK	CYP3A4	None	CYP3A4	MD PK, itraconazole-midazolam DDI
OH-itraconazole	NA	Minimal PBPK	CYP3A4, CL _{renal}	None	CYP3A4	
Fluconazole	1 st order	Minimal PBPK	CL _{iv}	None	CYP2C9, CYP2C19, CYP3A4/5	SD and MD PK, fluconazole-midazolam DDI, fluconazole-triazolam DDI, fluconazole-warfarin DDI, fluconazole-tolbutamide DDI
Rifampin	1 st order	Minimal PBPK	CL _{iv} , CL _{renal}	None	CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5	Rifampin-midazolam DDI, rifampin-warfarin DDI, rifampin-tolbutamide DDI
Erythromycin	1 st order	Minimal PBPK	CYP3A4/5, UGT1A4, CL _{renal}	None	CYP2D6, CYP3A4/5	Erythromycin-alprazolam DDI, erythromycin-midazolam DDI, erythromycin-triazolam DDI
Alprazolam	1 st order	Minimal PBPK	CYP3A4/5, CL _{renal}	None	None	Erythromycin-alprazolam DDI
Midazolam	ADAM	Minimal PBPK	CYP3A4, CL _{hep} , UGT1A4, CL _{renal}	None	None	SD PK
Cimetidine	1 st order	Minimal PBPK	CL _{hep} , MechKiM	OCT2 _{kidney} , OAT3 _{kidney} , MATEs _{kidney} , MRP4 _{kidney}	MATEs _{kidney} , OCT2 _{kidney}	SD and MD PK, cimetidine-metformin DDI

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Pyrimethamine	1 st order	Minimal PBPK	CL _{po}	None	MATE _{Skidney} , OCT2 _{kidney}	SD PK, pyrimethamine-metformin DDI
Metformin	1 st order	Full PBPK	CL _{hep} , MechKiM	OCT1 _{liver} , MATE _{Skidney} , OCT2 _{kidney} (EGD model)	None	cimetidine-metformin DDI, pyrimethamine-metformin DDI
Digoxin	ADAM	Full PBPK	CL _{hep} , CL _{renal}	P-gp _{intestine} , P-gp _{liver}	None	SD and MD PK,

A: Absorption, D: Distribution, E: Elimination, EGD: Electrochemical Gradient Driven; ADAM: Advanced Dissolution, Absorption and Metabolism; SD: single dose; MD: multiple dose; DDI: drug-drug interaction

It was noted that the Applicant made substantial changes to the Simcyp (V16) default compound files with justification. Specifically, changes were made to the midazolam, itraconazole and OH-itraconazole, metformin, and cimetidine files (see comparison in the Applicant's response to clinical pharmacology information request submitted on 30 November 2018).

The Applicant developed its own itraconazole and OH-itraconazole models which were different from the Simcyp library models in many parameters, such as logP, pKa, Fa, Ka, Vss, CYP3A4 clearance parameters (Vmax, Km, and f_{mic}), CYP1A2 CL_{int} (for itraconazole), CL_r (for OH-itraconazole), and CYP3A4 K_i (for OH-itraconazole) (Response to Clinical Pharmacology Information Request submitted on November 30, 2018). The Applicant verified the itraconazole/OH-itraconazole models with itraconazole and OH-itraconazole plasma concentration-time profiles observed following multiple dose administration of itraconazole and a itraconazole/OH-itraconazole-midazolam (using the Applicant's midazolam model) DDI study.

In the fluconazole model, the K_i towards CYP2C9 was changed from 7.92 μM to 20.4 μM. The model was verified with CYP2C9 substrates, warfarin and tolbutamide. Of note, the revised K_i value has been verified by the software developer and updated in V17.

In the revised midazolam model, the Applicant reduced the f_{up} value by 2-fold, developed an ADAM model for midazolam absorption, reduced the fugut value, and simplified the elimination by combining different nonlinear CYP3A4/5 pathways into linear CYP3A4 and additional clearance pathways. The revised midazolam model was verified by comparing the simulated against the observed mean plasma concentration time profiles for midazolam following a single oral administration of 7.5 mg from three publications.

