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**Memo: review of the sponsor's white paper on comparison of overall survival
between Erdafitinib clinical study BLC2001 patients and real-world control patients
from observational data**

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LIST OF ABBREVIATIONS

anti-PD-(L)1	Antibodies to programmed cell death receptor or ligand 1
ATC	Average treatment effects on the control
ATO	Average treatment effect for overlap population
ATT	Average treatment effects on the treated
CG	Clinic-genomic
CI	Confidence interval
DOP 1	Division of Oncology Products 1
ECOG	Eastern Cooperative Oncology Group
EHRs	electronic health records
FGFR	Fibroblast growth factor receptor
FGFR+	FGFR-positive (FGFR genetic alterations)
Flatiron-FMI	Flatiron-Foundation Medicine, Inc.
GC	cisplatin-gemcitabine regimen
HR	Hazard ratio
ICD	International Classification of Diseases
LOT	Line of Therapy
MAR	Missing at random
MDF	Social Security Master Death File
MI	Multiple imputation
mUC	metastatic Urothelial Cancer
MVAC	Methotrexate, Vinblastine, Doxorubicin, Cisplatin regimen
NDI	national death index
NGS	FoundationOne next-generation sequencing
OND	Office of New Drugs
OS	Overall Survival
OSE	Office of Surveillance and Epidemiology
PS	Propensity score
RECIST	Response Evaluation Criteria in Solid Tumors
RWD	Real-world data
RWE	Real-world evidence
SAP	Statistical Analysis Plan
sIPTW	Stabilized inverse probability treatment weighting
TKI	Tyrosine kinase inhibitor
UC	Urothelial carcinoma/cancer

EXECUTIVE SUMMARY

The Division of Oncology Products 1 (DOP 1) in the Office of New Drugs (OND) consulted the Office of Surveillance and Epidemiology (OSE) to review the sponsor's study report titled "*Comparison of Overall Survival Between Erdafitinib Clinical Study BLC2001 Patients and Real-World Control Patients from Observational Data*", along with the sponsor's statistical analysis plan (SAP). Results of DEPI review are reported in this document, along with DEPI's recommendations.

In this study, the sponsor compared overall survival among the fibroblast growth factor receptor-positive (FGFR+) patients with advanced or metastatic urothelial cancer from a Phase 2 clinical study (BLC2001) who received Erdafitinib, versus the patients identified from real-world Flatiron-Foundation Medicine, Inc. (Flatiron-FMI) database who received anti-PD-(L)1 or chemotherapy. The results suggested a significant improvement in overall survival in patients treated with Erdafitinib when compared to those treated with anti-PD-(L)1 or chemotherapy, with estimated hazard ratios between 0.265 (95%CI: 0.134-0.524) and 0.367 (95%CI: 0.233- 0.578) for four different comparison groups exposed to Erdafitinib. The sponsor concluded that patients treated with erdafitinib in the BLC2001 Study had a survival benefit compared to FGFR positive patients in the Flatiron Dataset treated with anti-PD-(L)1 therapies and chemotherapy.

However, several important methodological issues impact interpretability of these findings. These include 1) unmeasured confounders 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, trial patients were enrolled from academic medical centers primarily from Europe, while controls were enrolled from community oncology clinics in the US; 4) potential differential treatment misclassification; 5) incomplete capture of death information in controls, and 6) very small sample size in the real-world control cohorts. Because both internal and external validity are threatened by these methodological issues, DEPI does not consider the study sufficient for supporting the effectiveness of the drug.

1 INTRODUCTION

This review responds to a consult request from the Division of Oncology Products 1 (DOP1) for review of the sponsor's white paper titled "*Comparison of Overall Survival Between Erdafitinib Clinical Study BLC2001 Patients and Real-World Control Patients from Observational Data*", along with the sponsor's statistical analysis plan (SAP). Briefly, this report refers to a study comparing overall survival among patients with advanced or metastatic urothelial cancer (mUC) and fibroblast growth factor receptor (FGFR) alterations from a Phase 2 clinical study (BLC2001) who received Erdafitinib versus advanced mUC patients identified from real-world Flatiron-Foundation Medicine, Inc. (Flatiron-FMI) database who received the currently available standard of care.

1.1 BACKGROUND

Urothelial carcinoma (UC) of the bladder caused approximately 200,000 deaths worldwide in 2018 and is the sixth most common type of cancer in the U.S.^{1,2} Metastatic urothelial carcinoma carries a dismal prognosis, with 5-year survival rate of 5%¹ and with limited treatment options. First-line treatment for mUC typically includes cisplatin-based chemotherapy: cisplatin-gemcitabine (GC) regimen, and combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Immune check point inhibitors including programmed cell death protein 1 (PD1) inhibitors or programmed death-ligand 1 (PD-L1) inhibitors are now the standard of care for the treatment of mUC in second-line setting after cisplatin-based chemotherapy.³

FGFRs are present in many types of normal and tumor cells and have been shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis.⁴ FGFR mutations and gene fusions have been associated with neoplastic progression and tumor vascularization in multiple cancer types,⁵ and are detected in approximately 15 to 20% of locally advanced or metastatic UC.^{6,7}

1.2 REGULATORY HISTORY

Erdafitinib is a pan-FGFR tyrosine kinase inhibitor (TKI) with demonstrated clinical activity in subjects with solid tumors identified to have alterations in the FGFR pathway including urothelial carcinoma.⁸ The regulatory history of Erdafitinib is described below:

- On 26 Apr 2013, the sponsor submitted an investigational new drug application to FDA (IND 117490).
- On 13 Mar 2018, Erdafitinib was granted Breakthrough Therapy Designation for the proposed indication.
- On 2 Aug, 30 Aug, and 18 Sept 2018, the sponsor submitted new drug application (NDA 212018) in three portions for rolling review.

- On 18 Oct 2018, according to the agreement from pre-NDA meeting, the sponsor submitted the new report titled “*Comparison of Overall Survival Between Erdafitinib Clinical Study BLC2001 Patients and Real-World Control Patients from Observational Data*”, as supportive evidence for the NDA submission to address the unmet medical need in the FGFR positive population.

1.3 PRODUCT LABELLING

The proposed indication for BALVERSA (Erdafitinib) includes treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), (b) (4)



2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENT TO BE REVIEWED

- The sponsor’s white paper titled “*Comparison of Overall Survival Between Erdafitinib Clinical Study BLC2001 Patients and Real-World Control Patients from Observational Data*”.
- The corresponding Statistical Analysis Plan (Part 2).

2.2 CRITERIA APPLIED TO REVIEW

The reviewer used the following guidelines for the reference in the review of study report and SOP:

- Guidance for industry and FDA staff. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices.⁹
- Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data.¹⁰
- Guidance for industry. E 10 Choice of Control Group and Related Issues in Clinical Trials.¹¹

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The study evaluated the overall survival (OS) comparing FGFR-positive (FGFR+) advanced mUC patients who received Erdafitinib selected from a phase 2 clinical trial (BLC2001) versus those treated with currently available standard of care (SOC) from Flatiron-FMI database who were FGFR+ or regardless of FGFR status.

3.2 STUDY OBJECTIVES

- Primary: to compare OS among FGFR+ mUC patients treated with Erdafitinib and FGFR+ mUC patients treated with currently available treatment options, i.e., anti-PD-(L)1 and/or chemotherapy.
- Secondary: to compare OS among FGFR+ patients treated with Erdafitinib with mUC patients treated with anti-PD-(L)1, regardless of FGFR status.

3.3 STUDY METHODS

3.3.1 Design & Setting

In this study, the exposed group and unexposed group were derived from different data sources: the exposed (*refers to “Erdafitinib”*) subjects were selected from a phase 2 single arm clinical trial (BLC2001), while the unexposed (*refers to “external controls”*) subjects were identified from real-world Flatiron-FMI clinic-genomic database.

3.3.1.1 Population, Data Source & Time Period

The target population for this study consisted of adult 18+ with advanced or metastatic urothelial cancer and specific FGFR genetic alterations. The clinical study BLC2001 was used to obtain the exposed FGFR+ patients who received Erdafitinib for treatment of advanced mUC, and the real-world Flatiron-FMI database was used to obtain unexposed patients who received currently available standard of care.

Study BLC2001 is a Phase 2, multicenter, open-label study to evaluate efficacy and safety of single-agent Erdafitinib in subjects with metastatic or surgically unresectable UC with selected FGFR genetic alterations. Only patients from Regimen 3 of BLC2001 (i.e., dose of Erdafitinib 8 mg QD) were included in the analysis. Since the regimen 3 was added in the trial after Amendment 3, issued on 9 Aug 2016, the time frame for the Erdafitinib cohort was from 9 Aug 2016 to 15 Mar 2018 (the last date of data collected).

Flatiron Health collects real-world, longitudinal, de-identified patient-level clinical data from electronic health records (EHRs) from US community-based oncology clinics. In partnership with Foundation Medicine, Inc. (FMI), Flatiron patient EHRs are linked with FoundationOne next-generation sequencing (NGS) results to yield the Flatiron-FMI clinicogenomic database. The Flatiron-FMI cohort included patients with a confirmed diagnosis of advanced bladder cancer and with FoundationOne testing results for FGFR status. The time frame for the real-world control cohorts was from 1 Jan 2011 to 31 Jan 2018.

3.3.1.2 Selection, Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for exposed¹² and unexposed cohorts are summarized in table 1.

Table 1: Inclusion and exclusion criteria for the study cohort

Exposed (Erdafitinib)	Unexposed (anti-PD-(L)1 or chemo)
<p>Inclusion:</p> <ul style="list-style-type: none"> • Ages 18 Years and older, male and female; • Must have histologic demonstration of metastatic or surgically unresectable urothelial cancer (cT4b, N+, or M+). Minor components of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable; • Must have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at baseline; • Subjects met 1 of the following molecular eligibility criteria based on evaluation of appropriate tumor tissue: One of the following FGFR fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; OR One of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C. • Must have an ECOG performance status score 0, 1, or 2; • Must have adequate bone marrow, liver, and renal function as described in protocol; • Negative pregnancy test (urine or serum beta human chorionic gonadotropin [b-hCG]) at Screening for women of child bearing potential who are sexually active; • Must have shown disease progression according to RECIST, version 1.1, following prior chemotherapy for metastatic or surgically unresectable urothelial cancer. Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease recurrence or progression according to RECIST, version 1.1, within 12 months of the last dose are considered to have received chemotherapy in the metastatic setting. 	<ul style="list-style-type: none"> • Patient had at least 1 documented clinical visit in the Flatiron network on or after 1 Jan 2011; • Patient had an ICD code consistent with bladder cancer in their electronic health record (ICD-9: 188x, 189.1, 189.2, 189.3; or ICD-10: C65x, C66x, C67x, C68.0); • Patient had a confirmed diagnosis of advanced bladder cancer; confirmation was based upon (1) review of Flatiron unstructured data and (2) confirmation of histology from the patient’s tumor samples. • Patient underwent NGS testing by FMI on a tumor sample with pathologist-confirmed histology that was consistent with bladder cancer (i.e., urothelial/transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma), and • Patient had 1 of the following primary sites of disease confirmed: bladder, renal pelvis, ureter, or urethra. • FGFR+ patients were identified by FMI NGS if positive for 1 or more of the 9 FGFR mutations and gene fusions in the Janssen diagnosis panel.
<p>Exclusion:</p> <ul style="list-style-type: none"> • Receiving chemotherapy, targeted therapies, definitive radiotherapy, or treatment with an investigational anticancer agent within 2 weeks (in the case of nitrosoureas and mitomycin C, within 6 weeks; in the case of immunotherapy, within 4 weeks) before the first administration of study drug. 	<p>Primary analysis (anti-PD-(L)1 patients):</p> <ul style="list-style-type: none"> • anti-PD-(L)1 patients who received an unknown clinical study drug in the Flatiron Database.

<p>Exclusion (continued):</p> <ul style="list-style-type: none"> • Having persistent phosphate level greater than ULN during screening (within 14 days of treatment and prior to Cycle 1 Day 1) and despite medical management. • Having a history of or current uncontrolled cardiovascular disease. • Females being pregnant, breast-feeding, or planning to become pregnant within 3 months after the last dose of study drug and males who plan to father a child while enrolled in this study or within 5 months after the last dose of study drug. • Having not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, or Grade 1 neuropathy). 	
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3.3.2 Outcome

The primary endpoint was overall survival, which was measured from the index date to the date of patient’s death from any cause. If a patient was alive or the vital status was unknown, the patient’s OS was censored at the date the patient is last known to be alive. The index date was based on the starting date of any or a specific treatment line and was specified in table 2.

Table 2: Exposure of interest and definition of index date:

Exposed vs Unexposed patients		Definition of Index Date (Day 1)	
Exposed (Erdafitinib cohort)	Unexposed (Control cohorts)	Exposed	Unexposed
FGFR+ patients treated with Erdafitinib from BLC2001 (N*=99)	FGFR+ patients treated with anti-PD-(L)1 from Flatiron-FMI (N=25)	1 st dose date of Erdafitinib	1 st dose date of first anti-PD-(L)1 treatment
	All patients treated with anti-PD-(L)1 from Flatiron-FMI (regardless of FGFR status). (N=115)		
FGFR+ patients who progressed on or after at least one prior chemotherapy and were treated with Erdafitinib as 2 nd or higher line of treatment from BLC2001 (N*=82)	FGFR+ patients treated with anti-PD-(L)1 as 2 nd or higher line of treatment from Flatiron- FMI (N=16)	1 st dose date of Erdafitinib	1 st dose date of 2 nd or higher line anti- PD-(L)1 treatment
	FGFR+ patients treated with chemotherapy as 2 nd or higher line of treatment from Flatiron-FMI(N=17)		

* all numbers refer to the number of subjects included in the delayed entry model.

3.3.3 Exposure

The primary exposure of interest was Erdafitinib as a regimen of 8 mg once daily; the unexposed comparators of SOCs included anti-PD-(L)1 and chemotherapy, as specified below as well as in table 2.

- Initiation of erdafitinib vs Anti-PD-(L)1:
 - In any line of therapy (LOT)
 - ◆ for FGFR+ controls
 - ◆ for all control patients (regardless of FGFR status)
 - As second or higher line of therapy
- Initiation of erdafitinib vs Chemotherapy: as second or higher line of therapy

Among controls, anti-PD-(L)1 therapy includes Pembrolizumab, Nivolumab, Durvalumab, Atezolizumab, and Avelumab. Combination therapies with anti-PD-(L)1 drugs were also included, such as anti-PD-(L)1 plus immunotherapy combination was defined as treatment with any of the 5 anti-PD-(L)1 drugs above plus any other immunotherapy. Anti-PD-(L)1 plus chemotherapy combination was defined as any of the five anti-PD-(L)1 drugs above plus any chemotherapy.

The chemotherapy includes Gemcitabine, Cisplatin, MVAC-combination, Vinflunine, Docetaxel, Paclitaxel, Carboplatin, Bendamustine, Cabazitaxel, Capecitabine, Cyclophosphamide, Doxorubicin, Doxorubicin Pegylated Liposomal, Etoposide, Ifosfamide, Irinotecan, Methotrexate, Oxaliplatin, Paclitaxel Protein-Bound, Pemetrexed, Temozolomide, Topotecan, Vinblastine, Vinorelbine, Cabozantinib, Fluorouracil, and Mitomycin. Anti-PD-(L)1 plus chemotherapy combination and chemo-chemo therapy combination were included as well.

3.3.4 Covariates

Baseline covariates for the primary analysis included age, gender, line of treatment (at Erdafitinib, anti-PD-(L)1, or chemotherapy), smoking history, primary tumor location, hemoglobin level, and time since most recent therapy. ECOG score was included in the sensitivity analysis due to substantial missingness in ECOG value.

Baseline was defined as the last non-missing values on or before first dose date of Erdafitinib, or the last measurement taken within 60 days before the indicated line of therapy for Flatiron-FMI external controls.

3.3.5 Sample Size/Power

Power calculation was not performed; sample size for each analysis was listed in table 2.

3.3.6 Statistical Analyses

- Cox proportional hazard model was used to estimate the hazard ratio (HR) for the overall survival:
 - ◆ Univariate model
 - ◆ Multivariate model (covariate adjustment or PS weighting, respectively)
- Analysis was further adjusted for left truncation through delayed entry model;
- Propensity score approach with different weighting schemes were performed in the sensitivity analysis:
 - ◆ Stabilized inverse probability treatment weighting (sIPTW)
 - ◆ Average treatment effect for overlap population (ATO)
 - ◆ Average treatment effects on the treated (ATT)
 - ◆ Average treatment effects on the control (ATC)
- Sensitivity analysis for missingness of ECOG performance score
 - ◆ Complete-case analysis versus multiple imputation (MI) for missing value in ECOG

3.4 STUDY RESULTS

The main results on OS in four comparison groups were summarized in table 3 below. Results of sensitivity analysis for assessing the impact of missing ECOG are also included in the table.

