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APPLICATION NUMBER:

125147/0

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

BLA: 125147	Submission Date(s): 3/28/2006, 7/10/2006, 8/4/2006, 8/9/2006, 8/31/2006
Brand Name	Vectibix™
Generic Name	Panitumumab
Primary Reviewer	Angela Yuxin Men, M.D., Ph.D.
PM Reviewers	Rajnikanth Madabushi, Ph.D., Yaning Wang, Ph.D.
Team Leader	Hong Zhao, Ph.D.
Division	Clinical Pharmacology V
Clinical Division	Biologic Oncology Product
Sponsor	Amgen
Relevant IND(s)	BB-IND 8382
Submission Type; Code	NME, CMA Pilot 1 Program with Priority Review
Formulation; Strength(s)	Single- use 5 mL, 10 mL, or 20 mL vials containing a — ng/ml solution in a preservative-free solution containing — sodium acetate, — sodium chloride, and Water for Injection, USP, for intravenous infusion
Indication	

OCP Briefing was held on August 9, 2006 attended by:

Larry Lesko, Shiew-Mei Huang, Nam Atiqur Rahman, John Lazor, Mehul Mehta, Hong Zhao, Jang-Ik Lee, Ruthann Giusti, Anne Pilaro, Ken Thummel, Gilbert Burckart, Jenny Zheng, Jeffrey Tworzyanski, Lei Zhang, Yaning Wang, Sophia Abraham, Arzu Selen, Young M Choi, Hae Young Ahn, Apparaju Sandhya, Pravin Jadhav

Table of Contents

1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The to-be-marketed product manufactured from a — Chinese Hamster Ovary (CHO) process is considered pharmacokinetically comparable to the clinical trial product manufactured from a — CHO process. Clinical pharmacology and biopharmceutics studies in BLA125147 are acceptable and support approval of Vectibix from a clininal pharmacology perspective.

1.2 PHASE IV COMMITMENTS

Clinical Pharmacology related Post Marketing Commitments (PMCs):

1) Conduct a Phase 1 pediatric study, Protocol 20050252 entitled "A Phase I Study to Evaluate the Safety and Pharmacokinetics of Panitumumab in Children with Refractory Solid Tumors".
   Final Protocol Submission: —
   Study Start (FPE): —
   Report submission: —

2) Conduct a Phase 1 drug interaction study, entitled "Open Label, 2-Cohort, Randomized Study to Assess the Potential Pharmacokinetic Drug-Drug Interaction between Irinotecan and Panitumumab in Subjects with Colorectal Cancer".
   Protocol (or amendment) Submission: August 2007
   Study Start (FPE): December 2007
   Report submission: —

3) Submit a final study report for study 20040192 entitled, "A Phase 1 Clinical Study of ABX-EGF (Panitumumab) Evaluation of the Safety and PK of ABX-EGF in Japanese Subjects with Advanced Solid Tumors"-that characterizes the pharmacokinetic profile of Vectibix™ in the Japanese population. The final study report should provide summary analyses and primary data, including pharmacokinetic data, in both the Japanese and non-Asian population that will permit an assessment of differences in pharmacokinetics, if any, based on race/ethnicity.

For PMCs from other disciplines, please refer to Appendix 4.5.

1.3 CLINICAL PHARMACOLOGY FINDINGS

The sponsor is seeking an accelerated approval for Vectibix (Panitumumab), a fully human IgG2 monoclonal antibody directed against the epidermal growth factor receptor (EGFr), for the t

Fifteen clinical studies in subjects with a variety of solid tumors were conducted to support this license application, of which 13 included pharmacokinetic (PK) sample collection.

Mechanism of Action: EGFr is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFr (HER1/c-ErbB-1), HER2, HER3, and HER4. EGFr promotes cell growth in normal epithelial tissues including the skin and hair follicle, and is expressed on a variety of tumor cells, including those of the colon and rectum. Panitumumab binds to the ligand binding domain of EGFr on both normal and tumor cells with high affinity and competitively inhibits the binding of ligands for EGFr. Binding of Panitumumab to the EGFr prevents ligand-inducted receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased inflammatory and vascular growth factor production, and internalization of the EGFr. *In vitro* assays and *in vivo* animal studies have shown that Panitumumab inhibits the growth and survival of some tumor cell lines expressing EGFr. The addition of Panitumumab to chemotherapy and/or targeted therapeutic agents in selected tumor xenograft models in animals resulted in an increase in antitumor effects compared to chemotherapy or targeted therapeutic agents alone.

