

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125547Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

<b>BLA</b>	125547/0
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<b>Review Classification</b>	Standard
<b>PDUFA Due Date</b>	02-Dec-2015
<b>Brand Name</b>	PORTRAZZA
<b>Generic Name</b>	Necitumumab (IMC-11F8, LY3012211)
<b>Proposed Indication</b>	In combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)
<b>Proposed Dosage Regimen</b>	800 mg administered by intravenous (IV) infusion over (b) minutes on Days 1 and 8 of a 3-week treatment cycle
<b>Proposed Dosage Form</b>	16 mg/mL (800 mg/50 mL) sterile solution in single-dose vials
<b>Related IND</b>	102512
<b>Applicant</b>	Eli Lilly and Company
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## 1. EXECUTIVE SUMMARY

This new molecular entity (NME) BLA submission seeks marketing approval for PORTRAZZA (necitumumab) to be used in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). The proposed dosage regimen is 800 mg PORTRAZZA administered as an intravenous (IV) infusion over (b) (4) minutes on Days 1 and 8 of each 3-week cycle. The FDA recommends changing the infusion duration to **60 minutes** as this is one of the most conventionally used infusion durations.

The efficacy and safety of necitumumab were evaluated in a global, randomized, open-label, Trial JFCC (SQUIRE) that compared necitumumab in combination with gemcitabine/ cisplatin versus the standard chemotherapy regimen alone (gemcitabine and cisplatin) in the first-line treatment of patients with squamous NSCLC. Necitumumab in combination with chemotherapy improved the overall survival by 1.6 month (11.5 months versus 9.9 months) as compared to those receiving chemotherapy alone with a hazard ratio [HR] and 95% confidence interval values of 0.84 (0.74%, 0.96%;  $p=0.012$ ). The safety of necitumumab in combination with gemcitabine/ cisplatin was comparable to gemcitabine/cisplatin chemotherapy alone except for the incidence of skin reactions (79% versus 12% for all grades, 8.2% versus 0.6% for Grade  $\geq 3$ ) and hypomagnesemia (31% versus 16% for all grades, 9.3% versus 1.1% for Grade  $\geq 3$ ).

Population pharmacokinetics (popPK) analyses of pooled data from 807 patients who participated in five clinical trials suggest that the increased risk of rash and hypomagnesemia in patients who received necitumumab in combination with gemcitabine/cisplatin was independent of necitumumab concentration. Body weight was the only significant covariate in the final popPK model; however, simulations suggested that the influence of body weight on the variability of necitumumab exposure is not clinically meaningful to require a body weight based dosing. Age, sex, race, renal function (as measured by Cockcroft-Gault creatinine clearance), hepatic function (as defined by alanine aminotransferase, aspartate aminotransferase (AST) and total bilirubin) or concomitant medications (gemcitabine and cisplatin) appear not to have a clinically meaningful effect on necitumumab exposure to warrant dosage adjustment. No apparent correlation was identified between necitumumab exposure ( $C_{ss,ave}$ ) and safety or efficacy endpoints.

The popPK analysis supports the proposed 800 mg necitumumab on Days 1 and 8 of a 3-week cycle as an appropriate dosage regimen in the indicated NSCLC patient population. The exposure to gemcitabine tends to be higher when administered with necitumumab in the presence of cisplatin; this may have contributed to the higher toxicity observed in the combination of necitumumab with gemcitabine and cisplatin arm. The exposure of the commercial formulation manufactured with (b) (4) is comparable to the clinical formulation manufactured by (b) (4) in patients with solid tumors.

A total of 14.4% (141/981) of patients in the six clinical trials with PORTRAZZA tested positive for ADAs at baseline with 2.9% having neutralizing antibodies. After PORTRAZZA treatment, 8.7% (71/814) of patients were tested positive for ADAs. The incidence of treatment emergency anti-necitumumab antibodies (TE-ADAs) was 4.1% (33/814). For patients with post-treatment ADAs, mean  $CL_{tot}$  was 26% higher and mean  $C_{ss,ave}$  was 34% lower than in those without ADAs. No obvious relationship was found between immunogenicity and the incidence of infusion related reactions (IRRs). The impact of immunogenicity on the efficacy endpoint (OS) could not be assessed due to limited number of patients with TE-ADAs detected.

## 1.1 RECOMMENDATIONS

BLA 125547 is acceptable from a clinical pharmacology perspective provided the Applicant and the Agency come into mutual agreement regarding the labeling language.

## 1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

[None]

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An abbreviated Clinical Pharmacology (CP) Office-Level briefing was held for this BLA on July 6, 2015.

### 1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

**Efficacy and Safety:** Necitumumab (IMC-11F8, LY3012211) is a recombinant human DNA-derived monoclonal antibody of IgG1 that blocks the ligand binding site of EGFR. The efficacy and safety of necitumumab in the proposed patient population (first-line treatment of squamous NSCLC) were primarily evaluated in Trial JFCC (SQUIRE). A 1.6-month improvement in overall survival (OS) was observed among patients in the GC+N (gemcitabine/ cisplatin + necitumumab) Arm compared with those in the GC (gemcitabine/ cisplatin) Arm (HR = 0.842 [0.736, 0.962]; p=0.012). The most reported adverse events (AEs) occurring at higher rates for patients receiving GC+N compared to those receiving GC alone were skin reactions (79% versus 12% for all grades, 8.2% versus 0.6% for Grade  $\geq 3$ ) and hypomagnesemia (31% versus 16% for all grades, 9.3% versus 1.1% for Grade  $\geq 3$ ).

**Dose Selection Rationale:** The proposed dosage regimen of 800 mg necitumumab on Days 1 and 8 of each 3-week cycle was based on the safety and pharmacokinetics (PK) data from the dose-escalation Trial JFCE in 60 patients with advanced solid tumors. In this trial, necitumumab was administered either once weekly (Arm A) or once every 2 weeks (Arm B) for 6 weeks at doses ranged from 100 mg to 1000 mg. Although no necitumumab-related dose-limiting toxicities (DLTs) were observed in patients after the **QW** dosing up to 1000 mg and two out of the nine patients experienced necitumumab-related DLTs after the 1000 mg **Q2W** dosing, the **800 mg Q2W** dosing regimen was selected for future clinical trials. Exploratory population pharmacokinetics (popPK) simulations from 807 patients in clinical trials (Trials JFCA, JFCB (INSPIRE), JFCC (SQUIRE), JFCI and JFCJ) predicted that the average necitumumab steady state serum concentrations ( $C_{ss,ave}$ ) at the 800 mg **Q2W** were above the target concentration associated with the anti-tumor activity in murine tumor mice xenograft model ( $\geq 40$   $\mu\text{g/mL}$ ).

**Population PK (popPK) Analysis:** PopPK analysis was performed on the data from 807 patients in the five clinical trials: JFCA, JFCB, JFCC, JFCI and JICJ to characterize the PK of necitumumab, to determine the effect of various covariates, and to explore the exposure-response relationships with regard to safety and efficacy. Necitumumab was administered at 800-mg on Days 1 and 8 of a 3-week cycle (Trials JFCB, JFCC, JFCJ and subset of Trial JFCA), 800 mg once weekly (Trial JFCI), every 2 weeks (subset of Trial JFCA) and 600 mg on Days 1 and 8 of a 3-week cycle (subset of Trial JFCA). The PK of necitumumab were characterized by the target-mediated drug disposition model (TMDD), exhibiting dose-dependent effects on total clearance ( $CL_{tot}$ ) and steady state volume of distribution ( $V_{ss}$ ) in the popPK analysis. The population parameter estimates for  $CL_{tot}$  and  $V_{ss}$  are 14.1 mL/h (CV=39%) and 7.0 L (CV=31%), respectively at the 800 mg dose given on Days 1 and 8 of a 3-week cycle; this corresponds to an elimination half-life of approximately 14 days. The predicted time to reach steady state was approximately 100 days. Inter-patient variability in PK parameters ranged from 21% to 55%.

**Exposure-Efficacy Relationship:** Exploratory exposure response (E-R) analysis of data from Trial SQUIRE suggests that patients with higher serum necitumumab concentrations appear to have an improved efficacy (prolonged OS). The population median predicted necitumumab  $C_{ss,ave}$  of 216  $\mu\text{g/mL}$  resulted in an increase in survival time of about 48 days relative to control and an  $E_{max}$  of 42 days. The 90% predicted interval of  $C_{ss,ave}$  for the 800 mg dose regimen was 110-360  $\mu\text{g/mL}$ , an exposure range covering the efficacy range of 70%-100%  $E_{max}$  in the  $C_{ss,ave}$ -OS curve.

**Exposure-Safety Relationship:** Based on the final popPK model, there appeared to be an exposure-hypomagnesemia trend for all grades with the rates of 15%, 24%, 24% and 29% for exposure quartile Q1, Q2, Q3 and Q4, respectively. Exploratory E-R analysis of data from Trial SQUIRE indicates that there appeared to be a relationship for all grades of hypomagnesemia; higher hypomagnesemia rate associated with higher exposure to necitumumab, but such relationship was not observed for any of Grade3+ hypomagnesemia. No apparent relationship was observed for Grade3+ rash or Grade3+ thromboembolic event (venous and arterial).

**Specific Populations:** No dedicated PK studies have been performed in pediatric, elderly, hepatically impaired or renally impaired patients. In the final popPK model, body weight was identified as the only significant covariate affecting necitumumab disposition, with a less than proportional effect on both  $CL_{tot}$  and  $V_{ss}$  parameter estimates; however, simulations suggested that the effect of body weight is not clinically meaningful as dosing based on body weight would not lead to a decreased variability in PK or improvement in efficacy (OS). Age (range=19-84 years), sex (75% male), race (85% Whites), renal function [as measured by Cockcroft-Gault creatinine clearance ( $CL_{cr}$ ), range=11-250 mL/min] or hepatic function [as measured by alanine aminotransferase (range= 2-615 U/L), aspartate aminotransferase (range=1.2-619 U/L) and total bilirubin (range=0.1-106  $\mu$ mol/L)] appear not to have a significant effect on the PK of necitumumab. The lack of correlation between  $CL_{tot}$  and hepatic or renal function is expected given the known mechanisms involved for clearance of monoclonal antibodies (mAbs). Based on the Applicant's prespecified analyses, tumor EGFR protein expression as assessed by immunohistochemistry (H-score cutpoint of 200) was not predictive of efficacy outcomes in Trial JFCC (SQUIRE); however, additional exploratory analyses demonstrated that a small subset of patients lacking detectable tumor EGFR protein expression (H-score =0; n=47) did not appear to benefit in terms of OS or PFS when necitumumab was added to gemcitabine and cisplatin.

**Drug-Drug Interactions (DDI):** The popPK analysis performed with data from 807 patients in 5 clinical trials including Trial JFCJ indicates that gemcitabine and cisplatin have no effect on the exposure to necitumumab. The data from Trial JFCJ in 12 patients with advanced solid tumors indicate that the coadministration of necitumumab (800 mg) with gemcitabine (1250 mg/m<sup>2</sup>) and cisplatin increased the geometric mean dose-normalized gemcitabine  $AUC_{INF}$  by 22% and  $C_{max}$  by 63% compared to those after administration of gemcitabine and cisplatin alone. This increased exposure to gemcitabine may have contributed to the higher toxicity observed with the necitumumab containing arm. The coadministration of necitumumab did not have an effect on the exposure to cisplatin (as measured by dose-normalized  $AUC_{0-5h}$  and dose-normalized  $C_{max}$  for total platinum) in the presence of gemcitabine.

**Product Comparability:** The comparability of the to-be-marketed product manufactured by (b) (4) to the clinical trial product manufactured by (b) (4) was assessed in 18 patients with solid tumors in Trial JFCJ. The comparability was demonstrated in necitumumab PK parameters between the products manufactured by two drug substance (DS) processes with the ratio of geometric means and 90% confidence interval of 0.99 (84%, 115%) for  $AUC_{0-168h}$  and 1.08 (92%, 128%) for  $C_{max}$ .

**Immunogenicity:** The immunogenicity of necitumumab was assessed in 981 patients from six clinical trials, 814 out of 981 patients had serum samples collected and analyzed for anti-necitumumab antibodies (ADAs) at baseline and post-treatment. Seventy one out of 814 patients (8.7%) were tested positive for ADAs. Treatment-emergent ADAs (TE-ADAs) were detected in 33 patients (4.1%). Neutralizing antibodies (NABs) were detected in 28 patients (2.9%) at

baseline and in 11 patients (1.4%) post treatment. The development of TE-ADAs, and NAbs showed no correlation with safety outcomes. The incidence of skin rash and hypomagnesemia was similar between patients with ADAs detected and overall population (81.5 versus 79% and 32.1 versus 31%, respectively). The popPK analysis suggested that ADA-positive patients had 26% higher  $CL_{tot}$  and 34% lower  $C_{ss,ave}$  than those ADA-negative patients. The incidence of infusion related reactions (IRRs) was 1.7% with 0.2% of patients were ADA-positive. The impact of immunogenicity on the efficacy endpoint (OS) could not be assessed due to limited number of patients with TE-ADAs detected.

## 2. QUESTION BASED REVIEW (QBR)

### 2.1 GENERAL ATTRIBUTITES

#### *2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?*

Necitumumab (IMC-11F8, LY3012211) is a human monoclonal antibody composed of (b) (4) (see Figure 1). The necitumumab molecular mass, determined by mass spectrometry, (b) (4) resulting in a relative molecular mass for the necitumumab monoclonal antibody of (b) (4) kDa. (b) (4)

**Figure 1. Structure of Necitumumab\***

(b) (4)

The drug product will be commercially available as a sterile, preservative-free solution at a concentration of 16 mg/mL (800 mg/50 mL) in single dose vials.

#### *2.1.2 What are the proposed mechanisms of action and therapeutic indications?*

Necitumumab is a fully human IgG1 monoclonal antibody (mAb) that binds to the human epidermal growth factor receptor-1 (EGFR) and antagonizes binding of its cognate ligands

including transforming growth factor  $\alpha$  (TGF $\alpha$ ), epidermal growth factor (EGF), heparin-binding epidermal growth factor (HB-EGF), betacellulin, amphiregulin, epiregulin, and epigen. Necitumumab selectively blocks ligand-induced phosphorylation of EGFR and consequent phosphorylation of downstream signaling molecules. Furthermore, necitumumab inhibits EGFR-dependent tumor cell proliferation and targets EGFR-expressing tumor cells for killing through an antibody-dependent cell cytotoxic response.

The proposed indication is for the use of PORTRAZZA in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).

### 2.1.3 What are the proposed dosage and route of administration?

The proposed dosing regimen is 800 mg administered by intravenous (IV) infusion over (b) (4) minutes on Days 1 and 8 of a 3-week treatment cycle.

**Reviewer Comment:** FDA has a concern on the proposed (b) (4) minutes of infusion time for potential medical errors as this is not a standard infusion time to be used in clinical settings. FDA recommends change of the infusion time from (b) (4) minutes to 60-minutes (b) (4).

## 2.2 GENERAL CLINICAL PHARMACOLOGY

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

Seven clinical trials were submitted to this BLA submission which also contained pertinent clinical pharmacology information (see Table 1).

**Table 1: Clinical Studies Containing Clinical Pharmacology Pertinent Information**

Trial	Patient Population	Total N (N <sub>PK</sub> for PK Evaluation)	Study Design	Dosing Regimen
JFCA	Japanese patients with advanced solid tumors	15 (15)	Phase 1, open label, single-agent, dose-escalation	Cohort 1 (N=3): Necitumumab 600 mg (50 min IV) Q3W for 6 week Cohort 2 (N=6): Necitumumab 800 mg (50 min IV) Q2W IV for 6 weeks Cohort 3 (N=6): Necitumumab 800 mg (50 min IV) (Days 1 & 8) Q3W for 6 weeks
JFCB (INSPIRE)	Naïve patients with non-squamous NSCLC	633 (247)	Phase 3, open-label, randomized	Arm A: Necitumumab 800 mg (50 min IV) on Days 1 and 8 Q3W, pemetrexed 500 mg/m <sup>2</sup> (10 min IV) on Day 1 Q3W and cisplatin 75 mg/m <sup>2</sup> (2 h IV) on Day 1 Q3W for 3 weeks Arm B: Pemetrexed 500 mg/m <sup>2</sup> (10 min) D1 Q3W and cisplatin 75 mg/m <sup>2</sup> (2 h IV) on Day 1 Q3W for 3 weeks
JFCC (SQUIRE)	Naïve patients with squamous NSCLC	1093 (470)	Phase 3, open-label, randomized	Arm A: Necitumumab 800 mg (50 min IV) on Days 1 and 8 Q3W, gemcitabine 1250 mg/m <sup>2</sup> (30 min IV) on Days 1 and 8 Q3W and cisplatin 75 mg/m <sup>2</sup> (2 h IV) on Day 1 Q3W for 3 weeks

Trial	Patient Population	Total N (N <sub>PK</sub> for PK Evaluation)	Study Design	Dosing Regimen
				<b>Arm B:</b> Gemcitabine 1250 mg/m <sup>2</sup> (30 min IV) on Days 1 and 8 Q3W and cisplatin 75 mg/m <sup>2</sup> (2 h IV) on Day 1 Q3W for 3 weeks
JFCD	Naïve patients with locally advanced or metastatic colorectal cancer	44 (42)	Phase 2, open-label, combination, single-arm	<b>Necitumumab:</b> 800 mg (50 min IV) Q2W for 2 weeks <b>mFOLFOX-6 Q2W:</b> Oxaliplatin 85 mg/m <sup>2</sup> (2 h IV), Folinic acid 400 mg/m <sup>2</sup> (2 h IV), 5-FU 400 mg/m <sup>2</sup> (2-4 min IV bolus) and 5-FU 2400 mg/m <sup>2</sup> (46 h IV) continuously, immediately following bolus) for 2 weeks
JFCE	Patients with solid tumors who have failed standard therapy	60 (56)	Phase 1, open-label, single-agent, two-arm, dose-escalation	Necitumumab 100, 200, 400, 600, 800, or 1000 mg (50 min IV) QW for 6 weeks (Arm A, N=29) or Q2W for 6 weeks (Arm B, N=31)
<sup>a</sup> JFCI	Patients with advanced solid tumors	40 (40)	Phase 2, open-label, single agent, single-arm, QTc	Necitumumab 800 mg (50 min IV) QW for 6 weeks
<sup>b</sup> JFCJ	Patients with advanced solid tumors	35 (35)	Phase 2, sequential single-arm, DDI and comparability	<b>3-week PK run in period:</b> Gemcitabine 1250 mg/m <sup>2</sup> (30 min IV) on Day 1, cisplatin 75 mg/m <sup>2</sup> (2 h IV) on Day 1 and necitumumab 800 mg (50 min IV) on Day 3 of a 3-week cycle [Cohort 1 administered necitumumab as clinical drug substance manufactured by (b) (4) (N=18) and Cohort 2 administered necitumumab as commercial drug substance manufactured by (b) (4) (N=17)] <b>Cycles 1-6:</b> Necitumumab 800 mg (50 min IV) on Days 1 and 8 Q3W, gemcitabine 1250 mg/m <sup>2</sup> (30 min IV) on Days 1 and 8 Q3W and cisplatin 75 mg/m <sup>2</sup> (2 h) on Day 1 Q3W of a 3-week cycle

QW=once every week, Q2W= Once every other Q3W=once every 3 weeks

<sup>a</sup>[see Section 2.7 of this review for more details on the assay methodology]

<sup>a</sup>Registration Trial

<sup>a</sup>Study JFCI is ongoing. As a cut-off date of 29-Oct-2013, interim QTc data are available from 40 patients. The final study report, once completed, will be submitted to the IND along with datasets and additional documentation requested by FDA in its October 2011 advice letter. A consult was sent to the IRT group on 09-Jan-2015 for the evaluation of these interim QTc data.

<sup>b</sup>Study JFCJ had 2 cohorts: Cohort 1 received necitumumab drug substance (DS) manufactured using (b) (4) while Cohort 2 received necitumumab DS manufactured using (b) (4) [see Section 2.5 of this review for more details on DS comparability]

### 2.2.1.1 Registration Trial JFCC (SQUIRE)

The efficacy and safety of necitumumab in naïve patients with squamous NSCLC are based on the results from Trial JFCC (SQUIRE), entitled “*A Randomized, Multicenter, Open-Label Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy plus Necitumumab (IMC-11F8) Versus*

*Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)*”.

The primary objective of SQUIRE was to evaluate the OS in the target patient population (Stage IV squamous NSCLC) treated with necitumumab plus gemcitabine and cisplatin chemotherapy versus gemcitabine and cisplatin chemotherapy alone. SQUIRE was a Phase 3, open-label, global, multi-center, randomized study in 1093 patients with squamous Stage IV NSCLC. Baseline patient demographics and disease characteristics were balanced between arms, including patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 (9.0% versus 8.6%) and Asian patients (7.9% versus 7.7%). The patients’ median age was 62 years (range=32 to 86) with 83% of patients being male, and 84% being Caucasian. Patients were randomized (1:1) to receive either necitumumab plus gemcitabine and cisplatin chemotherapy (GC+N Arm, N=545) or gemcitabine and cisplatin alone (GC, N=548). In the **GC+N Arm**, patients received necitumumab (800 mg IV on Days 1 and 8), gemcitabine (1250 mg/m<sup>2</sup> IV on Days 1 and 8) and cisplatin (75 mg/m<sup>2</sup> IV on Day 1 only) of each 3-week cycle for a maximum of 6 cycles. Gemcitabine was administered following the completion of the necitumumab infusion; cisplatin was administered at least 30 minutes after the completion of the infusion of gemcitabine. In the **GC arm**, patients received the same chemotherapy dosage regimen as in the GC+N arm but without necitumumab.

**Efficacy Results:** The primary objective was met for this study, demonstrating a statistically significant and clinically relevant improvement in OS among patients in the GC+N Arm compared with that in the GC Arm (HR = 0.842 [0.736, 0.962]; p=0.012), with an estimated reduction in the risk of death of 16% in GC+N arm (see **Table 2**). The median OS time increased from 9.9 months to 11.5 months when necitumumab was administered with gemcitabine and cisplatin.

**Table 2: Summary of the Primary Efficacy Results**

	GC+N N = 545	GC N = 548
Number of deaths, n (%)	418 (76.7)	442 (80.7)
Number censored, n (%)	127 (23.3)	106 (19.3)
Log-rank p-value (two-sided) Stratified*	0.012	
Hazard ratio (95% CI) Stratified*	0.842 (0.736, 0.962)	
Median OS – months (95% CI)	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)

\*Stratified by the randomization strata (ECOG performance status [0-1 vs 2], and geographic region [North America, Europe, and Australia versus South America, South Africa and India vs Eastern Asia])

**Safety Results:** The most commonly reported adverse events (AEs) of **all grade** observed in SQUIRE with higher incidence rate in the GC+N Arm than in the GC Arm were skin reactions (79% versus 12%) and hypomagnesemia (31% versus 16%), dermatitis acneiform (15.1% versus 0.6%), acne (8.7% versus 0.6%), pruritus (7.1% versus 0.9%), dry skin (6.5% versus 1.5%), paronychia (6.7% versus 0.2%), rash generalized (5.2% versus 0.4%) and decreased weight (13.4% versus 6.3%). Among the **Grade ≥3** AEs reported in the GC+N Arm were skin rash (8.2% versus 0.6%) and hypomagnesemia (9.3% versus 1.1%).

**2.2.2. What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?**

The primary efficacy endpoint in the Trial JFCC (SQUIRE) was overall survival (OS), defined as the interval between the date of randomization and the date of death from any cause. The basis for selecting OS as a clinical endpoint in NSCLC is because it is a direct measure of clinical benefit to a patient, easily measured, unambiguous, objective and unaffected by the timing of assessment.

### 2.2.3 What is the basis of the dose selection?

The selection of the proposed dose of 800 mg for necitumumab was based on the safety and PK data from the Phase 1, dose-escalation Trial JFCE in 60 patients with advanced solid tumors. In this study, necitumumab was administered either once weekly (QW) (Arm A) or once every 2 weeks (Q2W) (Arm B) for 6 weeks at doses ranged from 100 mg to 1000 mg. No dose-limiting toxicities (DLTs) were observed in any patient treated with QW (including the 9 patients who received the 1000 mg dose). Of 9 patients receiving 1000 mg Q2W, 2 experienced necitumumab-related adverse events that qualified as DLTs. One patient experienced Grade 3 headache, Grade 3 vomiting, and Grade 3 nausea. The second patient experienced a DLT of Grade 3 headache; this patient was able to continue necitumumab at a reduced dose of 800 mg. The 800 mg dose either given QW or Q2W was defined as the maximum tolerated dose (MTD) and was selected to be used in future clinical trials.

Mostly, serum trough concentrations ( $C_{min}$ ) observed at necitumumab doses of 400 mg and above QW were well above the target serum trough concentrations of  $\geq 40$   $\mu\text{g/mL}$  associated with anti-tumor activity in the murine tumor xenograft model) (see Table 3).

**Table 3: Geometric Mean (%CV) Observed Serum Trough Concentrations ( $C_{min}$ ) Following Administration of Necitumumab Once Weekly (QW) or Every Other Week (Q2W) at Doses of 100 mg to 1000 mg (Trial JFCE)**

Dose (mg)	$C_{min}$ , $\mu\text{g/mL}$					
	QW (Arm A)			Q2W (Arm B)		
	Cycle 1 Pre-2 <sup>nd</sup> Infusion	Cycle 1 Pre-7 <sup>th</sup> Infusion	Cycle 2 Pre-13 <sup>th</sup> Infusion	Cycle 1 Pre-2 <sup>nd</sup> Infusion	Cycle 1 Pre-4 <sup>th</sup> Infusion	Cycle 2 Pre-7 <sup>th</sup> Infusion
100 mg	2.0 (31%) N=3	2.7, 5.3 N=2	NC	1.37, 1.73 N=2	1.26 N=1	NC
200 mg	7.7 (77%) N=6	28.8 (20%) N=3	21.6, 27.6 N=2	NC	1.3, 3.53 N=2	13.4 N=1
400 mg	32.6 (42%) N=6	80.9 (51%) N=3	47.9, 149 N=2	9.7 (87%) N=5	20.6, 74.3 N=2	30.1 N=1
600 mg	48.7 (25%) N=6	141 (68%) N=3	107 N=1	8.3 (49%) N=4	35.0, 96.5 N=2	22.3 N=1
800 mg	120 (46%) N=14	296 (22%) N=4	301, 496 N=2	47.2 (58%) N=13	100 (41%) N=6	46.7 N=1
1000 mg	165 (65%) N=17	343 (108%) N=5	440, 1190 N=2	66.4 (93%) N=16	88.1 (14%) N=3	162 N=1

NC=Not calculated

Population PK (popPK) modeling simulations of data from Trials JFCA, JFCB (INSPIRE), JFCC (SQUIRE), JFCI and JFCJ predicted that almost all patients had average serum necitumumab concentrations ( $C_{ss,ave}$ ) (observed or predicted) well above the target concentration associated with the anti-tumor activity in murine tumor mice xenograft model ( $\geq 40$   $\mu\text{g/mL}$ ) (see Figure 2). Thus, the popPK analysis supports the proposed 800 mg necitumumab on Days 1 and 8 of a 3-week cycle as an appropriate dosage regimen in the NSCLC patient population.