In summary, the results showed a substantial decrease in risk of overall mortality for Erdafitinib treated patients compared to all four control cohorts: (1) FGFR+ patients with anti-PD-(L)1, either as any LOT (HR: 0.265, 95%CI: 0.134-0.524), or (2) as second or higher LOT (HR: 0.317, 95%CI: 0.153-0.656); (3) all patients regardless of FGFR status who were treated with anti-PD-(L)1 (HR 0.367, 95%CI: 0.233- 0.578); (4) FGFR+ patients treated with chemotherapy as second or higher LOT (HR 0.364, 95%CI: 0.156, 0.848).

3.5 STUDY CONCLUSIONS

The sponsor concluded that:

- (1) The study results suggest that patients treated with Erdafitinib in study BLC2001 had a survival benefit when compared to FGFR positive patients from the Flatiron-FMI patients treated with available therapies (anti-PD-(L)1 or chemotherapy).
- (2) In the absence of head-to-head clinical studies, real-world, patient-level data can form the basis of an external control group to provide valuable insights regarding the effectiveness of Erdafitinib in this biomarker selected population of mUC patients.

Table 3: Summary of OS and the estimated HR for OS by Cox proportional hazard model with delayed entry

	FGFR+ Patients, Erdafitinib vs Anti-PD-(L)1						FGFR+ patients with Erdafitinib vs all patients with Anti-PD-(L)1 - As any LOT			FGFR+ Patients, Erdafitinib vs Chemotherapy - As 2 nd or higher LOT					
	As any LOT			As 2 nd or higher LOT			ERDA	Anti-PD-(L)1	P-value	ERDA	Anti-PD-(L)1	P-value	ERDA	Chemotherapy	
	ERDA	Anti-PD-(L)1	95% CI	HR	95% CI	P-value									HR
N. Patients	99	25		82	16		99	115		82	17				
Treatment duration (month) Median (range)	5.3 (0-17)	NA		NA	NA		NA	NA		NA	NA		NA		
Death: N (%)	40 (40.4)	17 (68.0)		34 (41.5)	12 (75)		40 (40.4)	72 (62.6)		34 (41.5)	12 (71)				
Overall survival (month) Median (IQR)	13.8 (6.18, NE)	3.12 (0.49, 7.89)		13.8 (5.98, NE)	3.12 (1.22, 6.67)		13.8 (6.18, NE)	4.96 (2.63, 11.40)		13.8 (5.98, NE)	5.55 (3.42, 9.56)				
6-month OS rate (95%CI)	78% (70%, 87%)	34% (18%, 67%)		75% (66%, 85%)	33% (15%, 76%)		78% (70%, 87%)	50% (40%, 62%)		75% (66%, 85%)	48% (25%, 93%)				
12-month OS rate (95% CI)	55% (45%, 68%)			54% (42%, 68%)			55% (45%, 68%)	22% (15%, 33%)		54% (42%, 68%)	9% (2%, 47%)				
<i>Primary Analysis (Excluding ECOG)</i>															
Unadjusted Analysis	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
sIPTW	0.323	0.182, 0.572	<.001	0.266	0.137, 0.518	<.001	0.413	0.279, 0.611	<.001	0.270	0.136, 0.536	<.001	0.270	0.136, 0.536	<.001
ATO	0.278	0.149, 0.520	<.001	0.397	0.164, 0.959	0.040	0.386	0.243, 0.611	<.001	0.280	0.148, 0.528	<.001	0.280	0.148, 0.528	<.001
Multivariable Model	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
PS Weighted - sIPTW	0.303	0.145, 0.635	0.002	0.379	0.163, 0.879	0.024	0.432	0.278, 0.671	<.001	0.347	0.177, 0.681	0.002	0.347	0.177, 0.681	0.002
PS Weighted - ATO	0.265	0.134, 0.524	<.001	0.317	0.153, 0.656	0.002	0.367	0.233, 0.578	<.001	0.364	0.156, 0.848	0.019	0.364	0.156, 0.848	0.019
<i>Sensitivity Analysis 1: (Including non-missing ECOG)</i>	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Multivariable Model	0.253	0.122, 0.528	<.001	0.378	0.165, 0.868	0.022	0.310	0.183, 0.523	<.001	0.326	0.150, 0.708	0.005	0.326	0.150, 0.708	0.005
Multivariable Model	0.259	0.124, 0.540	<.001	0.282	0.130, 0.609	0.001	0.372	0.228, 0.605	<.001	0.346	0.151, 0.793	0.012	0.346	0.151, 0.793	0.012
<i>Sensitivity Analysis 2: (Including MI for ECOG)</i>	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Multivariable Model	0.181	0.073, 0.450	<.001	0.193	0.075, 0.497	<.001	0.314	0.130, 0.760							
PS Weighted - sIPTW	0.329	0.123, 0.875	0.026	0.396	0.107, 1.470	0.166	0.324	0.125, 0.838							
PS Weighted - ATO	0.137	0.054, 0.348	<.001	0.113	0.047, 0.273	<.001	0.257	0.100, 0.660							

4 DISCUSSION

In this study, the sponsor compared OS in patients from a Phase 2 trial versus the external controls from real-world data (RWD) to provide evidence on treatment effectiveness of Erdafitinib among FGFR+ mUC patients. DEPI acknowledges the sponsor's efforts in applying several advanced analytic techniques to address the limitations pertaining to RWD, such as propensity score with various weighting schemes to adjust for measured confounders; sensitivity analysis with multiple imputation to assess the impact of missingness in baseline covariate (ECOG); Cox proportional hazard model with delayed entry to account for survival bias, etc. However, substantial methodological issues were identified, which may threaten the validity of the estimates.

Study population

Selection bias may be introduced as the control cohorts (anti-PD-(L)1 or chemotherapy) appear not comparable to the Erdafitinib cohort in term of several key characteristics at baseline:

- Erdafitinib patients were mostly enrolled in academic and medical centers, while Flatiron control patients were mostly from community oncology clinics. As the academic medical centers may have better performance in term of quality of care, capability of dealing with emergencies and frequency of patient visits, Erdafitinib patients were likely to have a better survival prognosis than Flatiron control patients; therefore, the results were likely be biased away from the null.
- Significant discrepancy of inclusion/exclusion criteria exists between Erdafitinib and control cohorts, especially for conditions with known adverse impact on prognosis for overall survival:
 - ◆ Patients with ECOG >2 were excluded in Erdafitinib cohort, however they were retained in the control cohorts. ECOG as a known independent prognostic factor for survival was not included in the primary analysis due to substantial missingness in the control cohorts; thus, the control cohorts likely included more patients with higher ECOG scores compared to the Erdafitinib cohort. Although the model was adjusted for ECOG in the sensitivity analysis, selection bias was not yet accounted for because ECOG was dichotomized as binary and the control patients with "ECOG>2" were included into ">=1" category in the sensitivity analysis; consequently, both primary analysis and sensitivity analysis likely biased the HR estimates away from null, i.e., in favor of better survival in the Erdafitinib cohort.
 - ◆ The Erdafitinib cohort had more stringent exclusion criteria than the unexposed group, such as, patients with inadequate bone marrow, liver, and renal function; history of or current uncontrolled cardiovascular disease, etc. These were the top reasons for excluding ineligible patients in the BLC2001

trial; however, the same criteria were not applied for the control patients. As a result, the control cohorts may include patients with more comorbidities or severe disease conditions at baseline. As the study didn't account for these differences in the analysis, potential confounding bias was introduced, and results are likely to be biased away from the null.

- ◆ Other exclusion criteria were applied for the Erdafitinib cohort but not the control cohorts, such as: (1) received anti-cancer therapy within 2-6 weeks from index date; (2) had persistent phosphate level greater than upper limit of normal (ULN); (3) unrecovered from reversible toxicity of prior anticancer therapy, etc. These factors imply that the Erdafitinib patients tended to be healthier with fewer overall toxicities compared to the control patients in Flatiron-FMI. Failure to address these issues may bias the results away from null.

In summary, these exclusion criteria may have resulted in Erdafitinib patients with fewer comorbidities and fewer toxicities from prior therapies; as the Flatiron control patients were not restricted by these exclusion criteria, their baseline health conditions could be comparatively worse. As demonstrated in the results table, 93% of the erdafitinib patients had baseline ECOG \leq 1, and half had ECOG=0; by contrast, only half of the control patients had baseline ECOG $<$ 1 (55%) and one fourth had ECOG=0 (26%). ECOG was missing in approximately 30% of control patients. Difference in baseline ECOG implies a better survival outcome expected in erdafitinib patients than control patients, which could result in biased estimates of improved survival favoring the trial patients.

- Geographically, all control subjects were in the US, while the majority of Erdafitinib subjects were in Europe (70%) and only 21 patients (21%) were in US,¹² There may exist heterogeneity in treatment effect due to different population and different healthcare system or clinical practice in different countries,¹³ however, the sponsor's original study report on BLC2001 didn't include such information.¹²
- The two groups were not comparable in the second objective: all 99 Erdafitinib subjects had FGFR+, while among 115 anti-PD-(L)1 patients from Flatiron-FMI database, only 25 patients had FGFR+. As the patients with FGFR+ may have different OS from FGFR- patients, inferences made from this analysis may be misleading.

Measure of exposure and outcome

The identification of mUC patient in real-world controls appeared appropriate in the way that they were identified not only based on ICD 9/10 diagnosis codes, but also based upon the review of Flatiron unstructured data and confirmation of histology from the patient's tumor sample. However, several issues were noticed below:

- Index date: The control patients may have gone to other facilities outside of Flatiron-FMI at an earlier time. However, as the patients' history may not be completely captured in the EHR data, the index date identified from Flatiron-FMI may not accurately represent the true first date of the therapy and may be incorrect.
- The ascertainment of anti-PD-(L)1, chemotherapy may subject to potential misclassification. Although the SAP provided the name of drugs that were included in anti-PD-(L)1 and chemotherapy, neither SAP nor study report described how a patients' treatment information was retrieved, from what source (doctor's prescription or patient's dispensing), and how it was validated. In addition, as most Flatiron patients were limited to community oncology clinics, some patients may have gone to other facilities for cancer care before they went to Flatiron community clinics. Conversely, treatment regimens for the BLC2001 patients were likely captured with high accuracy. Potential differential treatment misclassification may be introduced for these reasons.
- Per SAP, the control cohorts included both single regimens and combination regimens. However, the combined therapy may differ from single regimen in term of efficacy, safety and toxicity and may further affect overall survival.¹⁴ In addition, it was not appropriate to include Anti-PD-(L)1 plus chemotherapy in both Anti-PD-(L)1 cohort and chemotherapy cohort due to heterogeneity of treatment effect .
- In terms of primary endpoint (OS), both SAP and white paper didn't describe how the information on death was obtained in the real-world control cohorts (i.e.: EHR or chart review, linked to other data source, such as national death index (NDI) or social security master death file (MDF)). Furthermore, in the analysis, patients with unknown vital status were censored at the date they were last known to be alive. However, there was no information on how many patients were censored due to missing vital status in both cohorts; potential selection bias may be introduced if censoring was not uninformative (i.e. not random). In addition, censoring a patient to the date last seen alive assumes that the patient's status cannot be determined, which is questionable as the patient may be discharged from the clinic and died in home afterwards, and his death status was not recorded in the flatiron data. On the other hand, these patients may be still "at-risk" after their last seen in clinics but were no longer counted in the risk set after last-seen date. Therefore, the corresponding hazard rate estimates may be incorrect, because even a small change in denominator may have a large impact on hazard rate estimate, especially since sample size was very small.

Missingness in covariates and unmeasured confounders

The primary analysis adjusted for baseline covariates as potential confounders including: patient's age, gender, line of therapy, smoking history, primary tumor location,

hemoglobin level, and time since most recent therapy. However, some key adverse prognostic factors for OS that were distributed differently in the Erdafitinib and control groups, but were not accounted for in the study, include:

- Substantial missingness in ECOG: ECOG, a known independent prognostic factor for survival,¹⁵ was not included in the primary analysis due to substantial missingness (28-37%) in the control cohorts (all patients in BLC2001 had a recorded ECOG score). Although the sensitivity analysis included ECOG in covariate adjustment, ECOG was dichotomized as “>=1” vs. “0”. Consequently, residual confounding may exist due to persistent difference among ECOG>=1 category in the comparison groups.
- Baseline comorbidity and visceral metastases: As discussed earlier, the stringent inclusion/exclusion criteria in BLC2001 trial may result in much healthier Erdafitinib patients with fewer comorbidities compared to control cohorts. However, information on baseline comorbidity was not measured for both cohorts. Additionally, visceral metastasis is an established main adverse prognostic factor for OS,^{15 16} and was measured for the Erdafitinib cohort but not for the real-world control cohorts. Therefore, these factors were not accounted for in the analysis.
- Tumor diagnosis at index date and TNM stage at initial diagnosis: These are the known factors associated with cancer survival; however, this information was included in BLC2001 study but not reported in the control cohorts. Therefore, these factors were not included in the analysis.
- Treatment duration, discontinuation or interruption: these are important risk factors that may affect OS and may vary with different anti-cancer treatment and care settings. However, such information was only available for Erdafitinib cohort and missing for the real-world control cohorts. Therefore, these factors were not included in the analysis.
- Concomitant therapy and subsequent anti-cancer therapy: In BLC2001, 92% of Erdafitinib patients took concomitant medications, mainly for supportive care; and 34% of patients received subsequent anti-cancer therapy following Erdafitinib. Concomitant therapy and subsequent anti-cancer therapy may help to improve the patient’s survival. Comparing to the trial participants, availability of these types of care maybe be different in real-world settings; however, such information was not available for the control cohorts. Therefore, these factors were not included in the analysis.
- Health care services and utilization: The Erdafitinib patients in BLC2001 trial mostly received care and treatment in large academic medical centers, while most of control patients were treated in community oncology clinics. Thus, the frequency of clinic visits, clinical practices, and capability of dealing with

emergency situations were likely very different. These differences should be accounted for in the study; however, such information wasn't available in both cohorts. Therefore, these factors were not included in the analysis.

- **Temporal bias**: As noticed, the Erdafitinib cohort was assembled most recently, starting from Aug 2016 through Mar 2018; the control cohorts were collected from Jan 2011 and through Jan 2018. With rapid development in cancer care in recent years, and increased awareness of supportive care among cancer patients and their families, there may exist a potential temporal trend and the effect of calendar time needs to be considered in the study.
- **Other unmeasured potential confounders**, including the patient's race/ethnicity, BMI, social economic status and marital status, etc., which may also affect patient's cancer care and overall survival;¹⁷⁻²¹ however, such information was not available in both cohorts.

To estimate the potential magnitude of the bias arising from unmeasured confounders in this study, we conducted a quantitative bias analysis using E-value approach²²⁻²⁴. In the comparison of Erdafitinib vs. anti-PD-(L)1 as second or higher LOT, given the estimated HR (0.282, 95%CI: 0.130-0.609) from Cox proportional hazard model with delayed entry and ATO weighted propensity score approach, an unmeasured confounder should have a HR at least 4.17 to explain away the observed association in this analysis. ECOG performance score (<1 vs. ≥1) as a known prognostic factor for OS, has been reported in the literature with HR ranging from 1.2 to 4.56 among mUC patients,^{17 25-27} suggesting that unmeasured confounders, as one of several important threats to validity, are likely to explain away the observed HR in this study.

Sample size

Another concern identified in this review is very small sample size obtained in the control cohorts: only 25 GFR+ patients were treated with anti-PD-(L)1 as any LOT (16 for second or higher LOT), and 17 GFR+ patients were treated with chemotherapy as second or higher LOT. It is estimated that in US, there are about 700,000 patients currently living with urothelial cancer,¹ plus 12,000 new patients annually with locally advanced or mUC each year,²⁸ among whom 15-20% patients may have FGFR+.^{6 7} Given the limited size of the control cohorts from Flatiron-FMI database, it is unclear whether these represent the target population; thus results from this study may not be generalizable conclusions.

Statistical analysis

The overall methodology for the statistical analysis was sound. A few issues are noted about the sensitivity analysis and propensity score method.

- Sensitivity analysis on ECOG:

- ◆ In the sensitivity analysis, ECOG was dichotomized as binary (<1 vs. ≥1) and “ECOG>2” was combined into “≥1” category. As the erdafitinib cohort excluded all patients with ECOG>2, the selection bias was not accounted for in the sensitivity analysis, and residual confounding may also exist due to persistent difference among “ECOG≥1” category in the comparison groups.
- ◆ It may be not practical to use a multiple imputation approach due to small sample size (16-25 patients) in the control cohorts, as about one third of subjects did not have an ECOG value.
- ◆ Multiple imputation (MI) approach generally assume the data were at least missing at random (MAR), which is probably not the case in the real-world Flatiron-FMI data.
- Propensity score weighting
 - ◆ The study report did not describe the distribution of propensity score overlap between Erdafitinib and Flatiron-FMI cohorts. As the Erdafitinib patients and control patients were selected from very different data sources with many discrepancies in selection criteria, the overlap of PS between the two groups might be small. Lack of overlap in covariate structure may lead to erroneous estimates and 95% CIs. In general, if there is little overlap in PS, the two groups are inherently incomparable, and statistical strategies cannot overcome this problem.²⁹⁻³¹
 - ◆ Given that multivariate Cox proportional hazard models showed significant differences in OS between two exposure groups, with large effect size and HR estimates, and 95% CIs close to those estimated from PS with ATO weighting, the multivariable adjusted model is sufficient.