PBPK model verification

The erdafitinib PBPK model predictions were compared to PK studies in healthy subjects and cancer patients (EDI1001, EDI1002, EDI1003, EDI1004, EDI1006), a mass balance study (EDI1005), and a DDI study (EDI1007) with fluconazole (a moderate CYP2C9 and CYP3A

inhibitor), and itraconazole (a strong CYP3A inhibitor) in subjects with CYP2C9 *1/*1 and *1/*2 genotypes. The in vivo studies for model verifications were summarized in Table 142.

PBPK model application

The developed PBPK models were used to simulate the following conditions.

- Erdafitinib PK in subjects with CYP2C9 *2/*2, *2/*3, and *3/*3 genotypes
- Effects of CYP2C9 and CYP3A4 inhibitors (fluconazole and itraconazole) and inducer (rifampin) on the PK of erdafitinib in subjects with various CYP2C9 genotypes
- Effects of erdafitinib on the PK of sensitive CYP3A4 substrates (midazolam, alprazolam, and triazolam)
- Effects of erdafitinib on the PK of a P-gp substrate (digoxin)
- Effects of erdafitinib on the PK of an OCT2 substrate (metformin)

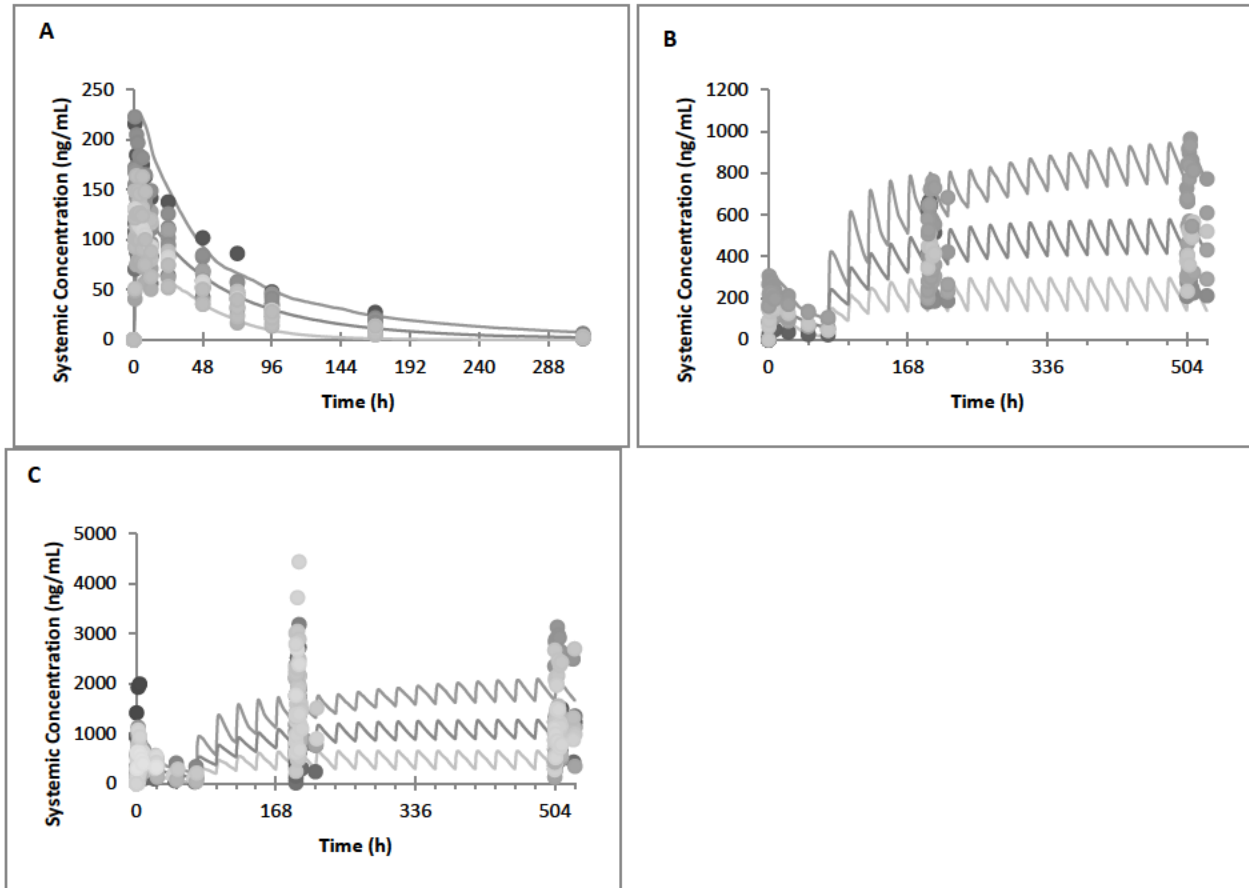
Results

1. Can the PBPK models provide a reasonable description of the PK of erdafitinib?

Yes, the PBPK models for erdafitinib described erdafitinib PK following a single dose of erdafitinib in healthy and cancer subjects (figures 1-3, and tables 1-3 in study report FK12149), and multiple dose of erdafitinib in cancer subjects (figures 2-3, and tables 2-3 in study report FK12149). The predicted versus the observed PK are shown in Figure 27 and Table 143.

Figure 27: Predicted and observed PK profiles

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Predicted and observed PK profiles following (A) 4 mg single dose of erdafitinib in healthy subjects (EDI1007), (B) 4 mg single dose followed by 4 mg QD from Day 4 in cancer patients (EDI1001), and (C) 9 mg single dose followed by 9 mg QD from Day 4 in cancer patients (EDI1001). The solid lines are simulated mean and 90% CI (green and grey lines) PK profiles. The dots are observed total erdafitinib plasma concentrations.

Source: Applicant's simulations output files.

Table 143: Comparison of predicted vs. observed erdafitinib PK parameters (expressed as geometric mean values)

Dosing	Population	Observed		Predicted		Predicted / Observed	
		Cmax (ng/mL)	AUC (ng*hr/mL)	Cmax (ng/mL)	AUC (ng*hr/mL)	CmaxR	AUCR