**Figure 2. Predicted Average Steady State Necitumumab Serum Concentrations ( $C_{ss,ave}$ ) at 800 mg Dose Administered on Day 1 and Day 8 of a Three-Week Cycle (Applicant's)**



Solid red line represents median, dotted lines the 90% prediction interval

A flat 800 mg dose was selected. Although body weight was found to be a significant covariate in the final popPK model, simulations suggested effect of body weight on PK of necitumumab appears to be clinically insignificant (see Section 2.3.2.4 of this review).

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

Necitumumab serum concentrations were measured using two bioanalytical assays. An earlier assay using surface plasmon resonance (Biacore) developed by ImClone (Branchburg, NJ) was used in the initial trials (Trials JFCD and JFCE). Subsequently, an enzyme-linked immunosorbent assay (ELISA) developed by (b) (4) was used in the other clinical trials (Trials JFCA, JFCB, JFCC, JFCI and JFCJ).

A cross-assay comparison performed in Trial JFCA indicated the lack of general agreement between the two bioanalytical methods (Biacore and ELISA). In addition, The Biacore assay validation was not fully compliant with the FDA Bioanalytical guidance. Due to lack of comparability between the two bioassay methods and due to deficiencies in the Biacore method validation, ELISA assay used in Trials JFCA, JFCB, JFCC, JFCI and JFCI are considered more reliable and therefore, were used for definitive PK analyses. The Biacore assay data for samples collected in Trials JFCD and JFCE were only considered for supportive evidence. The performance of these bioanalytical methods is summarized in Section 2.6 of this review.

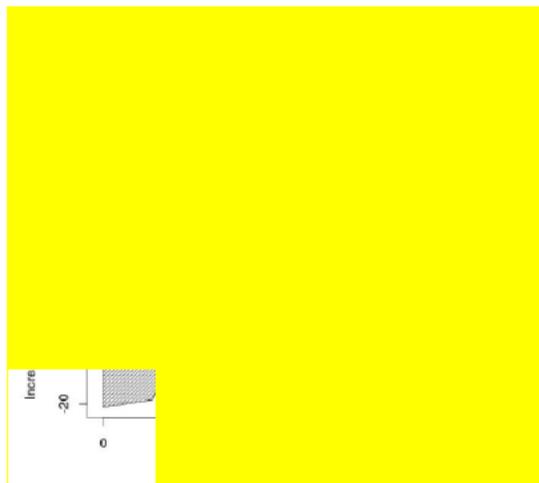
#### ***2.2.5 Exposure-response***

##### ***2.2.5.1 Is there an exposure-response relationship for overall survival (OS), the primary efficacy endpoint?***

Exploratory exposure-efficacy relationship was evaluated using the popPK analysis of data from Trial JFCC (SQUIRE). Most patients were Whites (84%), males (84%) and smokers (91%). Using the final PopPK model, simulations of survival time using various values of necitumumab  $C_{ss,ave}$  result in the exposure-response curve shown in **Figure 3** after excluding patients with no PK sampling. The population median of the maximum OS effect ( $E_{max}$ ) was estimated to be 63 days, i.e., the difference between 399 days for the GC+N arm and 336 days for the GC arm. The population median predicted necitumumab  $C_{ss,ave}$  of 216  $\mu\text{g/mL}$  resulted in an increase in survival time of about 48 days relative to control and an  $E_{max}$  of 42 days. The 90% predicted

interval of  $C_{ss,ave}$  for the 800 mg dose regimen was 110-360  $\mu\text{g/mL}$ , an exposure range covering the efficacy range of 70%-100%  $E_{max}$  in the  $C_{ss,ave}$ -OS curve. In other words, the  $C_{ss,ave}$ -OS relationship demonstrated that the 800 mg dose regimen would result in an OS of 70-100%  $E_{max}$ ; therefore, the regimen is reasonable from the primary efficacy perspective (see Appendix 3 - Pharmacometrics (PM) Review for more details).

**Figure 3. Necitumumab Exposure-Response Curve for Overall Survival Based on Final Model Excluding Patients with No PK Data**



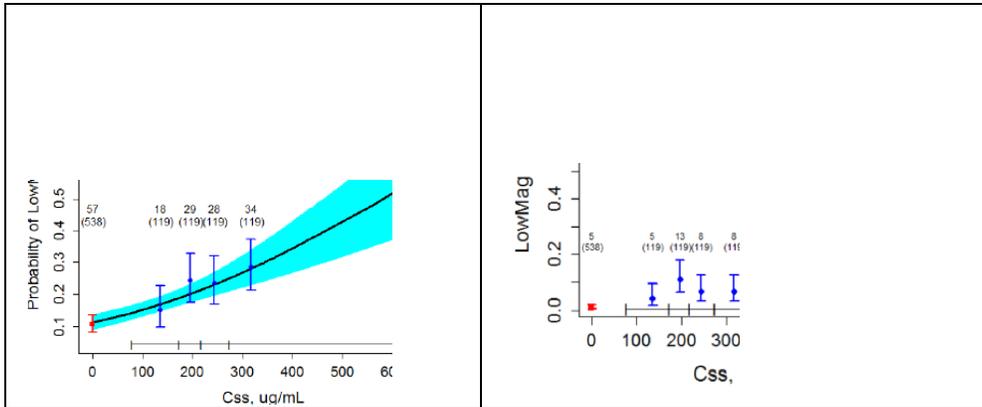
The shaded area is the 95% confidence interval of the median survival time relative to control. The vertical lines (median and 90% prediction interval) show the predicted range of  $C_{ss,ave}$  for patients in the JFCC study.

#### **2.2.5.2 Is there evidence of exposure-response for safety?**

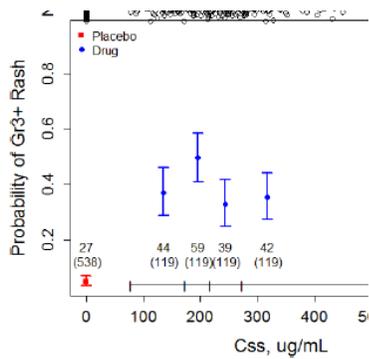
As per PM review, exploratory exposure-safety relationship was evaluated using the PopPK analysis of data from Trial JFCC (SQUIRE) after excluding the patients with no PK sampling. Based on the final PopPK model, there appeared to be an exposure-hypomagnesemia trend for **all grades** (left upper panel of **Figure 4**) but no trend for **Grade 3+** (left lower panel of **Figure 4**). For all grades hypomagnesemia, the rates were 15%, 24%, 24% and 29% for Q1, Q2, Q3 and Q4, respectively.

There appeared to be no exposure-response relationship for Grade 3+ rash (**Figure 5**). There also appeared to be no exposure-response relationship for either Grade 3+ arterial (ATE) (**Figure 6**) or Grade 3+ venous (VRE) thromboembolic events (**Figure 7**).

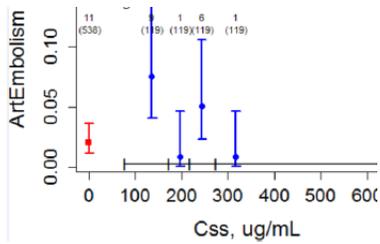
**Figure 4. Probability of Hypomagnesemia *versus* Exposure**



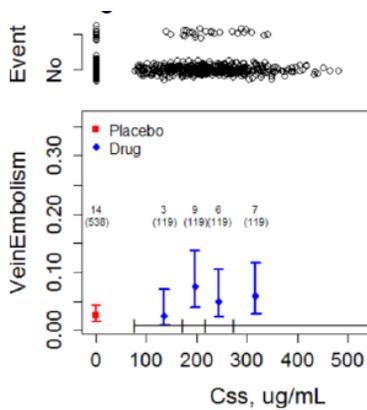
**Figure 5. Probability of Grade 3+ Rash *versus* Necitumumab Exposure**



**Figure 6. Probability of Grade 3+ ATE Thromboembolic Event versus Necitumumab Exposure**



**Figure 7. Probability of Grade 3+ VRE Thromboembolic Event versus Necitumumab Exposure**



**2.2.6 Does necitumumab prolong the QTc interval?**

(b) (4)  
 (see Attachment 1 - QTc-IRT review).

**2.2.7 Pharmacokinetic (PK) characteristics of the drug and its major metabolites**

**2.2.7.1 What are PK parameters in patients with NSCLC?**

Intensive PK sampling was performed in studies JFCE, JFCD, JFCA, JFCI and JFCJ. Sparse PK samples were obtained in 2 Phase 3 Trial JFCC (SQUIRE) and JFCB (INSPIRE). **Table 4** summarizes the PK sampling scheme utilized in all trials.

**Table 4: Summary of PK Sampling in Clinical Trials**

Trial	N <sub>PK</sub>	Bioanalytical Assay Used	PK Sampling
JFCA	15	ELISA	Cycle 1: <ul style="list-style-type: none"> <li>Day 1 and Day 29: pre-dose, EOI, 0.5, 1, 2, 6, 24, 96, 168, 264 and 336 hours after the EOI</li> </ul>
JFCB (INSPIRE)	247	ELISA	Arm A only Cycle 1 to Cycle 6: Day 1: pre-dose only
JFCC (SQUIRE)	470	ELISA	Arm A only Cycle 1 to Cycle 6: Day 1: pre-dose only
JFCD	42	Biacore	Cycle 1/Day 1: pre-dose, EOI, 0.5, 1, 2, 6, 24, 96 and 168, 264 and 336 hours after the EOI
JFCE	56	Biacore	Cycle 1/Day 1 (Arm A and Arm B): pre-dose, EOI, 0.5, 1, 2, 6, 24, 96, 168, 264 and 336 hours after the EOI
JFCI	40	ELISA	Cycle 1: <ul style="list-style-type: none"> <li>Day 1 and Day 36: pre-dose, EOI, 1, 2, 4, 24, 48 72 hours post EOI,</li> <li>Days 8, 15, 22 &amp; 29: pre-dose, EOI, 1, 2 4 hours post EOI</li> </ul>
JFCJ	35	ELISA	<b>Necitumumab Sampling:</b> Run in period/Day 3 (necitumumab alone) and Cycle 1/Day 1 (necitumumab plus gemcitabine and cisplatin): pre-dose, EOI, 0.5, 1, 3, 6.7, 24, 72 and 168 hours post EOI <b>Gemcitabine</b> <ul style="list-style-type: none"> <li>Run in period/Day 1 (gemcitabine and cisplatin) and Cycle 1/Day 1 (necitumumab plus gemcitabine and cisplatin): pre-dose, EOI, 0.5, 1, 2.5, 3.5, 6.2 and 24 hours post EOI</li> </ul> <b>Cisplatin:</b> <ul style="list-style-type: none"> <li>Run in period/Day 1(Gemcitabine and cisplatin) and Cycle 1/Day 1 (necitumumab plus gemcitabine and cisplatin): pre-dose, EOI, 2 min, 0.25, 1, 1.7 and 3.7 hours post EOI</li> </ul>

ELISA=Enzyme-linked immune-sorbent assay

EOI=End of Infusion

The PK of necitumumab was characterized using non-compartmental analysis (NCA) of the data collected in Trials JFCD and JFCE and population PK (PopPK) analysis of the pooled data collected in Trials JFCA, JFCB, JFCC, JFCI and JFCF.

Trials JFCD and JFCE used Biacore bioanalytical assay to measure serum necitumumab concentrations which was not adequately validated (as per FDA guidance) and it is considered not robust.

The other 5 studies used ELISA bioanalytical assay to measure serum necitumumab concentrations which was adequately validated as per the FDA guidance and it is considered more robust.

**PK Characterization – Non-Compartmental Analysis (NCA)**

The PK parameters of necitumumab in trials JFCA and JFCJ using NCA are summarized in **Table 5**.

**Table 5: Geometric Mean (Geometric %CV) NCA PK Parameters (ELISA Assay)**

Trial	Dose	N	C <sub>max</sub> (µg/mL)	t <sub>1/2</sub> (d)	AUC <sub>0-336</sub> (µg <sup>*</sup> h/mL)	CL (mL/h)	V <sub>ss</sub> (L)
<b>Day 1 of Cycle 1</b>							
JFCA	Cohort 1: 600 mg	3	306 (29%)	5.2 (14%)	NC	NC	NC
	Cohort 2: 800 mg	6	417 (46%)	8.6 (31%)	49500 (27%)	12.0 (21%)	2.8 (31%)
	Cohort 3: 800 mg	6	352 (20%)	6.1 (18%)	NC	NC	NC
<b>Day 29 of Cycle 1</b>							
JFCA	Cohort 1: 600 mg Days 1 & 8 Q3W Week 5/4 <sup>th</sup> Dose	3	396 (5%)	7.9 (36%)	56300 (21%)	NC	NC
	Cohort 2: 800 mg Q2W Week 5/3 <sup>rd</sup> Dose	6	523 (17%)	9.7 (18%)	81400 (19%)	9.8 (19%)	NC
	Cohort 3: 800 mg Day 1 & 8 Q3W Week 5/4 <sup>th</sup> Dose	5	629 (16%)	11.9 (18%)	105000 (12%)	NC	NC
	<b>Dose</b>	<b>N</b>	<b>C<sub>max</sub></b> (µg/mL)	<b>*t<sub>1/2</sub></b> (d)	<b>AUC<sub>0-168</sub></b> (µg <sup>*</sup> h/mL)	<b>CL</b> (mL/h)	<b>V<sub>ss</sub></b> (L)
<b>Run-In-Period/Day 3</b> (Necitumumab Alone, Commercial Drug Substance (b) (4))							
JFCJ	800 mg	17	300 (36%)	5.3 (3.1-8.3)	21580 (30%)	22.5 (35%)	4.1 (35%)
<b>Run-In-Period/Day 3</b> (Necitumumab Alone, Clinical Drug Substance (b) (4))							
JFCJ	800 mg	18	277 (22%)	4.8 (2.9-7.7)	21864 (24%)	23.7 (33%)	3.8 (22%)
<b>Day 1/Cycle 1</b> (Necitumumab Plus Gemcitabine and Cisplatin, Clinical Drug Substance (b) (4))							
JFCJ	800 mg	12	330 (23%)	3.1 (2.6-4.0)	23543 (34%)	30.3 (30%)	3.3 (32%)

\*Geometric mean (range)

As the intensive PK sampling was performed up to 336 hours (14 days) post infusion, with a drug having a long half-life (t<sub>1/2</sub>) as necitumumab (14 days, 3 x t<sub>1/2</sub> = 1008 hours), the non-compartmental data analysis (NCA) is considered inadequate to characterize the PK of necitumumab. The population PK (popPK) analysis performed on the data collected from Trials JFCA, JFCB, JFCC, JFCI and JFCJ was found to be acceptable to characterize the PK of necitumumab. In addition, the assay method (ELISA) used in the five trials was adequately validated.

**PK Characterization – Population (popPK) Analyses**

Population PK (popPK) analysis was performed on the data from 807 patients who participated the five clinical trials: JFCA, JFCB, JFCC, JFCI and JICJ. Patients were mostly administered necitumumab at 800-mg over a 50-minute IV infusion on Days 1 and 8 of a 3-week cycle. This

regimen was used in the Phase 3 Trials JFCB and JFCC as well as in the DDI Trial JFCJ and the Phase 1 Trial JFCA. Other patients in JFCA were dosed on this schedule at 600 mg. Necitumumab was also administered at 800-mg QW (Trial JFCI) or Q2W (subset of patients in Trial JFCA). **Figure 8** shows predicted mean serum concentration-time profile for necitumumab from the popPK model.

**Figure 8. Predicted Mean Serum Necitumumab Concentration-Time Profile (Applicant's)**

B  
of  
5

The population PK parameter estimates from the final popPK model are shown in **Table 6**.

**Table 6: Population PK Parameter Estimates for Necitumumab in Final PopPK Model**

Parameter	Population Estimate (%RSE)	Inter-Patient Variability (%RSE)
<sup>a</sup> Clearance (CL <sub>tot</sub> ) (mL/h)	11.4 (4%)	28.8% (10.5)
<sup>c</sup> K <sub>m</sub> (μg/mL)	7.97 (24%)	--
<sup>c</sup> V <sub>max</sub> (mg/h)	0.565 (13%)	--
<sup>b</sup> Central Volume of Distribution, V <sub>1</sub> (L)	3.41 (2.9)	21.1% (18.8)
Inter-compartmental Clearance, Q (L/h)	0.0183 (8.3)	--
<sup>b</sup> Peripheral Volume of Distribution, V <sub>2</sub> (L)	3.29 (4.1)	55.4% (20.7)
Inter-Patient Variability Correlation Coefficient (CL <sub>tot</sub> and V <sub>1</sub> )	0.609 (19.4)	

CL = clearance; K<sub>m</sub> = concentration at which the reaction rate is at half-maximum;

Q = intercompartmental clearance; RSE = relative standard error; V<sub>1</sub> = central volume of distribution;

V<sub>2</sub> = peripheral volume of distribution; V<sub>max</sub> = maximum rate of a Michaelis-Menten type reaction

<sup>a</sup>Total clearance (CL<sub>tot</sub>) is the sum of linear and nonlinear clearances  $CL_{tot} = CL + V_{max}/(C + K_m)$

<sup>b</sup>Volume at steady state (V<sub>ss</sub>) is the sum of central and peripheral volumes of distribution  $V_{ss} = V_1 + V_2$

<sup>c</sup>Fixed (constant) parameters described as follow: K<sub>m</sub> = concentration at which the reaction rate is at half-maximum and V<sub>max</sub> = maximum rate of a Michaelis-Menten reaction

PopPK modeling simulations were used to calculate the population parameter estimates of  $CL_{tot}$  and  $V_{ss}$  (14.1 mL/h and 6.97 L, respectively) at steady state following dosing with 800 mg on Day 1 and Day 8 of a 3-weekly cycle (see Table 7). Inter-patient variability in PK parameters was 21-55%.

**Table 7: Summary of Predicted PK Parameters at Necitumumab 800 mg Dose Given as a 50-minute IV Infusion on Days 1 and 8 of a 3-Week Cycle**

	<sup>a</sup> AUC <sub>0-21d</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	<sup>b</sup> C <sub>max</sub> ( $\mu\text{g}/\text{mL}$ )	<sup>c</sup> C <sub>ss,ave</sub> ( $\mu\text{g}/\text{mL}$ )	<sup>d</sup> CL <sub>tot</sub> (mL/h)	<sup>e</sup> V <sub>ss</sub> (L)
Geometric Mean	111000	508	221	14.1	6.97
Geometric CV%	38	32	38	39	31
Median	112000	509	223	14.0	6.89
5 <sup>th</sup> Percentile	59,900	302	119	7.61	4.34
95 <sup>th</sup> Percentile	201000	843	399	2.67	11.7

<sup>a</sup>AUC is the total AUC in cycle 6 over the 3-week cycle

<sup>b</sup>C<sub>max</sub> is the maximum of the reported simulated concentrations for the Cycle 6, Day 8 profile

<sup>c</sup>C<sub>ss,ave</sub> is the average steady-state concentration over the dosing interval:  $AUC_{0-21d}/21\text{days}$

<sup>d</sup>Total clearance (CL<sub>tot</sub>) is the sum of linear and nonlinear clearances:  $CL_{tot} = CL + V_{max}/(C+K_m)$  with "C" being Cycle 6 C<sub>ss,ave</sub>

<sup>e</sup>Volume at steady state (V<sub>ss</sub>) is the sum of central (V<sub>1</sub>) and peripheral (V<sub>2</sub>) volumes of distribution

From the above results, following a 800 mg dose over 50 min IV on Day 1 and Day 8 of every 3-week cycle, the PK of necitumumab was well described by an approximation of a target mediated drug disposition model (TMDD) as commonly seen with mAbs. Distribution followed a biphasic decline, while drug clearance was non-linear. Total systemic clearance (CL<sub>tot</sub>) and steady state volume of distribution (V<sub>ss</sub>) were 14.1 mL/h (CV=39%) and 6.9 L (CV=31%), respectively. This corresponds to a half-life of approximately 14 days. The predicted time to reach steady state was approximately 100 days. Inter-patient variability in PK parameters was 21.1-55.4%.

**2.2.7.2 How does the PK of the drug and its major active metabolites in healthy volunteers compared to that in patients?**

Necitumumab has not been evaluated in healthy subjects.

**2.2.7.3 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

No mass balance study has been conducted for necitumumab. Mass balance studies are not generally performed for monoclonal antibodies because they are degraded into amino acids those are then recycled into other proteins.

**2.2.7.4 What are the characteristics of drug metabolism?**

Metabolism studies are not generally performed for monoclonal antibodies because they are degraded into amino acids those are then recycled into other proteins.

**2.2.7.5 What are the characteristics of drug excretion?**

Excretion studies are not generally performed for monoclonal antibodies because their large molecular size prevents them from excreting via the kidney.

## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population PK (popPK) analysis was performed on the pooled necitumumab serum concentration-time data collected from 807 patients who participated in the 5 clinical trials JFCA, JFCB (INSPIRE), JFCC (SQUIRE), JFCI and JFCJ. Patients were mostly administered necitumumab at 800-mg over a 50-minute IV infusion on Days 1 and 8 of each 3-week cycle. This regimen was used in the Phase 3 trials JFCB and JFCC as well as in the DDI trial JFCJ and the Phase 1 trial JFCA. Other patients in JFCA were dosed on this schedule at 600 mg. Necitumumab was also administered at 800-mg QW (Trial JFCI) or Q2W (subset of patients in Trial JFCA). A summary of Patients' demographics is presented in **Table 8**. The various covariates (including age, sex, race, body weight, hepatic function and renal function) were evaluated for their influence on the disposition of necitumumab.

**Table 8:** Patients' Demographics; N (%)

Characteristics	Pooled data from Trials JFCA, JFCB, JFCC, JFCI and JFCJ	Data from JFCC (SQUIRE)
N	807	470
Dosing (mg)	600 mg or 800 mg	800 mg
<u>Regimen:</u>		
QW	40 (5%)	0
Q2W	6 (1%)	0
Q3W (Days 1 & 8)	761 (94%)	470 (100%)
*Age (years)	62 (19-84)	62 (32-84)
<u>Sex:</u>		
Male	607 (75%)	392 (83%)
Female	200 (25%)	78 (17%)
<u>Race:</u>		
White	688 (85%)	394 (84%)
Black/African American	17 (2%)	5 (1%)
Asian	55 (7%)	37 (8%)
American/Indian/Alaskan Native	2 (0%)	1 (0%)
Multiple	2 (0%)	0
Other	43 (6%)	33 (7%)
*Weight (kg)	71 (35-181)	70 (35-125)
*BSA (m <sup>2</sup> )	1.82 (1.23-2.81)	1.82 (1.23-2.48)
*ALT (U/L)	19 (1.4-387)	18 (1.4-121)
*AST (U/L)	20 (4.9-216)	19 (4.9-116)
Bilirubin (μmol/L)	7.0 (0.3-30.8)	7.1 (0.33-30.8)
CGCL (mL/min)	90.0 (36-250)	90.5 (38-250)
<u>Concomitant Medications:</u>		
With Cisplatin	717 (89%)	470 (100%)
Without Cisplatin	90 (11%)	0
With Gemcitabine	337 (42%)	0
Without Gemcitabine	470 (58%)	470 (100%)

Median (range)

BSA=body surface area; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CGC=Cockcroft-Gault creatinine clearance

### 2.3.1.1 Genetics: Tumor EGFR Expression

EGFR expression at the protein level is frequent in squamous NSCLC [PMID: 19046792]. The applicant conducted exploratory analyses to evaluate the potential value of EGFR protein expression in the tumor as a predictive biomarker of response to necitumumab. EGFR protein expression was assessed by immunohistochemistry (IHC) and an H-score cutpoint of 200 was pre-specified by the applicant based on the results of the phase 3 FLEX trial [PMID: 22056021]. In the FLEX trial, chemotherapy-naïve patients with advanced squamous or non-squamous NSCLC whose tumors had evidence of EGFR expression in at least one positively stained tumor cell by IHC (Dako PharmDx kit) received vinorelbine and cisplatin with or without cetuximab, an EGFR mAb. Post-hoc subgroup analyses of the FLEX trial suggested that patients whose tumors had high EGFR expression (H-score  $\geq 200$ ) derived greater survival benefit from the addition of cetuximab relative to patients whose tumors had low EGFR expression (H-score  $< 200$ ). Based on these findings and the mechanistic similarity between cetuximab and necitumumab, the applicant explored the relationship between EGFR expression (H-score high  $\geq 200$  vs. H-score low  $< 200$ ) and response to necitumumab in both SQUIRE and INSPIRE. EGFR protein expression was assessed in archived tumor tissue by IHC (Dako EGFR PharmDx kit). The H-score was calculated as = [0 x (% cells with no staining) + 1 x (% cells with staining intensity of +1) + 2 x (% cells with staining intensity of +2) + 3 x (% cells with staining of +3)], resulting in a possible continuous range of H-scores from 0 to 300. Only results from SQUIRE are discussed below, and the results presented correspond to the applicant's analyses and were not replicated by the reviewer.

Archived tumor tissue was available for 1060 / 1093 patients in the intent-to-treat (ITT) population (97.0%). A valid EGFR IHC assay result was available for 982 / 1093 patients (89.8%). There were no relevant differences in terms of baseline demographic and disease characteristics between arms or between the subset of patients included in these analyses and the ITT population. Efficacy outcomes in the EGFR IHC population were similar to those in the ITT population. H-score values were balanced across treatment arms and their distribution is shown in **Table 9**.

**Table 9. H-Score Distribution in SQUIRE**

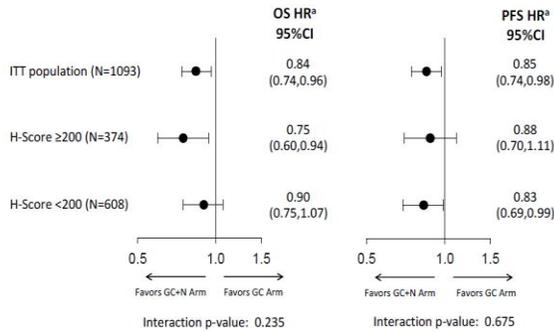
Study	H-score	GC + N (486) N (%)	GC (496) N (%)	Total N (%)
SQUIRE (N = 982)	$\geq 200$	191 (39.3)	183 (36.9)	374 (38.1)
	$< 200$	295 (60.7)	313 (63.1)	608 (61.9)
	$> 0$	462 (95.1)	473 (95.4)	935 (95.2)
	0	24 (4.9)	23 (4.6)	47 (4.8)

GC+N = necitumumab plus gemcitabine and cisplatin; GC = gemcitabine and cisplatin

Source: I4X-IE-JFCC (CP11-0806) CSR Table JFCC 14 59

The majority of patients (95.2%) had EGFR-expressing tumors, in agreement with published literature. The applicant analyses of OS and PFS by H-score ( $\geq 200$  vs.  $< 200$ ) did not show a consistent association, with no treatment-by-cutpoint interaction. A forest plot for OS and PFS by EGFR expression using the cutpoint of 200 ( $\geq 200$  vs.  $< 200$ ) is shown in **Figure 9**. Based on the applicant's analyses, the H-score with a cutpoint of 200 was not predictive of efficacy outcomes (OS, PFS) in SQUIRE.