Results inconsistent with the literature and other clinical trials

Table 4 lists the estimated median OS in this study as compared to other clinical trials among advanced mUC patients that evaluated the same anti-PD-(L)1 or chemotherapy as the control cohorts. The inclusion/exclusion criteria of the participants in these trials were similar with BLC2001 trial, except for the inclusion of FGFR+ in BLC2001.

As the sponsor failed to provide OS for all real-world control patients who were treated with anti-PD-(L)1 or chemotherapy as second or higher LOT, we were unable to draw an inference from the direct comparisons; however, as displayed in table 4, the median OS for real-world control patients treated with anti-PD-(L)1 as any LOT (4.96 months), was substantially shorter than median OS for patients treated with anti-PD-(L)1 as second or higher LOT (8.6-10.3 months),³²⁻³⁵ indicating a discrepancy of OS estimates between clinical trials and RWD. The sponsor acknowledged the gap in the discussion section and adjusted the analysis with several baseline covariates in the analysis. Nevertheless, due

to the substantial discrepancy in cohort selection criteria between the two groups, unavailability of several important confounding factors in the control cohorts, and the small sample size obtained from Flatiron-FMI database, both the internal invalidity and external validity of the study results were seriously threatened. Inferences drawn from these results are likely to be misleading.

Table 4. Median overall survival (months) in real-world Flatiron patients versus trial patients of advanced mUC treated with chemotherapy or anti-PD-(L)1

Source	Treatment	FGFR+		Regardless of FGFR status	
		Any LOT	2+ LOT	Any LOT	2+ LOT
Flatiron-FMI Database	Anti-PD-(L)1	3.12 (N=17)	3.12 (N=16)	4.96 (N=115)	?
	Chemotherapy		5.55 (N=17)		?
Phase 2 trial	Erdafitinib	13.8 (N=99)	13.8 (N=82)		
Phase 2 trial	Atezolizumab ^{34 35}				8.6 (N=310)
Phase 2 trial	Nivolumab ³³				8.7 (N=275)
Phase 3 trial	Pembrolizumab ³²				10.3 (N=270)
Phase 3 trial	Chemotherapy ³²				7.4 (N=255)

5 CONCLUSION

The study found a significant improvement in overall survival in FGFR+ patients treated with Erdafitinib for advanced mUC compared to FGFR+ patients from the Flatiron-FMI patients treated with anti-PD-(L)1 or chemotherapy. However, DEPI identified several methodological issues threatening study validity including differential selection of two comparison cohorts, missingness of important confounding factors, potential differential misclassification of exposures and outcome. Most of these issues could result in bias in favor of the study drug and may explain the observed improved overall survival in the study arm compared to external controls. Further, due to the very small sample size in the real-word control cohorts, it is unclear whether the control population is representative of patients on SOC. In conclusion, DEPI does not consider the current study sufficiently valid for supporting regulatory decisions pertaining to drug effectiveness. However, if this study is to be considered for regulatory decision making, the Sponsor should consider DEPI recommendations located in Appendix II.

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APPENDICES

I. LIST OF HIGH-LEVEL ISSUES IDENTIFIED IN THE STUDY

1. **Confounding bias** due to missingness in covariates and unmeasured confounders

- 1) Baseline ECOG as an important prognostic factor for survival was not included in the primary analysis due to substantial missingness (28-37%) in the control cohorts.
- 2) Baseline comorbidity was not measured in both cohorts;
- 3) Other key confounding factors that were measured in Erdafitinib cohort only and missed from the control cohorts:
 - a. Visceral metastases (lung, liver and bone)
 - b. Tumor diagnosis at index date and TNM stage at initial diagnosis
 - c. Treatment duration, discontinuation or interruption
 - d. Concomitant therapy and subsequent anti-cancer therapy
- 4) Health care utilizations were not available in both cohorts.
- 5) Other potential confounders, including the patient's race/ethnicity, BMI, social economic status and marital status, etc., were not available in both cohorts.

2. **Selection bias:**

- 1) Erdafitinib patients in BCL2001 trial were enrolled in academic medical centers, while control cohorts in Flatiron-FMI were mostly from community oncology clinics. Clinical practice, frequency of patient's visits, and capability of dealing with emergencies can be different, generally better performance in academic medical centers than community clinics, which implies better survival expectation for trial patients.
- 2) Erdafitinib patients were primarily in Europe (70%) and only 21% of the patients were in US; while all the control patients were in US.
- 3) Significant discrepancies in inclusion and exclusion criteria between two comparison groups. Specifically, more stringent exclusion criteria were applied to Erdafitinib cohort, but not applied to the control cohorts; listed as below:
 - Patients with Eastern Cooperative Oncology Group Performance Status (ECOG) score >2.
 - Patients with inadequate bone marrow, liver, and renal function;
 - Patient with history of or current uncontrolled cardiovascular disease;
 - Patients who received anti-cancer therapy within 2-6 weeks from index date;
 - Patients had persistent phosphate level greater than ULN;

- Patients who were unrecovered from reversible toxicity of prior anticancer therapy.

These exclusions left the Erdafitinib patients less sick and with fewer toxicities from the prior therapies. As demonstrated in the result table, 93% of the erdafitinib patients had baseline ECOG \leq 1, and half with ECOG=0; by contrast, only half of the control patients had baseline ECOG $<$ 1 and one fourth with ECOG=0. Difference in baseline ECOG implies a better survival outcome in erdafitinib patients than control patients.

3. **Potential misclassification on exposure with incorrect index date**

- 1) The control patient may have gone to the other facilities outside of Flatiron-FMI at the earlier time. Since such information was not available in Flatiron-FMI database, the index date identified from Flatiron-FMI maybe not the truly first date of therapy and hence incorrect;
- 2) Neither SAP nor study report described how and from what source the control patient's treatment information was retrieved, and how they were validated. Therefore, potential misclassification may exist for the control cohorts.
- 3) The combined therapy of Anti-PD-(L)1 plus chemotherapy was included in the chemotherapy control cohorts.

4. **Missed information on outcome ascertainment and follow-up time**

- 1) Both the SAP and study report didn't describe how the patient's death was ascertained, and whether the other death related databases (e.g., national death index or social security master death file) were linked to retrieve the death information. Unlike the trial patients, the community clinics generally don't follow-up the patient for their survival outcome after the last visit or discharge, therefore the death information in the control cohorts may be incomplete.
- 2) The study report didn't provide the distribution of follow-up time and number (%) of patients who were censored due to unknown vital status in both cohorts. Therefore, it's unclear whether loss to follow-up was differential in two groups, and if censoring was uninformative.

5. **Extremely small sample size** in control cohorts: only 16-25 patients were identified in the control cohorts for the primary objectives, which were too small to represent the target population and thus lack of the capability to draw generalizable conclusions.

II. RECOMMENDATIONS

DEPI has the following recommendations to the Sponsor to improve study validity. Please note, due to limitations in the Flatiron-FMI data source, these recommendations may not ensure sufficiently valid results to support regulatory decisions:

- 1) Selection of Erdafitinib cohort:
 - a. Investigate potential influence of geographic heterogeneity on the treatment effect for BLC2001 study before including patients from outside the US.
- 2) Selection of the control cohorts:
 - a. Additional data sources may be necessary to identify control cohorts with adequate sample size.
 - b. Linkage to other data sources, such as claims data, to capture more complete information about patients' medical history and exposures, and to improve the capability of applying exclusion/inclusion criteria as same as the Erdafitinib cohort. This may also increase the accuracy of index date and improve ascertainment of baseline comorbidities and other relevant covariates.
 - c. Apply the same inclusion/exclusion criteria to the control cohorts as were applied to the Erdafitinib cohort:
 - Patients with ECOG >2
 - Patients with inadequate bone marrow, liver, and renal function
 - Patients with history of or current uncontrolled cardiovascular disease
 - Patients who received anti-cancer therapy within 2-6 weeks from index date
 - Patients who had persistent phosphate level greater than ULN;
 - Patients who were unrecovered from reversible toxicity of prior anticancer therapy
 - Pregnant or breast-feeding females during study period
- 3) Ascertainment of exposure:
 - a. Describe how treatment regimen information was retrieved from the RWD and how it was validated.
 - b. Stratify the treatment into single and combined regimen in design stage and analysis stage.
 - c. Anti-PD-(L)1 plus chemotherapy should not be included in the chemotherapy cohort.
 - d. Include and describe the information on treatment duration, discontinuation, and interruption among the control cohorts.

- 4) Ascertainment of outcome:
 - a. Describe how death was ascertained for the Flatiron-FMI cohorts, if any external database (e.g., NDI, MDF) was linked to retrieve the death information.
 - b. Effort should be made to obtain the patient's complete, accurate information on vital status, such as linking to the external database (NDI, MDF).
 - c. Describe the distribution of follow-up time among Erdafitinib cohort and control cohorts.
 - d. Provide number (%) of patients who were censored due to unknown vital status in both Erdafitinib cohort and control cohorts.

- 5) Effort should be made to retrieve as much as possible information on important confounding factors in both comparison cohorts:
 - a. Baseline comorbidities for both comparison cohorts;
 - b. Visceral metastases, tumor diagnosis at index date and TNM stage at initial diagnosis for control cohorts;
 - c. Concomitant therapy and subsequent anti-cancer therapy in control cohorts;
 - d. Information on health care utilization, frequency of clinic visits, and type of care settings, etc.
 - e. Patient's race/ethnicity, BMI, SES, marital status, etc.

- 6) Statistical analysis:
 - a. Conduct a sensitivity analysis to restrict the Erdafitinib cohort to US patients.
 - b. All potential confounding factors as mentioned above should be considered in the analysis if they were not accounted for in the study design stage (e.g., matching or restriction).
 - c. Provide the plots for distribution of propensity score, and % of overlap between two comparison groups in each analysis to assess if there is sufficient overlap.
 - d. Given the similar results from multivariable adjusted model and PS with ATO weighting model, pursuing further analysis with various PS weighting schemes using data with inadequate sample size seems impractical and unnecessary in this study.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 20, 2019

To: Julia Beaver, MD
Director
Division of Oncology Products 1 (DOP 1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Emily Dvorsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): BALVERSA (erdafitinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 212018

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On September 18, 2018, Janssen Biotech, Inc. submitted for the Agency's review part 3 of 3 of a rolling submission of an original New Drug Application (NDA) 212018 for BALVERSA (erdafitinib) tablets. BALVERSA (erdafitinib) is a New Molecular Entity (NME) with a proposed indication for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC), ^{(b) (4)}



This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP 1) on September 26, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BALVERSA (erdafitinib) tablets.

2 MATERIAL REVIEWED

- Draft BALVERSA (erdafitinib) tablets PPI received on September 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 12, 2019.
- Draft BALVERSA (erdafitinib) tablets Prescribing Information (PI) received on September 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 12, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 15, 2019
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 212018
Product Name and Strength: Balversa (erdafitinib) tablets, 3 mg, 4 mg, and 5 mg
Applicant/Sponsor Name: Janssen Biotech, Inc.
FDA Received Date: February 12, 2019
OSE RCM #: 2018-1805-2
DMEPA Safety Evaluator: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container labels and carton labeling for Balversa (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

^a Gao, T. Label and Labeling Review for Balversa (NDA 212018). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Feb 1. RCM No.: 2018-1805-1.

2 DISCUSSION

Janssen acknowledges our previous recommendations and made the following changes related to the prominence of the daily dose statement:^b

- The secondary color, corresponding to tablet count, was applied behind the daily dosage statement.
- The daily dose font size was increased and bolded for additional emphasis.

We evaluated the proposed changes and determined that there are adequate differentiation between the different daily dose statement via the use of different colors and bolding (see Table 1).

Table 1. Same strength tablet for the different dose daily statement

(b) (4)



3 CONCLUSION

The revised Balversa container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^b Response to FDA Information Request of 01 February 2019. Horsham (PA): Janssen Biotech, Inc. 2019 Feb 7. Available at <\\cdsesub1\evsprod\nda212018\0042\m1\us\response-to-fda-01feb2019.pdf>.

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Clinical Inspection Summary

Date	February 4, 2019
From	Yang-min (Max) Ning, M.D., Ph.D. Susan Thompson, M.D. Kassa Ayalew, M.D., M.P.H. OSI/DCCE/GCPAB
To	Dow-Chung Chi, M.D. Chana Weinstock, M.D. Clara Lee, RPM OCE/OHOP/DOPI/
NDA #	212018
Applicant	Janssen Research and Development, LLC.
Drug	Erdafitinib tablets (BALVERSA)
NME	Yes
Therapeutic Classification	Inhibitor of fibroblast growth factor receptor (FGFR) tyrosine kinase
Proposed Indication(s)	Treatment of adult patients with locally advanced or metastatic urothelial carcinoma, (b) (4) 
Consultation Request Date	October 24, 2018
Summary Goal Date	February 11, 2019
Action Goal Date	March 8, 2019
PDUFA Date	May 18, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an open-label, randomized trial (Study BLC2001) were submitted to the Agency in support of New Drug Application (NDA) for erdafitinib for its use in patients with advanced urothelial carcinoma who have certain FGFR genetic alterations. Three study sites and the Sponsor, as listed in Section III of this summary, were selected for clinical inspections.

All the inspections were completed in a timely manner with no refusals. The inspectional findings, as summarized below, verified the sponsor's reported clinical data with source documents at the study sites and revealed that the sponsor had satisfactorily managed and monitored the conduct of this trial. There was no evidence of underreporting of adverse events.

Based on the inspectional findings of the three sites and the sponsor along with other relevant documents contained in the available Establishment Inspection Reports, the OSI reviewer considers that the trial was adequately conducted and that the submitted data from the inspected sites and sponsor appear acceptable in support of this NDA and respective indication for erdafitinib.

II. BACKGROUND

Erdafitinib is an inhibitor of FGFR tyrosine kinase. To support the proposed indication and dose schedule in this NDA, the Applicant submitted clinical data from Study 42756493BLC2001 (referred as BLC2001 in this summary), which was an open-label, multicenter Phase 2 trial of erdafitinib (conducted under IND 117490) in subjects with advanced urothelial carcinoma who had disease progression following prior chemotherapy. Subjects were also required to have one of the FGFR alterations detected in their tumor tissue (FGFR fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, or FGFR3-BAIAP2L1; FGFR3 point mutations: R248C, S249C, G370C, or Y373C). The primary endpoint was objective response rate (ORR) as assessed by Investigators and an Independent Radiologic Review Committee (IRRC) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Tumor responses to erdafitinib in the trial were assessed with imaging scans (CT/MRI) at baseline, once every 6 weeks (+/- 3 days) during the first 3 months, then once every 12 weeks (+/- 1 week) for the next 9 months, and thereafter, once every 4 to 6 months until disease progression or unacceptable toxicity. The central review by IRRC was triggered for subjects on Study Regimen 3 (erdafitinib 8 mg once daily every day, with pharmacodynamically guided up-titration to 9 mg once daily) after the Investigator-assessed ORR reached >25%, a prespecified threshold in the study protocol.

Between 5/20/2015 and 3/15/2018, the trial enrolled 210 subjects at 87 sites across 14 countries, including 16 study sites in the United States. Of the 210 enrolled, 99 subjects received erdafitinib at Regimen 3, which represents the proposed dose schedule for clinical use in the submitted erdafitinib label. The rest of subjects received other Regimens (6 mg or 10 mg daily) that were not recommended by the Data Review Committee in July 2016. The data cutoff date for the submitted efficacy and safety analyses to the NDA was March 15, 2018.

The review division requested clinical inspections to verify the reported efficacy and safety findings from this trial in terms of the proposed dose schedule. Three study sites, as listed in the following section, were selected. Relative to other sites, these three sites enrolled a high number of study subjects and had a high number of responders to treatment with erdafitinib. The sponsor inspection was also requested for this First-in-Class oncology product to confirm the selection of subjects positive for FGFR alterations, determination of Regimen 3 as the optimal dose regimen from the three studied dosing schedules, and implementation of IRRC as prespecified in the study protocol.

III. RESULTS (by site):

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: HHung1@its.jnj.com Site: Sponsor	Protocol: BLC2001	Nov. 26-30, 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data is unreliable.

*Preliminary classification based on preliminary communication with the field investigator.

This may be associated with: a) EIR has not been received from the field; b) complete review of EIR is pending. Final classification occurs after the final review of the EIR occurs or the post-inspectional letter has been sent to the inspected entity.