4mg SD	Healthy	134	8777	125	8653	0.93	0.99
4mg QD day1	Cancer	163	6022	179	7408	1.10	1.23
4mg QD SS	Cancer	630	12064	543	10896	0.86	0.90
9mg QD day1	Cancer	390	15091	403	16560	1.03	1.10
9mg QD SS	Cancer	1911	36608	1201	23994	0.63	0.66
Normalized to 8mg SD	Healthy	309	19840	266	17989	0.86	0.91
Normalized to 8mg QD SS	Healthy	NA	NA	863	18202	NA	NA

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Normalized to 8mg SD	Cancer	457	NA	380	24014	0.83	NA
Normalized to 8mg QD SS	Cancer	NA	29268	1068	21926	NA	0.75

Source: Tables 1-3 in study report FK12149, Tables 1-2 in Response to Clinical Pharmacology Information Request submitted on November 30, 2018, SD: single dose; MD: multiple dose; SS: steady state; AUC_{inf} for SD, AUC₇₂ for day 1 of MD, AUC_{tau} for SS of MD.

The Applicant developed two populations, the healthy subjects and the cancer population. The difference between the two populations is the protein unbound fraction in plasma. It was observed that erdafitinib binds preferentially to α 1-AGP and the unbound fraction was inversely related to α 1-AGP concentration. The α 1-AGP level was higher in cancer subjects than that in healthy subjects, which gave a lower unbound fraction in cancer subjects (mean 0.316% and CV 64.0%) than that in healthy subjects (mean 0.510% and CV 39.4%) (Table 10 in the Summary of Clinical Pharmacology Studies). The total exposure (C_{max} and AUC₂₄) to erdafitinib was 40% to 50% higher, and the free exposure (C_{max} and AUC₂₄) was about 20% higher in cancer subjects than those in healthy subjects (Table 2 in Response to Clinical Pharmacology Information Request submitted on November 30, 2018). The PBPK model incorporated f_{up} values of 0.0028 and 0.0044, respectively, in cancer subjects and healthy subjects to describe the observed PK differences in the two populations. The PBPK models were able to describe the PK of erdafitinib in healthy and cancer subjects as shown in Figure 27. It appears that the model underestimated the observed variability in cancer subjects following 9 mg QD of erdafitinib (Figure 27 (C)). As it is unknown whether other physiology functions, such as renal, and liver functions which affect clearance and PK, might be different in the cancer subjects, the erdafitinib cancer PBPK model is considered as exploratory.