**Figure 9. Forest Plots of OS and PFS by H-score  $\geq 200$  vs.  $<200$  in SQUIRE**



CI = confidence interval; GC+N = necitumumab plus gemcitabine and cisplatin; GC = gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival

<sup>a</sup> Stratified HR for ITT population; unstratified HR for H-Scores  $\geq 200$  and  $<200$

Source: I4X-IE-JFCC (CP11-0806) CSR Figure JFCC 11 8

An additional exploratory subgroup analysis was conducted to evaluate OS and PFS in a small subset of patients (n = 47) with no detectable EGFR expression (H-score =0). A summary and a forest plot of OS and PFS by H-score ( $>0$  vs. =0) are shown in **Table 10** and **Figure 10**, respectively. The results suggest that patients lacking detectable tumor EGFR protein expression by IHC (H-score =0) do not derive an OS (HR 1.86) or PFS (HR 1.19) benefit from the addition of necitumumab to gemcitabine and cisplatin compared to gemcitabine and cisplatin alone.

**Table 10. Summary of OS and PFS by H-score ( $>0$  vs. =0)**

	H-score $>0$		H-score =0 <sup>d</sup>	
	GC+N N = 462	GC N = 473	GC+N N = 24	GC N = 23
<b>Overall Survival</b>				
p-value <sup>a</sup>		0.004		0.072
HR (95% CI) <sup>b</sup>		0.81 (0.70, 0.93)		1.86 (0.94, 3.65)
Median – months	11.73	9.99	6.47	17.35
Interaction p-value <sup>a</sup>			0.018	
<b>Progression-free Survival</b>				
p-value <sup>a</sup>		0.015		0.611
HR (95% CI) <sup>c</sup>		0.83 (0.72, 0.97)		1.19 (0.61, 2.30)
Median – months	5.72	5.49	4.24	5.59
Interaction p-value <sup>a</sup>			0.305	

CI = confidence interval; GC+N = necitumumab plus gemcitabine and cisplatin; GC = gemcitabine and cisplatin; HR = hazard ratio

<sup>a</sup> p-value obtained from Likelihood Ratio chi-square test of significance

<sup>b</sup> Hazards ratio for death from any cause comparing GC+N to GC within protein expression subgroup Hazards ratio greater than 1 indicates increasing hazards with GC+N compared to GC within protein expression subgroup

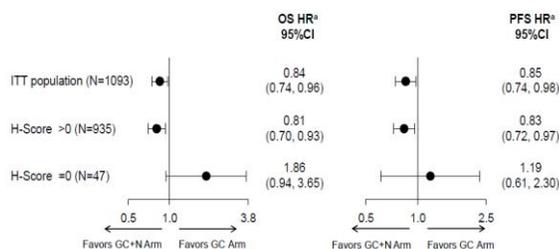
<sup>c</sup> Hazards ratio for death from any cause or progressive disease comparing GC+N to GC within protein expression subgroup

Hazards ratio greater than 1 indicates increasing hazards with GC+N compared to GC within protein expression subgroup

<sup>d</sup> H-score =0 is equivalent to 100% of cells negative for EGFR staining

Source: I4X-IE-JFCC (CP11-0806) CSR Table JFCC 11 13

**Figure 10. Forest Plots of OS and PFS by H-score >0 vs. =0 in SQUIRE**



CI = confidence interval; GC+N = necitumumab plus gemcitabine and cisplatin; GC = gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival

<sup>a</sup> Stratified HR for ITT population; unstratified HR for H-Scores >0 and =0

Source: I4X-IE-JFCC (CP11-0806) CSR Figure JFCC 11 11

**Reviewer Comment:** Although exploratory and of limited sample size (n=47), this particular analysis coupled with the biological plausibility of lacking the target of necitumumab (EGFR) suggests a potential for risk without benefit in patients receiving necitumumab who lack detectable tumor EGFR protein expression.

The applicant presented the results of additional exploratory biomarker analyses that were not included in the BLA submission at the Oncologic Drugs Advisory Committee Meeting on July 9, 2015. Specifically, the applicant evaluated other potential biomarkers related to the EGFR-pathway and necitumumab mechanism of action in SQUIRE, including HER2 and HER3 protein expression (measured by IHC), and EGFR gene copy number (measured by FISH). eCadherin protein expression (by IHC) and fibroblast growth factor receptor 1(FGFR1) gene copy number could be analyzed if the patient provided consent and sufficient tissue was available. In addition, the applicant planned germline polymorphisms (in blood) to be assessed included fragment C gamma receptor (FC $\gamma$ R) polymorphisms (such as FCGR2A and FCGR3A). According to the applicant, the only other marker that showed a potential predictive benefit was EGFR copy number assessed by FISH. The applicant considered this finding to be hypothesis generating as data were only available in 51% of the ITT.

**Reviewer Comment:** Given the benefit-risk profile of necitumumab, the exploration and identification of functional and/or genomic biomarker(s) that are predictive of response to necitumumab in future clinical studies remains important.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

#### 2.3.2.1 Age, Sex and Race

PopPK analysis showed that age (range=19-84 years), sex (75% males) and race (85% Whites) had no significant effect on the exposure to necitumumab (predicted average steady state concentrations ( $C_{ss,ave}$ )).

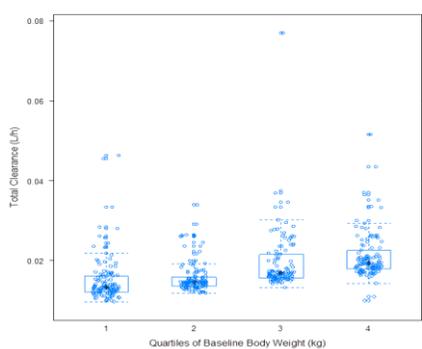
#### 2.3.2.2 Pediatric patients

The safety and effectiveness of necitumumab have not been evaluated in pediatric patients. The Applicant requested a full waiver of pediatric studies for the proposed indication.

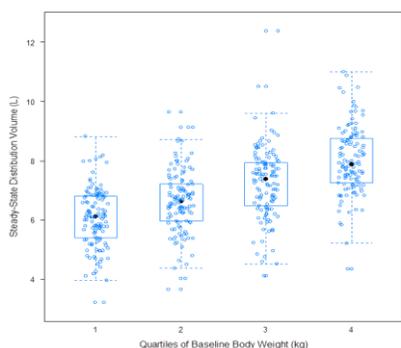
### 2.3.2.3 Body Weight

Body weight was found to be the only significant covariate affecting the PK of necitumumab in the final popPK model, with a less than proportional effect on both  $CL_{tot}$  and  $V_{ss}$  parameter estimates (typical  $CL_{tot}$  ranged from 77% to 131% and typical  $V_{ss}$  from 84% to 120% of median at 5<sup>th</sup> and 95<sup>th</sup> weight percentile in comparison to overall variability (see **Figures 11** and **12**, respectively). Although body weight was a significant covariate, PopPK model simulations suggested that the effect of body weight is not clinically significant as dosing based on body weight would not lead to a decreased variability in PK or an improvement in OS (see **Figure 13** below). In this Figure, it appears that heavier patients had similar OS to lighter patients.

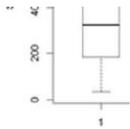
**Figure 11.** Scatter Plot of the Effect of Body Weight on Total Clearance ( $CL_{tot}$ )



**Figure 12.** Scatter Plot of the Effect of Body Weight on Steady State Volume of Distribution ( $V_{ss}$ )



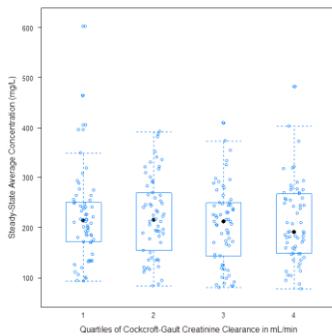
**Figure 13. Overall survival stratified by body weight quartiles for necitumumab arm only and by drug exposure ( $C_{ss,ave}$ ) quartiles as observed in Trial SQUIRE (Applicant's)**



#### 2.3.2.4 Renal impairment

No specific studies of necitumumab in patients with renal impairment have been conducted. As a mAb, necitumumab is not expected to be excreted via the kidney, but rather through proteolytic degradation. Thus renal impairment study is considered unnecessary. PopPK analysis indicates that renal function (as assessed by Cockcroft-Gault creatinine clearance [CGCL=11-250 mL/min]) has no effect on the PK of necitumumab (see **Figure 14**).

**Figure 14. CGCL Versus Exposure ( $C_{ss,ave}$ )**

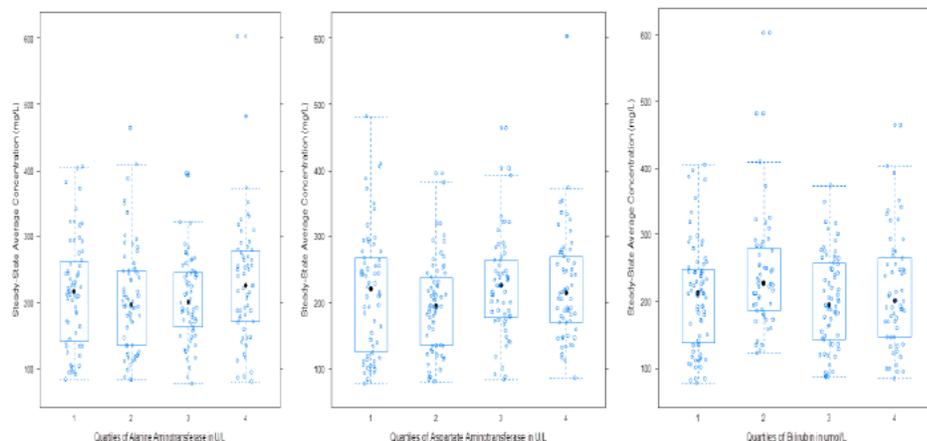


#### 2.3.2.5 Hepatic impairment

No specific studies of necitumumab in patients with hepatic impairment have been conducted. Necitumumab is a mAb that is eliminated by proteolytic degradation not by hepatic CYP enzyme metabolism, thus hepatic impairment study is considered unnecessary.

PopPK analysis indicates that hepatic function (as assessed by alanine aminotransferase [ALT=2-615 U/L], aspartate transaminase [AST=1.2-619 U/L] and total bilirubin [Total Bilirubin=0.1-106  $\mu$ mol/L]) has no effect on the PK of necitumumab (see **Figure 15**).

**Figure 15. ALT, AST and Total Bilirubin Versus Exposure ( $C_{ave,ss}$ )**



**2.3.2.6 What are other factors important to understand the drug's efficacy and safety?**

**Immunogenicity:**

Blood samples were collected in six clinical trials for the analysis of anti-necitumumab antibodies (ADAs). In addition to scheduled samples, samples were taken for ADA assessment in the setting of an infusion-related reaction (IRR), at the onset of the reaction, at the resolution of the reaction, and 30 days following the resolution of the reaction. **Table 11** below shows the sampling schedule for immunogenicity evaluations.

**Table 11: Immunogenicity Sampling Schedule in Clinical Trials**

Trial	Sampling Schedule
JFCA	Cohorts 1 and 3: Prior to 1 <sup>st</sup> infusion, prior to 4 <sup>th</sup> infusion (Cycle 1/Week 5), prior to 1 <sup>st</sup> infusion of Cycles 2 and 4, and 30-day follow-up visit Cohort 2: Prior to 1 <sup>st</sup> infusion, prior to 4 <sup>th</sup> infusion (Cycle 2/Week 7), prior to 1 <sup>st</sup> infusion of Cycles 4, and 30-day follow-up visit
JFCC (SQUIRE)	Arm A only: prior to infusion on Day 1 of Cycles 1, 3, and 5, and 30-day follow-up visit
JFCB (INSPIRE)	Arm A only: prior to infusion on Day 1 of Cycles 1, 3, and 5, and 30-day follow-up visit
JFCD	Screening, prior to the initial necitumumab infusion (Cycle 1) and every other cycle thereafter (Cycles 3, 5, etc), at End of Therapy, and 45 days after the last infusion
JFCE	Prior to initial necitumumab dose in PK sampling period; prior to the final infusion of each treatment cycle; and at 30-day follow-up visit
JFCJ	Prior to the first infusion; Day 1 of Cycles 2, 4, and 6; at 30-day follow-up visit

The immunogenicity results from these studies are summarized in **Table 12**.

**Table 12: Immunogenicity Results for Necitumumab-Treated Patients**

Trial	Baseline Immunogenicity Evaluations				Post-Treatment Immunogenicity Evaluations		
	# of Patients Analyzed (N)	ADA-Positive Patients N (%)	Neutralizing-Antibody-positive patients N (%)	# of Patients Analyzed	ADA-Positive Patients N (%)	TE-ADA-Positive Patients N (%)	Neutralizing-Antibody-positive patients N (%)
JFCA	15	2 (13.3%)	0 (0%)	15	0 (0%)	0 (0%)	0 (0%)
JFCB (INSPIRE)	301	37 (12.3%)	18 (6.0%)	229	13 (5.7%)	9 (3.9%)	6 (2.6%)
JFCC (SQUIRE)	528	81 (15.3%)	5 (0.9%)	448	39 (8.7%)	15 (3.3%)	1 (0.2%)
JFCD	42	6 (14.3%)	1 (2.4%)	40	5 (12.5%)	4 (10.0%)	1 (2.5%)
JFCE	60	12 (20%)	4 (6.7%)	48	11 (22.9%)	4 (8.3%)	3 (6.3%)
JFCJ	35	3 (8.6%)	0 (0%)	34	3 (8.8%)	1 (2.9%)	0 (0%)
<b>Total</b>	<b>981</b>	<b>141 (14.4%)</b>	<b>28 (2.9%)</b>	<b>814</b>	<b>71 (8.7%)</b>	<b>33 (4.1%)</b>	<b>11 (1.4%)</b>

ADA= anti-drug antibodies; NIK = number of patients with immunogenicity data available; TE ADA = treatment-emergent anti- drug antibodies

\*Percentages were calculated using the number of patients with post-treatment immunogenicity samples as the denominator

Of the 981 patients with immunogenicity data reported, 814 patients had samples collected and analyzed after necitumumab treatment (post-treatment immunogenicity evaluations). Seventy-one patients (8.7%) had samples positive for ADAs (post-treatment ADAs positive). Treatment-emergent ADAs (TE-ADAs) were detected for 33 out of 814 patients (4.1%). TE-ADAs are defined as ADA-positive patients who had a post baseline positive response that involved a  $\geq 4$ -fold increase in antibody titer compared to baseline, or in the case of a baseline sample without the presence of antibody [or a missing baseline] a titer  $\geq 1:20$ . Neutralizing-Antibodies (Nab) were observed in 11 patients (1.4%).

In **Trial JFCC**, 528 patients who received necitumumab were analyzed for immunogenicity at any time during the study. The majority (448/528) of patients had both pre- and post-treatment immunogenicity samples evaluated. Of these, 39 patients (8.7%) had post-treatment ADA-positive samples and 15 patients (3.3%) had TE-ADAs during the study. One patient (0.2%) had a NAbs detected.

#### Effect of Immunogenicity on PK

Necitumumab serum concentrations for samples with detected ADAs were generally lower than those in samples negative for ADAs. Individual concentration-time profiles for ADA positive patients are shown in **Figure 16**.

**Figure 16. Necitumumab Concentration-Time Data for Patients Included in the Population PK Analysis Having at Least One Post-treatment ADA Positive Sample (Applicant's)**

An information request (IR) was sent to the Applicant via an email on 26-May-2015 for the following information regarding immunogenicity incidence, evaluation of impact of ADAs on efficacy, safety and PK of necitumumab. The following are the applicant's responses to the IR.

**Immunogenicity Incidence**

**FDA's IR Question #1:** Your proposed labeling states (b) (4)

However, your immunogenicity data report shows (b) (4) incidence of treatment-emergent anti-necitumumab antibodies [33/814 (4.1%)]. Please clarify this discrepancy",

**In response to FDA's Question #1,** the Applicant considered this an error and is committed to revise the labeling to include the following corrected statement:

(b) (4)

**Impact of ADA Formation on the Safety of Necitumumab**

**FDA's IR Question #2:** In your BLA submission, in Module 2.5 Clinical Overview subsection 2.5.3.1.5. *Immunogenicity of Necitumumab*, you state "The development of ADAs, treatment-emergent ADAs, and neutralizing antibodies showed no correlation with safety outcomes. There was no relationship between immunogenicity and IRRs (infusion-related reaction) or treatment-emergent adverse events (TEAEs). Please point out the location of these analyses in your BLA submission or provide report of these analyses.

**In response to FDA's IR Question #2,** the Applicant submitted IRRs data from patients who tested positive for ADAs from five clinical trials (JFCA, JFCB [INSPIRE], JFCC [SQUIRE], JFCD, JFCE AND JFCJ).

**Impact of ADAs on IRRs:** The results are summarized in Table 13. Out of the 981 patients analyzed for immunogenicity, 17 (1.7%) experienced IRRs. Two patients out of 17 (0.2%) who experienced IRRs were tested ADA-positive.

**Table 13: Relationship between Immunogenicity and IRRs**

Trial	# of Patients Analyzed (N)	ADA-Positive Patients N (%)	Experienced IRR (N (%))	Experienced IRR and ADA- Positive
JFCA	15	2 (13.3%)	0 (0%)	0 (0%)
JFCB (INSPIRE)	301	37 (12.3%)	6 (2.0%)	0 (0.0%)
JFCC (SQUIRE)	528	81 (15.3%)	8 (1.5%)	2 (0.38%)
JFCD	42	6 (14.3%)	0 (0.0%)	0 (0.0%)
JFCE	60	12 (20%)	1 (1.7%)	0 (0.0%)
JFCJ	35	3 (8.6%)	2 (5.7%)	0 (0%)
<b>Total</b>	<b>981</b>	<b>141 (14.4%)</b>	<b>17 (1.7%)</b>	<b>2 (0.2%)</b>

**Reviewer Comment:** Based on the data submitted, the incidence of IRRs in clinical trials was generally low (1.7%) with only 0.2% of patients had ADAs detected suggesting TE-ADAs are not associated with observed IRRs.

**Impact of ADAs on Safety besides IRRs:** A summary of treatment-emergent adverse events (TEAEs) for the 81 patients who had at least one positive ADA in Trials SQUIRE is provided in the following Applicant’s **Table APP\_4\_11**. The incidence of most commonly TEAEs in overall population was skin reactions and hypomagnesemia (79% and 31%, respectively in the necitumumab plus gemcitabine and cisplatin treatment arm). In the 81 patients who were tested positive for ADAs, the incidence of skin reaction and hypomagnesemia was 81.5% and 32.1%, respectively. The incidence of rash and hypomagnesemia is similar between patients with positive ADAs and overall population.

**Table APP\_4\_11: Treatment-Emergent Adverse Events**

Dry skin  
Rash genes  
Pruritus  
Rash macul  
Erythema  
Exfoliativ  
Rash prur:  
  
SKIN REACTI  
Rash  
Dermatitis  
Acne  
Dry skin

01111111  
VENOUS THR  
Pulmonar  
Deep vei

**Reviewer Comment:** Based on the safety data submitted, the incidence of skin reaction and hypomagnesemia was 81.5% and 32.1%, respectively, in the 81 patients who were ADA-positive and was similar to the overall population (79% and 31%, respectively).

*Impact of ADA Formation on the PK of Necitumumab*

**FDA's IR Question #3:** In your BLA 2.5 submission, in Module 2.5 Clinical Overview subsection 2.5.3.1.5 *Immunogenicity of Necitumumab*, you state "The low immunogenic profile of necitumumab precludes a definitive analysis of the effect of development of ADAs and treatment-emergent ADAs on the PK of necitumumab." However, your plots of necitumumab exposure (or clearance) versus ADA status (positive or negative) show all ADA positive patients except one had low necitumumab exposure and higher clearance as compared to ADA negative patients. Please provide the magnitude of the difference in exposure and clearance and propose labeling language to describe the impact of ADAs on necitumumab exposure.

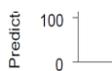
**In response to FDA's IR Question #3,** the Applicant submitted a comparison between total clearance and predicted average steady-state concentrations for patients who had tested for immunogenicity in Trial SQUIRE. The results are summarized in Applicant's **Tables 14** and **Figures 17** and **18** below.

**Table 14: Necitumumab Total Clearance and Predicted Average Steady-State Concentration Stratified by ADA Status for Patients Included in the Exposure-Response Analysis in SQUIRE**

Geo CV<sup>2</sup>  
Median  
90% PI

<sup>a</sup>81 patients in SQUIRE were ADA-positive at any time 77 of those patients were included in the exposure response analysis 4 patients did not have PK data due to lack of post-treatment PK samples

**Figure 17.  $C_{ss,ave}$  Predictions in SQUIRE Stratified by Necitumumab ADA Status**



Plot with data for patients included in exposure response analysis and having ADA data available

**Figure 18. Necitumumab Exposure-Response Curve for Overall Survival Based on Final Model**

The black shaded area is the 95% confidence interval of the increase in median survival time relative to control. The red continuous vertical line is the median  $C_{ss,ave}$  for all patients whilst the red broken lines show the 90% prediction interval of the  $C_{ss,ave}$  for patients in SQUIRE. The blue continuous line is the median  $C_{ss,ave}$  for ADA post treatment positive patients, whilst the blue broken lines show the 90% prediction interval for ADA post-treatment-positive patients in SQUIRE.

Total clearance ( $CL_{tot}$ ) tends to be higher and predicted average serum concentration ( $C_{ss,ave}$ ) from the final PopPK model tends to be lower in patients with ADAs than in those patients without ADAs. Patients with ADAs detected only pre-treatment had 8.8% higher  $CL_{tot}$  and 12.2% lower  $C_{ss,ave}$  than those without ADAs. For patients with ADA detected post-treatment,  $CL_{tot}$  was 26% higher and  $C_{ss,ave}$  was 34% lower than in those without ADAs. Although lower exposure ( $C_{ss,ave}$ ) was associated with the presence of ADAs, the exposure is still within the therapeutic range with significant overlap in  $C_{ss,ave}$  for patients with ADA detected to those without ADAs (**Figure 18**).

Based on the above data, the Applicant proposes the following label language:

(b) (4)

**Reviewer Comment:** Based on the data submitted, there is a higher clearance in patients with detected ADAs than in patients without ADAs.

**FDA's Question #4 (Request for Line Listings):**

Please provide line listing of patient ID and corresponding ADA status (binding and neutralizing antibodies), PK data, efficacy outcome (OS), IRR and major TEAEs in Trial JFCC (SQUIRE) for FDA review and further analyses.

**In response to FDA's Question #4,** the Applicant provided the requested listings for the 81 patients with ADAs from Trial SQUIRE.

## 2.4 EXTRINSIC FACTORS

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**

### 2.4.2 Drug-drug interactions

No studies on the metabolism of necitumumab have been performed *in vitro* or in humans. Like most therapeutic proteins, necitumumab is not expected to be metabolized by liver cytochrome P450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction. Therefore, necitumumab is unlikely to have clinically relevant metabolism-based drug-drug interactions (DDI).

#### 2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

No, as necitumumab is a mAb.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No, as necitumumab is a mAb.

#### 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes? Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No, as necitumumab is a mAb.

#### 2.4.2.4 Are there other metabolic/transporter pathways that may be important?

No. As biologics are degraded into amino acids that then recycled into other proteins, classical biotransformation studies performed for small molecule drugs are generally not needed for biologics.

#### 2.4.2.5 Does the label specify co-administration of another drug (e.g., Combination Therapies in oncology) and, if so, has the interaction potential between these drugs been evaluated?

### Effect of Necitumumab on the PK of Gemcitabine and Cisplatin

The effect of necitumumab on the PK of gemcitabine and cisplatin was assessed in Trial JFCJ, an open-label, non-randomized study in 18 patients with advanced cancers. The study was conducted in two consecutive periods for both cohorts (Cohort 1 and 2): a 3-week PK run-in period and a combination treatment period in each of the cohorts in Cycle 1 and subsequent cycles. Cohort 2 was included for product comparability assessment (b) (4) (see Section 2.5.3 below).

### Three-week PK Run-In Period:

**Cohort 1**, 18 patients were treated sequentially with single doses of gemcitabine and cisplatin and necitumumab alone using drug substance (DS) manufactured (b) (4) at the following doses at cycle one and subsequent cycles:

- Gemcitabine 1250 mg/m<sup>2</sup> as a 30-min IV infusion on **Day 1**
- Cisplatin 75 mg/m<sup>2</sup> as a 2-hour IV infusion on **Day 1**
- Necitumumab 800 mg as 50 min IV infusion on **Day 3**

Intensive PK sampling for necitumumab only was conducted during the PK run-in period, while pre- and post-infusion PK sampling for necitumumab only was performed on Day 1 of cycle 1 (Sampling scheme for this study is presented in Section 2.2.7 above, Table 4).

**Results:**

A summary of PK parameters and a summary of statistical analysis for gemcitabine without (Day 1 of Run-In-Period) or with necitumumab (Day 1 of Cycle 1) are shown in Tables 15 and 16, respectively.

**Table 15: Geometric Mean (%CV) PK Parameters for Gemcitabine Following a Dose of 1250 mg/m<sup>2</sup> over 30 Minutes IV Infusion on Day 1 of Run-In Period (Gemcitabine and Cisplatin Alone Therapy) and on Day 1 of Cycle 1 (Necitumumab plus Gemcitabine and Cisplatin)**

Parameter	Gemcitabine Day 1/Run-In Period (Gemcitabine and Cisplatin)	Gemcitabine Day 1/Cycle 1 (Necitumumab Plus Gemcitabine and Cisplatin)
N	18	12
C <sub>max</sub> (ng/mL)	11500 (69%)	18500 (44%)
C <sub>max</sub> /Dose (ng/mL/mg)	4.8 (66%)	7.8 (43%)
AUC <sub>INF</sub> (ng.h/mL)	6490 (47%)	7890 (37)
AUC <sub>INF</sub> /Dose (ng.h/mL/mg)	2.7 (45%)	3.3 (33%)
t <sub>1/2</sub> (h)	7.59 (5.29 - 12.0)	7.74 (4.35 - 13.6)
CL (L/h)	368 (45%)	301 (33%)
V <sub>ss</sub> (L)	259 (69%)	188 (44%)

\* Geometric mean (range)

**Table 16: Statistical Summary of Treatment Comparison for Gemcitabine**

Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
	Test (Gemcitabine and Cisplatin Plus Necitumumab)	Reference (Gemcitabine and Cisplatin)		
AUC <sub>INF</sub> /Dose (ng.h/mL/mg)	3.3	2.7	1.18	(96%, 146%)
C <sub>max</sub> /Dose (ng/mL/mg)	7.8	4.8	1.65	(118%, 232%)

Coadministration of necitumumab increased the geometric mean dose-normalized AUC<sub>INF</sub> and dose-normalized C<sub>max</sub> for gemcitabine by 22% and 63%, respectively, compared to

coadministration of gemcitabine and cisplatin alone therapy; this may be contributed to the higher toxicity observed with the combination of necitumumab with gemcitabine and cisplatin.