Single-Dose PK Parameters at Various Dose Levels: The PK of Panitumumab after single doses ranging from 0.75 to 9 mg/kg have been characterized in a broad range of studies and tumor types. Panitumumab administered as a single agent exhibits nonlinear PK. Following a single dose administration of Panitumumab as a 1-hour infusion, the area under the concentration time curve (AUC) increased in a greater than dose proportional manner. As the dose of Panitumumab increased from 0.75 to 9 mg/kg, the clearance decreased from 30.6 to 4.6 mL/day/kg and the half-life increased from 0.8 day to 6.5 days. However, at doses above 2 mg/kg, the AUC of Panitumumab increased in an approximately dose propotional manner. The concentration-time profile was best described by a 2-compartmental PK model with linear and nonlinear clearance pathways, likely to be mediated by the reticuloendothelial system (RES) and EGFr, respectively.

Multiple-Dose PK: Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), Panitumumab concentrations reached steady-state levels by the third infusion with mean (±SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 μg/mL, respectively. Panitumumab peak and trough concentrations were comparable across studies. The mean (±SD) AUC and CL were 1306± 374 μg•day/mL and 3.7 ± 1.4 mL/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

Drug Metabolism and In Vitro Drug-Drug Interaction: No studies on the metabolism of

Panitumumab have been performed in humans or in animals. In ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), it states "the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids". Therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P_{450} enzyme system is not expected to play any role in Panitumumab biotransformation.

In Vivo Drug-Drug Interaction: No formal drug-drug interaction studies have been conducted with Panitumumab. Potential effects of PK drug-drug interactions between Panitumumab and Irinotecan were evaluated through a cross-study comparison. Irinotecan did not have an effect on the PK of Panitumumab. A decrease of approximately 30% on C_{max} and AUC of Irinotecan, and its active metabolite, SN-38, was observed when Irinotecan-containing chemotherapy was administered concurrently with Panitumumab. The clinical relevance of this finding is unknown. The sponsor — has proposed to conduct a formal phase 1 drug interaction study between Vectibix and Irinotecan as a Post Marketing Commitment (PMC).

Rationale for Dose Selection: In the Phase 1 dose-escalation study examining doses from 0.75 to 5 mg/kg once a week (QW), 6 mg/kg once every two weeks (Q2W) and 9 mg/kg once every three weeks (Q3W), an acceptable safety profile was observed and no maximal tolerated dose (MTD) was reached. Skin toxicities [referred to as "integument/eye toxicities" (I/E toxicity) in this license application] were considered an on-target pharmacodynamic effect of EGFr blockade. A plateau in the incidence and severity of I/E toxicity was observed at 2.5 mg/kg QW. Additionally, Panitumumab trough concentrations (C_{trough}) achieved at 2.5 mg/kg QW exceeded the IC_{90} (represents the serum Panitumumab concentration at which the nonlinear clearance pathway mediated by EGFr saturated by 90%) established in animal xenograft models. The dose of 2.5 mg/kg was considered an optimal QW dose. PK simulations demonstrated that less-frequent dosing schedules (6 mg/kg Q2W and 9 mg/kg Q3W) could result in similar trough concentrations as to that of 2.5 mg/kg QW. Thus, Panitumumab dose for the pivotal clinical trial was selected at 6 mg/kg given Q2W by IV infusion over 60 minutes.

PK in Special Populations: A population PK analysis was performed to explore the potential effects of selected covariates on Panitumumab PK. Results suggest that age (26-85 years), gender, race (15% non-White), tumor type (mCRC, lung cancer or renal cancer), mild to moderate renal dysfunction, mild to moderate hepatic dysfunction and EGFR membrane staining intensity (1+, 2+, or 3+) in tumor cells had no apparent impact on the PK of Panitumumab. Serum Panitumumab concentrations appeared to be lower in Japanese subjects than those observed in non-Japanese subjects. Because this study in Japanese population is ongoing, the conclusion regarding the effect of race on the PK of Panitumumab can not be drawn at this time. No formal PK studies of Panitumumab have been conducted in pediatrics or in patients with renal or hepatic impairment. A Phase 1 pediatric study has been proposed as a PMC to be conducted in —

Inter-Individual Variability in PK Data: The integrated PK analysis has been conducted

to investigate the inter-individual variability associated with the PK data. The inter-subject variability was 25% and 54% for volume of distribution and clearance, respectively. The population PK analysis identified that the body weight was a potentially influential covariate. Data from PK simulations suggest that a weight-based dose would result in less variability in exposure to Panitumumab across body weights than a fixed dose, supporting the current use of body weight-based doses (mg/kg).

Comparability among Product Lots: To support the manufacturing changes from an expression system of hybridoma to a — CHO and then scaling up to — CHO, PK of these Panitumumab materials were evaluated in cancer patients. The PK profiles of Panitumumab were comparable between the hybridoma and — CHO materials at 6 mg/kg Q2W. The 90% CIs of the parameter ratios between products manufactured from the — process and — CHO process after the first and third dose of 6 mg/kg Q2W were slightly outside the 80 to 125% range. They are considered comparable because these differences are likely due to cross-study comparison with limited number of patients. In addition, these PK differences between the — and — materials are not expected to affect clinical efficacy and safety.