2. Can the PBPK models be used to predict the PK of erdafitinib in various CYP2C9 genotype populations?

Yes. Erdafitinib is cleared by multiple pathways. The estimated contribution from each pathway varies depending on CYP2C9 genotype (see Table 144). The highest contribution from a specific pathway is about 40%.

Table 144: Estimated contribution (%) of each clearance pathway to total clearance

CYP2C9 genotype	CYP2C9	CYP3A4	Additional Hep	Renal	Biliary
*1/*1	41	18	7	14	19
*1/*2	39	19	7	15	20
*1/*3	30	22	8	17	23
*2/*2	33	21	8	16	22
*2/*3	25	24	9	16	25
*3/*3	8	29	11	22	30

Relative CYP2C9 enzyme abundance was incorporated into the model in order to simulate erdafitinib PK in various CYP2C9 genotype populations. The relative enzyme abundance values were back-calculated from published studies on tolbutamide (a CYP2C9 probe

substrate). There have been literature reports on successful prediction of clearance for CYP2C9 substrates (Kusama M et al. Pharm Res. 2009 Apr;26(4):822-35) considering enzymatic activity, expression levels, and the contribution of CYP2C9 to total clearance. Table 145 is a summary of the CYP2C9 mediated clearance in various genotypes relative to *1/*1 for several CYP2C9 substrates, and erdafitinib. Large variability was observed with respect to relative clearance in various CYP2C9 genotypes. The designated relative clearance via CYP2C9 for erdafitinib was within the range observed for several CYP2C9 substrates.

Table 145: CYP2C9 mediated clearance relative to *1/*1 genotype for CYP2C9 substrates (values from Kusama M et al. were mean values)

Drugs	fm _{CYP2C9}	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	Reference
S-flurbiprofen	0.96	1	0.73	0.56	NA	NA	NA	Kusama M et al. Pharm Res. 2009 Apr;26(4):822-35
Losartan [E3174 formation]	0.84	1	0.52	0.64	0.68	0.23	0.01	
Phenytoin	0.83	1	0.70	0.71	0.62	0.40	0.70	
Tolbutamide	0.98	1	0.84	0.64	0.75	0.46	0.15	
Tolbutamide	0.94 (Simcyp default model)	1	0.91	0.64	0.72	0.49	0.17	Table 7 of Response to Clinical Pharmacology Information Request (November 30, 2018)
Torsemide	0.97	1	0.98	0.54	0.94	0.44	0.33	Kusama M et al. Pharm Res. 2009 Apr;26(4):822-35
S-warfarin	0.94	1	0.67	0.53	0.44	0.28	0.11	Kusama M et al. Pharm Res. 2009 Apr;26(4):822-35
S-warfarin	NA	1	0.58	0.52	0.32	0.23	0.09	Scordo MG et al. Clin Pharmacol Ther. 2002 Dec;72(6):702-10.
Erdafitinib	0.39	1	0.89	0.65	0.71	0.46	0.11	Table 6 of Response to Clinical Pharmacology Information Request (November 30, 2018)

The values extracted from Kusama M et al. were mean values. Only substrates with fm_{CYP2C9} higher than 0.8 were included. Celecoxib was not included as large discrepancies were observed among the reported values. The number of subjects was less than two for phenytoin (*3/*3) and the data should be interpreted with caution. It was reported that genetic polymorphisms of both OATP1B1 and CYP2C9 affected the clearance of torsemide.

The predicted erdafitinib PK in healthy subjects with various CYP2C9 is summarized in Table 146.