A summary of PK parameters and a summary of statistical analysis for total platinum (from cisplatin) without (Day 1 of Run-In-Period) or with necitumumab (Day 1 of Cycle 1) are shown in Tables 17 and 18, respectively.

**Table 17: Geometric Mean (%CV) PK Parameters for Total platinum (from Cisplatin) Following a Dose of 75 mg/m<sup>2</sup> over 2 Hours IV Infusion on Day 1 of Run-In Period (Gemcitabine and Cisplatin Alone Therapy) and on Day 1 of Cycle 1 (Necitumumab plus Gemcitabine and Cisplatin)**

Parameter	Cisplatin Day 1/Run-In Period (Gemcitabine and Cisplatin)	Cisplatin Day 1/Cycle 1 (Necitumumab Plus Gemcitabine and Cisplatin)
N	18	12
C <sub>max</sub> (ng/mL)	2750 (15%)	3130 (21%)
C <sub>max</sub> /Dose (ng/mL/mg)	19.2 (21%)	22.1 (30%)
AUC <sub>0-5h</sub> (ng.h/mL)	8740 (14%)	9530 (16%)
AUC <sub>0-5h</sub> /Dose (ng.h/mL/mg)	61.5 (20%)	67.3 (24%)

**Table 18: Statistical Summary of Treatment Comparison for Total Platinum (From Cisplatin)**

Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
	Test (Cisplatin and Gemcitabine Plus Necitumumab)	Reference (Cisplatin and Gemcitabine)		
AUC <sub>0-5h</sub> /Dose (ng.h/mL/mg)	67.3	61.5	1.09	(106%, 115%)
C <sub>max</sub> /Dose (ng/mL/mg)	22.1	19.2	1.15	(111%, 125%)

Coadministration of necitumumab increased the geometric mean dose-normalized AUC<sub>0-5h</sub> and dose-normalized C<sub>max</sub> for total platinum (from cisplatin) by 9% and 15%, respectively, compared to coadministration of gemcitabine and cisplatin alone suggesting that the coadministration of necitumumab may not have an effect on the PK of cisplatin when given with gemcitabine.

**Effect of Gemcitabine and Cisplatin on the PK of Necitumumab**

- The popPK analysis of data from 807 patients from 5 clinical trials, including Trial JFCJ, indicates that gemcitabine and cisplatin chemotherapy has no effect on the PK of necitumumab.

- The effect of gemcitabine and cisplatin on the PK of necitumumab was also assessed in Trial JFCJ. A summary of PK parameters and a summary of statistical analysis for necitumumab without (Day 3 of Run-In-Period) or with gemcitabine and cisplatin (Day 1 of Cycle 1) are shown in Tables 19 and 20, respectively.

**Table 19: Geometric Mean (%CV) PK Parameters for Necitumumab Following a Dose of 800 mg over 50 Minutes IV Infusion on Day 3 of Run-In Period (Necitumumab Alone) and on Day 1 of Cycle 1 (Necitumumab Plus Gemcitabine and Cisplatin)**

Parameter	Necitumumab Day 3/Run-In Period (Alone)	Necitumumab Day 1/Cycle 1 (Necitumumab Plus Gemcitabine and Cisplatin)
N	18	12
C <sub>max</sub> (µg/mL)	277 (22%)	330 (23%)
AUC <sub>0-168h</sub> (µg.h/mL)	21864 (24%)	23543 (34%)
t <sub>1/2</sub> (d)	4.87 (2.92 - 7.29)	3.14 (2.61 - 4.00)
CL (mL/h)	23.7 (33%)	30.3 (30%)
V <sub>ss</sub> (L)	3.79 (22%)	3.28 (32%)

\*Geometric mean (range)

**Table 20: Statistical Summary of Treatment Comparison for Necitumumab**

Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
	Test (Necitumumab Plus Gemcitabine and Cisplatin)	Reference (Necitumumab (Alone))		
AUC <sub>0-168h</sub> (µg.h/mL)	23543	21864	1.08	(99%, 117%)
C <sub>max</sub> (µg/mL)	330	277	1.19	(109%, 130%)

Coadministration of gemcitabine and cisplatin with necitumumab increased the geometric mean AUC<sub>0-168</sub> and C<sub>max</sub> for necitumumab by 8% and 19%, respectively, compared to coadministration of gemcitabine and cisplatin alone suggesting that the coadministration of cisplatin and gemcitabine may not have an impact on the PK of necitumumab.

#### **2.4.2.6 What other co-medications are likely to be administered to the target patient population?**

A variety of supportive medicines and nutritional supplements include antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and other supportive care agents are likely to be given to the targeted patient population.

**2.4.2.7 Are there any other in vivo drug-drug interaction (DDI) studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

[None]

**2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

Not applicable because necitumumab is a therapeutic mAb administered by the IV route.

**2.5.2 What is the composition of the to-be-marketed formulation?**

The proposed commercial necitumumab drug product is supplied as a sterile solution at a concentration of 16 mg/mL in 50-mL (800 mg/50 mL) Type I single use glass vials. The drug product is diluted with 0.9% Sodium Chloride Injection (normal saline) prior to administration by intravenous infusion. The composition of necitumumab drug product is provided in **Table 21**.

**Table 21: Composition of Necitumumab Drug Product, 800 mg/50 mL**

Ingredient	Quantity (mg/mL)	Function
Necitumumab	16	Active Ingredient
Sodium Citrate, Dihydrate	2.55	(b) (4)
Citric Acid, Anhydrous	0.256	
Glycine	9.984	
Sodium Chloride	2.338	
Mannitol	9.109	
Polysorbate 80	0.1	
Water for Injection	q.s. (b) (4)	

q.s. = quantity sufficient

**2.5.3 What moieties should be assessed in bioequivalence studies?**

The following Four different processes were used to manufacture necitumumab drug substance (DS) during clinical development:

- (b) (4) used in Trial JFCE (the Phase 1, dose-escalation).
- (b) (4) used in Trial JFCD (Phase 2 combination).
- (b) (4) used in later clinical trials including the Phase 3 Trial JFCC (SQUIRE).
- (b) (4) the proposed commercial manufacturing process for necitumumab drug product and (b) (4) was used in Cohort 2 of Trial JFCJ (a DDI trial).

In response to an FDA's comment at the Type C meeting on 19-Feb-2013 that the comparability of drug products made (b) (4) should be assessed in humans, the Applicant incorporated this assessment during the 3-week Run-In Period of Trial JDCJ by inclusion the following Cohort 2 in the trial:

**Cohort 2**, 17 patients were treated sequentially with single doses of gemcitabine and cisplatin and necitumumab alone using DS manufactured by commercial (b) (4) at the following doses with the same dose regimens in Cohort 1 (see Section 2.4.2.5 above).

The results from this trial are presented in Tables 22 and 23.

**Table 22: Geometric Mean (%CV) PK Parameters for Necitumumab from Drug Product Manufactured (b) (4) Following 800 mg Dose Over 50 Minutes IV Infusion on Day 3 of Run-In Period in Cohort 1 and Cohort 2**

Parameter	(b) (4) Day 3/ Run-In Period (Cohort 1)	(b) (4) Day 3/ Run-In Period (Cohort 2)
N	18	17
C <sub>max</sub> (µg/mL)	277 (22%)	300 (36%)
AUC <sub>0-168h</sub> (µg.h/mL)	21864 (24%)	21580 (30%)
t <sub>1/2</sub> (d)	4.87 (2.92 - 7.29)	5.3 (3.09 - 8.37)
CL (mL/h)	23.7 (33%)	22.5 (35%)
V <sub>ss</sub> (L)	3.79 (22%)	4.05 (35%)

\* Geometric mean (range)

**Table 23: Statistical Summary of Treatment Comparison for Necitumumab**

Parameter	Geometric Mean		Ratio (Test/Reference)	90% CI
	Test (b) (4)	Reference (b) (4)		
AUC <sub>0-168h</sub> (µg.h/mL)	21580	21864	0.99	(84%, 115%)
C <sub>max</sub> (µg/mL)	300	277	1.08	(92%, 128%)

The PK parameters for necitumumab using DS manufactured (b) (4) were similar. The ratio of geometric means for AUC<sub>0-168h</sub> was close to 1 with 90% CI within the 80-125%. Although the upper limit of 90% CI for C<sub>max</sub> is 128% (>125%), this difference is not considered clinically important.

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

Not applicable.

**2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?**

Not applicable.

**2.6 ANALYTICAL SECTION**

**2.6.1 Were the active moieties identified and measured in the clinical pharmacology studies?**

Serum concentrations of the active moiety, necitumumab, were measured in clinical pharmacology trials. In Trial JFCJ, plasma samples were analyzed for gemcitabine and its inactive metabolite, 2',2'-difluorodeoxy-uridine (dFdU) and for total platinum (from cisplatin).

**2.6.2 What bioanalytical procedures and methods were used to determine drug concentrations? Are they acceptable for this BLA?**

**Necitumumab:** Originally, a surface plasmon resonance (Biacore) assay method was developed by ImClone and was used in early trials (Trials JFCD and JFCE). Subsequently, an enzyme-linked immune-sorbent assay (ELISA) method was developed for the determination of serum necitumumab concentrations and was used in other trials including the Phase 3 Trial JFCC (SQUIRE). Although the principle of both assays is similar in that necitumumab is binding to its functional ligand, EGFR, there are differences inherent in the conduct of each assay. For instance, EGFR is covalently immobilized to the Biacore sensor chip whereas it is non-covalently adsorbed to the ELISA plate. In the Biacore, the mass of necitumumab binding to the sensor chip is directly measured by change in a physical phenomenon (surface plasmon resonance) whereas in the ELISA assay an indirect quantitation using secondary antibody-enzyme conjugates and colorimetric readouts are utilized to quantitate bound necitumumab.

**Cross-Comparison:** Serum samples from Trial JFCA were used to conduct a cross-comparison of the serum concentrations analyzed using these two bioanalytical assay methods. A total of 400 samples from Trial JFCA initially assayed using the Biacore bioanalytical method were subsequently re-analyzed using the ELISA bioanalytical method. A pre-specified acceptance criterion for determining comparability was the demonstration of the percent difference of (b) (4) % in measured serum necitumumab concentrations between the two assay methods for at least 2/3 of the samples (i.e., 267 samples). This cross-comparison analysis between the two assays showed that the serum necitumumab concentrations obtained using the Biacore method were not comparable to the concentrations obtained using ELISA method based on the pre-specified criterion. The concentrations produced by the Biacore bioanalytical method (b) (4) than those produced by the ELISA bioanalytical method. The percent difference of (b) (4) % was observed in 209 out of 400 samples (52.3%).

In addition, the Biacore assay was not adequately validated as per the FDA Guidance for Bioanalytical Method Validation (FDA 2001). As the lack of comparability between the two assay methods and the deficiencies in the Biacore validation method, ELISA assay method was considered more robust and reliable and was used for definitive PK analysis. The PK data from the Biacore assay method were only used as supportive evidence (Trials JFCD and JFCE).

**Gemcitabine:** In Trial JFCJ, gemcitabine and its inactive metabolite, 2',2'-difluorodeoxy-uridine (dFdU), were measure in plasma samples using a LC-MS/MS method.

**Cisplatin:** In Trial JFCJ, total platinum (from cisplatin) concentrations in plasma samples were analyzed using an Inductively Coupled Plasma Mass Spectrometry (ICP-MS) assay method.

**2.6.4.1** *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

**2.6.4.2** *What are the lower limits of quantification (LLOQ)?*

**2.6.4.3** *What are the accuracy, precision, and selectivity at these limits?*

**2.6.4.4** *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

**Necitumumab:**

- **ELISA Assay Validation:** The calibration curve was linear over the serum concentration range of 1.75-25.0 µg/mL. The LLOQ was 1.75 µg/mL. The inter-assay precision, as expressed as % relative standard deviation (%RSD) ranged from 4.1% to 9.6%. The intra-assay precision (% RSD) ranged from 2.0% to 10.5%. The inter-assay accuracy (%RE) ranged from -6.6% to 6.8%. The intra-assay accuracy (%RE) ranged from -7.9% to 13.1%. Necitumumab in human serum was stable following 5 freeze/thaw cycles at approximately -70°C, and at room temperature and at refrigerated temperature (between 2°C to 8°C) for at least 24 hours. Necitumumab in serum was stable for up to 24 months (749 days) when stored at approximately -70°C.
- **Gemcitabine:** The calibration curves were linear over plasma concentration range of 0.25-100 ng/ml for gemcitabine and 1.0-1000 ng/mL for dFdU. The LLOQ was 0.25 ng/mL for gemcitabine and 1.0 ng/mL for dFdU. Samples above the limit of quantification were diluted to yield results within the calibrated range. The inter-assay accuracy (% relative error) ranged from -5.2% to -0.3% for gemcitabine and -3.5% to 1.2% for dFdU. The inter-assay precision (% relative standard deviation) ranged from 2.1% to 7.6% for gemcitabine and 4.9% to 8.4% for dFdU. Gemcitabine and dFdU were stable for approximately 3 months when stored -20°C.
- **Cisplatin:** The calibration curve for total platinum (from cisplatin) was linear over plasma concentration range of 50-2000 ng/mL. The LLOQ was 50 ng/mL. Samples above the limit of quantification were diluted to yield results within the calibrated range. The inter-assay accuracy (% relative error) ranged from -3.5 % to 1.1 %. The inter-assay precision (% relative standard deviation) ranged from 1.1 % to 2.5 %. Platinum was stable for up to 12 months when stored at approximately -20°C.

**3. OCP LABELING RECOMMENDATIONS**

Edits were made in Sections 6.2, 7 and 12.3 of the labeling. The left hand column of the table is the language from the Applicant's proposed package insert. The right hand column of the table is the edits made to the Applicant's proposed labeling by the clinical pharmacology team, in concurrence with the clinical team. The entirety of the Applicant's proposed package insert is appended to this review (Appendix 4.1).

Applicant's Proposed Labeling	Clinical Pharmacology Reviewer's Revisions to Applicant's Proposed Labeling
<p data-bbox="152 380 626 625">6.2 Immunogenicity  <span style="background-color: gray; color: gray;">(b) (4)</span>  <span style="background-color: gray; color: gray;">[Redacted]</span>  <span style="background-color: gray; color: gray;">[Redacted]</span></p> <p data-bbox="152 995 626 1262">The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to PORTRAZZA with the incidences of antibodies to other products may be misleading.</p>	<p data-bbox="646 380 1123 604">6.2 Immunogenicity  As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, <span style="background-color: gray; color: gray;">(b) (4)</span>  <span style="background-color: gray; color: gray;">[Redacted]</span>  <span style="background-color: gray; color: gray;">[Redacted]</span></p> <p data-bbox="646 604 1123 968">Treatment-emergent ADAs were detected in 4.1% (33/814) of patients. Neutralizing antibodies were detected in <span style="background-color: gray; color: gray;">(b) (4)</span> 1.4% (11/814) of patients at post <span style="background-color: gray; color: gray;">(b) (4)</span>  <span style="background-color: gray; color: gray;">[Redacted]</span>  <span style="background-color: gray; color: gray;">[Redacted]</span>  -No relationship was found between the presence of ADAs and incidence of infusion related reactions. The impact of <span style="background-color: gray; color: gray;">(b) (4)</span> overall survival could not be assessed due to limited number of patients with treatment-emergent ADAs. In Study 1, the exposure to necitumumab was lower in patients with <span style="background-color: gray; color: gray;">(b) (4)</span>  <span style="background-color: gray; color: gray;">[Redacted]</span>  <i>[see Clinical Pharmacology (12.3)].</i></p> <p data-bbox="646 995 1123 1262">The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to PORTRAZZA with the incidences of antibodies to other products may be misleading.</p> <p data-bbox="1084 1272 1123 1293" style="text-align: right;"><span style="background-color: gray; color: gray;">(b) (4)</span></p>
<p data-bbox="152 1465 626 1486">8 USE IN SPECIFIC POPULATIONS</p>	<p data-bbox="646 1465 1123 1486">8 USE IN SPECIFIC POPULATIONS</p> <p data-bbox="646 1514 1123 1688"><b>8.6 Renal Impairment</b>  No formal studies have been conducted to evaluate the effect of renal impairment on the exposure to necitumumab. Renal function has no influence on the exposure to necitumumab based on the population pharmacokinetic analysis of data from clinical trials. <i>[see Clinical Pharmacology (12.3)].</i></p>



Applicant's Proposed Labeling	Clinical Pharmacology Reviewer's Revisions to Applicant's Proposed Labeling
<p>(b) (4)</p> <p>Renal Impairment — (b) (4)</p>	<p>(b) (4)</p> <p><i>Renal Impairment —</i></p> <p>(b) (4)</p>
<p>Hepatic Impairment — (b) (4)</p>	<p><i>Hepatic Impairment —</i></p> <p>(b) (4)</p>
<p>Drug Interaction Studies — (b) (4)</p>	<p>Drug Interaction: (b) (4)</p>
	<p><i>Effect of Necitumumab on Gemcitabine and Cisplatin</i></p> <p><u>In 12 patients with advanced solid tumors who received gemcitabine and cisplatin in combination with PORTRAZZA, the geometric mean dose-normalized AUC of gemcitabine was increased by 22% and C<sub>max</sub> increased by 63% compared to administration of gemcitabine and cisplatin alone while exposure to cisplatin was unchanged.</u></p> <p><i>Effect of Gemcitabine and Cisplatin on Necitumumab</i></p> <p><u>Concomitant administration of gemcitabine</u></p>

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Applicant's Proposed Labeling	Clinical Pharmacology Reviewer's Revisions to Applicant's Proposed Labeling
	<p><u>and cisplatin had no effect on the exposure of necitumumab.</u></p> <p><u><b>Immunogenicity</b></u></p> <p><u>In Study 1, the CL<sub>tot</sub> of necitumumab was 26% higher and C<sub>0.5, AVE</sub> was 34% lower in patients with (b) (4)</u></p>

**4 APPENDICES**

- 4.1 Appendix 1 - Applicant's Proposed Labeling**
- 4.2 Appendix 2 - Analytical Method Validation**
- 4.3 Appendix 3 - Pharmacometrics Review**
- 4.4 Appendix 4 - OCP Filing Memo**

**Attachment 1: QTc-IRT Review**

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**OFFICE OF CLINICAL PHARMACOLOGY:  
PHARMACOMETRIC REVIEW**

BLA Number	125547
Drug Name	PORTRAZZA™ (necitumumab)
Dose Regimen	800 mg (absolute dose) administered as an intravenous infusion over (b) (4) minutes on Days 1 and 8 of each 3-week cycle
Indication	Necitumumab as an epidermal growth factor receptor (EGFR) antagonist, used in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung (NSCLC)
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Secondary Reviewer	Yaning Wang, Ph.D.
Sponsor	Eli Lilly and Company

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## 1 SUMMARY OF FINDINGS

The Phase III pivotal trial for this BLA was JFCC conducted in squamous non-small cell lung cancer (NSCLC) patients. The primary efficacy endpoint of JFCC was overall survival duration (OS). Based on sponsor’s exposure-response (E-R) analysis on the OS data of JFCC, the dose regimen of 800 mg necitumumab was reasonable for the proposed indication. This dose regimen was identified as the maximum tolerable dose (MTD) in JCFE, the Phase I dose-escalation study conducted in patients with advanced solid tumors.

Baseline ECOG was identified as a confounder for the exposure-OS relationship, ECOG0-1 being associated with longer OS than ECOG2.

Based on FDA reviewer’s exploratory E-R analysis on the safety data of JFCC, there appeared to be an E-R relationship for hypomagnesemia, higher necitumumab exposure being correlated with higher hypomagnesemia rate. Although necitumumab arm showed higher rates than the placebo arm for Grade3+ hypomagnesemia, Grade3+ rash, Grade3+ venous and Grade3+ arterial thromboembolic events, there appeared to be no E-R relationship for any of those adverse events (AEs).

### 1.1 KEY REVIEW QUESTIONS

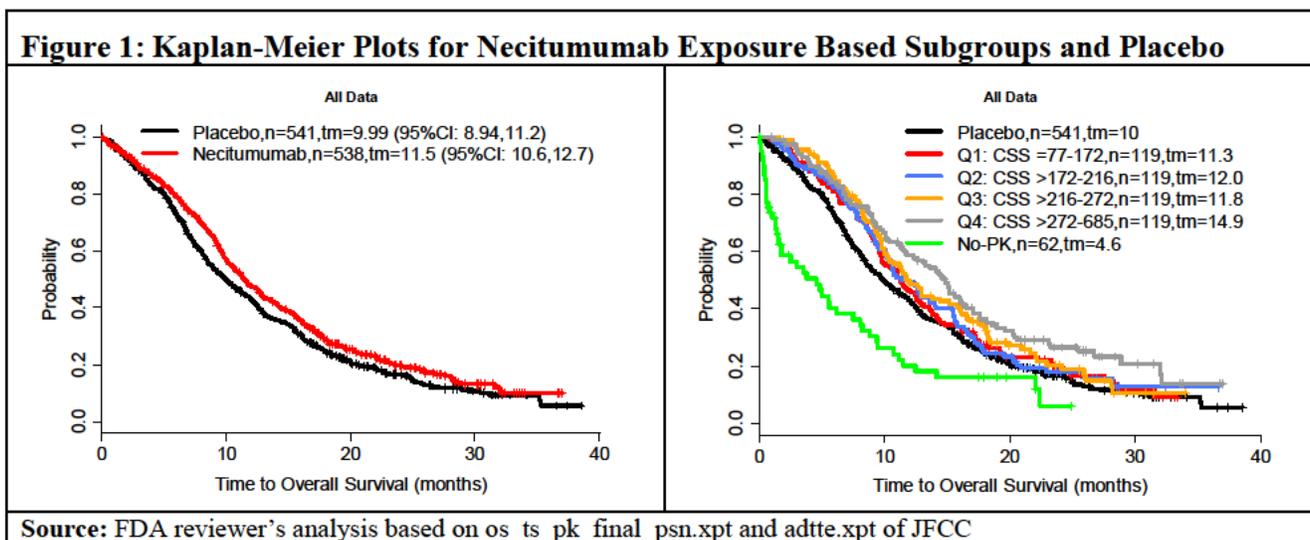
The purpose of this review is to address the following key questions.

#### 1.1.1 Does E-R relationship support the proposed dose regimen: 800 mg IV infusion on Days 1 and 8 of every 3-week cycle?

Based on sponsor’s E-R analysis on the OS data of Study JFCC (the Phase III pivotal trial conducted in the squamous NSCLC patients for this BLA), the dose regimen of 800 mg necitumumab was reasonable.

The primary efficacy endpoint of JFCC was OS. The median OS ( $t_m$ ) was 9.9 months for the placebo arm and 11.5 months for necitumumab arm (**Figure 1**). The steady-state mean serum concentrations ( $C_{ss,ave}$ ) of necitumumab for Quartiles (Q) 1-4 were 77-172, 172-216, 216-272 and 272-685  $\mu\text{g/mL}$  (upper bound inclusive), respectively. As shown in the right panel of **Figure 1**, the  $t_m$  values were 11.3, 12.0 and 11.8 months for Q1-3, respectively, all close to 11.5 months--the  $t_m$  for the whole necitumumab arm. In contrast, Q4 showed the longest  $t_m$  of 14.9 months. It should be noticed that, these four subgroups based on  $C_{ss,ave}$  are not randomized and the distribution of known risk factors such as ECOG across these four subgroups is unbalanced as

shown in Figure 2. In addition, there were 62 patients with missing PK data, who are referred to as No-PK patients in this review. No-PK patients showed the shortest  $t_m$  of 4.6 months. The  $t_m$  value highly correlates with ECOG as shown in **Figure 2**; Q4 had the most ECOG0-1 patients with the longest  $t_m$ , while No-PK group had the most ECOG2 patients with the shortest  $t_m$  in the 6 groups.



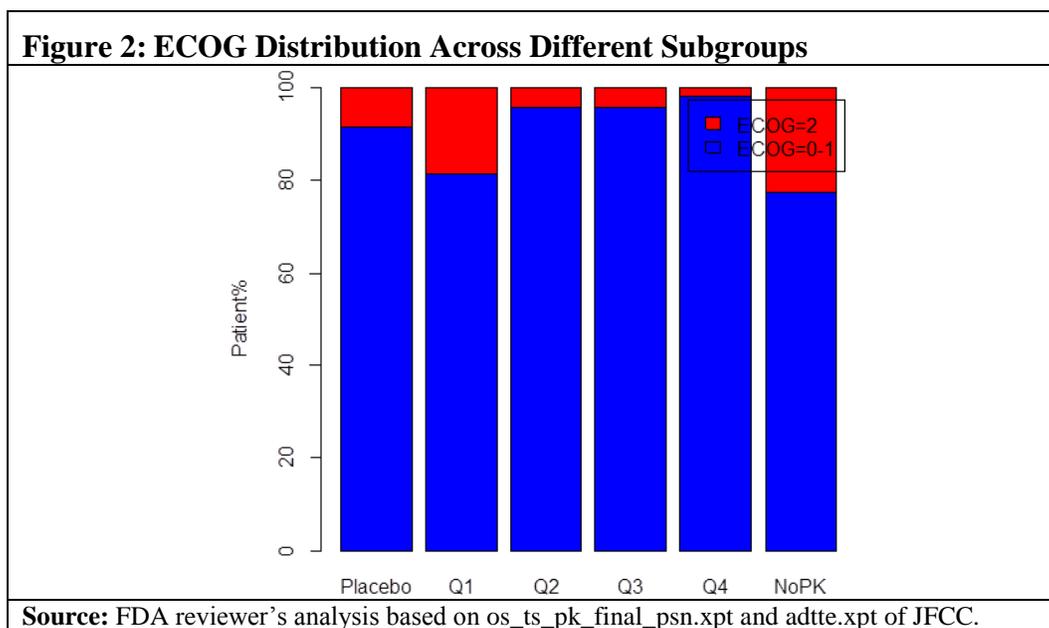
Sponsor's original E-R analysis excluded No-PK patients and included baseline ECOG as the covariate in the baseline tumor model. The impact of ECOG on OS was incorporated through the longitudinal tumor response, which was dependent on the baseline tumor size and modeled as a combination of exponential shrinking process and a linear growth process. The shrinking process also included a delayed resistance that reduced the shrink rate over time in an exponential way. The hazard for time-to-OS was modelled as a function of both the longitudinal tumor size and the exposure through an independent  $E_{max}$  model. The predicted  $C_{ss,ave}$ -OS profile is presented in the left panel of **Figure 3**. The population median of the maximum OS effect ( $E_{max}$ ) was estimated to be 63 days, i.e., the difference between 399 days for necitumumab and 336 days for the placebo. At the population median predicted necitumumab  $C_{ss,ave}$  of 216  $\mu\text{g/mL}$ , an increase in survival time of about 60 days relative to control was estimated. The sponsor converted this increase of 60 days to a model predicted hazard ratio of 0.85, which was compared to the observed value of 0.84. However, the comparison of 60 days to the observed OS differences from the two data sources indicated that the predicted OS difference underestimated the observed OS difference from the data used to build the model and overestimated the observed OS difference from the complete data (**Table 1**).