1. Dr. Scott Tagawa, Site US00014

This site was inspected as a data audit for Study BLC2001. This was the first FDA inspection for the Principal Investigator. The inspection found that 6 of 31 screened subjects were enrolled at the site. Five of the 6 subjects were in the 8 mg cohort. At the time of this inspection, three subjects remained on erdafitinib and had ongoing study visits per the protocol. Two subjects were discontinued secondary to progressive disease and one subject due to the occurrence of a serious adverse event (SAE). Source records of the 6 enrolled subjects were reviewed. These included informed consent documents, eligibility criteria, study protocol and amendments, medical histories, electronic case report forms (eCRFs), adverse event (AE) reporting, protocol deviations, delegation of authority, financial disclosure, Institutional Review Board (IRB) approvals, and investigational product accountability. The inspection also reviewed the protocol-specific training, monitoring, and relevant documents provided by the sponsor before the site initiation and during the study.

The inspection revealed no major regulatory violations or deficiencies. No FDA Form 483 was issued. The reported data in eCRFs were verified at the study site and found consistent with the data listings submitted to the NDA by the Applicant. Reporting of adverse events including SAEs appeared to be complete and accurate. One study subject was found to have three scans performed out of the allowed maximum time window (delayed from three to seven days). This appeared to be associated with the subject's missed appointments and rescheduling difficulties. This deviation was discussed with the Investigator at the close-out meeting.

2. Dr. Arlene Siefker-Radtke, Site US00011

This site was also inspected as a data audit for Study BLC2001, the first FDA Inspection for this Principal Investigator. There were 53 subjects screened at the site and 5 of them enrolled (4 in the 8 mg cohort). At the time of the inspection, one subject was on erdafitinib treatment and four subjects were discontinued from study treatment. The reasons for discontinuation included disease progression (two) and deaths (two). The inspection reviewed Regulatory Binders containing approved protocol and amendments, investigator agreements, training documents, IRB approvals, continuing reviews, eligibility criteria, Informed Consent forms, protocol deviations, monitoring logs and sponsor's correspondence. Source documents were examined for all five subjects and compared to the reported data listings and relevant eCRFs.

The inspection revealed no objectionable observations in the conduct at this site. The submitted data listings were confirmed against source records and/or documents. Imaging studies were performed and documented as per study protocol and were submitted to the IRRC accordingly. The overall response for each study subject was documented at the site and found to be complete. Two SAEs (one case of sepsis/colitis and one case of retinopathy) were well documented, and there was no evidence of

under-reporting of adverse events based on source data.

3. Dr. Yohann Lorient, Site FR00005

This foreign site was inspected as a data audit for BLC2001. There was no previous FDA inspection history for the investigator. Since the inspection was just completed two weeks ago, the EIR has not been received. The following key inspectional findings are based on the email correspondence provided by the field investigator who conducted the inspection. An amendment would be made should the EIR contain significant differences that could change the current assessment.

The site screened 104 subjects and enrolled 10 subjects in the study. Five subjects were in the 8 mg cohort. As of the time of this inspection, one subject was actively on study treatment, two remained in follow-up, and seven discontinued due to disease progression and thereafter died.

The inspection revealed no significant deficiencies. Source data for the primary endpoint ORR were verifiable. There was no evidence of under-reporting of adverse events or SAEs. For one subject ((b) (6) on 6 mg erdafitinib) 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.

4. Sponsor: Janssen Research and Development, LLC

The sponsor inspection was issued to evaluate the conduct of Study BLC2001. This inspection included a review of the sponsor's organizational charts, standard operating procedures and policies, CRO/vendor task orders and agreements, data management plans, monitoring visit reports, financial disclosures, investigator agreements (FDA Form 1572s) and qualifications (e.g. curriculum vitae), site training records, and certificate of analysis for study drug batches and related shipping and handling. The inspection also focused on sponsor's monitoring and agreements regarding the selection of subjects with certain FGFR alterations, determination of the 8 mg regimen as the recommended dose schedule and use of the IRRC for efficacy analysis. During the inspection, documents relevant to the above selected clinical sites for clinical inspections were retrieved from the sponsor's Trial Master File and examined accordingly.

The inspection found no major regulatory violations or deficiencies, with no Form 483 issued. Data consistency between original eCRFs in the RAVE eDC system and the datasets submitted to the NDA was verified in several randomly selected study subjects. One study site (US00029) that was found to be non-compliant with the study protocol was identified by the sponsor in a timely manner, and the enrollment at the site was

terminated. The inspection identified a few protocol deviations, for which the sponsor provided corresponding documents to show their reporting and/or communication with responsible study investigators. The involved study subjects in the deviations were not placed at undue risk. Concerning the incomplete list of CROs found in the BIMO folder of the NDA, the sponsor was able to provide an updated list of all CROs along with corresponding signed service agreements and related work orders.

Overall, the inspectional findings showed that the sponsor had proper management and adequate oversight of the conduct of Study BLC2001 and verified that the clinical investigation of erdafitinib in the intended study population was carried out in accordance with the investigational plan and study protocol. The sponsor's submitted data, associated with Study BCL2001, appear reliable based on available information.

{See appended electronic signature page}

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Review Division /Division Director/J Beaver
Review Division /Cross Discipline Team Leader/C Weinstock
Review Division /Project Manager/C Lee
Review Division/Medical Officer/D.C. Chi
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Knin
OSI/DCCE/Branch Chief/K Ayalew
OSI/DCCE/Team Leader/SD Thompson
OSI/DCCE/GCP Reviewer/YM Ning
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 1, 2019
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 212018
Product Name and Strength: Balversa (erdafitinib) tablets, 3 mg, 4 mg, and 5 mg
Applicant/Sponsor Name: Janssen Biotech, Inc.
FDA Received Date: January 28, 2019
OSE RCM #: 2018-1805-1
DMEPA Safety Evaluator: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container labels and carton labeling for Balversa (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 DISCUSSION

Janssen agrees to utilize the FDA recommended expiration date format.^b Additionally, Janssen only provided the representative mock-ups of the [REDACTED] (b) (4) [REDACTED] 3 mg, 56-tablet Carton (Box) to facilitate review, but intends to update all labels in Module 1.14.1.1 with these changes following agreement with FDA.^c

Janssen implemented most of our recommendations, except our recommendation to replace the “# mg” strength statement with the statement “# mg daily dose (number # mg tablets once

^a Gao, T. Label and Labeling Review for Balversa (NDA 212018). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 18. RCM No.: 2018-1805.

^b Response to FDA Information Request of 22 January 2019. Horsham (PA): Janssen Biotech, Inc. 2019 Jan 28. Available at <\\cdsesub1\evsprod\nda212018\0035\m1\us\response-to-fda-22jan2019.pdf>.

^c NDA 212018. erdafitinib (JNJ-42756493). Response to FDA Information Request of 22 January 2019. Horsham (PA): Janssen Biotech, Inc. 2019 Jan 28. Available at <\\cdsesub1\evsprod\nda212018\0035\m1\us\cover.pdf>.

daily)”

(b) (4)

Janssen would like to retain the dosage strength of each individual tablet to maintain consistency across the product portfolio (i.e., the bottle labels and bottle cartons), so instead, Janssen added the daily dose statement in the line below the “# mg” strength statement on the container labels and to the right of to the “# mg” strength statement on the carton labeling.

While the addition of the daily dose statement to the labels and labeling is acceptable, the revision still does not fully address our concern

(b) (4)



Figure 1. Same strength tablet for the different dose daily

(b) (4)



3 CONCLUSION

The revised Balversa container labels, and carton labeling are unacceptable from a medication error perspective.

4 RECOMMENDATIONS FOR JANSSEN BIOTECH, INC.

We recommend the following be implemented prior to approval of this NDA:

- A. General Comments for Container Labels – Pull Out Blister Cards, Carton Labeling – Blister Card Sleeves, and Carton Labeling – Carton box
 - a. We acknowledge your addition of the daily dose statement in the line below the “# mg” strength statement on the container labels and to the right of to the “# mg” strength statement on the carton labeling and find this addition acceptable. However, as currently presented, we are concerned that the daily dose statement lacks prominence, and thus, does not fully address our concern

(b) (4)



tablets.

(b) (4)

We recommend revising the container labels and carton labeling to provide additional differentiation between (b) (4) packs that contain the same strength (i.e., 3 mg and 4 mg) by means of different colors, bolding, or boxing, or by other means. For example, you may consider using the color already utilized to highlight the net quantity statement as the color to also highlight or box the daily dose statement. We note the purple color highlighting the 42-count statement for 3 mg tablets overlap with the purple color highlighting the strength statement for 5 mg tablets. If you choose to use colors for differentiating, please ensure same or similar colors do not overlap among the different strengths.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 18, 2019
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 212018
Product Name and Strength:	Balversa (erdafitinib) tablets, 3 mg, 4 mg, and 5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Biotech, Inc.
FDA Received Date:	September 18, 2018
OSE RCM #:	2018-1805
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this NDA, this review evaluates the proposed container label, carton labeling, Prescribing Information (PI) and Medication Guide for Balversa for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Janssen proposed to provide Balversa in bottles (b) (4) we requested intend-to-market samples of Balversa on December 6, 2018.^a Janssen provided the requested samples on December 21, 2018, and the following clarification in an email^b:

Please note that upon approval of the NDA, the Sponsor intends to commercialize Erdafitinib tablets, 3mg, 4 mg and 5 mg, in the HDPE bottle configurations as described in the NDA; (b) (4)

^a Fahnbulleh, F. NDA 212018 Balversa IR. Silver Spring (MD): FDA, CDER, OSE (US); 2018 Dec 6.

^b Hsiao-Ling, H. RE: NDA 212018 Balversa IR. Raritan (NJ): Janssen Research & Development, LLC; 2018 December 14. NDA 212018.

We shared this information with the Review Team, and the Review Team confirmed that it is acceptable (b) (4) information in Section 16 How Supplied/Storage and (b) (4)

Therefore, we evaluated the proposed PI, container label and carton labeling for the bottles, and the container label and carton labeling (b) (4) determined that they can be improved to ensure safe medication use.

Since the proposed tablets are “film-coated” (b) (4), we asked the Review Team to consider adding the statement “Do not chew, crush, or split tablets” if there is a product quality or pharmacokinetics reason that the film-coated tablets should not be chewed, crushed, or split. The Review Team confirmed that the “Do not chew, crush, or split tables” statement does not need to be added to the PI.

4 CONCLUSION & RECOMMENDATIONS

The proposed Balversa PI, container labels, and carton labeling may be improved to ensure safe medication use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

- a. In Section 2.2 Recommended Dosage and Administration, include the number of tablets the patient need to take for the 8 mg and 9 mg dose. For example: “8 mg (two 4 mg tablets)” and “9 mg (three 3 mg tablets)” to prevent confusion and wrong dose errors.
- b. Revise the statement “The tablets should be (b) (4) (b) (4) “Swallow tablets whole with or without food.” for clarity.
- c. In Section 2.4 Dose Modification, consider including the number of tablets and the tablet strength required to make the X mg dose in Table 1 to prevent confusion and wrong dose errors. For example:

Table 1: BALVERSA Dose Reduction Schedule

Dose	1 st dose reduction	2 nd dose reduction	3 rd dose reduction	4 th dose reduction	5 th dose reduction
9 mg → (three 3 mg tablets)	8 mg (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop
8 mg → (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop	

B. Patient Information

1. In “How Should I take Balversa” section, we recommend including the number of tablets the patient need to take for the 8 mg and 9 mg dose to prevent confusion and wrong dose errors. For example: “8 mg (two 4 mg tablets) once a day” and “9 mg (three 3 mg tablets) once a day”.

4.2 RECOMMENDATIONS FOR JANSSEN BIOTECH, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act- Questions and Answers*.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

(b) (4)







2. Revise the Dosage statement for “x mg daily dose” from “Dosage: See package insert.” to “Usual Dosage: Take [three/two/one] X mg tablets at the same time once daily, with or without food. Swallow tablets whole.” This will ensure the patients understand that they need to take two or three tablets all at once.

D. Carton Labeling – Carton box

1.

(b) (4)

We recommend revising the container labels and carton labeling to prominently display the daily dose followed by the quantity of tablets required for the dose (e.g., “8 mg daily dose (two 4 mg tablets once daily)”) to prevent wrong selection errors.

Ensure that this statement (e.g., “8 mg daily dose (two 4 mg tablets once daily)”) is more prominent than the net quantity statement (e.g., “56 film-coated tablets”) by using a bigger font size.

For example, see the 8 mg daily dose carton labeling below. Please note that the example layout below is just to demonstrate our recommendations above.

NDC 0000-0000-00

Balversa
(erdafitinib) tablets

8 mg daily dose
(two 4 mg tablets once daily)

Contents: 2 individual weekly blister packs.
Each blister pack contains 28 tablets (4 mg per tablet).

Rx only
56 film-coated tablets

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Balversa received on September 18, 2018 from Janssen Biotech, Inc..

Table 2. Relevant Product Information for Balversa																			
Initial Approval Date	N/A																		
Active Ingredient	erdafitinib																		
Indication	Treatment of adult patients with locally advanced or metastatic urothelial carcinoma, (b) (4) <div style="background-color: #cccccc; width: 100%; height: 50px; margin-top: 5px;"></div>																		
Route of Administration	oral																		
Dosage Form	tablets																		
Strength	3 mg, 4 mg, and 5 mg																		
Dose and Frequency	<p>The recommended starting dose of BALVERSA is 8 mg orally once daily; with pharmacodynamically guided up-titration, based on serum phosphate levels, to 9 mg daily if criteria are met.</p> <p>For adverse reactions</p> <p>BALVERSA Dose Reduction Schedule</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th style="width: 15%;">Dose</th> <th style="width: 15%;">1st dose reduction</th> <th style="width: 15%;">2nd dose reduction</th> <th style="width: 15%;">3rd dose reduction</th> <th style="width: 15%;">4th dose reduction</th> <th style="width: 15%;">5th dose reduction</th> </tr> </thead> <tbody> <tr> <td>9 mg</td> <td>→ 8 mg</td> <td>6 mg</td> <td>5 mg</td> <td>4 mg</td> <td style="background-color: #cccccc;">Stop</td> </tr> <tr> <td>8 mg</td> <td>→ 6 mg</td> <td>5 mg</td> <td>4 mg</td> <td style="background-color: #cccccc;">Stop</td> <td></td> </tr> </tbody> </table>	Dose	1 st dose reduction	2 nd dose reduction	3 rd dose reduction	4 th dose reduction	5 th dose reduction	9 mg	→ 8 mg	6 mg	5 mg	4 mg	Stop	8 mg	→ 6 mg	5 mg	4 mg	Stop	
Dose	1 st dose reduction	2 nd dose reduction	3 rd dose reduction	4 th dose reduction	5 th dose reduction														
9 mg	→ 8 mg	6 mg	5 mg	4 mg	Stop														
8 mg	→ 6 mg	5 mg	4 mg	Stop															
How Supplied	<p>3 mg tablets</p> <p>Bottle of 56-tablets with child resistant closure</p> <p>Bottle of 84-tablets with child resistant closure</p> <p>Two dose pack wallets of 28-tablets each in a box of 56-tablets</p> <p>Two dose pack wallets of 42-tablets each in a box of 84-tablets</p> <p>4 mg tablets</p> <p>Bottle of 28-tablets with child resistant closure</p> <p>Bottle of 56-tablets with child resistant closure</p> <p>One starter pack wallet of 14-tablets in a box</p>																		

	One dose pack wallet of 28-tablets in a box Two dose pack wallets of 28-tablets each in a box of 56-tablets 5 mg tablets Bottle of 28-tablets with child resistant closure One dose pack wallet of 28-tablets in a box
Storage	Store at 20°C 25°C (68°F 77°F); excursions permitted between 15°C and 30° (59°F and 86°F)
Container Closure	HDPE Bottle - white 40 cc HDPE bottle with a child-resistant (b) (4) closure and an induction seal liner.  (b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Balversa labels and labeling submitted by Janssen Biotech, Inc.

- Container labels received on September 18, 2018
- Carton labeling received on September 18, 2018
- Blister Cards received on September 18, 2018
- Prescribing Information (Image not shown) received on September 18, 2018

G.2 Label and Labeling Images



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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212018
Submission Number	004
Submission Date	9/18/2018
Date Consult Received	9/28/2018
Clinical Division	DOP1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation submitted in NDA 212018. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 117490 dated 09/06/17 in DARRTS;
- Study 42756493EDI1001 [protocol](#), [study report](#), [cardiac safety report](#) (Submission 0002) and [concentration-QT analysis report](#) (Submission 0004);
- [Proposed label](#) (Submission 0004); and
- [Highlights of clinical pharmacology and cardiac safety](#) (Submission 0002).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 ms) of erdafitinib was observed in this QT assessment.