Table 146: Predicted steady state PK (geometric means) following 9 mg QD erdafitinib in healthy subjects with various CYP2C9 genotypes

	Erdafitinib model with CYP3A interaction				Erdafitinib model without CYP3A interaction			
	C _{max} (ng/mL)	AUC _{tau} (ng*hr/mL)	C _{max} R*	AUCR*	C _{max} (ng/mL)	AUC _{tau} (ng*hr/mL)	C _{max} R*	AUCR*
*1/*1	964.81	20198.03	1.00	1.00	927.13	19022.46	0.96	0.94

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*1/*2	1012.64	21035.54	1.05	1.04	960.40	19813.58	1.00	0.98
*1/*3	1131.10	24196.60	1.17	1.20	1066.82	22391.16	1.11	1.11
*2/*2	1090.52	23216.22	1.13	1.15	1033.34	21581.13	1.07	1.07
*2/*3	1213.10	26184.75	1.26	1.30	1057.04	22146.73	1.10	1.10
*3/*3	1454.52	32025.49	1.51	1.59	1338.29	28948.59	1.39	1.43
CYP2C9 activity = 0	1576.15	34698.52	1.63	1.72	1423.49	31004.63	1.48	1.54

Source: The Applicant's submitted output files and the reviewer's simulation using submitted workspace files.

*Predicted ratios are expressed as the fold changes compared to the corresponding parameter in CYP2C9 *1/*1

There are two uncertainties in the model predicting erdafitinib PK in subjects with various CYP2C9 genotypes: (1) the effects of erdafitinib on itself as a CYP3A4 perpetrator and substrate, and (2) the effects of erdafitinib on itself as a P-gp perpetrator and substrate).

In general, the confidence in predicting the time-dependent inhibition and inductions effects of erdafitinib on a CYP3A substrate is low (see discussion in the following section). The effects of erdafitinib on itself as a CYP3A4 perpetrator are expected to be low considering that the contribution of the CYP3A4 pathway to erdafitinib total clearance was about 20% in CYP2C9 extensive metabolizers, and linear and time-independent PK was observed. The reviewer explored the effects of erdafitinib as a CYP3A perpetrator by turning on and off the CYP3A4 interaction in the erdafitinib model and the results are shown in Table 146. The difference in PK was generally less than 10% between with and without the CYP3A4 interaction comparing the corresponding genotype groups. In addition, the reviewer conducted simulations to estimate erdafitinib PK in subjects without CYP29C activity. Overall, the simulations suggested that steady state AUC could be increased by 60% in CYP2C9 poor metabolizers compared to extensive metabolizers.

The effect of erdafitinib on itself as a P-gp inhibitor is expected to be low. Erdafitinib has high solubility and high permeability. The intestinal P-gp transport is likely to be saturated (above 0.3 μM , i.e. 0.134 $\mu\text{g}/\text{mL}$) following 9 mg dose of erdafitinib (36 $\mu\text{g}/\text{mL}$ estimated by 9 mg/250mL). Less than 20% of total dose was eliminated via renal clearance, suggesting that involvement of renal P-gp is not significant. The Applicant stated that the inhibitory effects of erdafitinib on renal P-gp is expected to be low, given that the value of $I_{\text{max,u}}/IC_{50}$ was 0.0172 and less than basic cut-off value of 0.1 (Table 4 in Pharmacokinetics Written Summary). Because the erdafitinib exposure is linear across the dose range of 0.5 to 12 mg and time-independent, and itraconazole (a CYP3A and P-gp inhibitor) only increased erdafitinib AUC by 33% and did not affect C_{max} , the effect of erdafitinib on itself as a P-gp inhibitor is expected to be low.

Based on the above assessment and considering that erdafitinib is not a substrate of major liver uptake transporters, the Applicant's approach is acceptable using PBPK analyses to predict erdafitinib PK in subjects with CYP2C9 *2/*2, *2/*3, and *3/*3 genotypes. The model predicted that erdafitinib exposure was about 60% higher in CYP2C9 poor metabolizers compared to that in CYP2C9 extensive metabolizers.