The reviewer believed that the discrepancy between the predicted OS difference and the observed OS difference from the complete data could be due to the exclusion of the No-PK patients from the E-R analysis. Upon the FDA's request, the sponsor reanalyzed the exposure-

OS data by including the No-PK patients, for whom the  $C_{ss,ave}$  values were predicted using the final population pharmacokinetics model. The new exposure-OS profile is shown in the right panel of **Figure 3**, with  $E_{max}$  estimated to be 42 days (i.e., the difference of 385 days for necitumumab and 343 days for the placebo). At the population median predicted necitumumab  $C_{ss,ave}$  of 216  $\mu\text{g/mL}$ , an increase in survival time of about 42 days relative to control was estimated. This estimate is more consistent with the observed effect of 48 days. However, the median OS times (estimated 343 days vs observed 311 days for placebo arm; estimated 385 days versus observed 359 days for necitumumab arm) are over-estimated for both arms even though the difference (42 days) is closer to the observed value (48 days).

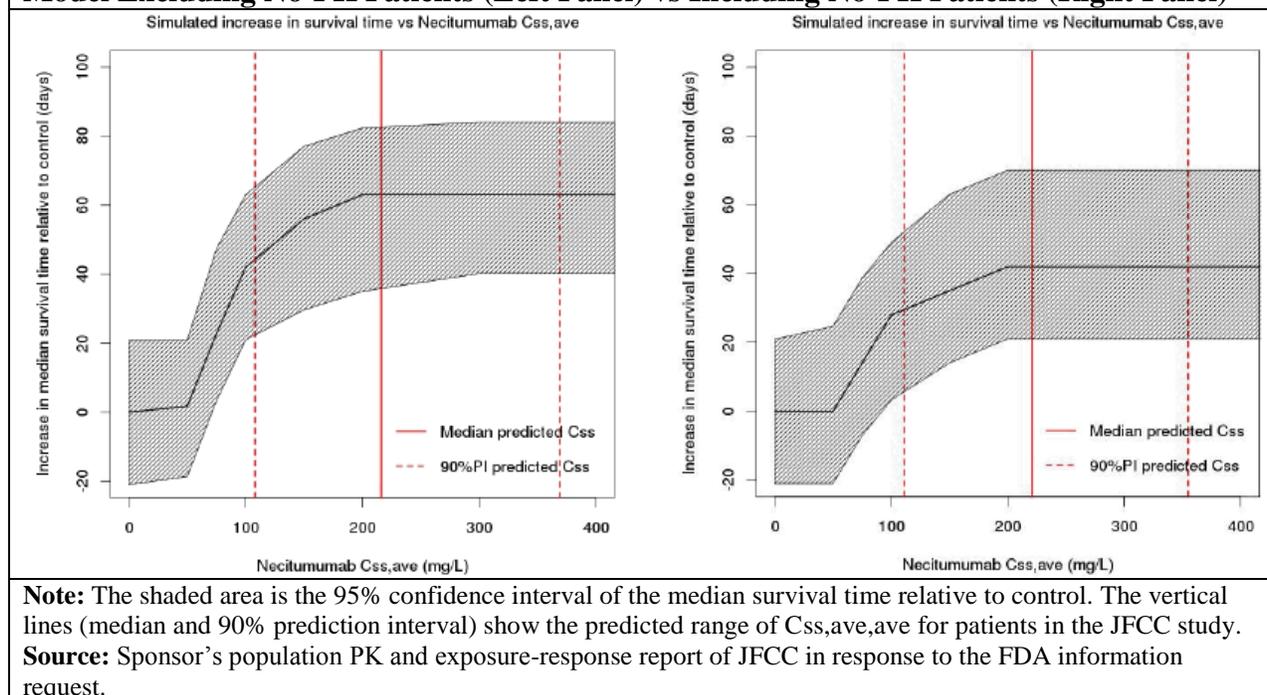
**Table 1: Median Overall Survival Time Comparison**

Data	Placebo	Necitumumab	Difference
Data Excluding No-PK Patients	311	385	74
Data Including No-PK Patients	311	359	48



As shown in both panels of **Figure 3**, the 90% predicted interval (PI) of  $C_{ss,ave}$  for the 800 mg dose regimen was 110-360  $\mu\text{g/mL}$ , an exposure range covering the efficacy range of 70%-100%  $E_{max}$  in the  $C_{ss,ave}$ -OS curve. In other words, the  $C_{ss,ave}$ -OS relationship demonstrated that the 800 mg dose regimen would result in an OS of 70-100%  $E_{max}$ , therefore the regimen is reasonable from the primary efficacy perspective.

**Figure 3: Necitumumab Exposure-Response Curve for Overall Survival Based on Final Model Excluding No-PK Patients (Left Panel) vs Including No-PK Patients (Right Panel)**



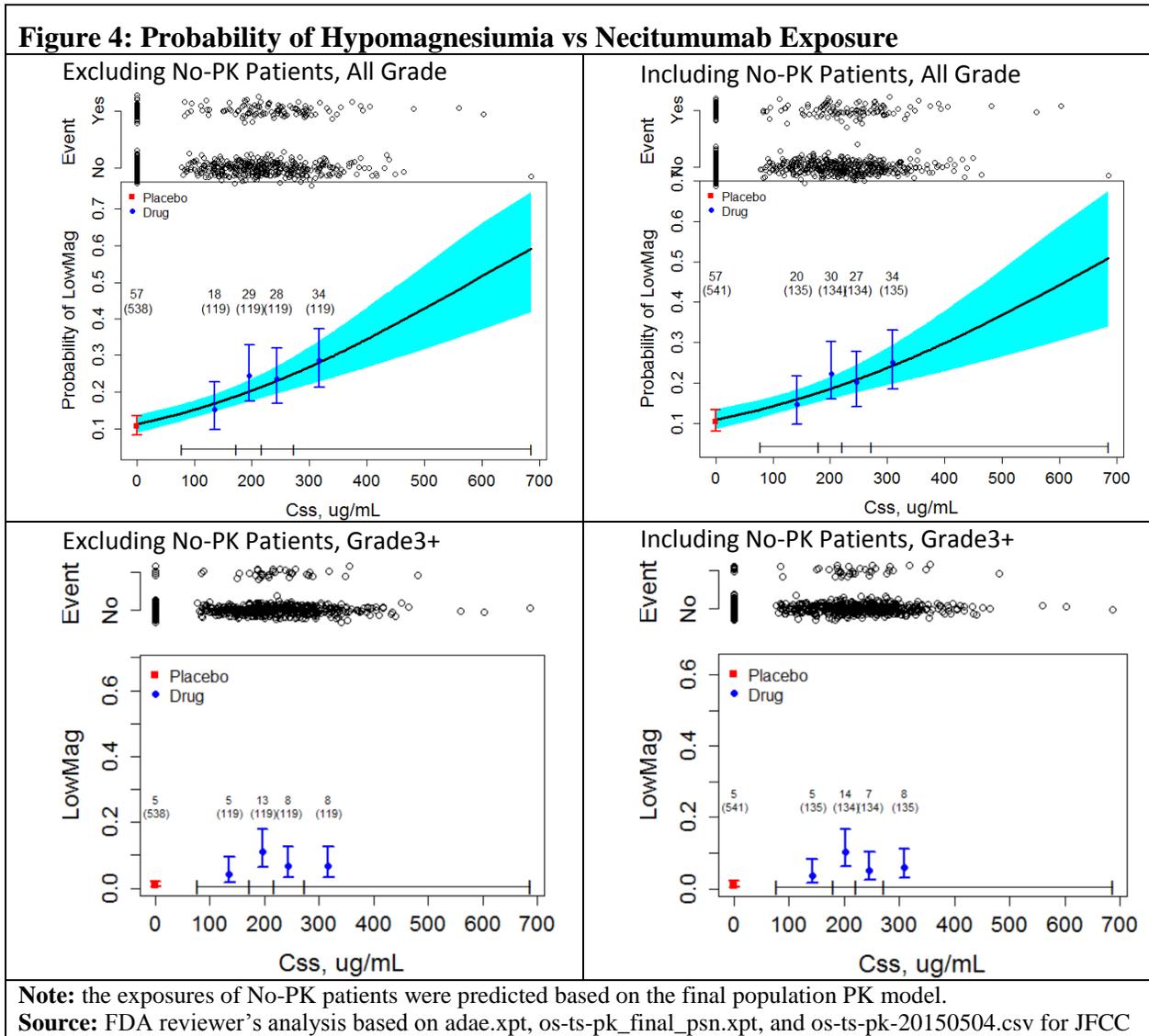
Refer to FDA reviewer's comments about the limitation of the sponsor's exposure-OS analysis at the end of Section 3. This limitation did not affect the relative exposure-OS relationship. The overall flat exposure-safety data, as shown in Section 1.1.3 of this review, also support necitumumab 800 mg dose regimen.

### 1.1.2 Given the apparent exposure-OS relationship, are there any confounders for that relationship?

Baseline ECOG was identified as the confounder for the exposure-OS relationship; in general ECOG0-1 associates with longer OS and ECOG2 associates with shorter OS. As shown in **Figure 2**, Q4 was the subgroup with the most ECOG0-1 patients, which had the longest OS ( $t_m=14.9$  months) in Study JFCC. In contrast, No-PK was the subgroup with the least ECOG0-1 patients, which had the shortest OS ( $t_m=4.6$  months) in the study. ECOG, as a confounder of exposure-OS for necitumumab, was considered in the sponsor's exposure-OS analysis.

**1.1.3 Are there any exposure-response relationships for drug related Grade3+ AEs (such as rash, hypomagnesemia, arterial/venous thromboembolic events)?**

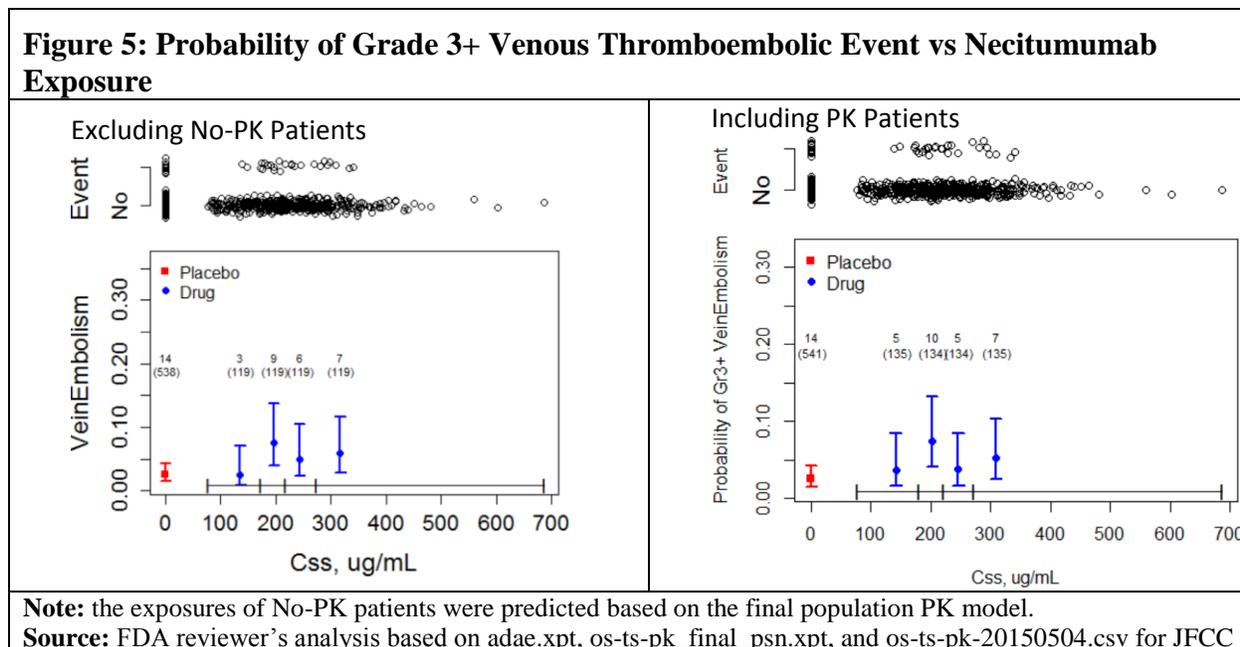
In JFCC, there appeared to be an E-R relationship for hypomagnesemia; higher necitumumab exposure correlated with higher hypomagnesemia rate. There appeared to be no E-R relationship for any these four AEs: Grade3+ hypomagnesemia, Grade3+ rash, Grade3+ venous or Grade3+ arterial thromboembolic event in the study.



When No-PK patients were excluded, there appeared to be an E-R relationship for all grade hypomagnesemia (left upper panel of **Figure 4**) but no relationship for Grade 3+ hypomagnesemia (left lower panel of **Figure 4**). For all hypomagnesemia grades, the rates were 15%, 24%, 24% and 29% for Q1, Q2, Q3 and Q4, respectively, versus 11% for the placebo arm.

For Grade 3+ hypomagnesemia, the rates were 4%, 11%, 7% and 7% for Q1, Q2, Q3 and Q4, respectively, versus 0.9% for the placebo arm. The results remained similar when No-PK patients were included in the analysis (right panels of **Figure 4**). Necitumumab increased hypomagnesemia rates significantly whether all grade or Grade3+ was considered.

As for Grade 3+ venous thromboembolic events, there appeared to be no E-R relationship whether No-PK patients were excluded (left panel of **Figure 5**) or included (right panel of **Figure 5**). The response rate of necitumumab arm was numerically higher than the placebo arm.

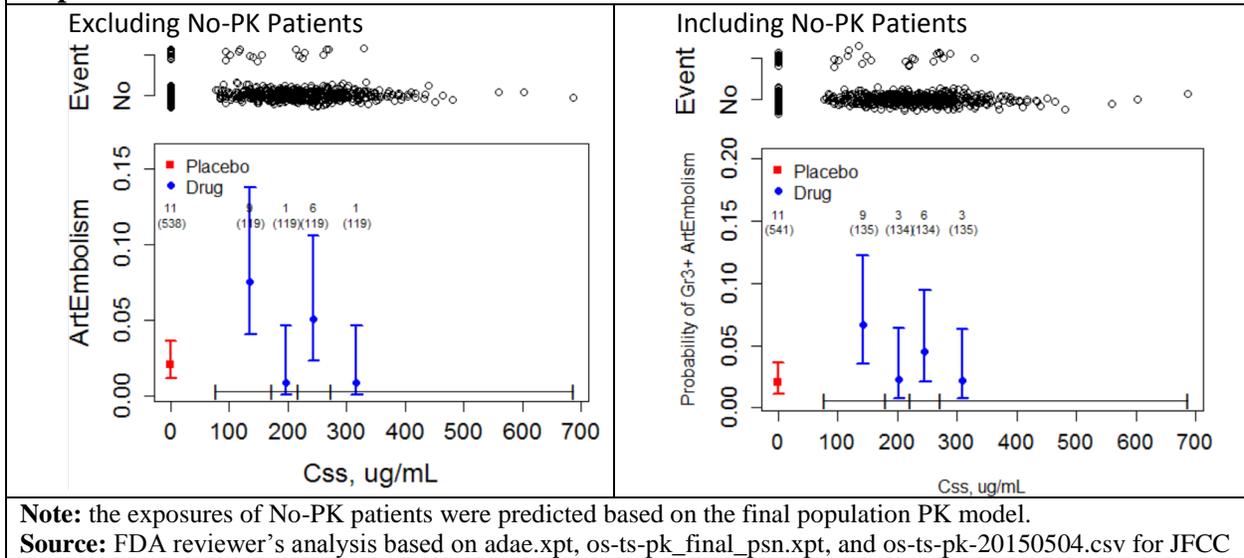


As for Grade 3+ arterial thromboembolic events, there appeared to be no E-R relationship whether No-PK patients were excluded (left panel of **Figure 6**) or included (right panel of **Figure 6**). The overall response rate for necitumumab arm was higher than the placebo arm.

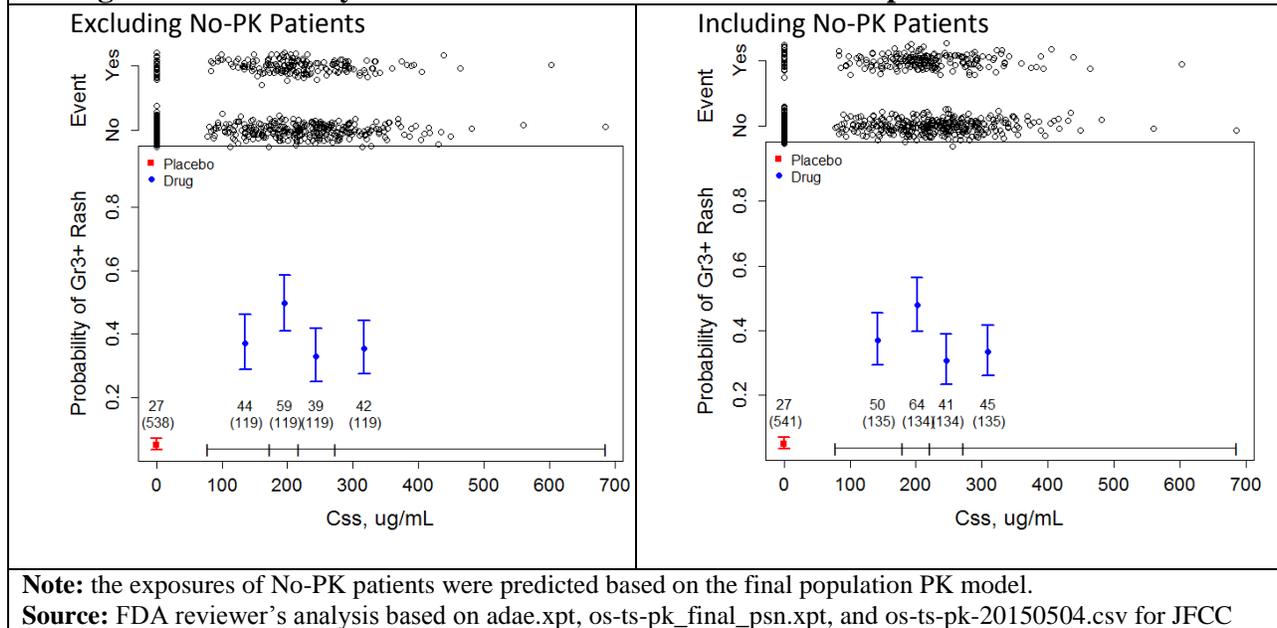
As for Grade 3+ rash, there appeared to be no E-R relationship whether No-PK patients were excluded (left panel of **Figure 7**) or included (right panel of **Figure 7**), although the response rates for all Q1-4 were significantly higher than the placebo arm.

In summary, there appeared to be an E-R relationship for hypomagnesemia. No E-R relationship was identified for any of these four AEs: Grade 3+ hypomagnesemia, Grade 3+ rash, Grade 3+ venous or Grade 3+ arterial thromboembolic event in Study JFCC.

**Figure 6: Probability of Grade 3+ Arterial Thromboembolic Event vs Necitumumab Exposure**



**Figure 7: Probability of Grade 3+ Rash vs Necitumumab Exposure**



## 1.2 RECOMMENDATIONS

None

## **2 PERTINENT REGULATORY BACKGROUND**

Necitumumab is a recombinant human IgG1 monoclonal antibody that binds with high affinity and specificity to the human epidermal growth factor receptor (EGFR) and blocks the ligand binding site, blocking activation by all known ligands and inhibiting relevant biological consequences in-vitro. Activation of EGFR has been correlated with malignant progression, induction of angiogenesis and inhibition of apoptosis or cell death. In addition, necitumumab induces EGFR internalization and degradation in vitro. In vivo studies in mouse xenograft models of human cancer, including non-small cell lung carcinoma, demonstrate that necitumumab has antitumor activity both as a single agent and in combination with gemcitabine and cisplatin.

The initial Investigational New Drug (IND) application (IND 102512) for necitumumab in solid tumors was submitted for US Food and Drug Administration (FDA) review on 17 November 2008. The following are key regulatory events pertaining to the clinical development of necitumumab in combination with gemcitabine and cisplatin, for treatment of patients with advanced or metastatic NSCLC. Copies of pertinent FDA meeting minutes can be found in Module 1.6.3.

Phase 3 SQUIRE Protocol: The SQUIRE protocol was submitted on 21 September 2009. The FDA letter dated 05 November 2009 provided comments but included no revision to the primary endpoint, choice of control arm, key inclusion/exclusion criteria, or statistical design.

Supplemental Pharmacokinetic (PK) Data: On 31 March 2014, FDA feedback was received noting that an additional PK comparability study is not necessary to support the description in the Biologics License Application (BLA) filing of drug product manufactured using drug substance produced (b) (4) as the commercial drug product.

SQUIRE pre-BLA meeting: On 23 June 2014, Lilly met with FDA to discuss and reach agreement on content and format for the SQUIRE BLA.

## **3 RESULTS OF SPONSOR'S ANALYSIS**

### **3.1 PIVOTAL TRIAL (STUDY JFCC)**

Study JFCC (I4X-IE-JFCC) was a global, Phase 3, randomized (1:1), open-label trial of necitumumab plus placebo (gemcitabine-cisplatin) versus placebo. Through this trial, necitumumab plus placebo was developed as the first-line treatment for Stage IV squamous Non-Small Cell Lung Cancer. The primary objective was to evaluate the OS and the secondary objectives were to evaluate PFS (time to disease progression), objective response rate (ORR), time to treatment failure (TTF), safety and toxicity profile, PK and immunogenicity of necitumumab. The median OS was 11.5 months (95% CI: 10.6, 12.7) for the necitumumab plus placebo arm and 9.9 months (95%CI: 8.9, 11.2) for the placebo arm. The 1.6 months difference

in median OS demonstrated a statistically significant and clinically meaningful improvement with necitumumab plus placebo treatment with a HR of 0.84 (95%CI: 0.74, 0.96) at p-value=0.012. The Grade  $\geq 3$  treatment-emergent adverse events (preferred terms) with highest incidence for which incidence was higher in the necitumumab arm than in the control arm were hypomagnesemia (8.7% vs. 1.1%), rash (3.7% vs. 0.2%), pulmonary embolism (3.5% vs. 1.8%), hypokalemia (3.0% vs. 1.5%), and vomiting (2.8% vs. 0.9%).

### 3.2 SPONSOR'S POPULATION PHARMACOKINETICS AND E-R ANALYSIS

#### 3.2.1 Studies Included in the Analysis

Population PK data of necitumumab were obtained from five Phase 1, 2 and 3 studies (JFCA, JFCB, JFCC, JFCI, and JFCJ). The cancer indication, necitumumab dose and dosing regimen, PK sampling schedule and number of patients for each study are summarized in **Table 2**. Overall, the dose and dosing regimen of necitumumab was either 600 mg or 800 mg on Day 1 and Day 8 of 21-day cycle. The cancer indications consisted of advanced solid tumor, nonsquamous and squamous non-small cell lung cancer.

<b>Table 2: Summary of Six Studies Included in the Population PK analysis</b>				
<b>Study Code</b>	<b>Design</b>	<b>Treatment (infusion duration or rate) [Cycle length]</b>	<b>Necitumumab PK Timepoints (post end of infusion)</b>	<b>N<sub>PK</sub></b>
<b>14X-IE-JFCA</b> [IMCL CP11-0907]  A Phase 1 Study of IMC-11F8 in Patients with Advanced Solid Tumors	Phase 1, single-agent, dose-escalation study in Japanese patients	<u>Cohort 1:</u> Necitumumab 600 mg ( $\leq 25$ mg/min), D1 D8 Q3W  <u>Cohort 2:</u> Necitumumab 800 mg ( $\leq 25$ mg/min), Q2W  <u>Cohort 3:</u> Necitumumab 800 mg ( $\leq 25$ mg/min), D1 D8 Q3W  [6W]	<b>Cohorts 1 and 3:</b> <u>C1, D1 (I1):</u> P, E, 0.5, 1, 2, 6, 24, 96 h <u>C1, D8 (I2) and D22 (I3):</u> P, 1 h <u>C1, D29 (I4):</u> P, E, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 264 h <u>C2+, D1 D8:</u> P, 1 h <u>30d follow up</u>  <b>Cohort 2:</b> <u>C1, D1 (I1) and D29 (I3):</u> P, E, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 264 h <u>C1, D15 (I2):</u> P, 1h <u>C2+, D1, D15, and D29:</u> P, 1h	15
<b>14X-IE-JFCJ</b> [IMCL CP11-1115] <sup>a</sup>  An Open-Label, Non-controlled, Non-randomized Sequential Design, Drug-Interaction Study of Necitumumab (IMC-11F8) in Combination with Gemcitabine-Cisplatin in Patients with Advanced Solid Cancers	Open-label, single-arm study (Phase 2)	<u>3-week PK run in period:</u> Gemcitabine 1250 mg/m <sup>2</sup> (30 min), D1 Cisplatin 75 mg/m <sup>2</sup> (2 h), D1 Necitumumab 800 mg (50 min), D3  <u>Cycles 1-6:</u> Necitumumab 800 mg (50 min), D1 D8 Q3W Gemcitabine 1250 mg/m <sup>2</sup> (30 min), D1 D8 Q3W Cisplatin 75 mg/m <sup>2</sup> (2 h), D1 Q3W  [3W]	<u>PK run in period, D3:</u> P, E, 0.5, 1, 3, 6.7, 24, 72, 168 h <u>C1, D1<sup>b</sup>:</u> P, E, 0.5, 1, 3, 6.7, 24, 72, 168 h <u>C2-C6, D1:</u> P, 1 h	35

<b>14X-IE-JFCI [IMCL CP11-1114]</b>  A Study to Determine Whether Necitumumab (IMC-11F8) Monotherapy Affects the Corrected QT (QTc) Interval in Patients With Advanced Solid Tumors	Multicenter, open-label, single-arm monotherapy study (Phase 2)	Necitumumab 800 mg (50 min) QW  [6W]	C1, D1 and D36; P, E, 1, 2, 4, 24, 48, 72 h C1, D8, D15, D22, and D29; P, E, 1, 2, 4 h C2-C4 D1; P, E	40
<b>14X-IE-JFCC [IMCL CP11-0806] SQUIRE</b>  A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3, randomized, open-label study	<u>Arm A:</u> Necitumumab 800 mg (≥50 min), D1 D8 Q3W Gemcitabine 1250 mg/m <sup>2</sup> (30 min), D1 D8 Q3W Cisplatin 75 mg/m <sup>2</sup> (2 h), D1 Q3W  <u>Arm B:</u> Gemcitabine 1250 mg/m <sup>2</sup> (30 min), D1 D8 Q3W Cisplatin 75 mg/m <sup>2</sup> (2 h), D1 Q3W  [3W]	<u>Arm A</u> C1-C6, D1; P 30d follow up	470  N <sub>ITT</sub> = 545 (Arm A); 548 (Arm B)
<b>14X-IE-JFCB [IMCL CP11-0805] INSPIRE</b>  A Randomized, Multicenter, Open-Label Phase 3 Study of Pemetrexed-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Pemetrexed-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Nonsquamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3, randomized, open-label study	<u>Arm A:</u> Necitumumab 800 mg (≥50 min), D1 D8 Q3W Pemetrexed 500 mg/m <sup>2</sup> (10 min) D1 Q3W Cisplatin 75 mg/m <sup>2</sup> (2h) D1 Q3W  <u>Arm B:</u> Pemetrexed 500 mg/m <sup>2</sup> (10 min) D1 Q3W Cisplatin 75 mg/m <sup>2</sup> (2h) D1 Q3W  [3W]	<u>Arm A</u> C1-C6, D1; P 30d follow up	247  N <sub>ITT</sub> = 315 (Arm A); 318 (Arm B)

Abbreviations: C# = Cycle # (ie, C1 = Cycle 1); D# = Day # (ie, D8 = Day 8); E = end of infusion; I# = Infusion # (ie, I1 = Infusion 1); N<sub>ITT</sub> = number of patients in intent-to-treat population; N<sub>PK</sub> = number of patients included in the population PK analysis; P = pre-infusion; Q2W = once every 2 weeks; Q3W = once every 3 weeks; QW = once every week

a Study JFCJ had 2 cohorts: Cohort 1 received DP using DS manufactured using (b) (4) while the Cohort 2 received DP using DS manufactured using (b) (4) Necitumumab PK sampling for Cohort 2 on Day 1 of Cycle 1 was scheduled for pre-infusion, 1 and 168 hours post end of infusion.  
(Source: Table 7.1 on Pages 21-22 of population PK meta-analysis and E-R analysis of study JFCC)

Population PK of necitumumab was evaluated in a total of 6021 evaluable necitumumab concentrations obtained from 920 patients. Out of these data, 113 patients and 1101 serum data of necitumumab were excluded in the population PK analysis with reasons detailed in **Table 3**.