The effect of erdafitinib was evaluated in Study 42756493EDI1001. The highest dose that was evaluated was 12 mg once daily (QD), which covered steady state exposure at the maximum therapeutic dose (9 mg QD). Data from the dose expansion cohorts (9 mg QD continuous dosing and 10 mg QD 7d on/7d off) were assessed using central tendency analysis by visit (cycle, day and time), which did not suggest that erdafitinib is associated with large mean increases in the QTc interval (see Table 1 for overall results). There was no placebo or positive control in the study. The findings of this analysis are further supported by categorical analysis (section 4.4) and exposure-response analysis (section 4.5).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	Mean (ms)	90% CI (ms)
QTcF	9 mg	C1D1-2h	6.9	(4.2, 9.6)
QTcF	10 mg (7d on/7d off)	C1D7-2h	3.9	(0.5, 7.4)

ECG data used to support the exposure-response analysis were generated by a different method from those used to support the central tendency analysis. Due to limitations in terms of ECG acquisition and interpretation (section 4.5), exposure-response analysis was used as a supportive analysis in this review.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

None.

2 PROPOSED LABEL

Below are proposed edits to the [label](#) submitted to Submission 0004 from the QT-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Based on evaluation of QTc interval in a Phase 1, open-label, dose escalation and dose expansion study in 187 patients with cancer, erdafitinib had no large effects (i.e. 20 ms) on QTc interval (b) (4)



Reviewer's comments: Study 42756493EDI1001 does not include a placebo or positive control arm or a large exposure margin. Therefore, results only support a lack of large effect (i.e., >20 ms) on QTc interval per ICH E14 Q&A 6.1 and cannot be used to exclude a small effect (i.e., <10 ms).

We propose not to report results of the exposure-response analysis because the analysis is supportive of the by-time analysis. Due to the limitations in study design, small effects cannot be excluded using concentration-QTc analysis.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Study 42756493EDI1001 is a Phase 1, 4-part study to evaluate the safety, pharmacokinetics, and pharmacodynamics of erdafitinib in subjects with solid tumors or lymphoma. The QT-IRT reviewed the QT assessment plan previously (under IND 117490 dated [09/06/2017](#)). It was concluded that Study 42756493EDI1001 may be adequate to exclude large mean QTc effects (20 ms) at the therapeutic exposures to support registration.

In Part 1 of the study, 39 patients received continuous dosing regimen (0.5-12 mg QD) and 27 subjects in the intermittent dosing regimen (10 or 12 mg QD, 7 days on/7 days off). Triplicate 12-lead ECGs and time-matched PK samples were collected at the time-points listed in Appendix 5.2. In addition, the sponsor collected continuous Holter data from patients in Part 1. The primary purpose of the Holter data was for rhythm analysis.

In Part 2 (tumor biopsy cohort), 1 patient received 6 mg QD and 10 patients received 9 mg QD doses. In Part 3 (dose expansion cohort), 46 patients received continuous dosing regimen (9 mg QD). In Part 4, 64 patients received intermittent dosing regimen (10 mg QD, 7 days on/7 days off). Triplicate 12-lead ECGs and time-matched PK samples were collected at the time-points specified in Appendix 5.2.

Sponsor submitted a cardiac safety analysis using 12-lead ECG data reported in 3 groups for the central tendency analysis and the outlier analysis: 1) Parts 1 (each cohort separately and 2 pooled groups: daily dosing, intermittent dosing); 2) Parts 2 and 3 (9 mg QD continuous dosing); and 3) Part 4 (10 mg QD, intermittent dosing). These data (available in Submission 0002) supported an interim analysis before NDA submission and are referred to as “primary ECG dataset” in the current review. Predose baseline was used in this dataset.

Sponsor also submitted a concentration-QTs analysis using PK data from Part 1 paired with ECG re-extractions at the time-points described in Appendix 5.2. These data (available in Submission 0010) are referred to as “supportive ECG dataset” in the current review. The baseline in this analysis was time-matched using ECGs extracted from a Holter ECG collected during screening.

3.2 SPONSOR’S RESULTS

3.2.1 Central tendency analysis

No large QTc effect was observed in 9 mg QD or 10 mg QD either in the reviewer’s analysis or in the sponsor’s analysis. Please see section 4.3 for the details. We focus on Part-3 dose expansion cohort (9 mg QD) and Part-4 intermittent dosing regimen (10 mg QD (7 days on/ 7 days off) up to cycle 2 Day 1.

3.2.1.1 Assay Sensitivity

Not applicable. The purpose is to exclude large effect.

3.2.1.1.1 QT bias assessment

Not applicable. The purpose is to exclude large effect.

3.2.2 Categorical Analysis

Our categorical analyses concurred with the sponsor’s conclusion - 1 subject QTcF values >500 ms and no subject’s change from baseline was above 60 ms. Please see section 4.3 for the details.

3.2.3 Safety Analysis

Four subjects (2%) had electrocardiogram QT prolonged reported as a TEAE. These are Subject (b) (6) highest QT value was 529 msec at end of treatment, baseline 511 msec), Subject (b) (6) (highest QT value was QTcB 486 msec predose on Cycle 1 Day 8, baseline 467 msec), Subject (b) (6) (highest QT value was QTcB 478 msec on Cycle 4 Day 1, baseline value 444 msec), and Subject (b) (6). This last subject (Subject (b) (6) with Grade 3 elevated QTcF and QTcB discontinued treatment due to electrocardiogram QT prolonged.

Subject (b) (6) was a 67-year old male on the 10-mg intermittent regimen with medical history of atrial fibrillation, chronic kidney disease, hypertension, and valvular cardiomyopathy. At baseline QTcB for this subject was 496 msec and QTcF 481 msec. Grade 1 electrocardiogram QT prolongation was reported on Study Day 36 (QTcB=481 msec, QTcF=462 msec), which worsened on Study Day 43 to Grade 3 (QTcB=526 msec, QTcF=501 msec). The investigator considered the event to be possibly related to erdafitinib, and erdafitinib was discontinued. The event resolved on Study Day 56.

TEAEs considered to be “arrhythmia-related” included the following PTs: 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 on the 8/9-mg daily regimen were reported to have arrhythmia-related TEAEs. Two subjects had Grade 3 events of syncope; no Grade 4 events were reported. None of the arrhythmia-related events were serious, or resulted in reduction, interruption, or discontinuation of erdafitinib. No cases of torsades de pointes were reported. A brief narrative for the 1 subject with ventricular arrhythmia is provided below. Grade 1 ventricular arrhythmia and Grade 3 syncope (9-mg regimen): Subject (b) (6) was a 63-year-old male. He had ventricular arrhythmia which was reported from Study Day 1, and which persisted throughout the duration of the subject’s study participation. At screening, the subject’s ECG showed intraventricular conduction defect with ventricular premature complexes (Mod5.3.3.2/EDI1001InterimReport/eRT report/Listing16.2.6.2). The subject had a medical history of hypertension and a baseline QTc of 412 msec (Mod5.3.3.2/EDI1001InterimReport/LEG02). On Day 1, ECG showed first degree atrioventricular block; the QTcB value 450 msec. The investigator considered this event unrelated to erdafitinib and the subject continued study treatment until Day 163 without any additional cardiac events (he had one event of syncope on Day 141 at which time he also had groin pain and urinary retention), after which he was subsequently discontinued due to disease progression.

Across all dose regimens, 15 subjects (3.6%) had arrhythmia-related TEAEs. Two subjects had their dose interrupted as a result, and 1 subject had erdafitinib discontinued. One subject on the 6-mg daily regimen had a fatal event of loss of consciousness that occurred 3 days after discontinuation of erdafitinib due to progressive disease; additional details are provided below.

Grade 5 loss of consciousness (6-mg regimen): Subject (b) (6) was a 71-year-old male with medical history of fatigue, anemia, and hypertension. The subject had non-serious Grade 3 TEAEs of decreased appetite and fatigue on Study Day 11. Treatment with the study drug was permanently discontinued on Study Day 15 due to progressive disease, with the last dose of the study drug received on Study Day 14. On Study Day 17, the subject died at home due to an SAE of Grade 5 loss of consciousness considered to be due to clinical deterioration due to disease progression. The investigator considered this event not related to erdafitinib treatment. An autopsy was not performed.

3.2.4 Exposure-Response Analysis

The sponsor used QTcI as the primary endpoint in the concentration-QTc analysis.

After confirming the lack of hysteresis and the linearity of the drug effect, the linear mixed effect model including Δ QTcI as the dependent variable, the erdafitinib plasma concentration (total or free), C_p , as a continuous covariate and each nominal post-dose timepoint as categorical factors was used to analyze the data. The slopes for total and free erdafitinib plasma concentrations were estimated 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 to -1.5 msec) and -5.1 msec (90% CI: -8.3 to -2.0 msec), respectively.

Sponsor obtained similar results using Δ QTcF as the dependent variable.

Reviewer conducted concentration-QTc analysis using QTcF as the primary endpoint. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. mean < 20 bpm) were observed (see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study (i.e. the primary ECG dataset using 12-lead ECG data from 4 parts) appears acceptable.

ECG acquisition and interpretation of the supportive ECG dataset (i.e. generated by re-extraction of Holter recording after the interim analysis) could not be evaluated because raw data was not submitted to ECG Warehouse.

4.2.2 QT bias assessment

Not performed.

4.3 CENTRAL TENDENCY ANALYSIS

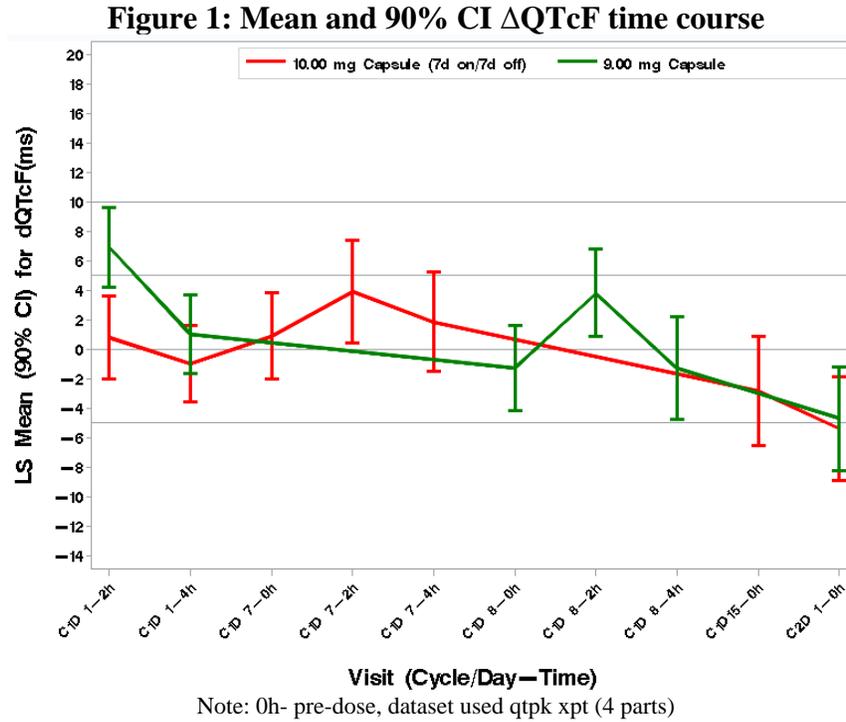
We used the primary ECG dataset to perform the Center Tendency Analysis for dose expansion cohorts in Parts 3 and 4. ECG data after Cycle 2 was excluded from analysis because the sampling time relative to dosing was random.

4.3.1 QTc

The primary endpoint is the change from baseline of QTcF. We focus on Part-3 (dosed at 9 mg capsule) and Part-4 (dosed at 10 mg capsule (7d on/7d off)) and performed central

tendency by visit (cycle, day and time) up to cycle 2 Day 1. Figure 1 presents the mean and 90% CI on mean change from baseline in QTcF by visit and dose group.

The largest upper limit of 90% CI mean change from baseline in QTcF was 9.6 ms and 7.4 ms for 9 mg QD (at cycle 1 day 1 - 2h post-dose) and 10 mg QD (7d on/7d off) at cycle 1 day 7 - 2h post-dose, respectively.



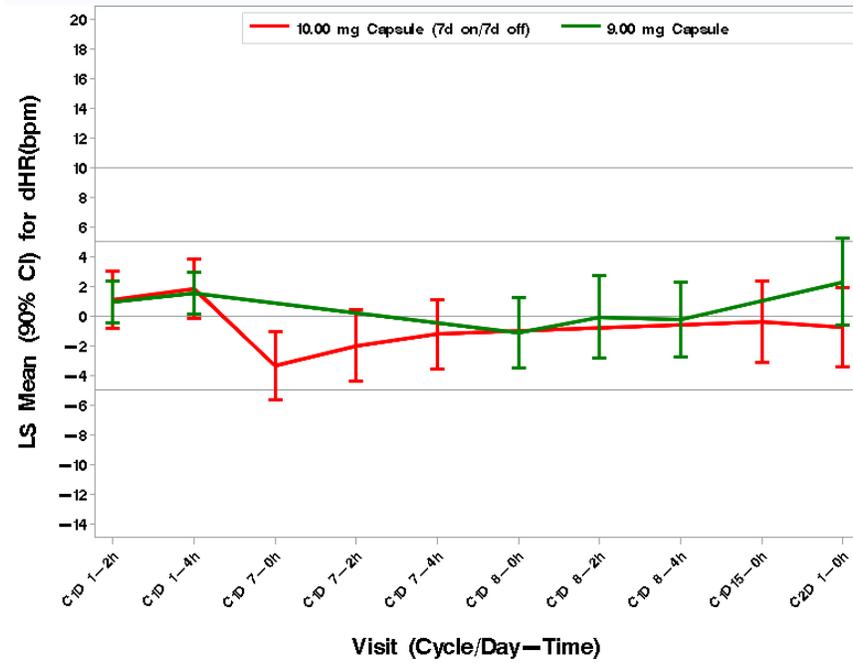
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

The same statistical analysis was performed based on HR. The largest upper limit of 90% CI mean change in HR were 5.2 bpm and 3.8 bpm for dosed at 9 mg QD (at cycle 2 day 1 - pre-dose) and 10 mg QD (7d on/7d off) at cycle 1 day 1 - 4h post-dose, respectively. Figure 2 displays the time profile of Δ HR for different dose groups.

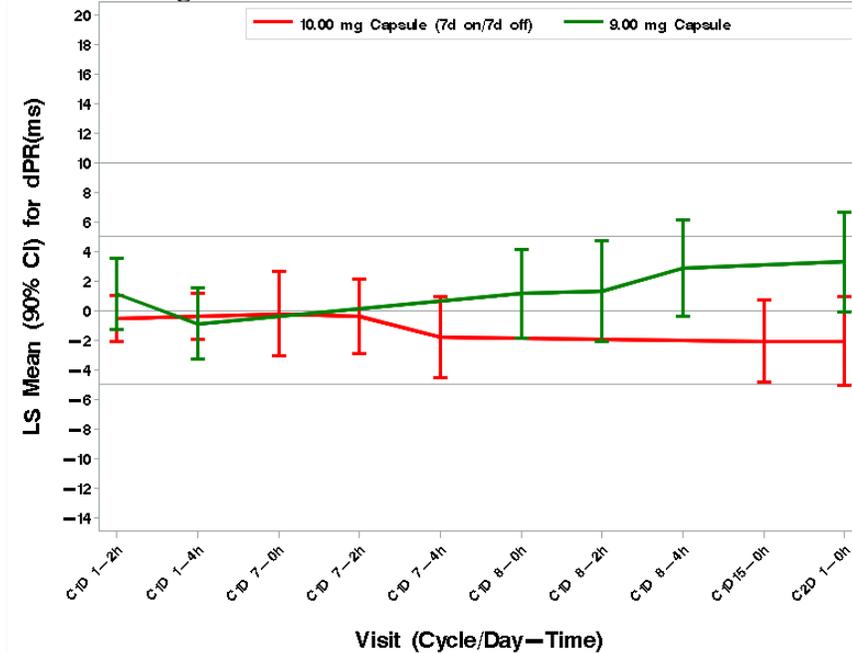
Figure 2: Mean and 90% CI Δ HR time course



4.3.3 PR

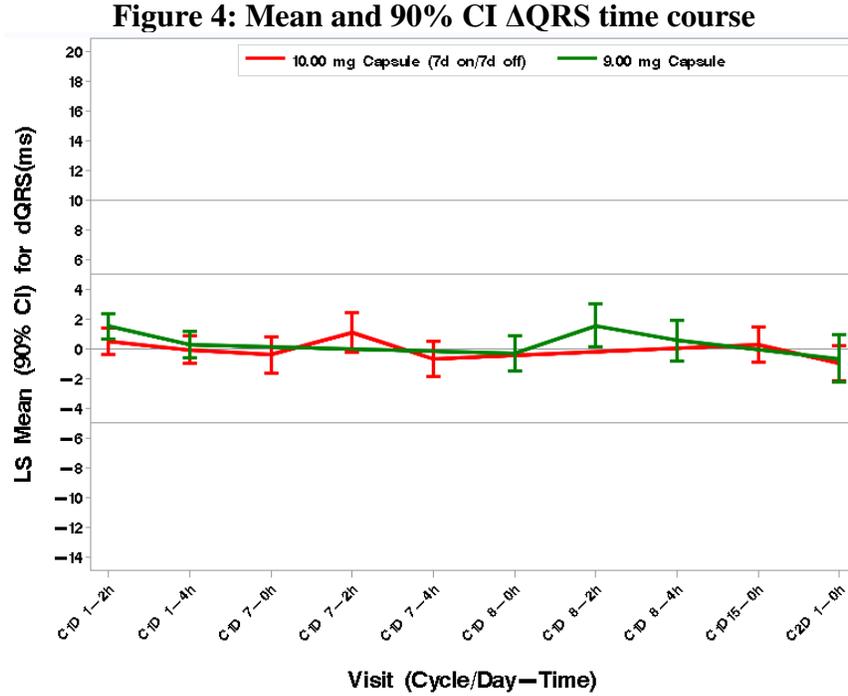
The same statistical analysis was performed based on PR interval. The largest upper limits of 90% CI mean change from baselines in PR were 6.7 ms and 2.6 ms for 9 mg QD at cycle 2 day 1 - pre-dose and 10 mg QD (7d on/7d off) at cycle 1 day 7 - pre-dose, respectively. Figure 3 displays the time profile of Δ PR for different dose groups.