3. Can the PBPK models be used to estimate the effects of CYP2C9/CYP3A modulators on erdafitinib PK?

Yes. The effects of CYP2C9/CYP3A modulators were verified with in vivo DDI study (EDI1007) between erdafitinib and itraconazole (a CYP3A and P-gp inhibitor) or fluconazole (a CYP2C9 and CYP3A inhibitor). The simulated geometric mean PK parameters (C_{max}, AUC, C_{maxR}, and AUCR) were within 20% difference of the observed values (Table 147). The model slightly under predicted the effects of itraconazole on erdafitinib (1.18 vs. 1.34). Of note, the in vivo DDI study was a parallel design due to the long half-life of erdafitinib while the simulation was conducted using a cross-over design. The Applicant simulated multiple trials and compared erdafitinib PK in the absence and presence of itraconazole cross different trials, and an AUCR of 1.32 was obtained, which was close to the observed AUCR of 1.34.

Table 147: Predicted and observed erdafitinib PK (geometric means) in the absence and presence of fluconazole and itraconazole

Observed (EDI1007; CYP2C9*1/*1 + *1/*2)				Predicted				Predicted / observed			
C _{max} (ng/mL)	AUC (ng*hr/mL)	C _{maxR}	AUCR	C _{max} (ng/mL)	AUC (ng*hr/mL)	C _{maxR}	AUCR	C _{max}	AUC	C _{maxR}	AUCR
No inhibitor											
134	8777	NA	NA	125	8653	NA	NA	0.93	0.99	NA	NA
Fluconazole 400 mg QD from day 1 to day 11 and 4 mg erdafitinib on day 5											
162	13060	1.21	1.49	137	14265	1.04	1.65	0.85	1.09	0.86	1.11
Itraconazole 200 mg QD from day 1 to day 11 and 4 mg erdafitinib on day 5											
140	11785	1.04	1.34	125	10376	1.02	1.18	0.89	0.88	0.98	0.88

Source: Table 5 in Study report FK12149, C_{maxR} and AUCR were expressed as with perpetrator / without perpetrator

The reviewer repeated the DDI simulations using the Applicant submitted workspace files and obtained similar results with numerical differences. The reviewer also conducted DDI simulation using the Simcyp (V17) default itraconazole/OH-itraconazole, and fluconazole models. The predicted DDI results were similar to the that obtained by the Applicant's models with numerical differences. The simulated itraconazole and OH-itraconazole PK profiles following 200 mg QD were similar using the Applicant's model vs. the Simcyp V17 default model for the first 10 days. The predicted plasma concentrations were higher using the Applicant's model than using the Simcyp V17 model after about 10 days of administration. The difference did not appear affecting the prediction of itraconazole's effect on erdafitinib PK probably because of the low contribution of the CYP3A pathway to the overall erdafitinib clearance.

Predicted erdafitinib exposure changes at steady state in the presence or absence of CYP2C9 or CYP3A4 modulators are summarized in Table 148. In each simulation, both the perpetrator and substrate were given from day 1 to day 22. The perpetrators were given either once daily (QD) or twice daily (BID). The erdafitinib exposure ratios were expressed as fold changes relative to the exposure in subjects with CYP2C9 *1/*1 without comedications. A dual CYP2C9 and CYP3A4 inhibitor (such as fluconazole) may increase the erdafitinib exposure by approximately 60% to 100%, and a dual CYP2C9 and CYP3A inducer may decrease the erdafitinib exposure by

approximately 30%-60% compared to the exposure in subjects with CYP2C9 *1/*1 without comedications (Table 148). The erdafitinib CYP3A interaction effects on the DDI predictions are expected to be low due to the little contribution of CYP3A to erdafitinib clearance. Shutting down the erdafitinib CYP3A interaction in the model, the estimated AUC ratios were increased by 3% or 6% in CYP2C9 *1/*1 and *1/*3 subjects, respectively, with fluconazole or itraconazole, and no change with rifampin.