**Table 3: Summary of Necitumumab Data for the Population PK Analysis**

Study	Data Counts (Number of Patients/Number of Observations)							
	Excluded Data							VIII Included in analysis
	I Available source data	II Sample age >36 months	III Necitumumab concentrations obtained prior to first recorded dose	IV Lack of adequate dosing information	V Implausible <sup>a</sup> necitumumab concentrations	VI Different concentrations reported for same patient/date/time	VII Non-quantifiable necitumumab concentrations	
JFCA	15/466	--	15/15	--	1/8	--	--	15/443
JFCB	301/1168	1/2	283/283	3/4	--	--	36/58	247/821
JFCC	529/2457	2/5	502/504	--	--	1/2	81/119	470/1827
JFCI	40/1255	--	39/41	--	--	--	2/2	40/1212
JFCJ	35/675	--	35/53	--	--	--	4/5	35/617
Total	920/6021	3/7	874/896	3/4	1/8	1/2	123/184	807 <sup>b</sup> /4920

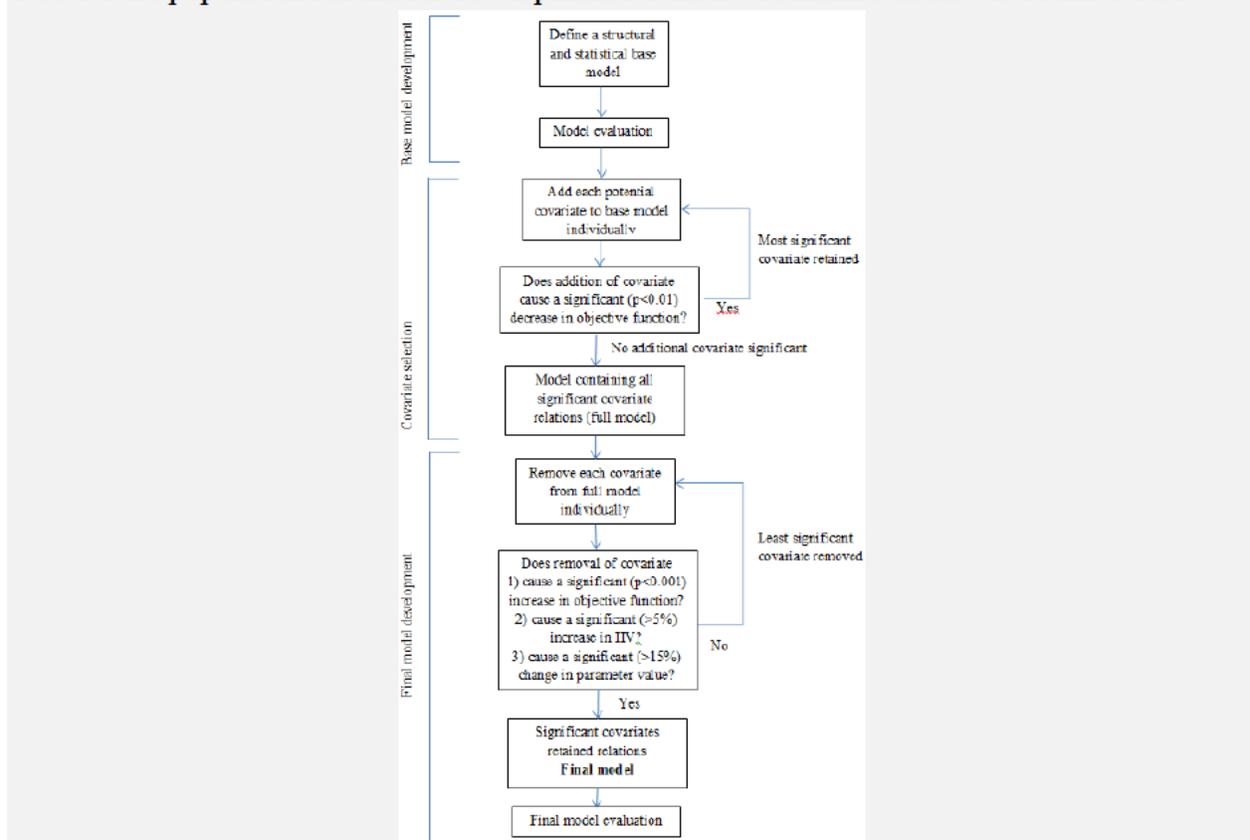
<sup>a</sup> Concentration reported at predose higher than that reported 1-h post end of infusion; or high concentrations reported following sample reported BQL with no additional dosing recorded.  
<sup>b</sup> An additional 15 patients in the dataset had dosing information and only concentrations which were not included in the analysis.  
(Source: Table 7.2 on Page 24 of population PK meta-analysis and E-R analysis of study JFCC)

**Exposure-Efficacy Analysis:** The exposure-efficacy analysis included OS and tumor size data from the necitumumab plus gemcitabine and cisplatin arm and gemcitabine and cisplatin arm from Study JFCC. Five patients who did not have any tumor size data were excluded from the joint model of OS and tumor size. Data from patients in the necitumumab plus gemcitabine and cisplatin arm were included in the exposure efficacy analysis only if exposure measures were available. Data from a total of 1014 patients were included in the exposure-efficacy analysis, 538 of whom were in the gemcitabine and cisplatin arm, whilst 476 were in the necitumumab plus gemcitabine and cisplatin arm.

**Exposure-Safety Analysis:** The exposure-safety analysis included data from the necitumumab plus gemcitabine and cisplatin arm and the gemcitabine and cisplatin arm from Study JFCC. Data from patients in the necitumumab plus gemcitabine and cisplatin arm were included in the exposure-safety analysis only if exposure measures were available. For exposure-safety analysis, data from a total of 1014 patients were included in the analysis, 538 of whom were in the gemcitabine and cisplatin arm, whilst 476 were in the necitumumab plus gemcitabine and cisplatin arm.

### 3.2.2 Population PK and E-R Model Development

Population PK analyses were performed using NONMEM (Version 7.3). The general process used for the population PK model development for the necitumumab dataset is outlined below:



Selection of the most appropriate PK base model was based upon agreement between predicted and observed serum concentrations, lack of pattern (that is, randomness) in the weighted residuals versus the predicted values, non-positive average changes in the inter-patient variability and significant decreases in the MOF.

Once a structural and statistical model was established, the effect of patient factors was assessed for their clinical relevance on the disposition of necitumumab. Covariate testing was performed without eta correlation to limit inclusion bias.

Stepwise covariate modeling (SCM) was implemented using Perl-Speaks NONMEM (PsN) (Lindbom et al. 2005) for remaining demographic, liver function, disease state, and concomitant medication covariates. The criterion for forward inclusion was a p-value no greater than 0.01 ( $\Delta 6.635$  MOF for inclusion of one parameter) with a backward deletion threshold of 0.001 ( $\Delta 10.828$  MOF) for exclusion of one parameter). The final model was developed using the following criteria:

- Convergence of the estimation and covariance routines
- Reasonable parameter and error estimates based upon the known pharmacokinetics of the compound
- Good precision of the parameter and error estimates
- Statistically significant difference in MOF, criterion:  $\geq 10.828$  point drop in MOF ( $p < 0.001$ )
- Decrease in the inter-subject variability in the relevant parameters of  $> 5\%$
- Agreement between predicted and observed plasma concentrations, as assessed by visual inspection
- Random distribution of the weighted residuals versus the predicted values, as assessed by visual inspection
- Clinical relevance of the change in the parameter estimate caused by the addition of the covariate in the model. Covariate parameter effect being  $> 15\%$  difference for a dichotomous covariate or a  $> 15\%$  covariate effect at the highest or lowest observed value for a continuous variable.

**Overall Survival and Tumor Growth Inhibition:** Overall survival was described using a time to event modeling approach implemented using NONMEM Version 7.3 with the Stochastic Approximation Expectation-Maximization (SAEM) estimation algorithm. Models were executed using PsN. Various hazard models were tested including exponential, Weibull, Gompertz, combined Weibull and Gompertz, and log-logistic distributions of event times. The survival was calculated as the inverse of the exponent of the cumulative hazard from time=0 to time=j in the study according to the following equation:

$$Surv_t = e^{-\int_{t_0}^t haz_t \cdot dt}$$

Where  $Surv_t$  was the survival at time  $t$  and  $haz_t \cdot dt$  was the hazard. The likelihood of death at time  $t$  (probability density function, pdf) was calculated as follows:

$$pdf = haz_t \times Surv_t$$

Therefore, for individuals who died at time= $t$  in the study had their pdf at that time estimated, whilst those who survived (or were censored) had their survival at time= $t$  estimated. Patient demographic covariates tested on the baseline hazard included:

- Geographical region that is, Region 1 (North America, Europe and Australia) versus region 2 (South America, South Africa and India) versus region 3 (Eastern Asia). Other classifications were also tested including East Asian versus non-East Asian; and Eastern Europe versus Eastern Asian versus the rest of the world.
- Race (white versus non-white)
- Sex
- ECOG performance status at enrollment (0, 1 or 2)
- Smoking history (non-smoker or light ex-smoker versus smoker)
- Histological subtype (basaloid, clear cell, small cell, papillary or other)

As tumor size may be a significant predictor of survival, a model describing the change in tumor size (CTS) with time in the study was implemented and combined with the OS model. Throughout this document, tumor size in the model refers to the sum of the longest diameters of the target lesions. Target lesions were defined as all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Change in tumor size was determined from a summation of tumor growth and tumor shrinkage. Various growth models were tested including linear, exponential and Gompertz growth, whilst a first order process was used to describe tumor shrinkage. Differential equations describing these models are shown below:

$$\frac{dSize}{dt} = Size_0 \cdot e^{-shrink \cdot t} \cdot (-shrink) + growth \quad ; \text{linear growth and first order shrinkage}$$

$$\frac{dSize}{dt} = -shrink \times Size_t + growth \times Size_t \quad ; \text{exponential growth and first order shrinkage}$$

$$\frac{dSize}{dt} = -shrink \times Size_t + growth \times \log\left(\frac{Size_{max}}{Size_t}\right) \quad ; \text{Gompertz growth and first order shrinkage}$$

Where  $Size_0$  is the baseline tumor size,  $Shrink$  is the first order exponential decrease in the size of the tumor,  $growth$  is the growth rate constant and  $Size_{max}$  is the maximum possible tumor size. The development of resistance was tested by means of a time-dependent reduction in the first order process of tumor shrinkage as shown below:

$$Shrink_t = Shrink_0 \times e^{-resist \times t}$$

Where  $Shrink_t$  is the first order shrink rate of the tumor at time,  $t$ ,  $Shrink_0$  is the shrink rate at the beginning of treatment, and  $resist$  is the rate of decline of the shrink rate. The tumor size at any time during treatment was then tested as a predictor of the hazard of death at the corresponding time in a model simultaneously describing OS and CTS.

Due to numerical difficulties with the Laplacian estimation algorithm, the SAEM method was used for the integrated OS-CTS model. Where parameters were mu-referenced and inclusion of variability was not desired (for example,  $EC_{50}$ ), a fixed value of 15% inter-individual variability was used to optimize the efficiency of the SAEM search algorithm (NONMEM Users Guide 2011). Since the MOF derived from SAEM is not suitable for hypothesis testing, the SAEM estimation process was followed by an evaluation step using importance sampling (IMP) to obtain an MOF that can be used for model comparison (NONMEM Users Guide 2011). Due to the Monte Carlo noise in the MOF derived from expectation-maximization methods, values were interpreted with caution and changes in the MOF were viewed in light of improvements in other model evaluation tools, including convergence, VPCs and goodness of fit plots (for tumor size data). The Monte Carlo noise in the IMP MOF was also kept to a minimum by increasing the number of random samples per subject (ISAMPLE) to 12000 such that MOF would oscillate by an average of about 1-3 points between iterations in the IMP evaluation step. Fifteen iterations of the evaluation step were carried out for each model, and the MOF for a model would be calculated as the average MOF from iteration 10 to 15, whereupon it would have stabilized.

The final PK model was used to obtain individual patient posthoc PK parameters. Using the mean dose a patient received in the study (some patients had dose reductions initiated by the clinic investigator for various reasons) and the individual PK parameters, an average steady state concentration was obtained for each patient ( $C_{ave,ss}$ ). For graphical exploration and presentation purposes  $C_{ave,ss}$  data was stratified in exposure quartiles for treatment arm, resulting in five stratas; placebo (i.e. control arm), Q1, Q2, Q3 and Q4. Since the final model had a non-linear component to it, the (quasi)  $C_{ave,ss}$  was obtained by integrating the drug concentration between the 10<sup>th</sup> and 11<sup>th</sup> cycle of necitumumab administration then dividing by the time interval (504 h). The drug concentration ( $C_{ave,ss}$ ) was then tested in the integrated OS-CTS model using sigmoidal maximum effect models as shown below:

$$DrugEffect = 1 + \frac{E_{max} \times Conc^{Hill}}{EC_{50}^{Hill} + Conc^{Hill}}$$

The drug effect was tested as a fractional decrease (-) in the baseline hazard for the OS and as a fractional increase (+) in the first order shrink rate of the tumor (separate  $E_{max}$  and  $EC_{50}$  estimated). Difficulties were encountered in estimating the hill coefficient therefore values fixed to 1 (ordinary  $E_{max}$  model), 2, 5, 10 and 15 were tested.

**Thromboembolic Events:** Arterial and venous thromboembolic events were recorded based on the adverse event of special interest (AESI) definition (I4X-IE-JFCC CSR). The time to onset of an arterial thromboembolic event was described using time to event modeling. The Laplacian estimation algorithm in NONMEM was used. Various hazard models including exponential, Weibull, Gompertz and log-logistic distributions of event times were tested. Similar to OS described above, the pdf was calculated for patients who had a thromboembolic event and survival was estimated for patients who did not have an event (right-censored). Due to unavailability of data with regard to the censoring time, patients who did not experience any thromboembolic event were censored at the final time that they were in the study.

Stepwise covariate modeling (SCM) implemented using PsN was used for covariate testing (including drug effect). The criterion for forward inclusion was a p-value no greater than 0.01 with a backward deletion threshold of 0.001. Apart from MOF-based criteria, covariates were retained in the model if they were precisely estimated and the confidence intervals for the parameter did not include zero.

Patient demographic covariates tested on the baseline hazard included:

- Geographical region that is, Region 1 (North America, Europe and Australia) versus region 2 (South America, South Africa and India) versus region 3 (Eastern Asia). Other classifications were also tested including Eastern Asian versus non-Eastern Asian; and Eastern Europe versus Eastern Asian versus the rest of the world.
- Race (white versus non-white)
- Sex
- Smoking history (non-smoker or light ex-smoker versus smoker)

In addition to the covariates listed above, study arm (presence or absence of necitumumab administration) was tested, as well as individual drug exposure ( $C_{\min,ss}$ ,  $C_{\text{ave},ss}$ ) using linear and maximum effect models respectively as shown below:

$$\text{StudyArmEffect} = 1 + \theta \times \text{ARM}$$

$$\text{DrugEffect} = 1 + \frac{E_{\max} \times \text{Conc}}{EC_{50} + \text{Conc}}$$

Where ARM had a value of zero (control arm) or 1 (necitumumab arm). Venous thromboembolism was modeled in the same manner as arterial thromboembolism as described above. When suitable, the same stratification according to exposure quartiles

**Hypomagnesemia:** Two approaches were used in the analysis of the occurrence of hypomagnesemia in the study. The first included developing a model to predict the grade of the first incidence of hypomagnesemia that a patient experienced. The second approach included developing a model to predict the highest grade of hypomagnesemia that a patient experienced for those patients who had one or more hypomagnesemia event recorded. In each case, a

proportional odds model was developed to describe the likelihood of occurrence of the various grades of hypomagnesemia in the study. This likelihood was estimated using logit transformations to constrain the values to be between 0 and 1 as shown in the equations below:

$$LOGIT = \theta_1$$

$$L = \frac{e^{LOGIT}}{1 + e^{LOGIT}}$$

Where  $\theta_1$  represents the estimated value of the logit parameter for a particular grade of hypomagnesemia and L is the likelihood of a patient experiencing hypomagnesemia of that grade.

Since there were several possible grades of hypomagnesemia (0-4), the logits were calculated from values which were coded as shown below:

$$B_1 = \theta_1$$

$$B_2 = B_1 + \theta_2$$

$$B_3 = B_2 + \theta_3$$

$$B_4 = B_3 + \theta_4$$

$B_{1-4}$  would then be used to calculate the probability of a particular grade as shown below:

$$Like_n = \frac{e^{B_n}}{1 + e^{B_n}}$$

where  $like_n$  is the likelihood of having greater than or equal to grade n of hypomagnesemia

The probability of a particular grade of hypomagnesemia was then calculated as follows:

$$P_0 = 1 - like_1$$

$$P_1 = like_1 - like_2$$

$$P_2 = like_2 - like_3$$

$$P_3 = like_3 - like_4$$

$$P_4 = like_4$$

Where  $P_0$ ,  $P_1$ ,  $P_2$ ,  $P_3$  and  $P_4$  are the probabilities of no hypomagnesemia, grade 1, 2, 3, and 4 respectively

Covariates tested on the base values of the logit parameters ( $B_{1-4}$ ) included the following:

- Geographical region that is, Region 1 (North America, Europe and Australia) versus region 2 (South America, South Africa and India) versus region 3 (Eastern Asia). Other classifications were also tested including East Asian versus non-East Asian, and Eastern Europe versus Eastern Asian versus the rest of the world.
- Race (white versus non-white)
- Sex

In addition to the covariates listed above, study arm (presence or absence of necitumumab administration) was tested, as well as individual drug exposure ( $C_{\min,ss}$  and  $C_{\text{ave},ss}$ ) using linear and maximum effect models respectively as shown below:

$$\text{StudyArmEffect} = \theta \times \text{ARM}$$

$$\text{DrugEffect} = \frac{E_{\max} \times \text{Conc}}{EC_{50} + \text{Conc}}$$

where ARM had a value of zero (control arm) or 1 (necitumumab arm), and  $E_{\max}$  and  $EC_{50}$  were parameters that were estimated accordingly.

Since the covariates, study arm and drug effect were being tested on logits, they were tested in an additive manner as exemplified below:

$$\text{LOGIT} = \theta_1 + \text{COV}$$

Where COV is the covariate relationship of interest.

This translates to a proportional effect in the untransformed domain. Only statistically significant parameters were kept in the model ( $\geq 10.828$  drop in MOF ( $p < 0.001$ ) for backward inclusion). Standard errors from the NONMEM covariance step were obtained as measures of parameter precision. Parameters were kept in the model if the RSE was less than 30% and the confidence interval did not include zero. Visual predictive checks were used for model evaluation.

**Rash:** Similar to hypomagnesemia, two analysis approaches were used for rash, one describing the grade of the first episode, and another describing the most severe grade a patient experienced during the study. The modeling procedure, covariates tested and model evaluation was conducted in a manner identical to that described for hypomagnesemia above. Visual predictive checks were used for model evaluation.

### 3.2.3 Population PK and E-R Results

**Final POP-PK Model:** After application of pre-specified inclusion/exclusion criteria, only patient body weight remained as a significant covariate for clearance and volume parameters. Parameters were estimated to be less than proportionally dependent on weight; for clearance parameters the power coefficient was estimated to 0.768 and for volume parameters 0.498. The population pharmacokinetic parameters  $CL$ ,  $K_m$ ,  $V_{\max}$ ,  $V_1$ ,  $V_2$ , and  $Q$  were well estimated, as were the covariate body weight effects. Final parameter estimates are shown in Table 4.

The goodness of fit plots for the final population PK model is shown in **Figure 8**. Post hoc estimates of  $CL$ , volume of distribution at steady-state ( $V_{ss}$ ) and terminal half-life ( $t_{1/2}$ ) were derived for all patients and their mean values [95% coefficient of variation (CV)] are listed in Table 5.

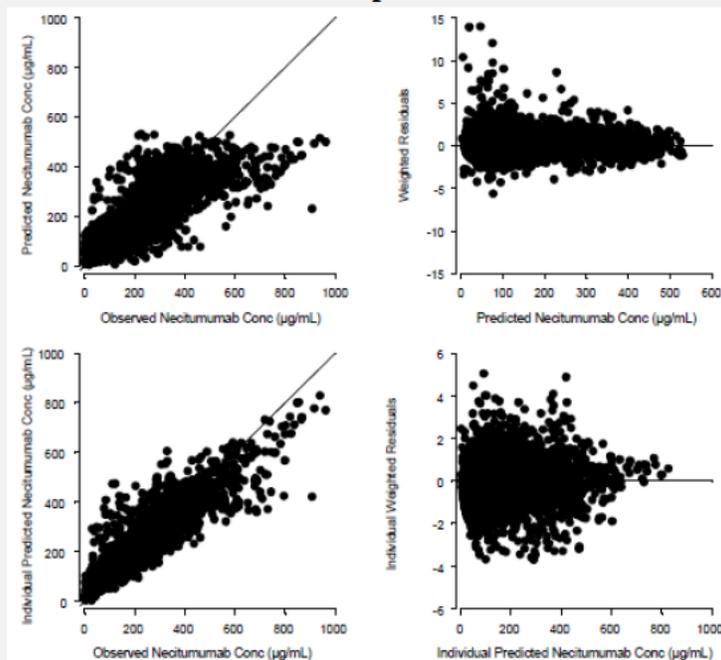
**Table 4: Population PK Parameters for Necitumumab in Final Model**

Parameter Description	Population Estimate (%RSE)	Inter-Patient Variability (%RSE)
Clearance <sup>a</sup> (CL <sub>tot</sub> )		28.8% (10.5)
CL (L/h)	0.0114 (4.0)	
K <sub>m</sub> (µg/mL)	7.97 (24.1)	
V <sub>max</sub> (mg/h)	0.565 (13.2)	
Central Volume of Distribution, V <sub>1</sub> (L) <sup>b</sup>	3.41 (2.9)	21.1% (18.8)
Inter-compartmental Clearance, Q (L/h)	0.0183 (8.3)	
Peripheral Volume of Distribution, V <sub>2</sub> (L) <sup>b</sup>	3.29 (4.1)	55.4% (20.7)
Weight-CL <sup>c</sup> and Q <sup>d</sup>	0.768 (8.7)	
Weight-V <sub>1</sub> <sup>e</sup> and V <sub>2</sub> <sup>f</sup>	0.498 (15.7)	
Inter-Patient Variability Correlation Coefficient (CL <sub>tot</sub> and V <sub>1</sub> )		0.609 (19.4)
Residual Error		
Additive (µg/mL)		10.8 (11.5)
Proportional		23.7% (3.4)

Abbreviations: RSE= relative standard error.  
<sup>a</sup>Total clearance (CL<sub>tot</sub>) is the sum of linear and nonlinear clearances.  $CL_{tot} = CL + V_{max}/(C+K_m)$   
<sup>b</sup>Volume at steady state (V<sub>ss</sub>) is the sum of central and peripheral volumes of distribution.  $V_{ss} = V_1 + V_2$   
<sup>c</sup> $CL_{ind} = CL * (bodyweight/70)^{0.768}$ ; <sup>d</sup> $Q_{ind} = Q * (bodyweight/70)^{0.768}$   
<sup>e</sup> $V_{1,ind} = V_1 * (bodyweight/70)^{0.498}$ ; <sup>f</sup> $V_{2,ind} = V_2 * (bodyweight/70)^{0.498}$

(Source: Table 8.2 on Page 43 of population PK meta-analysis and E-R analysis of study JFCC)

**Figure 8: Goodness of Fit Plots of the Final Population PK Model of Necitumumab**



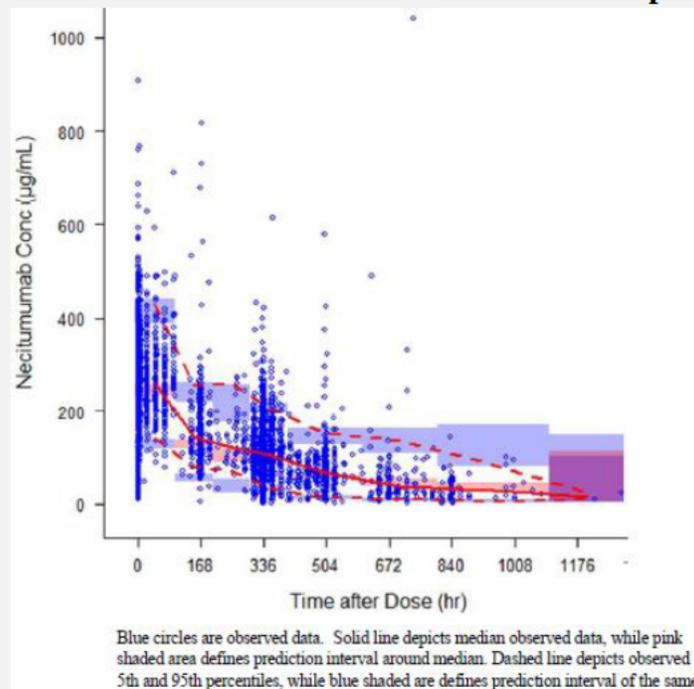
(Source: Figure 8.5 on Page 44 of population PK meta-analysis and E-R analysis of study JFCC)

**Table 5: Bootstrap Results of Final Population PK Model for Necitumumab**

Parameter	Model Estimate (Bootstrap 95% CI)	
	Parameter	Interpatient Variability
Clearance		28.8% (25.5% – 31.9%)
CL (L/h)	0.0114 (0.0106-0.0124)	
$K_{el}$ ( $\mu\text{g/mL}$ )	7.97 (3.97-15.4)	
$V_{max}$ (mg/h)	0.565 (0.406-0.731)	
Central Volume of Distribution, $V_1$ (L)	3.41 (3.23-3.66)	21.1% (17.4% – 27.1%)
Inter-compartmental Clearance, Q (L/h)	0.0183 (0.0155-0.0215)	
Peripheral Volume of Distribution, $V_2$ (L)	3.29 (3.04-3.56)	55.4% (41.4% – 68.6%)
Weight-CL and Q	0.768 (0.640-0.912)	
Weight- $V_1$ and $V_2$	0.498 (0.317-0.647)	
Inter-Patient Variability	0.609	
Correlation Coefficient (CL and $V_1$ )	(0.437-0.793)	
Residual Error		
Additive ( $\mu\text{g/mL}$ )	10.8 (8.42 – 16.1)	
Proportional (%)	23.7 (21.6 – 25.4)	

(Source: Table 8.3 on Page 45 of population PK meta-analysis and E-R analysis of study JFCC)

**Figure 9: Prediction Corrected Visual Predictive Check of Final Population PK model**



(Source: Figure 8.6 on Page 46 of population PK meta-analysis and E-R analysis of study JFCC)

Objective function mapping and visual predictive check (VPC) were used to evaluate the validity and robustness of the final population model and the precision of PK parameter estimates. The PK parameters of necitumumab in final model and their corresponding 95% confidence interval (CI) calculated based on the method of objective function mapping are listed in Table 5. 95<sup>th</sup> percentiles by VPC and the observed concentrations for both 8 mg/kg and 10 mg/kg are presented in Figure 9.