Figure 3: Mean and 90% CI Δ PR time course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval. The largest upper limits of 90% CI mean change from baselines in QRS were 3.0 ms and 2.4 ms for 9 mg QD at cycle 1 day 8 – 2h post-dose and 10 mg QD (7d on/7d off) at cycle 1 day 7 – 2h post-dose, respectively. Figure 4 displays the time profile of Δ PR for different dose groups.



4.4 CATEGORICAL ANALYSIS

For categorical analysis, the reviewer used the primary ECG dataset and pooled 4-parts by dosing regimen.

4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, and above 500 ms. One subject's QTcF from 10 mg capsule (7d on/7d off) was 501 ms at the end of treatment and had a baseline 454 ms.

Table 2: Categorical Analysis for QTcF

Treatment Group	Total N		Value ≤ 450 ms		450 ms < Value ≤ 480 ms		480 ms < Value ≤ 500 ms		Value > 500 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
0.50 mg Liquid	3	58	1 (33.3%)	56 (96.6%)	2 (66.7%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2.00 mg Liquid	4	65	4 (100%)	65 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Treatment Group	Total N		Value ≤ 450 ms		450 ms < Value ≤ 480 ms		480 ms < Value ≤ 500 ms		Value > 500 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
4.00 mg Liquid	(b) (6)	97	(b) (6) (100%)	97 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.00 mg Capsule	(b) (6)	73	(b) (6) (60.0%)	71 (97.3%)	(b) (6) (40.0%)	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6.00 mg Liquid	(b) (6)	89	(b) (6) (80.0%)	82 (92.1%)	(b) (6) (20.0%)	7 (7.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
9.00 mg Capsule	(b) (6)	724	(b) (6) (90.8%)	701 (96.8%)	(b) (6) (7.7%)	22 (3.0%)	(b) (6) (1.5%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
10.00 mg Capsule (7d on/7d off)	(b) (6)	888	(b) (6) (87.2%)	856 (96.4%)	(b) (6) (11.5%)	31 (3.5%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.1%)
12.00 mg Capsule	(b) (6)	111	(b) (6) (8	105 (94.6%)	(b) (6) (14.3%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
12.00 mg Capsule (7d on/7d off)	(b) (6)	238	(b) (6) (92.3%)	237 (99.6%)	(b) (6) (7.7%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 3: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value ≤ 30 ms		30 ms < Value ≤ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
0.50 mg Liquid	(b) (6)	39	(b) (6) (66.7%)	38 (97.4%)	(b) (6) (33.3%)	1 (2.6%)
2.00 mg Liquid	(b) (6)	52	(b) (6) (75.0%)	51 (98.1%)	(b) (6) (25.0%)	1 (1.9%)
4.00 mg Liquid	(b) (6)	82	(b) (6) (100%)	82 (100%)	(b) (6) (0.0%)	0 (0.0%)
6.00 mg Capsule	(b) (6)	59	(b) (6) (100%)	59 (100%)	(b) (6) (0.0%)	0 (0.0%)
6.00 mg Liquid	(b) (6)	65	(b) (6) (100%)	65 (100%)	(b) (6) (0.0%)	0 (0.0%)
9.00 mg Capsule	(b) (6)	409	(b) (6) (96.9%)	406 (99.3%)	(b) (6) (3.1%)	3 (0.7%)
10.00 mg Capsule (7 d on/7 d off)	(b) (6)	597	(b) (6) (92.3%)	587 (98.3%)	(b) (6) (7.7%)	10 (1.7%)
12.00 mg Capsule	(b) (6)	79	(b) (6) (100%)	79 (100%)	(b) (6) (0.0%)	0 (0.0%)
12.00 mg Capsule (7 d on/7 d off)	(b) (6)	193	(b) (6) (76.9%)	187 (96.9%)	(b) (6) (23.1%)	6 (3.1%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 4. Eleven subjects who experienced PR interval greater than 220 ms in 4.00 mg QD, 9 mg QD and 10 mg QD (7d on/7d off) dose groups. One subject in 9 mg and 2 subjects in 10 mg groups had baseline values >220 ms.

Table 4: Categorical Analysis for PR

Treatment Group	Total N		Value≤200 ms		200<PR≤220 ms		PR>220 ms	
	# Subj. (b) (6)	# Obs.	# Subj. (b) (6)	# Obs.	# Subj. (b) (6)	# Obs.	# Subj. (b) (6)	# Obs.
0.50 mg Liquid	(b) (6)	42	(b) (6)	42 (100%)	(b) (6)	0 (0.0%)	(b) (6)	0 (0.0%)
2.00 mg Liquid	(b) (6)	56	(b) (6)	56 (100%)	(b) (6)	0 (0.0%)	(b) (6)	0 (0.0%)
4.00 mg Liquid	(b) (6)	89	(b) (6)	77 (86.5%)	(b) (6)	7 (7.9%)	(b) (6)	5 (5.6%)
6.00 mg Capsule	(b) (6)	64	(b) (6)	57 (89.1%)	(b) (6)	7 (10.9%)	(b) (6)	0 (0.0%)
6.00 mg Liquid	(b) (6)	70	(b) (6)	70 (100%)	(b) (6)	0 (0.0%)	(b) (6)	0 (0.0%)
9.00 mg Capsule	(b) (6)	472	(b) (6)	430 (91.1%)	(b) (6)	34 (7.2%)	(b) (6)	8 (1.7%)
10.00 mg Capsule (7 d on/7d off)	(b) (6)	674	(b) (6)	606 (89.9%)	(b) (6)	38 (5.6%)	(b) (6)	30 (4.5%)
12.00 mg Capsule	(b) (6)	86	(b) (6)	86 (100%)	(b) (6)	0 (0.0%)	(b) (6)	0 (0.0%)
12.00 mg Capsule (7 d on/7 d off)	(b) (6)	206	(b) (6)	204 (99.0%)	(b) (6)	2 (1.0%)	(b) (6)	0 (0.0%)

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 5. Thirteen subjects who experienced QRS interval greater than 110 ms in 6 mg QD, 9 mg QD and 10 mg QD (7d on/7 d off). One subject in 6 mg, 3 in 9 mg, and 4 in 10 mg groups had baseline values >110 ms.

Table 5: Categorical Analysis for QRS

Treatment Group	Total N		Value≤100 ms		100 ms<Value≤110 ms		Value>110 ms	
	# Subj. (b) (6)	# Obs.	# Subj. (b) (6)	# Obs.	# Subj. (b) (6)	# Obs.	# Subj. (b) (6)	# Obs.
0.50 mg Liquid	(b) (6)	42	(b) (6)	28 (66.7%)	(b) (6)	14 (33.3%)	(b) (6)	0 (0.0%)
2.00 mg Liquid	(b) (6)	56	(b) (6)	56 (100%)	(b) (6)	0 (0.0%)	(b) (6)	0 (0.0%)
4.00 mg Liquid	(b) (6)	89	(b) (6)	85 (95.5%)	(b) (6)	4 (4.5%)	(b) (6)	0 (0.0%)
6.00 mg Capsule	(b) (6)	64	(b) (6)	44 (68.8%)	(b) (6)	13 (20.3%)	(b) (6)	7 (10.9%)
6.00 mg Liquid	(b) (6)	70	(b) (6)	67 (95.7%)	(b) (6)	3 (4.3%)	(b) (6)	0 (0.0%)
9.00 mg Capsule	(b) (6)	478	(b) (6)	416 (87.0%)	(b) (6)	37 (7.7%)	(b) (6)	25 (5.2%)
10.00 mg Capsule (7 d on/7 d off)	(b) (6)	674	(b) (6)	615 (91.2%)	(b) (6)	31 (4.6%)	(b) (6)	28 (4.2%)
12.00 mg Capsule	(b) (6)	86	(b) (6)	83 (96.5%)	(b) (6)	3 (3.5%)	(b) (6)	0 (0.0%)
12.00 mg Capsule (7 d on/7 d off)	(b) (6)	206	(b) (6)	203 (98.5%)	(b) (6)	3 (1.5%)	(b) (6)	0 (0.0%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 5. Twenty-six subjects who experienced HR interval greater than 100 bpm were in 0.5 mg QD, 6.00 mg capsule, 6.00 mg QD, 9.00 mg QD, 10.00 mg QD (7d on/7d off), 12 mg capsule and 12.00 mg QD (7d on/7d off) dose groups. Two subjects in 9 mg, 5 in 10 mg groups, 1 in 12 mg capsule and 1 in 12 mg QD (7 d on/7 d off) had baseline values >100 bpm.

Table 6: Categorical Analysis for HR

Treatment Group	Total N		Value ≤ 100 bpm		Value > 100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
0.50 mg Liquid	(b) (6)	42	(b) (6) 66.7%	41 (97.6%)	(b) (6) 33.3%	1 (2.4%)
2.00 mg Liquid		56	100%	56 (100%)	0 (0.0%)	0 (0.0%)
4.00 mg Liquid		89	100%	89 (100%)	0 (0.0%)	0 (0.0%)
6.00 mg Capsule		64	80.0%	63 (98.4%)	20.0%	1 (1.6%)
6.00 mg Liquid		70	80.0%	69 (98.6%)	20.0%	1 (1.4%)
9.00 mg Capsule		478	90.8%	458 (95.8%)	9.2%	20 (4.2%)
10.00 mg Capsule (7 d on/7 d off)		674	83.3%	644 (95.5%)	16.7%	30 (4.5%)
12.00 mg Capsule		86	85.7%	79 (91.9%)	14.3%	7 (8.1%)
12.00 mg Capsule (7 d on/7 d off)		206	76.9%	195 (94.7%)	23.1%	11 (5.3%)

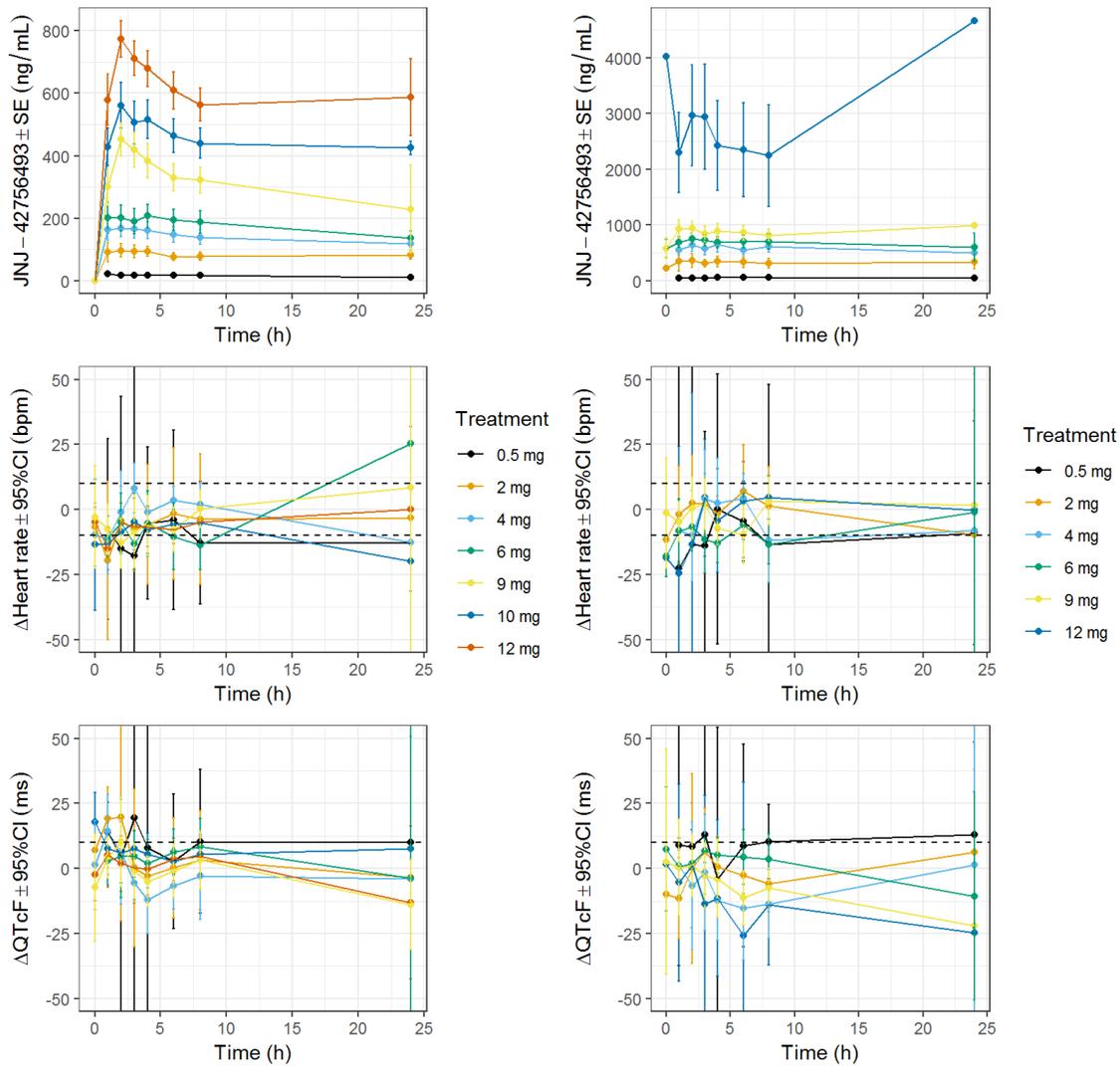
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and Δ QTcF using time-matched PK/ECG data from continuous Holter recording in Part 1 of the study (the supportive ECG dataset). The dataset was chosen for the initial analysis because it provided more time-matched PK/ECG data to evaluate potential HR effect, hysteresis, and linearity.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship.

An evaluation of the time-course of drug concentration and changes in Δ HR and Δ QTcF on C1D1 and at steady state (continuous dosing regimen only) is shown in Figure 5. The figures for C1D1 data show an increase in exposure with dose and an absence of dose-response in Δ HR or Δ QTcF. Despite of small sample size and large confidence interval, there does not appear to be significant changes in HR or signs of hysteresis and delayed effect. The figures for Cycle 2 and Cycle 3 data confirm a lack of apparent dose-response on Δ HR or Δ QTcF. Due to dose reduction in the continuous dosing treatment arms, accumulation appears lower than expected at dose levels higher than 6 mg QD.

Figure 5: Time course of drug concentration (top), heart rate (middle) and QTcF (bottom) on Cycle 1 Day 1 (Left) or Cycle 2/3 Day 1 (Right).



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and Δ QTcF was evaluated to determine if a linear model would be appropriate. Figure 6 showed the relationship between drug concentration and Δ QTcF and supports the use of a linear model. The figure also suggested the absence of a positive relationship between erdafitinib concentration and Δ QTcF in both the observations from C1D1 or from pooled data from all dosing regimens in Part 1 of the study. While the exposure-response relationship in the pooled dataset appeared to be driven by a few observations at high exposure, slopes from both models were negative. The final model is Δ QTcF \sim 1 + CONC + baseline_adjustment where USUBJID was included a random effect on intercept and concentration. Goodness-of-fit plots are shown in Figure 7. Overall, concentration-QTc analysis does not suggest large effect at the therapeutic dose level (8 mg QD, predicted $C_{max,ss}$ = 1399 ng/mL [50.8%]) or the maximum therapeutic dose (9 mg QD).

Figure 6: Assessment of linearity of concentration-QTc relationship. C1D1 from Part 1: Left; All data from Part 1: Right.