Table 148: Summary of simulated effects of CYP2C9 and CYP3A4 inhibitors and inducer on erdafitinib (9 mg QD) PK at steady state

CYP2C9 Genotype	*1/*1		*1/*2		*1/*3		*2/*2		*2/*3		*3/*3	
	CmaxR*	AUCR*	CmaxR*	AUCR*	CmaxR*	AUCR*	CmaxR*	AUCR*	CmaxR*	AUCR*	CmaxR*	AUCR*
Inhibitors												
Itraconazole 200 mg QD	1.11	1.13	1.16	1.19	1.33	1.38	1.27	1.32	1.34	1.40	1.79	1.82
Itraconazole 200 mg BID	1.13	1.15	1.18	1.21	1.35	1.40	1.29	1.34	1.36	1.43	1.82	1.85
Fluconazole 400 mg QD	1.54	1.64	1.57	1.67	1.67	1.78	1.64	1.75	1.61	1.71	1.87	1.94
Itraconazole 200 mg QD + Fluconazole 400 mg QD	1.60	1.70	1.63	1.73	1.73	1.85	1.70	1.81	1.67	1.78	1.94	2.01
Fluconazole 200 mg BID + Fluconazole 400 mg QD	1.61	1.71	1.64	1.74	1.73	1.85	1.70	1.82	1.68	1.79	1.94	2.01
Inducers												
Rifampin 600 mg QD	0.48	0.38	0.51	0.41	0.57	0.48	0.55	0.46	0.56	0.49	0.77	0.81

Source: Reviewer's analyses using the Applicant's submitted workspace. *Ratios are expressed as the fold change relative to *1*1 without inhibitors or inducers

4. Does the Applicant's PBPK analysis quantitatively predict the effects of erdafitinib on a sensitive CYP3A4 substrate?

No. In vitro, erdafitinib showed time-dependent inhibitory and induction potential towards CYP3A4. The inhibitory effect and the induction effect were integrated into the model separately. To quantitatively predict the in vivo inhibitory effect of erdafitinib from the in vitro system, the Applicant used erythromycin, the in vitro positive control compound, as the bridge. Specifically, the Applicant modified the Simcyp erythromycin model by using the in vitro determined inhibition parameters (CYP3A4 $K_{app} = 2.26$ vs. $23.2 \mu\text{M}$ in Simcyp, $K_{inact} = 1.72$ vs. 2.25 1/h in Simcyp) and verified its effects on the PK of alprazolam (a sensitive CYP3A substrate). In response to a Clinical Pharmacology Information Request, the Applicant further

verified erythromycin model using midazolam and triazolam as substrates. The Although the modified erythromycin could predict its effects on the PK of alprazolam (predicted AUCR 3.15 vs. observed AUCR 2.47), the model over-predicted its effects on the PK of midazolam (predicted AUCR 13.8 vs. observed AUCR 4.41) and triazolam (predicted AUCR 12 vs. observed AUCR 3.65) by approximately 3-fold. These results demonstrated the uncertainties in predicting TDI effects of erythromycin directly using the in vitro parameters. Similarly, the uncertainties in predicting TDI effects of erdafitinib from in vitro parameters is expected. Additional analysis and experiences are needed to scale the in vitro TDI parameters for in vivo quantitative predictions indirectly from other perpetrator compounds.

The Ind_{slope} (slope of the fold induction vs. concentration plot) for erdafitinib model was obtained from the in vitro induction study and calibrated against the rifampin CYP3A induction slope value derived from Simcyp V16 and E_{max}/EC_{50} of rifampin from the same donor. A sensitivity analysis on the Ind_{slope} , in the range of 50-fold lower to 50-fold higher compared to the default value, suggested that erdafitinib does not have much induction effect on a sensitive CYP3A substrate.

Due to the uncertainties in predicting TDI effects of erdafitinib from in vitro parameters, the Applicant's PBPK analysis was not adequate to quantitatively predict the effects of erdafitinib on a sensitive CYP3A4 substrate.

5. Can the PBPK model be used to qualitatively support the effects of erdafitinib on a P-gp substrate?

Yes. The Applicant used digoxin compound file provided in the Simcyp library as a P-gp substrate. Although the digoxin model did not incorporate P-gp in the kidney, it is not expected to affect the prediction of erdafitinib effects on a P-gp substrate (see discussion under Results #2). The IC_{50} values for P-gp obtained from the in vitro study were 0.67 μ M (based on extracellular concentration in medium) or 0.026 μ M (unbound intracellular concentration), respectively. A K_i of 0.026 μ M was used in the erdafitinib model to P-gp inhibition. Our in-house data suggested that in vitro K_i values generally under-predicted observed in vivo DDI between a P-gp perpetrator and digoxin. Sensitivity analysis on K_i was performed and showed that the maximal digoxin C_{max} and AUC ratio could be 1.58 and 1.25, respectively, in the presence and absence of erdafitinib.