**Exposure-OS Analysis:** The model that best described change in tumor size was comprised of linear growth and first order shrinkage (Wang et al. 2009). The tumor size at time t was determined using the differential equation below:

$$\frac{dSize}{dt} = Size_0 \cdot e^{-shrinkt} \cdot (-shrink) + growth$$

Where **Size** is the sum of longest diameters at time t, **Size<sub>0</sub>** is the estimated baseline tumor size, **shrink** is the first order shrink rate of the tumor and **growth** is the growth rate of the tumor.

Inter-individual variability on the baseline tumor size, shrink rate and growth rate was estimated in the model. A Box-Cox transformation of the random effects for the baseline tumor size was included, showing that the distribution was not exactly log-normal, but was negatively skewed. Furthermore, there was a positive correlation between the random effects for baseline tumor size and the growth rate.

The development of resistance was incorporated into the model using a first order decline in the shrink rate of the tumor as shown below:

$$Shrink_t = Shrink_0 \cdot e^{-resist \times (t - delay)}$$

Where **Shrink<sub>t</sub>** is the shrink rate at time t, **Shrink<sub>0</sub>** is the shrink rate at the beginning of treatment, **resist** is the first order rate at which the shrink rate declines and **delay** is an estimated time at which resistance starts to develop. If the difference between t and **delay** was negative, the difference was made to be zero so that **Shrink<sub>t</sub> = Shrink<sub>0</sub>** until the time of onset of resistance.

The time to event model that best described the overall survival was a combination of a Weibull function and Gompertz function for the hazard at time t. A significant predictor of the hazard at time t during the course of the study was the tumor size at that time ( $\Delta$ MOF = -209). Therefore, the hazard function in the final model was described according to the equation below:

$$\frac{dHaz}{dt} = Basehaz \times e^{[Gomp \times t + Weib \times LOG(t)]} \times e^{DPHAZ \times Size}$$

Where **Basehaz** is the baseline hazard at the beginning of the study, **Camp** is the shape parameter representing the Gompertz distribution of event times, **Weib** is the shape parameter representing the Weibull distribution, **DPHAZ** is the estimated link between tumor size at time t and the hazard.

Eastern Cooperative Oncology Group (ECOG) status at baseline was the only significant clinical covariate. Patients with a higher ECOG status at baseline also had a greater tumor size at baseline ( $\Delta\text{MOF} = -9$ ). As can be seen from the confidence intervals in the table of parameter estimates (**Table 6**), this difference is mainly for patients with an ECOG score of 2, whilst there is no significant difference between patients with a score of zero or 1. Although the covariate did not meet the backward deletion criteria for retention in the model, it was kept in the model based on prior clinical knowledge.

In separate models, necitumumab  $C_{ss,ave}$  was a significant predictor of both the shrink rate of the tumor ( $\Delta\text{MOF} = -16$ ,  $p < 0.001$ ) and the hazard for OS ( $\Delta\text{MOF} = -13$ ,  $p < 0.0025$ ). The  $\Delta\text{MOFs}$  are relative to the base model with ECOG status as a covariate. The final model had the effect of necitumumab increasing the shrink rate of the tumor as well as decreasing the baseline hazard ( $\Delta\text{MOF} = -25$ ,  $p < 0.001$ ). Parameter estimates of the final model are shown in **Table 6** below. The 95% CIs reported are from a bootstrap of 500 replicates.

**Table 6: Pharmacodynamic and Covariate Parameters in Final Tumor Growth Inhibition and Overall Survival Model**

Parameter Description	Population Estimate (95% CI)	Inter-Patient Variability (95% CI) %
<b>Tumor size model</b>		
Baseline tumor size (mm)	103 (96-108)	61 (58-64)
Box-Cox shape parameter for random effects of baseline tumor size <sup>a</sup>	-0.33 (-0.38-0.19)	--
Tumor growth rate (mm/day)	0.049 (0.035-0.068)	155 (137-170)
Correlation between random effects of baseline tumor size and tumor growth rate		0.47 (0.38-0.56)
Shrink rate of tumor (day <sup>-1</sup> )	0.0056 (0.0054-0.0069)	73 (64-82)
Time of onset of resistance (days)	43 (23-44)	90 (96-132)
Rate of development of resistance (day <sup>-1</sup> )	0.039 (0.026-0.039)	--
Emax for necitumumab increasing shrink rate <sup>b</sup>	0.35 (0.16-0.63)	--
EC50 ( $\mu\text{g/mL}$ ) <sup>b</sup>	150 (143-199)	--
Increase in baseline tumor size for ECOG=1 relative to ECOG=0 (%) <sup>c</sup>	7 (0-16)	--
Increase in baseline tumor size for ECOG=2 relative to ECOG=0 (%) <sup>c</sup>	27 (9-48)	--
Additive error (mm)	2.6 (0.9-3.6)	--
Proportional error (%)	8.8 (7.8-10)	--
<b>Overall Survival Model</b>		
Baseline hazard (day <sup>-1</sup> )	$1.2 \times 10^{-5}$ ( $5.0 \times 10^{-6}$ - $3.2 \times 10^{-5}$ )	--
Effect of tumor size on hazard (mm <sup>-1</sup> )	0.0067 <sup>d</sup> (0.0053-0.0080)	--
Weibull shape parameter	0.95 (0.74-1.15)	--
Gompertz shape parameter	-0.0020 (-0.0028-0.0013)	--
Emax for necitumumab decreasing baseline hazard <sup>e</sup>	0.19 (0.08-0.3)	--
EC50 ( $\mu\text{g/mL}$ ) <sup>e</sup>	71 (60-75)	--

<sup>a</sup>  $ETA_{box} = \frac{(e^{ETA_i}) - 1}{\theta_{box}}$  where  $ETA_{box}$  is the Box-Cox transformed random effect (from  $ETA_i$ ) for baseline tumor size and  $\theta_{box}$  is the estimated shape parameter

<sup>b</sup> Fractional increase in shrink rate of tumor =  $1 + \frac{Emax \times C_{ss}^\gamma}{EC50^\gamma + C_{ss}^\gamma}$  where  $\gamma$  was fixed to 10

<sup>c</sup> Fractional increase in baseline tumor size =  $1 + \theta_{ECOG}$  where  $\theta_{ECOG}$  is the relevant value for a score of 1 or 2

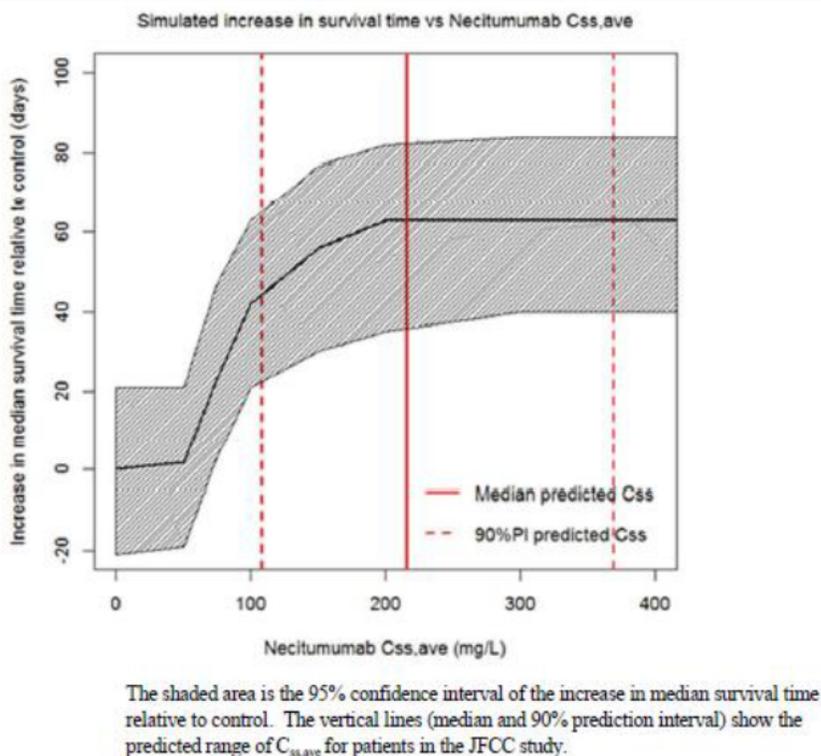
<sup>d</sup> Translates to a doubling in the hazard for every 103 mm of tumor

<sup>e</sup> Fractional decrease in hazard =  $1 - \frac{Emax \times C_{ss}^\gamma}{EC50^\gamma + C_{ss}^\gamma}$  where  $\gamma$  was fixed to 10

(Source: Table 8.4 on Page 49 of population PK meta-analysis and E-R analysis of study JFCC)

Using the final model, simulations of survival time using various values of necitumumab  $C_{ss,ave}$  resulted in the exposure-response curve shown in **Figure 10**. The figure shows that the population median predicted necitumumab  $C_{ss,ave}$  of 216  $\mu\text{g/mL}$  results in an increase in survival time of about 60 days relative to control, with an effective  $EC_{50}$  of 82  $\mu\text{g/mL}$  and an  $E_{max}$  of 63 days. The model-predicted median survival time for patients in the control arm was 336 days (observed value 311 days). Therefore the increase of 60 days approximates to a model predicted hazard ratio of 0.85, which can be compared to the observed value of 0.84. Patients in the 5<sup>th</sup> percentile would experience an increase in survival time of over 40 days, whilst those in the 95<sup>th</sup> percentile would have an increase of over 60 days. Based on the dosing regimen in SQUIRE, 474 (99.6%) of the 476 patients in the necitumumab arm had a  $C_{ss,ave}$  greater than  $EC_{50}$ . Therefore, near-maximum benefit is attained by nearly all patients receiving the proposed dosing regimen of 800 mg on day 1 and 8 of a 3 week cycle.

**Figure 10: Necitumumab Exposure-Response Curve for Overall Survival Based on Final Model**



**Source:** Figure 8.11 on Page 53 of population PK meta-analysis and E-R analysis of study JFCC

**Exposure-Arterial Thromboembolic Rate:** A time to event model with a Gompertz distribution of event times best described the arterial thromboembolism data. The shape parameter was negative, meaning that the hazard of treatment emergent thromboembolism decreased with time in the study. After testing demographic covariates and necitumumab  $C_{ss,ave}$  on the baseline hazard and Gompertz shape parameters, no covariates were found to be of

significance. Despite not meeting predefined backward retention criteria ( $\Delta\text{MOF} > 10.828$ ), study arm was retained as a covariate on the shape parameter due to observed improvement in the VPC. The negative shape parameter was 50% smaller in the necitumumab arm, meaning that the risk of treatment emergent thromboembolism persisted longer than that of patients in the control arm, in accordance with the longer treatment duration. Final model parameters were well estimated, and are presented in **Table 7**. VPC (**Figure 11**) shows the appropriateness of the model.

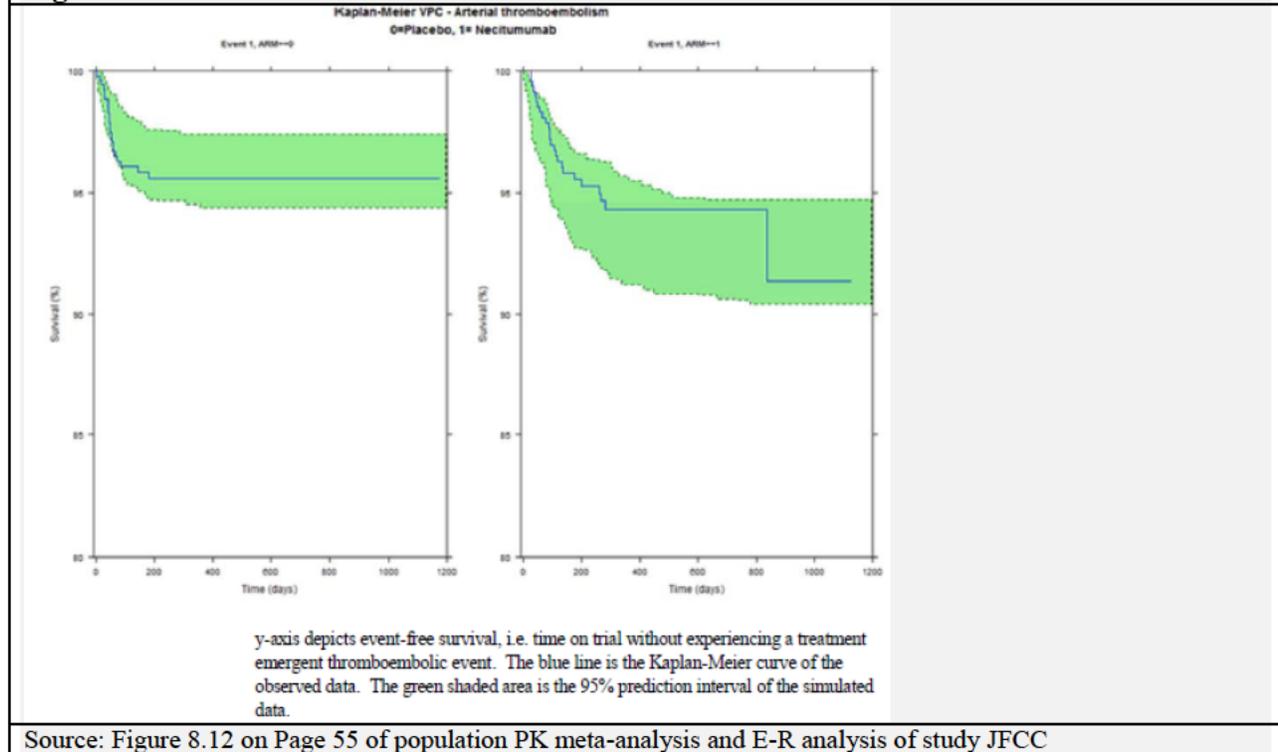
**Table 7: Parameter Estimates of Final Model for Arterial Thromboembolism**

Parameter	Population value (%RSE)
Baseline hazard ( $\text{day}^{-1}$ )	0.000467 (2.9)
Shape	-0.0124 (18)
Necitumumab arm on shape <sup>a</sup>	-0.502 (28)

<sup>a</sup>  $\text{Shape} = \theta_1 \times (1 + \theta_2 \times \text{COV})$  where  $\theta_1$  is the estimated shape parameter (-0.0124) and  $\theta_2$  is the estimated covariate effect (-0.502), COV is 0 for the control arm and 1 for the necitumumab arm

(Source: Table 8.5 on Page 54 of population PK meta-analysis and E-R analysis of study JFCC)

**Figure 11: Visual Predictive Check for Arterial Thromboembolism Model**



**Exposure-Arterial Thromboembolic Rate:** Similar to arterial thromboembolism, a time to event model with a Gompertz distribution of event times best described the venous thromboembolism data. The shape parameter was negative, meaning that the hazard of treatment emergent thromboembolism decreased with time in the study. After testing demographic

covariates and necitumumab  $C_{ss,ave}$  on the baseline hazard and Gompertz shape parameters, geographical origin was found to be of significance, with patients from Eastern Europe and Eastern Asian having a higher baseline hazard than patients from the rest of the world. However, the standard errors from the NONMEM covariance step were high and the CI included zero therefore that covariate was not retained in the model. Similar to arterial thromboembolism, incorporating study arm did not meet the inclusion criteria ( $\Delta MOFV \leq -10.828$ ) but was included in the model as a covariate on the shape parameter as it improved the VPC ( $\Delta MOF = -10.4$ ,  $p < 0.01$ ). The negative shape parameter was 48% smaller in the necitumumab arm, meaning that the risk of treatment emergent thromboembolism persisted longer than that of patients in the control arm, in accordance with the longer treatment duration. Final model parameters were well estimated, and are presented in **Table 8**. A VPC showing the appropriateness of the model is shown in **Figure 12**.

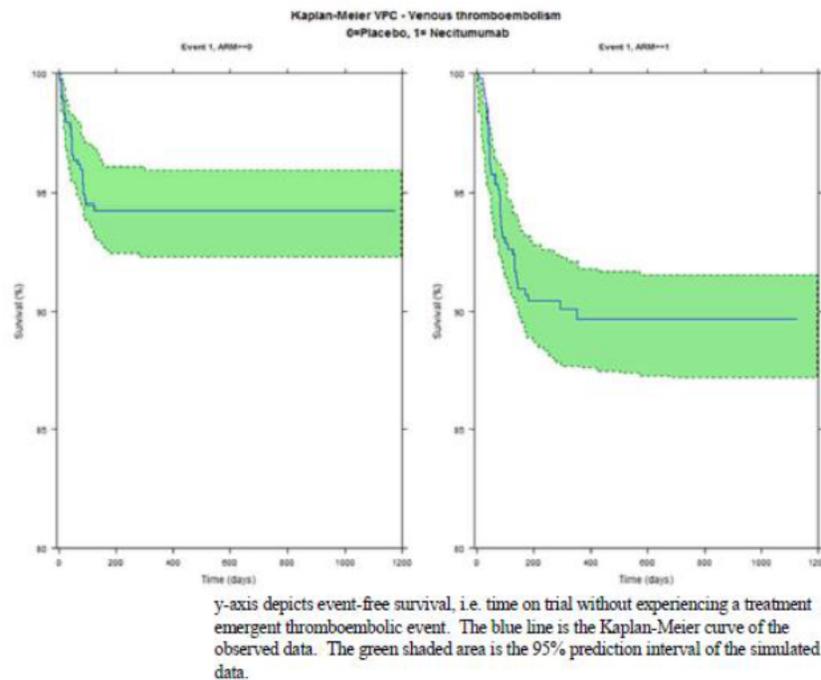
**Table 8: Parameter Estimates of Final Model for Venous Thromboembolism**

Parameter	Population value (%RSE)
Baseline hazard ( $\text{day}^{-1}$ )	0.000106 (2.1)
Shape	-0.0184 (14)
Necitumumab arm on shape <sup>a</sup>	-0.480 (19)

<sup>a</sup>  $Shape = \theta_1 \times (1 + \theta_2 \times COV)$  where  $\theta_1$  is the estimated shape parameter (-0.0184) and  $\theta_2$  is the estimated covariate effect (-0.480), COV is 0 for the control arm and 1 for the necitumumab arm.

(Source: Table 8.6 on Page 56 of population PK meta-analysis and E-R analysis of study JFCC)

**Figure 12: Visual Predictive Check for Venous Thromboembolism Model**



Source: Figure 8.13 on Page 57 of population PK meta-analysis and E-R analysis of study JFCC

**Exposure-Hypomagnesaemia:** Hypomagnesaemia occurred in a total of 251 patients, 165 (66%) of whom were in the necitumumab arm. Some patients who experienced hypomagnesaemia experienced several such events during follow-up, which would be a continuation of the previous event. However, there was no trend in the severity of hypomagnesaemia with time on treatment that could be modeled. Separate proportional odds models were created to determine the probability of the first recorded incidence of hypomagnesaemia as well as the most severe grade that a patient experienced as will be described below. **Table 9** shows the numbers of patients with each grade of hypomagnesaemia grouped by placebo (control arm) and necitumumab  $C_{ss,ave}$  quartiles. The table shows that there are more incidences of hypomagnesaemia in the necitumumab arm, but the occurrences are not related to drug exposure. **Figure 13** also shows that the severity of hypomagnesaemia was not related to drug exposure.

**Table 9: Occurrence of Hypomagnesaemia Stratified by Necitumumab  $C_{ss,ave}$  Quartiles, N (% of patients in corresponding stratum)**

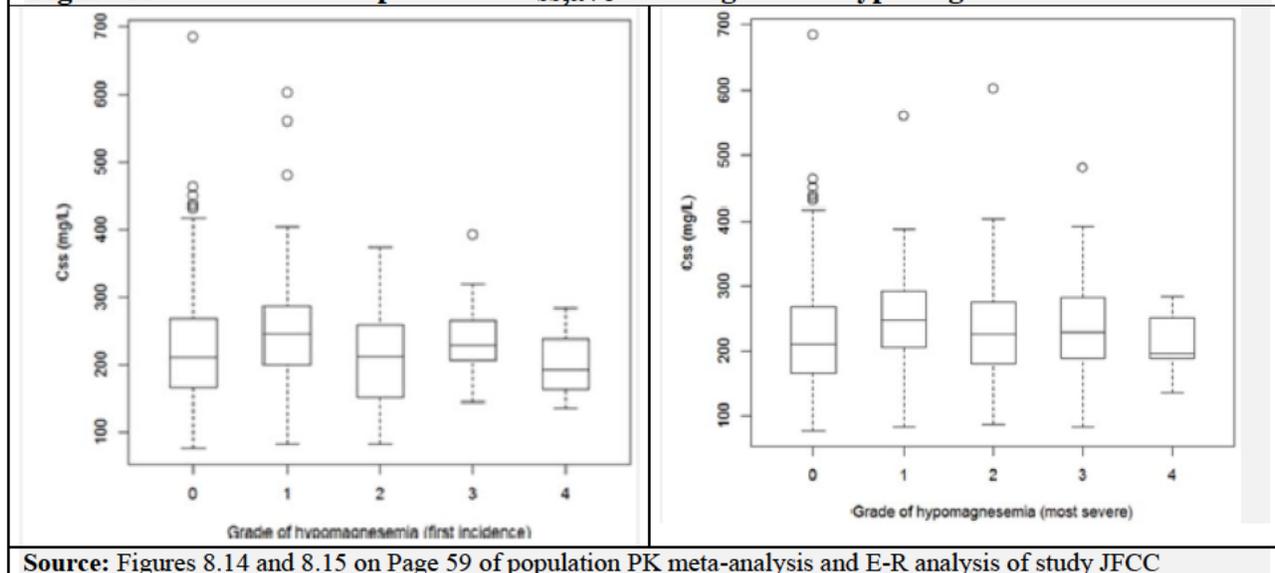
Grade (first incidence)	Necitumumab arm	Control arm	Q1	Q2	Q3	Q4
0	311 (65.3%)	452(84.0%)	90(75.6%)	82(68.9%)	69(58.0%)	70(58.8%)
1	103 (21.6%)	60(11.1%)	12(10.1%)	23(19.3%)	35(29.4%)	33(27.7%)
2	40 (8.4%)	23(4.3%)	14(11.8%)	8(6.7%)	9(7.6%)	9(7.6%)
3	19 (4.0%)	3(0.6%)	3(2.5%)	5(4.2%)	6(5.0%)	5(4.2%)
4	3 (0.6%)	0(0.0%)	1(0.8%)	1(0.8%)	0(0.0%)	1(0.8%)
<b>Grade (most severe)</b>						
0	311 (65.3%)	452(84%)	90(75.6%)	82(68.9%)	69(58.0%)	70(58.8%)
1	49 (10.3%)	48(8.9%)	5(4.2%)	11(9.2%)	15(12.6%)	18(15.1%)
2	66 (13.9%)	32(5.9%)	15(12.6%)	12(10.1%)	22(18.5%)	17(14.3%)
3	37 (7.8%)	6(1.1%)	8(6.7%)	9(7.6%)	9(7.6%)	11(9.2%)
4	13 (2.7%)	0(0%)	2(1.7%)	5(4.2%)	4(3.4%)	2(1.7%)

(Source: Table 8.7 on Page 58 of population PK meta-analysis and E-R analysis of study JFCC)

The final proportional odds model for the first incidence of hypomagnesaemia included study arm and race (white versus non-white) as significantly influencing the probability of developing hypomagnesaemia. Patients in the necitumumab arm or those who were white had a higher probability of developing hypomagnesaemia. Other covariates were not significant. A maximum effect model of  $C_{ss,ave}$  had the same MOF as study arm alone (but with an additional parameter), therefore using individual measures of drug exposure was not more informative than study arm alone (refer to sponsor's report for more information).

The final proportional odds model for the most severe grade of hypomagnesaemia was structurally similar to that described for the first incidence, except that the parameter estimates were slightly different. Similarly, a model with  $C_{ss,ave}$  as a covariate was not more informative than study arm alone (but with an additional parameter), with the predicted EC50 going towards a boundary of zero. Once again, race (white versus non-white) was a significant covariate (refer to sponsor's report for more information).

**Figure 13: Necitumumab predicted  $C_{ss,ave}$  versus grade of hypomagnesaemia in JFCC**



Source: Figures 8.14 and 8.15 on Page 59 of population PK meta-analysis and E-R analysis of study JFCC

**Exposure-Rash:** Rash occurred in a total of 440 patients, 385 (88%) of whom were in the necitumumab arm. Some patients who experienced rash experienced several such events during follow-up, which would be a continuation of the previous event. However, there was no trend in the severity of rash with time on treatment that could be modeled. Separate proportional odds models were created to determine the probability of the first recorded incidence of rash as well as the most severe grade that a patient experienced as will be described below. **Table 10** shows the numbers of patients with each grade of rash grouped by placebo and necitumumab  $C_{ss,ave}$  quartiles. The table shows that there are more incidences of rash in the necitumumab arm, but the occurrences are not related to drug exposure. **Figure 14** also shows that the severity of rash was not related to drug exposure.