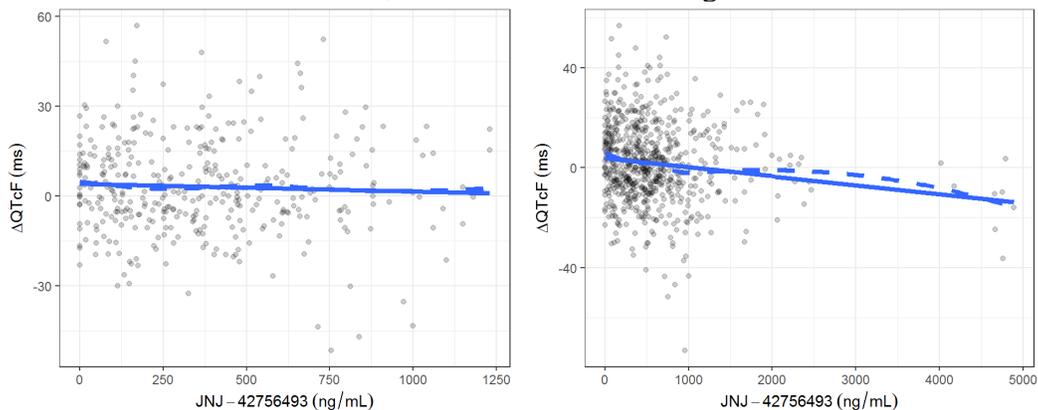
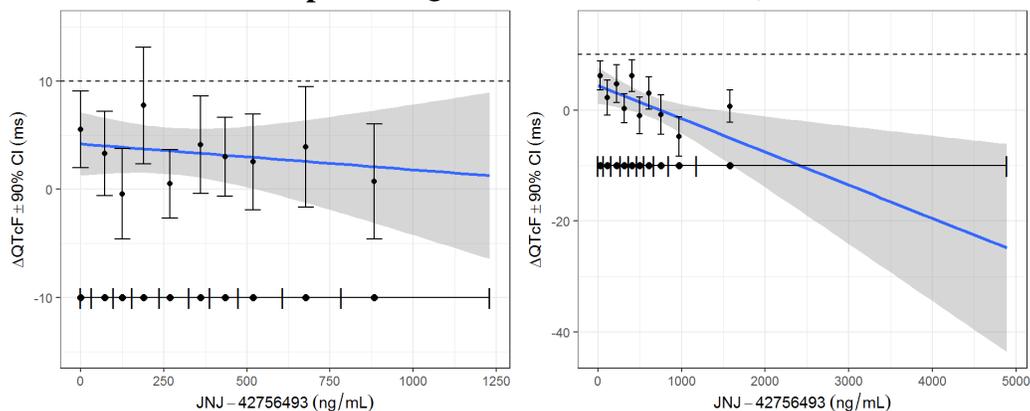


Figure 7: Goodness-of-fit plot for QTc. C1D1 of Part 1: Left; All data of Part 1: Right.



ECG data used in the concentration-QTc analysis were generated by re-extraction of Holter recording after an interim analysis based on 12-lead ECG data. Time-matched baseline from the Screening visit was used in the supportive ECG dataset, which potentially contributed to the large variability in $\Delta QTcF$. In addition, raw data were not submitted to ECG Warehouse. Because of these limitations in terms of ECG acquisition and interpretation, concentration-QTc analysis was used as a supportive analysis in this review. In a sensitivity analysis, exposure-response analysis was conducted using Part 1 of the primary ECG dataset with $\Delta QTcF$ as the dependent variable. The sensitivity analysis yielded similar results, supporting a lack of large effect on QTc interval at the maximum therapeutic dose level.

4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.3

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed.

5 APPENDIX

5.1 IRT'S HIGHLIGHT OF CLINICAL PHARMACOLOGY AND CARDIAC SAFETY

Therapeutic dose	8 mg once daily starting dose with pharmacodynamically-guided individualized up-titration to 9 mg once daily depending on serum phosphate levels and tolerability	
Maximum tolerated dose (MTD)	MTD not determined based on formal definition. Maximal dose administered was 12 mg once daily. 2 RP2D were identified: 9 mg QD or 10 mg 7 days on/7 days off	
Principal adverse events	Incidence of treatment-emergent adverse events (all doses combined, Safety Analysis Set): hyperphosphatemia (67%), stomatitis (44%), dry mouth (44%), diarrhea (39%)	
Maximum dose tested	Single Dose	12 mg
	Multiple Dose	12 mg once daily
Exposures achieved at maximum tested dose: 12 mg once daily, Mean (%CV)	Single dose (n=7 in subjects with cancer)	<u>Erdaftinib total concentrations</u> : Cmax 745 ng/mL (33.1%), AUC0-24 12374 ng.h/mL (35.6%) <u>Erdaftinib unbound concentrations</u> : Cmax,u 2.09 ng/mL (29.2%), AUC0-24,u 34.5 ng h/mL (26.7%)
	Multiple dose (n=3 in subjects with cancer)	<u>Erdaftinib total concentrations</u> : Cmax 3057 ng/mL, (53.1%), AUC0-24 64085 ng.h/mL (67.9%) <u>Erdaftinib unbound concentrations</u> : Cmax,u 7.99 ng/mL (33.2%), AUC0-24,u 157 ng.h/mL (26.2%)
Exposures achieved at proposed clinical dose regimen: 9 mg once daily, Mean (%CV)	Single dose (n=10 subjects with cancer EDI1001 Part 2)	<u>Erdaftinib total concentration</u> : Cmax 578 ng/mL (36.9%), AUC0-24 10069 ng.h/mL (25.4%) <u>Erdaftinib unbound concentrations</u> : Cmax,u 1.43 ng/mL (48.8%), AUC0-24,u 25.4 ng h/mL (31.9%)
	Multiple dose (n=6 subjects with cancer EDI1001 Part 2)	<u>Erdaftinib total concentration</u> : Cmax 2018 ng/mL (41.1%), AUC0-24 39587 ng.h/mL (44.4%) <u>Erdaftinib unbound concentrations</u> : Cmax,unb 5.12 ng/mL (55.9%), AUC0-24,u 98.7 ng h/mL (37.0%)
Range of linear PK	0.5 to 12 mg	
Accumulation, mean (%CV)	4.07 (32.0%) based on AUC (C2D1 upon once daily dosing)	
	3.44 (28.4%) based on Cmax (C2D1 upon once daily dosing)	
Metabolites	No circulating metabolites	
Absorption	Absolute/relative bioavailability	Near complete absorption. All formulations (solution, capsules, tablets with different particle size) demonstrated bioequivalence
	Tmax, median (EDI1001)	Single dose erdaftinib: median tmax=2.07 h Multiple dose erdaftinib: median tmax=2.87 h
Distribution	Vd/F	28.8 L (51.2%) in subjects with cancer
	Mean (%CV)	37.4 L (33.1%) in healthy subjects
Elimination	% bound	99.76% (in subjects with cancer from BLC2001, population PK)
	Route	Metabolism (67%), renal clearance (13%), and intestinal secretion (21%) (estimated by PBPK model) Enzymatic pathways: CYP2C9 and CYP3A4
	Terminal t1/2	Mean (%CV): 59.3 h (57.5%) (pooled healthy)
Intrinsic factors	CL/F	Pooled across all daily doses in EDI1001: 0.362 L/h (51.4%)
	Age	Not a clinically meaningful covariate in population PK model
	Sex	Sex was a covariate in population PK model. Model estimated 23% higher steady-state AUC in women
	Race	Not a clinically meaningful covariate in population PK model
	Hepatic impairment	Mild hepatic impairment was not a clinically meaningful covariate in in population PK model
	Renal impairment (EDI1001)	Comparable exposure between subjects (with cancer) with normal renal function and mild or moderate renal impairment
Disease state	Total exposure higher in subjects with cancer than healthy subjects primarily due to higher AGP levels. Disease state was	

		not a covariate in the population PK model after AGP was taken into consideration
Extrinsic factors	Drug interactions (EDI1007)	<u>Effect of other drugs on erdafitinib</u> : Fluconazole (CYP2C9 and CYP3A inhibitor) increase erdafitinib Cmax and AUC by 21% and 48% respectively; itraconazole (CYP3A4 and P-gp inhibitor) increase erdafitinib Cmax and AUC by 5% and 34% respectively
	Food effects	No food effect (EDI1006)
Expected high clinical exposure scenario	Drug-drug interaction with strong CYP2C9 inhibitor (AUC increase by 48%, observed); CYP2C9 poor metabolizer (*3/*3) with strong CYP3A4 inhibitor (AUC increase by 79%, predicted by PBPK)	
Nonclinical Cardiac Safety		
In vitro assays	The effects of erdafitinib at 1 to 10 µM in the guinea pig right atrium assay were suggestive of potential multiple ion-channel blocking properties. The hERG current was slightly to strongly decreased from 0.03 to 10 µM in hERG-transfected HEK293 cells, with an IC50 of 0.41 µM. In the rabbit ventricular wedge preparation, markers of proarrhythmia significantly increased starting at 0.1 µM	
In vivo: anesthetized guinea pig (non-GLP)	Prolongation of the QT and QTcB intervals and ECG abnormalities were observed at >2.5 mg/kg (total concentration ≥770 ng/mL or unbound concentration of 81.4 ng/mL)	
In vivo: anesthetized dogs (non-GLP)	QTc prolongation observed following oral administration at ≥0.63 mg/kg (total concentration [Cmax] ≥820 ng/mL or unbound concentration of 111 to 114 ng/mL free concentrations)	
Telemetric evaluation of cardiovascular safety in conscious dog (GLP)	No adverse effects on cardiovascular, ECG, and respiratory parameters were found up to 2.5 mg/kg (mean Cmax=90.2 ng/mL), with signs of benign arrhythmia in 1 dog given the dose of 5 mg/kg (Cmax=228 ng/mL) with QT and QTc prolongation, decrease in heart rate and ECG abnormalities	
Clinical cardiac safety	<p>The effects of erdafitinib on 12-lead ECGs and 24-hour Holter data as assessed by a central laboratory found no clinically significant findings during the treatment period following erdafitinib doses up to 12 mg in Study EDI1001.</p> <p>Blinded analysis of ECG parameters by a central vendor showed no clinically significant effect of erdafitinib on heart rate, no signal of any clinically significant effect of erdafitinib on atrioventricular conduction or cardiac depolarization as measured by the PR and QRS interval duration, and no evidence of a clinically significant effect of erdafitinib on cardiac repolarization by timepoint and categorical outlier analysis</p> <p>Three exposure-QT analyses were conducted based on 12-lead ECG, manually read ECGs, and Holter-extracted ECG (time-matched) from Study EDI1001. No significant relationship between erdafitinib plasma concentration and change in QTc were observed. The upper bound of the 2-sided 90% CI of predicted baseline-corrected QTcF value at the steady-state Cmax from the highest clinical dose (9 mg) was 2.5 ms or less, well below the accepted threshold of 20 ms in all 3 exposure-response analyses. Therefore, erdafitinib does not have a clinically relevant effect on QTc prolongation</p>	

5.2 ECG AND PK COLLECTION SCHEDULE

ECGs were collected in triplicate according to the following schedule:

Part 1: daily dosing

- Screening (2 sets at least 24 hours apart)
- Cycle 1 Day 1: predose, 2, 4, 8 hours postdose
- Cycle 1 Day 8: predose, 2, 4 hours postdose
- Cycle 1 Day 15: predose, 2, 4 hours postdose
- Cycle 2 Day 1: predose, 2, 4, 8 hours postdose
- Subsequent Cycles Day 1: post dose
- End of Treatment: 30 Days after dosing

Part 1: intermittent dosing (7 days on, 7 days off)

- Screening (2 sets at least 24 hours apart)
- Cycle 1 Day 1: predose, 2, 4, 8 hours postdose
- Cycle 1 Day 7: predose, 2, 4 hours postdose
- Cycle 1 Day 15: predose, 2, 4 hours postdose
- Cycle 1 Day 21: predose, 2, 4 hours postdose
- Cycle 2 Day 1: predose, 2, 4, 8 hours postdose
- Subsequent Cycles Day 1: post dose
- End of Treatment: 30 Days after dosing

Part 2 and Part 3: daily dosing

- Screening (2 sets at least 24 hours apart)
- Cycle 1 Day 1: predose, 2, 4 hours postdose
- Cycle 1 Day 8: predose, 2, 4 hours postdose
- Cycle 2 Day 1: predose
- Subsequent Cycles Day 1: post dose
- End of Treatment: 30 Days after dosing

Part 4: intermittent dosing

- Screening (2 sets at least 24 hours apart)
- Cycle 1 Day 1: predose, 2, 4 hours postdose
- Cycle 1 Day 7: predose, 2, 4 hours postdose
- Cycle 1 Day 15: predose
- Cycle 2 Day 1: predose
- Subsequent Cycles Day 1: post dose
- End of Treatment: 30 Days after dosing

Pharmacokinetic samples were collected according to the following schedule:

Part 1

- Cycle 1 Day 1: predose, 30 min, 1, 2, 3, 4, 6, 8, 24, 48, 72 hours postdose
- Cycle 1 Day 8 (for continuous daily dosing): predose, 30 min, 1, 2, 3, 4, 6, 8, 24 hours postdose
- Cycle 1 Day 7 (for intermittent dosing): predose, 30 min, 1, 2, 3, 4, 6, 8, 24 hours postdose
- Cycle 2 Day 1: predose, 30 min, 1, 2, 3, 4, 6, 8, 24 hours postdose
- Cycles 3, 4: predose

Part 2

- Cycle 1 Day 1: predose, 30 min, 1, 2, 3, 4, 6, 8, 24 hours postdose
- Cycle 2 Day 1 (for continuous daily dosing): predose, 30 min, 1, 2, 3, 4, 6, 8, 24 hours postdose
- Cycle 3, 4 Day 1: predose

Parts 3 and 4

- Cycle 1 Day 1: predose, 2, 4 hours
- Cycle 1 Day 8 (for continuous daily dosing): predose, 2, 4 hours
- Cycle 1 Day 7 (for intermittent dosing): predose, 2, 4 hours
- Cycles 2, 3, 4 Day 1: predose

Time-points for Holter re-extraction:

Cycle	Day	Timepoints	PK	Holter
Screening				Continuous
1	1	Predose, and at 1, 2, 3, 4, 6, 8, and 24 hours	X	Continuous
2	1	Predose, and at 1, 2, 3, 4, 6, 8, and 24 hours	X	Continuous
3	1	Predose	X	Continuous

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/s/

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LARS JOHANNESSEN
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CHRISTINE E GARNETT
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Medical Officer's Review of NDA 212018
Ophthalmology Consult

NDA 212018 Submission Dates: October 31 and November 9, 2018
Consult Review Review completed: December 17, 2018

Product Name: Erdafitinib

Sponsor: Janssen Biotech, Inc

Requested: The purpose of this ophthalmology consult is to review Janssen's NME NDA 212018 for ocular toxicity.

Submitted:

Original NDA Submission:

2.1.6.1.1. Central Serous Retinopathy

For the 8/9-mg daily regimen, 16% of subjects were reported to have TEAEs of central serous retinopathy (Table 21). The most commonly reported events were chorioretinopathy, retinal detachment, and detachment of retinal pigment epithelium. For all dose regimens combined, the incidence was slightly lower (11%). The same 3 TEAEs were most common.