Because there is an uncertainty in translating in vitro K_i to in vivo K_i towards P-gp, the PBPK model prediction was considered qualitative but not quantitative. The model suggested that erdafitinib had inhibitory potential towards intestinal P-gp.

The erdafitinib absorption was modeled by the ADAM model which incorporated a mean gastric transit time of 0.4 hour and a mean small intestinal transit time of 3.3 hours. Based on the erdafitinib absorption model simulation, majority of erdafitinib has moved out of small intestine after 6 hours of administration. After 6 hours of erdafitinib oral administration, the

simulated luminal and enterocyte concentrations were lower than the IC₅₀ values based on extracellular concentration and unbound intracellular concentration, respectively (Figures 8 and 9 in study report FK12149). Therefore, staggered dosing between erdafitinib and a P-gp substrate may mitigate the risk of erdafitinib effects on a P-gp substrate.

6. Can the PBPK models be used to estimate the effects of erdafitinib on an OCT2 substrate?

No. The Applicant indicated that the effects of cimetidine (an OCT2 and MATE inhibitor) and pyrimethamine (a MATE inhibitor) on metformin were verified for a dose of 250 mg metformin. The model under-predicted the interactions with cimetidine and pyrimethamine at a dose of 500 mg metformin. The reviewer tested the metformin model by completely blocking the OCT2 pathway, the MATEs pathway, and both OCT2 and MATEs pathways. The simulation suggested that the maximum AUCR (with vs. without an inhibitor) of metformin could be 2.16 at 250 mg dose level, and 1.76 at 500 mg dose level. A search in the University of Washington Drug Interaction Database Program suggested that dolutegravir (an OCT2 and MATEs inhibitor) could increase metformin AUC by 79% to 145% at metformin 500 mg dose level. Pyrimethamine could increase metformin AUC by 170% at metformin 500 mg dose level. The above analyses suggested that the metformin model could not capture the full spectrum of known DDIs. Therefore, the PBPK models could not be used to estimate the effects of erdafitinib on an OCT2 substrate.

Conclusions

In summary, the erdafitinib PBPK model is adequate to predict the PK in CYP2C9 poor metabolizers. The model predicted that erdafitinib exposure (AUC) could be increased approximately by 60% in subjects with CYP2C9 *3/*3 genotype compared to that in subjects with CYP2C9 *1/*1 genotype. The PBPK models are adequate to predict the effects of fluconazole (a moderate CYP2C9 and CYP3A inhibitor), itraconazole (a strong CYP3A inhibitor), and rifampin (a strong CYP3A and moderate CYP2C9 inducer) on erdafitinib PK. The model predicted that a dual CYP2C9 and CYP3A4 inhibitor (such as fluconazole) may increase the erdafitinib exposure by approximately 60% to 100%, and a dual CYP2C9 and CYP3A inducer may decrease the erdafitinib exposure by approximately 30%-60% compared to the exposure in subjects with CYP2C9 *1/*1 without comedications. The simulation suggested that erdafitinib had inhibitory potential towards intestinal P-gp. However, the PBPK analysis could not provide a quantitative estimation due to the uncertainty in translating in vitro Ki to in vivo Ki.

The PBPK models are not adequate to quantitatively predict the effects of erdafitinib on a sensitive CYP3A substrate (such as midazolam) because the link between in vitro and in vivo was not appropriately established. The PBPK models are not adequate to predict the effects of erdafitinib on metformin (an OCT2 substrate) because the model under-predicted the effects of cimetidine and pyrimethamine on metformin at a dose level of 500 mg.

19.5. Additional Clinical Outcome Assessment Analyses

Not Applicable

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/s/

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I agree with the recommendation for accelerated approval for this application. Amna Ibrahim MD, Deputy Director, DOP1

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