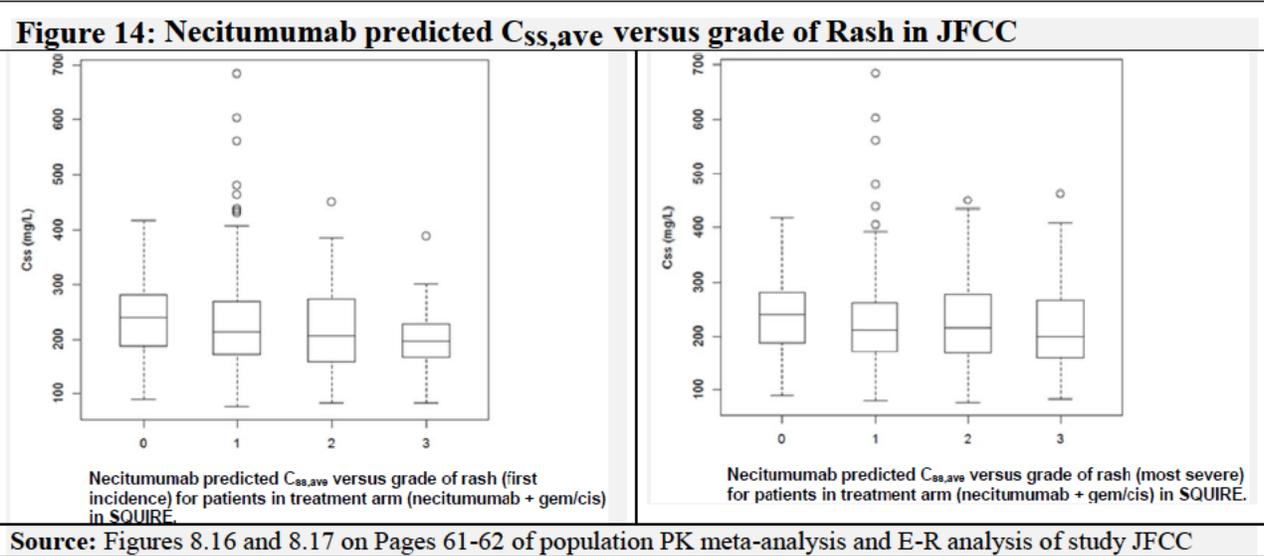
**Table 10: Occurrence of Rash Stratified by Necitumumab  $C_{ss,ave}$  Quartiles, N (% of patients in corresponding stratum)**

Grade (first incidence)	Necitumumab arm	Control arm	Q1	Q2	Q3	Q4
0	91 (19.1%)	483(89.8%)	18(15.1%)	18(15.1%)	28(23.5%)	27(22.7%)
1	274 (57.6%)	44(8.2%)	71(59.7%)	71(59.7%)	68(57.1%)	64(53.8%)
2	100 (21.0%)	9(1.7%)	28(23.5%)	27(22.7%)	20(16.8%)	25(21.0%)
3	11 (0.02%)	2(0.4%)	3(2.5%)	3(2.5%)	3(2.5%)	2(1.7%)
Grade (most severe)						
0	91 (19.1%)	483(89.8%)	18(15.1%)	18(15.1%)	28(23.5%)	27(22.7%)
1	187 (39.3%)	42(7.8%)	48(40.3%)	52(43.7%)	47(39.5%)	40(33.6%)
2	163 (34.2)	11(2.0%)	43(36.1%)	40(33.6%)	37(31.1%)	43(36.1%)
3	35 (7.4%)	2(0.4%)	11(9.2%)	9(7.6%)	7(5.9%)	8(6.7%)

(Source: Table 8.9 on Page 61 of population PK meta-analysis and E-R analysis of study JFCC)

The final proportional odds model for the first incidence of rash included study arm as the significant factor that influenced the probability of rash development. Patients in the necitumumab arm had a higher probability of developing rash. Other covariates were not significant. A maximum effect model of  $C_{ss,ave}$  had the same MOF as study arm alone (but with an additional parameter), therefore using individual measures of drug exposure was not more informative than study arm alone.

The final proportional odds model for the most severe grade of rash was structurally similar to that described for the first incidence, except that the parameter estimates were slightly different. Similarly, a model with  $C_{ss,ave}$  as a covariate was not more informative than study arm alone, with the predicted EC50 going towards a boundary of zero.



**Table 11: Comparison between Model Simulated and Observed Median OS by Exposure Group with No-PK patients Excluded or Included in the Exposure-Response Analysis**

GROUP	Median-OS Obs	No-PK Patients Included		No-PK Patients Excluded	
		Median-OS Sim	Difference	Median-OS Sim	Difference
No-PK	156	379.75	223.75	400.75	244.75
Placebo	311	343	32	343	32
Q1	357	371	14	392	35
Q2	378	383.25	5.25	402.5	24.5
Q3	376	385	9	406	30
Q4	457	392	-65	406	-51

**Source:** Figure 15 and Figure 16 of this review.

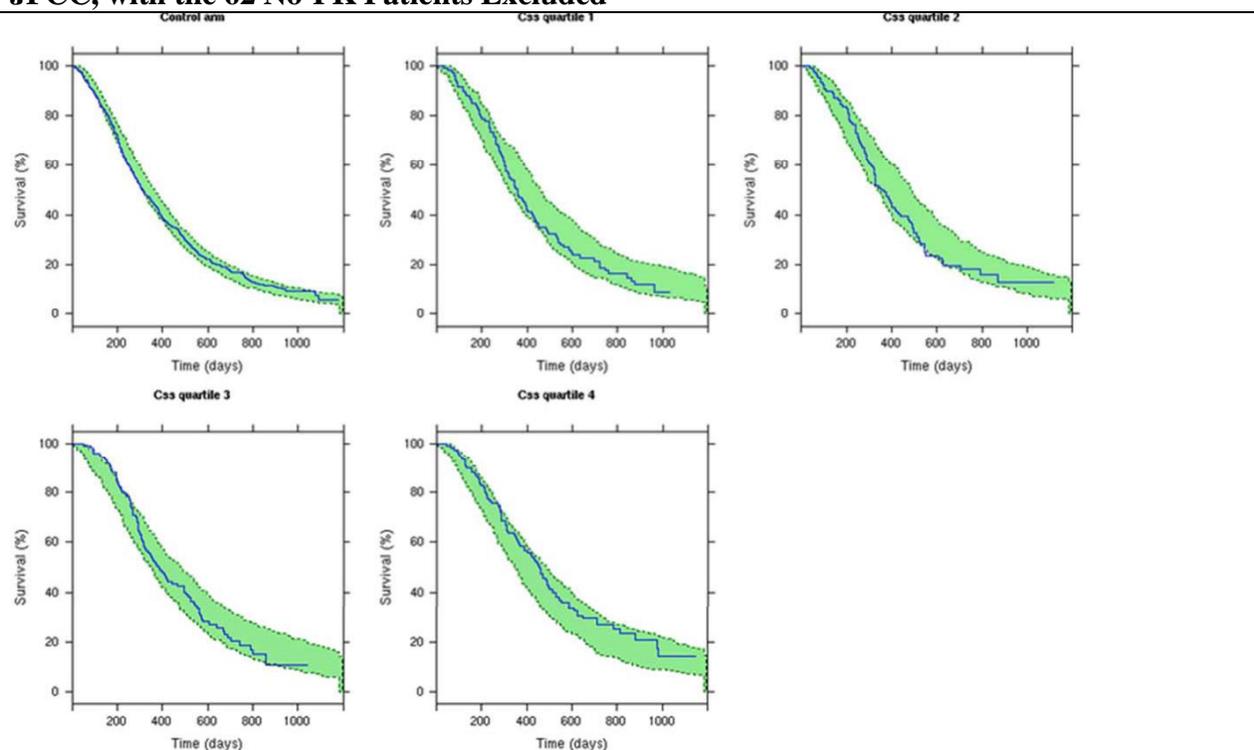
**Figure 15: The Revised Kaplan-Meier VPC for the Final Model on Exposure-OS Data of JFCC, with the 62 No-PK Patients Included**



**Note:** The blue line is the Kaplan-Meier curve of the observed data. The green shaded area is the 95% confidence interval of the simulated data.

**Source:** In response to FDA information request, sponsor's updated Figures APP.4.1 of population PK meta-analysis and E-R analysis of study JFCC when the 62 patients were included.

**Figure 16: The Original Kaplan-Meier VPC for the Final Model on Exposure-OS Data of JFCC, with the 62 No-PK Patients Excluded**



**Note:** The blue line is the Kaplan-Meier curve of the observed data. The green shaded area is the 95% confidence interval of the simulated data.

**Source:** Sponsor's Figures APP.4.1 of population PK meta-analysis and E-R analysis of study JFCC when the 62 patients were excluded.

*Reviewer's Comments:*

*In general, the applicant's population PK model appears reasonable. It was noticed that approximately 18% of the PK data (1101/6021) were not evaluable and was excluded from the population PK modeling analysis.*

*In the exposure-OS analysis, the exclusion of No-PK patients introduced bias towards the overestimation of necitumumab's OS effect. An information request was issued, and the sponsor updated the exposure-OS analysis by including the No-PK patients. The new estimate on necitumumab OS effect was more consistent with the observed result.*

*However, both analyses had bias towards overestimating OS for low exposure subgroups (placebo, No-PK and Q1-3) and underestimating OS for the highest exposure subgroup (Q4) as listed in **Table 11**. For the revised analysis, the 62 No-PK patients were included with exposure data predicted by the population PK model. The exclusion of the 62 No-PK patients resulted in larger bias for all subgroups except Q4 (**Table 11**, **Figure 15** and **Figure 16**). For better*

*prediction of OS based on necitumumab exposure, the sponsor needs to improve the exposure-OS model.*

## 4 REVIEWER’S ANALYSIS

### 4.1 INTRODUCTION

As shown in right panel of **Figure 1**, necitumumab seemingly had no OS effect on the No-PK patient subpopulation; the median OS of No-PK patients, 24% of whom (15/62) discontinued the study before the 3<sup>rd</sup> necitumumab dose, was 5.3 months shorter than that for the placebo arm (4.6 months vs. 9.9 months). In contrast, Q4 showed the longest OS, 14.9 months. The lack of OS benefit for No-PK patients could be attributable to the baseline characteristics including disease condition. Therefore, it is not appropriate to compare the survival benefit among patients without accounting for the baseline characteristics influencing OS. Analysis was conducted by the reviewer to identify the key confounding baseline risk factors associated with OS.

In addition, exploratory exposure-safety analyses were conducted for the 4 concerned Grade 3+ AEs: hypomagnesemia, rash, arterial thromboembolic event and venous thromboembolic event.

### 4.2 OBJECTIVES

The FDA reviewer’s analyses were to evaluate the E-R relationship for efficacy and safety between patients in the necitumumab arm and placebo arm.

### 4.3 METHODS

#### 4.3.1 Data Sets

Data sets used are summarized in Table 12.

Study Number	Name	Link to EDR
JFCC	os_ts_pk_final_psn.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-pk\os_ts_pk_final_psn.xpt
JFCC	os-ts-pk-20150504.csv	\\cdsesub1\evsprod\bla125547\0016\m5\datasets\population-pk\analysis\programs\datasets\os-ts-pk-20150504-csv.txt
JFCC	adae.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\i4x-ie-jfcc\analysis\adam\datasets\adae.xpt
JFCC	art_emb_final_psn.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-pk\art_emb_final_psn.xpt
JFCC	ven_emb_final_psn.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-pk\ven_emb_final_psn.xpt
JFCC	magnesium_first_incidence_final_psn	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-

	n.xpt	pk\magnesium_first_incidence_final_psn.xpt
JFCC	magnesium_most_severe_final_psn.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-pk\magnesium_most_severe_final_psn.xpt
JFCC	magnesium_first_incidence_final_psn.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-pk\magnesium_first_incidence_final_psn.xpt
JFCC	rash_severe_final_psn.xpt	\\cdsesub1\evsprod\bla125547\0001\m5\datasets\population-pk\analysis\legacy\datasets\jfcc-pk\rash_severe_final_psn.xpt

### 4.3.2 Software

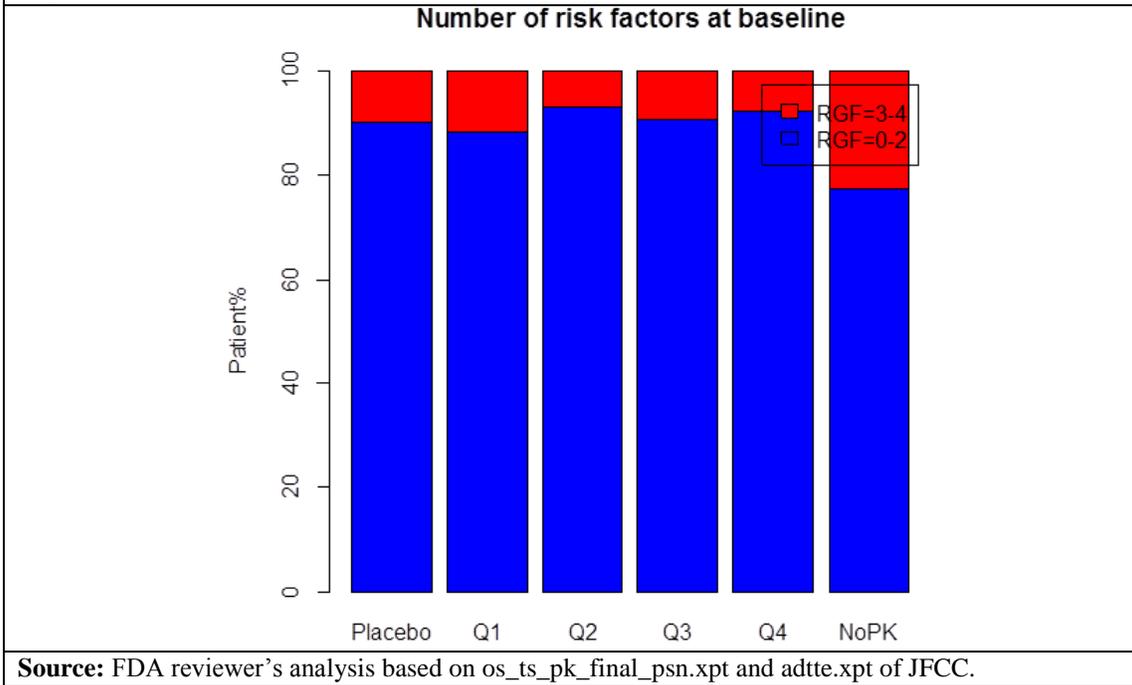
SAS and R were used for the FDA reviewer’s analysis.

## 4.4 RESULTS

### 4.4.1 Identify the Key Confounding Baseline Risk Factor

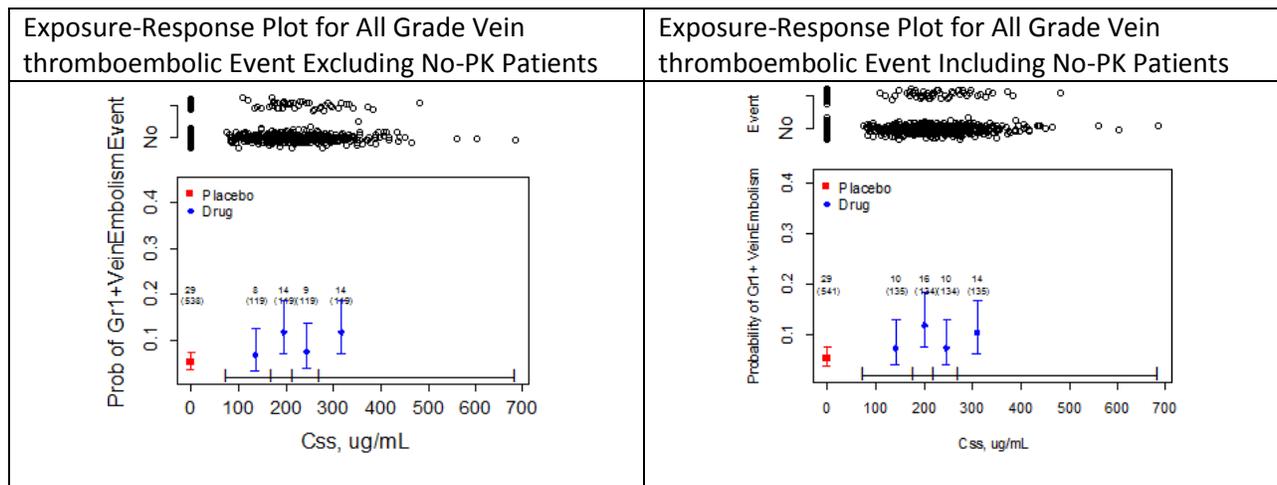
A stepwise Cox regression model was used to identify the key confounding baseline risk factors associated with OS in the placebo arm. Total 11 baseline variables (i.e., histologic subtype code, race, baseline ECOG, age, gender, smoking history category code, Baseline Leukocytes Category, Baseline Hemoglobin Category, Baseline BMI Category, Baseline Platelets Category, and Pooled Risk Factor Group) related to demographics, disease characteristics, and baseline health condition were explored in the multivariate analysis. Two key baseline risk factors were retained in the final model by showing statistically significant association with OS (p value < 0.05): the ECOG performance status (ECOG PS: 0-1 vs. 2), and Pooled Risk Factor Group (RFGR1N: 0-2 vs 3-4) as shown in **Figure 2** and **Figure 17**. An imbalance in ECOG distribution was observed across Q1-4 subgroups, such as poorer ECOG performance status in Q1, suggesting the short median OS time in Q1 patients with low exposure could be due to both low concentration of necitumumab and baseline ECOG (**Figure 2**). However, RFGR1N did not show such a clear imbalance across Q1-4.

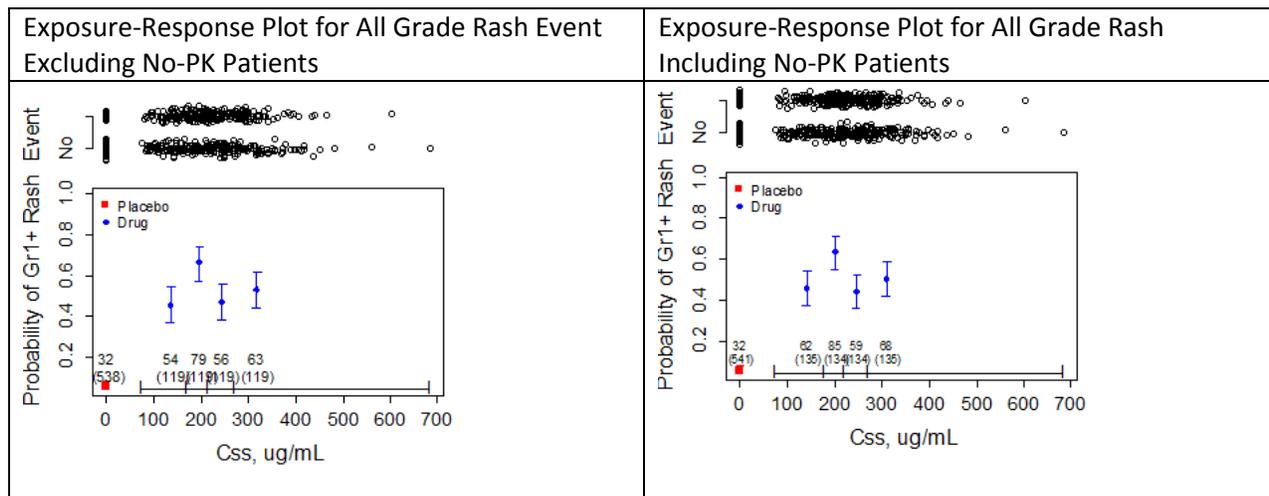
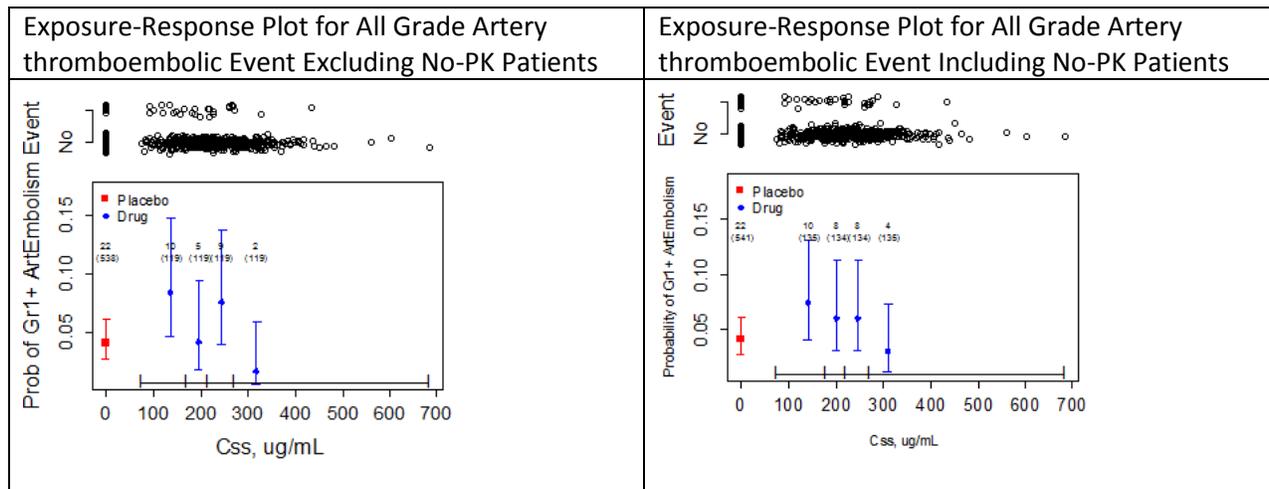
**Figure 17: The Distribution of Pooled Risk Factor Number**



#### 4.4.2 Exposure-Response Analyses for Major Adverse Events

The exploratory E-R analyses for the 4 concerned Grade 3+ AEs (hypomagnesemia, rash, arterial thromboembolic event and venous thromboembolic event) were conducted and the result is presented in Section 1.1.3. The results are overall consistent with sponsor's conclusion on the 4 AEs, except for a new finding on E-R for all grade hypomagnesemia. In addition, exposure-response analysis results for three all-grade AEs are presented below.





There appeared to be no exposure-response relationship for any of the three AEs (all-grade rash, all-grade artery thromboembolic events, and all-grade vein thromboembolic events) whether No-PK patients were included or excluded.

#### **4.4 Appendix 4 - OCP Filing Memo**

**Office of Clinical Pharmacology (OCP)**  
***New Drug Application Filing and Review Form***

**General Information About the Submission**

<b>BLA Number</b>	125547/0	<b>Brand Name</b>	PORTRAZZA
<b>OCP Division (I, II, III, IV, V)</b>	V	<b>Generic Name</b>	Necitumumab (IMC-11F8, LY3012211)
<b>Medical Division</b>	Oncology/DOP2	<b>Drug Class</b>	Human monoclonal (mAb) IgG1 antibody blocking the ligand binding site of epidermal growth factor receptor (EGFR)
<b>OCP Reviewers</b>	Safaa Burns, Ph.D. Hongshan Li, Ph.D. (PM)	<b>Proposed Indication</b>	In combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)
<b>OCP Team Leaders</b>	Hong Zhao, Ph.D. Liang Zhao, Ph.D. (PM)	<b>Dosage Form</b>	Sterile, preservative-free solution at a concentration of 16 mg/mL (800 mg/50 mL) in single dose vial
<b>Date of Submission</b>	02-Dec-2014	<b>Proposed Dosing Regimen</b>	800 mg administered by intravenous (IV) infusion over (b) (4) minutes on Days 1 and 8 of a 3-week treatment cycle
<b>Due Date of OCP Review</b>	08-August-2015	<b>Route of Administration</b>	Intravenous (IV) infusion
<b>Priority Classification</b>	Standard	<b>Applicant</b>	Eli Lilly and Company
<b>PDUFA Due Date</b>	02-Dec-2015		

**Clinical Pharmacology Information**

	<b>“X” if included at filing</b>	<b>Number of studies submitted</b>	<b>Number of studies reviewed</b>	<b>Critical Comments If any</b>
<b>STUDY TYPE</b>				
<b>Table of Contents present and sufficient to locate reports, tables, data, etc.</b>	x			
<b>Tabular Listing of All Human Studies</b>	x			
<b>HPK Summary</b>	x			
<b>Labeling</b>	x			
<b>Reference Bioanalytical and Analytical Methods</b>	x	11	11	<ul style="list-style-type: none"> <li>• Two Biacore assay validation reports for Phase 1 Study JFCE and Phase 2 Study JFCD</li> <li>• Five ELISA assay validation reports for Phase 1 Study JFCA, Phase 2 Studies JFCI (ongoing ) and JFCJ and Phase 3 Studies JFCB and JFCC</li> <li>• One assay validation report for gemcitabine (&amp; its metabolite)</li> <li>• One assay validation report for total &amp; free platinum from cisplatin</li> <li>• Two ADA assessment assay validation reports</li> </ul>
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				

<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:	x	7	7	<ul style="list-style-type: none"> <li>• Two Phase 1 studies (JFCA and JFCE)</li> <li>• Three Phase 2 studies (JFCD, JFCI and JFCJ)</li> <li>• Two Phase 3 studies (JFCB and JFCC)</li> </ul>
multiple dose:				
<b>Dose proportionality -</b>	x	1		Phase 1 Study JFCE (100-1000 mg doses)
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	x	5		PopPK analyses of data from Studies JFCA, JFCB, JFCC, JFCI, and JFCJ
In-vivo effects of primary drug:	x	1		<ul style="list-style-type: none"> <li>• Study JFCJ (effect of necitumumab on gemcitabine and cisplatin)</li> <li>• PopPK analyses (effect of gemcitabine and cisplatin on necitumumab)</li> </ul>
In-vitro:				
in-silico				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
<b>PD:</b>				
Phase 2:				
Phase 3:	x	1		Phase 3 Study JFCC (SQUIRE)
QT study	x	1		Interim QTc-Evaluation of data from ongoing Study JFCI, an IRT consult sent on 1/9/2015
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:	x	5		Intensive sampling in Studies JFCA, JFCD, JFCE, JFCI and JFCJ. Non-compartmental analysis performed on data from Studies JFCA, JFCD, JFCE and JFCJ.
Data sparse:	x	2		Sparse sampling in Studies JFCB and JFCC. PopPK analyses of data from Studies JFCA, JFCB, JFCC, JFCI and JFCJ.
<b>Immunogenicity</b>	x	6		Studies JFCA, JFCB, JFCC, JFCD, JFCE and JFCJ

<b>II. Biopharmaceutics</b>				
<b>Compatibility</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Biliary Elimination</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>18</b>	<b>18</b>	

On **initial** review of the BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	N/A. To-be-marketed product was used in the pivotal clinical trial.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	N/A. IV Formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose	x			

	individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	N/A
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

*Yes, the application is fileable from a clinical pharmacology perspective.*

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.**

Safaa Burns, Ph.D.

23-Jan-2015

Reviewing Clinical Pharmacologist

Date

Hong Zhao, Ph.D.

23-Jan-2015

Team Leader

Date

**Attachment 1: QTc-IRT Review**

3 Page(s) has been Withheld in Full as duplicate copy of OtherR  
3.9.15 review immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SAFAA BURNS  
08/06/2015

HONGSHAN LI  
08/06/2015

SARAH E DORFF  
08/07/2015

JINGYU YU  
08/07/2015  
On behalf of Yaning Wang

ROSANE CHARLAB ORBACH  
08/07/2015

HONG ZHAO  
08/07/2015  
I concur.

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***New Drug Application Filing and Review Form***

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<b>Labeling</b>	x			
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10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose	x			

	individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	N/A
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

*Yes, the application is fileable from a clinical pharmacology perspective.*

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.**

Safaa Burns, Ph.D.	23-Jan-2015
Reviewing Clinical Pharmacologist	Date
Hong Zhao, Ph.D.	23-Jan-2015
Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SAFAA BURNS  
01/23/2015

HONG ZHAO  
01/23/2015  
I concur.