Central Serous Retinopathy by Preferred Term; Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	< 6 mg QD	6 mg QD	8 or 9 mg QD	≥10 mg QD	All Intermittent Doses	All Doses Combined
Total number of subjects	20	91	164	7	134	416
Central serous retinopathy	0	11 (12%)	26 (16%)	0	8 (6%)	45 (11%)
Retinal detachment	0	8 (9%)	6 (4%)	0	3 (2%)	17 (4%)
Chorioretinopathy	0	2 (2%)	9 (5%)	0	3 (2%)	14 (3%)
Detachment of retinal pigment epithelium	0	2 (2%)	5 (3%)	0	2 (1%)	9 (2%)
Retinal oedema	0	0	4 (2%)	0	1 (1%)	5 (1%)
Retinopathy	0	0	3 (2%)	0	0	3 (0.7%)
Vitreous detachment	0	0	2 (1%)	0	0	2 (0.5%)
Detachment of macular retinal pigment epithelium	0	1 (1%)	0	0	0	1 (0.2%)

Reviewer's Comment: *Except for vitreous detachment and retinal edema, the remaining events are likely to represent different terms for the same event.*

Other Eye Disorders by Preferred Term; Safety Analysis Set (JNJ-42756493 (Erdafitinib))

	< 6 mg QD	6 mg QD	8 or 9 mg QD	≥10 mg QD	All Intermittent Doses	All Doses Combined
Total number of subjects	20	91	164	7	134	416
Eye toxicity	1 (5%)	37 (41%)	73 (45%)	3 (43%)	42 (31%)	156 (37%)
Dry eye	0	7 (8%)	30 (18%)	2 (29%)	14 (10%)	53 (13%)
Vision blurred	0	5 (5%)	23 (14%)	0	10 (7%)	38 (9%)
Lacrimation increased	0	13 (14%)	13 (8%)	0	8 (6%)	34 (8%)
Conjunctivitis	1 (5%)	7 (8%)	16 (10%)	2 (29%)	6 (4%)	32 (8%)
Visual impairment	0	3 (3%)	8 (5%)	0	3 (2%)	14 (3%)
Keratitis	0	2 (2%)	6 (4%)	1 (14%)	4 (3%)	13 (3%)
Cataract	0	4 (4%)	6 (4%)	0	2 (1%)	12 (3%)
Blepharitis	0	2 (2%)	5 (3%)	2 (29%)	1 (0.7%)	10 (2%)
Eye pain	0	1 (1%)	4 (2%)	0	3 (2%)	8 (2%)
Visual acuity reduced	0	1 (1%)	5 (3%)	1 (14%)	1 (0.7%)	8 (2%)
Xerophthalmia	0	2 (2%)	3 (2%)	1 (14%)	2 (1%)	8 (2%)
Photophobia	0	1 (1%)	2 (1%)	0	3 (2%)	6 (1%)
Eye irritation	0	0	1 (0.6%)	0	3 (2%)	4 (1%)
Foreign body sensation	0	0	2 (1%)	0	1 (0.7%)	3 (0.7%)
Conjunctival hyperaemia	0	0	1 (0.6%)	0	1 (0.7%)	2 (0.5%)
Corneal erosion	0	1 (1%)	1 (0.6%)	0	0	2 (0.5%)
Ocular hyperaemia	0	1 (1%)	1 (0.6%)	0	0	2 (0.5%)
Cataract subcapsular	0	1 (1%)	0	0	0	1 (0.2%)
Conjunctival haemorrhage	0	1 (1%)	0	0	0	1 (0.2%)
Conjunctival irritation	0	0	0	0	1 (0.7%)	1 (0.2%)
Corneal infiltrates	0	1 (1%)	0	0	0	1 (0.2%)
Eye inflammation	0	0	1 (0.6%)	0	0	1 (0.2%)
Retinal thickening	0	1 (1%)	0	0	0	1 (0.2%)
Xanthopsia	0	0	0	0	1 (0.7%)	1 (0.2%)

Reviewer's Comment: *The reported dry eye complaints, represented by a number of terms in this table (dry eye, vision blurred, lacrimation increased, conjunctivitis, keratitis, visual acuity reduced, xerophthalmia, eye irritation, foreign body sensation, conjunctival hyperemia, conjunctival irritation) occurred in the setting where the investigators attempted to prophylactically treat the eyes for dry eye symptoms.*

November 9, 2018 submission

As outlined in the 31 October 2018 response, there were 38 subjects for whom central serous retinopathy (CSR) was reported as TEAE in the BLC2001 clinical database. Of these 38 subjects, 23 subjects were from the 8 mg cohort and 15 subjects were from 6 mg and 10 mg cohorts. OCT images are available for 37 of the 38 subjects; all available OCT images for these 37 subjects are provided in this submission. One subject (b) (6) with Grade 1 CSR reported as an AE (detachment of macular retinal pigment epithelium) that led to withdrawal of treatment, did not have any OCT images available from OCT examination; however, supplemental information regarding results of the ocular examination is provided for this subject.

In addition to the OCT scans requested in the Information Request, the Sponsor has provided supplemental information from ocular examination reports (visual acuity, tonometry, funduscopy and slit lamp results) where available. This supplemental information is available for 32 of the 38 subjects.

A list of each of the 38 subjects with CSR reported and a hyperlink to their OCT images (Subject number, OCT scans) and supplemental ocular information (Subject number, eye exam reports). For each subject, all available OCT images and supplemental ocular information are provided in chronological order.

Reviewer's Comment: *The submitted information confirmed that the patients had been appropriately followed with ophthalmic examinations, and although the follow-up information was not available on the case report forms, adequately detailed information was available and submitted. Optical Coherence Tomography (OCT) scans confirmed the retinal pigment epithelial detachments (also known by other terms including serous detachments). Some detachments were central, others were not. Some were singular, others were multiple. Some were unilateral, others were bilateral. Some resolved with discontinuation and/or reduction of the erdafitinib dose, others resolved without a change in dose. Some recurred following re-administration of erdafitinib.*

Summary/Recommendations:

1. It is recommended that the labeling of the drug product, if approved, include a recommendation for prophylactic treatment for dry eye symptoms which are likely to occur. All patients should be initially treated for dry eye syndrome when initiating erdafitinib. Dry eye treatment should include topical ocular demulcents as needed. Continued dry eye syndrome management should be made by the ophthalmic specialist following the patient.
2. It is recommended that the labeling of the drug product, if approved, alert the treating physician that retinal pigment epithelial detachments (RPED) may occur with treatment. Events tended to occur in approximately 20% of patients treated with erdafitinib and generally occurred within the first nine months of treatment. RPED detachments will often cause visual field defects, which may not be initially noticed and may not be permanent if reversed. Grading of RPEDs based on symptoms is not helpful and should be discouraged. RPEDs should be monitored with optical coherence tomography (OCT). Dose reduction is not always necessary but should be considered if the RPED does not start to diminish within 3 weeks.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
12/18/2018

Medical Officer's Review of NDA 212018
Ophthalmology Consult

NDA 212018
Consult Review

Submission Dates:	September 28, 2018
Consult Request Date:	October 1, 2018
Review completed:	October 17, 2018

Product Name: Erdafitinib

Sponsor: Janssen Biotech, Inc

Requested: The purpose of this ophthalmology consult is to review Janssen's NME NDA 212018 for ocular toxicity.

Case Report Form for Study 42756493BLC2001

Form: Ophthalmologic Examination Page

Visual Acuity Result	Normal	<input type="checkbox"/>
	Abnormal	<input type="checkbox"/>
	Not Evaluable	<input type="checkbox"/>

Tonometry Result	Normal	<input type="checkbox"/>
	Abnormal	<input type="checkbox"/>
	Not Evaluable	<input type="checkbox"/>

Fundoscopy Result	Normal	<input type="checkbox"/>
	Abnormal	<input type="checkbox"/>
	Not Evaluable	<input type="checkbox"/>

Optical Coherence Testing Result	Fixed Unit: μm
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Optical Coherence Testing Analysis	Normal	<input type="checkbox"/>
	Abnormal	<input type="checkbox"/>
	Not Evaluable	<input type="checkbox"/>

If one or more of the results are 'Abnormal', Clinically significant?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>

If result was considered clinically significant, choose the primary corresponding AE log line, start date, and term

Reviewer's Comment: *The case report form did not capture the information needed to adequately evaluate potential ocular adverse events. For example:*

1. *Visual acuity should be recorded as a numeric value. A value should be recorded for each eye. Normal would need to be defined within a narrow range to provide informative information.*
2. *Tonometry should be recorded as a numeric value. A value should be recorded for each eye. Normal would need to be defined within a narrow range to provide informative information.*
3. *Each eye should have the fundoscopy findings recorded.*
4. *The case report form should have included potential findings from the slit lamp examination (i.e., anterior portion of the eye).*
5. *The optical coherence tomography (OCT) scan should have been included in the case report form. It should be included in the case report form for future studies. There is no single thickness measurement which provides an informative assessment of retinal pigment epithelial detachments. The OCT thickness measurement location was not specified.*
6. *Measures for each eye should be recorded separately.*

Amsler Grid	Normal	<input type="checkbox"/>
	Abnormal	<input type="checkbox"/>
	Not Evaluable	<input type="checkbox"/>

Reviewer's Comment: *Amsler grid testing provides an evaluation of the central macular distortion. It is not an accurate screening test for retinal pigment epithelial detachments.*

Eye Disorders Management Guideline/Physician Education Material

CONTRAINDICATIONS

Sponsor's Conclusions: The original exclusion criteria pertaining to history of CSR, RVO, AMD, diabetic retinopathy, uncontrolled glaucoma, or corneal pathology should not be retained as contraindications for use of erdafitinib.

Reviewer's Comment: *Concur.*

SCREENING FOR BASELINE OCULAR CONDITIONS

Sponsor's Conclusions: All patients should have an ophthalmologic examination, performed by an ophthalmologist or retinal specialist, before starting treatment with erdafitinib. The assessment should include:

- Evaluation of visual acuity,
- Tonometry,
- Slit lamp examination including screening for dry eye, i.e., Schirmer test (fluorescein staining of the cornea to check for epithelial defects and tear breakup time),
- Fundoscopy (dilated fundus examination of both central and peripheral zones should be performed), and

- Amsler grid test.

If indicated by retinal findings on funduscopy, an Optical Coherence Tomography (OCT) should also be performed at screening.

Should any sign of active CSR/RPED, Grade 2 or higher, be found, the patient should not start treatment with erdafitinib, but should hold start until resolution of CSR/RPED.

Reviewer's Comment:

1. *Visual acuity should be tested as best corrected distance visual acuity.*
2. *There is no indication that tonometry (i.e., eye pressure measurement) needs to be performed.*
3. *The Amsler grid is not expected to be a useful screen for the adverse events likely to be caused by erdafitinib.*
4. *All patients should have an OCT at each ophthalmic evaluation. Ophthalmic evaluations should be performed at baseline and then at regular intervals determined by the ophthalmic specialist following the patient. RPE detachments should be monitor at approximately 2-3 week intervals. Dose reduction should be considered if the RPE detachment is not starting to resolve without dose reduction.*

Prophylaxis for Dry Eye

Applicant's Summary: Events of dry eye syndrome are often encountered during treatment with erdafitinib. Furthermore, dry eye is a relatively common entity associated with aging. In order to prevent dry-eye syndrome and associated signs and symptoms such as feeling of a foreign body in the eye, eye pain, lacrimation changes, or visual disturbance as well as interference of dry-eye related symptoms with signs of retinal conditions, patients should be instructed to maintain eye hydration by intensive/aggressive use of artificial tear substitutes, hydrating or lubricating eye gels or ointments. Prophylaxis should begin concurrent with the start of treatment and continue during the entire treatment period and should be used frequently, e.g., at least every 2 hours while the patient is awake. Treatments such as RESTASIS® may be prescribed. Severe treatment-related dry eye should be evaluated by an ophthalmologist.

Reviewer's Comment:

1. *All patients should be initially treated for dry eye syndrome when initiating erdafitinib. Dry eye treatment should include ocular demulcents as needed.*
2. *There are no approved lubricating eye gels.*
3. *Continued dry eye syndrome management should be made by the ophthalmic specialist following the patient.*

Patients with onset of eye disorders must be referred to an ophthalmologist within 7 days. Administration of erdafitinib should be managed according to Table 1 according to the proposed USPI. In general, patients should follow specific treatment per the ophthalmologist's recommendation.

Table 1: Erdafitinib Dose Adjustments and Patient Monitoring for Eye Disorders

Grade and Definition	Erdafitinib Drug Administration Management And Subsequent Patient Monitoring
Prophylactic	From start of treatment use artificial tear substitute, hydrating or lubricating eye gels or ointments at least every 2 hours while awake. For dry eye that is not responding to this prophylactic treatment, ophthalmologist evaluation and tailored treatment is recommended.
Grade 1 Asymptomatic or mild symptoms; clinical or diagnostic observations only or abnormal Amsler grid test	<p>Immediate action: If an ophthalmologic examination cannot be performed within 7 days, withhold treatment with erdafitinib until an examination can be performed.</p> <p>Following ophthalmologic examination: If there is no evidence of eye toxicity on ophthalmologic examination, continue erdafitinib at the same dose level.</p> <p>If diagnosis from ophthalmologic examination is Grade 1 keratitis or retinal abnormality such as central serous retinopathy (CSR)/retinal pigment epithelial detachments (RPED): Continue erdafitinib at the same dose level. Observe for progression and monitor with monthly Amsler grid with no acute intervention. Should the patient indicate any visual disturbance during follow-up (could point to extramacular CSR), a dilated fundoscopic examination is indicated. If Grade 1 persists for over 3 months, this may warrant evaluation by a retinal specialist.</p> <p>Subsequent monitoring: Monitor for recurrence at 1 month post recovery with dilated fundoscopic examination, then at 3, 6, and 12 months repeat the ophthalmologic evaluation (including dilated fundoscopic examination and OCT if recurrence is suspected). Ophthalmologic examination should be performed at any time following recovery, in the case of clinical suspicion of recurrence.</p>
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)	<p>Immediate action: Immediately withhold erdafitinib.</p> <p>Following ophthalmologic examination: If there is no evidence of drug-related corneal or retinal pathology upon ophthalmologic examination, withhold erdafitinib until signs and symptoms have resolved. Resume erdafitinib therapy at the next lower dose level.</p> <p>If diagnosis from ophthalmologic examination is Grade 1 keratitis or retinal abnormality such as CSR/RPED, see above.</p> <p>If diagnosis from ophthalmologic evaluation is Grade 2 keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved or stabilized.</p> <p>If toxicity is reversible (upon weekly assessment leading to complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level. If not reversible within 4 weeks, consider monthly monitoring with ophthalmologic examination (inclusive of OCT and fundoscopic examination).</p>

	<p>Subsequent monitoring: Monitor for recurrence at 1 month post recovery with dilated fundoscopic examination, then at 3, 6, and 12 months repeat ophthalmologic evaluation (including dilated fundoscopic examination and OCT if recurrence is suspected). Ophthalmologic examination should be performed at any time following recovery, in the case of clinical suspicion of recurrence.</p>
Grade 3: Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	<p>Immediate action: Immediately withhold erdafitinib. Following ophthalmologic examination: If the toxicity is Grade 3 and reversible (upon weekly assessment leading to complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and continuation of treatment is in the best interest of the subject, then drug may be resumed at 2 dose levels lower if appropriate. If not reversible within 4 weeks, consider monthly monitoring with ophthalmologic examination (inclusive of OCT and fundoscopic examination).</p> <p>Subsequent monitoring: Monitor for recurrence at 1 month post recovery with dilated fundoscopic examination, then at 3, 6, and 12 months repeat ophthalmologic evaluation (including dilated fundoscopic examination and OCT if recurrence is suspected). Ophthalmologic examination should be performed at any time following recovery, in the case of clinical suspicion of recurrence.</p> <p>For cases of recurrence of Grade 3, consider permanent discontinuation.</p>
Grade 4: Sight threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	<p>Immediate action: Permanently discontinue treatment with erdafitinib. Monitor resolution of the event until complete resolution or stabilization.</p>

Reviewer's Comments:

(b) (6)

Summary/Recommendations/Comments for the Applicant:

1. The ophthalmic case report forms for Study 42756493BLC2001 did not capture the information needed to adequately evaluate potential ocular adverse events of erdafitinib or to be able to compare the events to those ocular events which occur in other members of this class of products.
 - a. Visual acuity should have been tested as best corrected distance visual acuity and should have been recorded as a numeric value. There is a large range of values which could be considered in the normal range. Later values could also be considered in the normal range while the change would be abnormal. A specific value should have been recorded for each eye.
 - b. Tonometry should have been recorded as a numeric value. There is a large range of values which could have been considered in the normal range. Later values could also be considered normal while the change would be abnormal. A specific value should have been recorded for each eye.
 - c. Each eye should have the funduscopy findings recorded.
 - d. The case report form should have included findings from the slit lamp examination (i.e., anterior portion of the eye).
 - e. The optical coherence tomography (OCT) scan should have been included in the case report form. A single thickness measurement does not provide sufficient information to assess the retina. Retinal pigment epithelial detachments are identified by their image on OCT, not by a thickness measurement. The location that the OCT thickness measurement was to be taken was not specified. Measures for each eye should be recorded separately.
 - f. OCT scans performed on patients treated with erdafitinib to date are recommended to be collected, reviewed and submitted to the NDA for review.
2. For future studies:
 - a. Optical coherence tomography (OCT) scans of each eye should be performed and included in the case report for each ophthalmologic visit for all future studies.
 - b. Visual acuity should be tested as best corrected distance visual acuity in each eye separately. The results for each eye should be included on the case report form.
 - c. Tonometry readings do not need to be taken or recorded for studies of erdafitinib.
 - d. Slit lamp findings for each eye separately should be included on the case report form.
3. Amsler grid testing provides an evaluation of the central macular distortion. It is not an accurate screening test for retinal pigment epithelial detachments.
4. It is acceptable to remove all ophthalmic conditions from the contraindications for erdafitinib.

The Eye Disorders Management Guideline/Physician Education Material should be modified in the following manner:

1. Visual acuity should be tested as best corrected distance visual acuity.
2. Tonometry should be removed since there is no indication that tonometry needs to be performed.
3. The Amsler grid should not be expected to serve as a useful screen for the adverse events likely to be caused by erdafitinib.
4. Ophthalmic evaluations should be performed at baseline and then at regular intervals as determined by the ophthalmic specialist following the patient. RPE detachments, if observed should be monitored at approximately 2-3 week intervals until they start resolving. Dose reduction should be considered if the RPE detachment is not starting to resolve in 2-3 weeks without dose reduction.
5. All patients should be initially treated for dry eye syndrome when initiating erdafitinib. Dry eye treatment should include ocular demulcents as needed. Continued dry eye syndrome management should be made by the ophthalmic specialist following the patient.
6. Recommendations to use lubricating eye gels are discouraged since there are no approved dry eye therapy gels.
7. The potential for a retinal pigment epithelial detachment to cause permanent vision loss is not dependent on whether the initial presentation limits activities of daily living. The use of the proposed scale is therefore not useful in adjusting therapy.

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Supervisory Medical Officer, Ophthalmology

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

/s/

WILEY A CHAMBERS
10/17/2018