Pharmacodynamic Findings: The efficacy of Panitumumab was evaluated with a primary endpoint of progressive-free survival (PFS) and secondary endpoints including overall response rate (ORR) and overall survival (OS). Based upon Independent Review Committee (IRC) determination, a statistically significant prolongation ($p< 0.001$; stratified log-rank test) in PFS was observed in patients receiving Panitumumab compared to those receiving best supportive care (BSC) alone. Median PFS was 56 days and 51 days, and mean PFS were 96 days and 60 days in the Panitumumab arm and BSC alone arm, respectively. ORR were 8% in the Panitumumab arm and 0% in BSC alone arm. No difference in OS between the two arms was observed.

Exposure-Response: The correlation between Panitumumab exposure and efficacy endpoints could not be determined because of lacking sufficient PK data and low overall response rate (8%). The relationship between Panitumumab doses and the incidence of I/E toxicity within 28 days of Panitumumab treatment was evaluated using logistic regression model. A plateau in the incidence of I/E toxicity was observed at 2.5 mg/kg QW. Doses higher than 2.5 mg/kg QW would not be expected to result in further enhancement of biological activity, whereas doses below this level would produce partial EGFr blockade. Incidence and duration of I/E toxicity were correlated with the duration of Panitumumab exposure, but not with C_{trough} of Panitumumab. The duration of severe I/E toxicity was not correlated with the duration of Panitumumab exposure.

EGFr Expression and Response: The potential relationship between EGFr expression and Panitumumab exposure or the clinical response was assessed. The intensity of EGFr membrane expression in tumor cells had no effect on the PK of Panitumumab. PFS and ORR did not correlate with either percentage of positive cells or the intensity of EGFr expression in an exploratory univariate analysis.

Immunogenicity: The incidence of non-transient anti-Panitumumab antibodies was 4.3% (19/447). For those patients whose sera tested positive in the screening immunoassays, an *in vitro* biological assay was performed to detect neutralizing antibodies. Seven of 19

patients with post-dose samples and 1/4 patients with follow-up samples were tested positive for neutralizing antibodies. There were no observed differences in PK profile and toxicity profile between patients who developed antibodies to Panitumumab and those who did not.

Adverse Events: The most common adverse events seen in patients receiving Panitumumab were skin toxicity (91%), paronychia (19%), diarrhea (13%) and fatigue (13%). Serious adverse reactions associated with the administration of Panitumumab included hypomagnesemia, dehydration, and hypersensitivity (1% each occurring during treatment).

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Signatures:

9/20/06

Angela Yuxin Men, M.D., Ph.D.
Clinical Pharmacology Reviewer, Biologic Product Team
Division of Clinical Pharmacology V

Hong Zhao 9/20/06

Hong Zhao, Ph.D.
Team Leader, Biologic Product Team
Division of Clinical Pharmacology V

Atiqur Rahman 9/20/06

Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology V

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

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

Chemistry and Physical-Chemical Properties: Panitumumab is a recombinant, human IgG_2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFr) with affinity of 0.05 nM (K_d). Panitumumab consists of — and has an approximate molecular weight of 147 kDa. Panitumumab is produced in genetically engineered mammalian cells.

Formulation: Vectibix (Panitumumab) is a sterile, colorless, pH 5.6 to 6.0, liquid for intravenous (IV) infusion, which may contain a small amount of visible amorphous Panitumumab particulates. Each single-use 5 mL, 10 mL, or 20 mL vial contains 100 mg, 200 mg, or 400 mg of Panitumumab, respectively. Vectibix is formulated with Panitumumab at a concentration of 20 mg/mL in a preservative-free solution containing — sodium acetate, — sodium chloride, and Water for Injection, USP.

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

Mechanism of Action: EGFr is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFr (HER1/c-ErbB-1), HER2, HER3, and HER4. EGFr promotes cell growth in normal epithelial tissues, including the skin and hair follicle, and is expressed on a variety of tumor cells (including colon, lung, breast, prostate, pancreatic, and head and neck carcinomas). Panitumumab binds to the ligand binding domain of EGFr with high affinity and competitively inhibits receptor autophosphorylation induced by all known EGFr ligands. Binding of Panitumumab to EGFr results in the internalization of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 (IL-8) and vascular endothelial growth factor (VEGF) production.

In vitro assays and *in vivo* animal studies have shown that Panitumumab inhibits the growth and survival of tumor cells expressing EGFr. No anti-tumor effects of Panitumumab were observed in human tumor xenografts lacking EGFr expression. The addition of Panitumumab to chemotherapy and/or targeted therapeutic agents in animal studies resulted in an increase in antitumor effects compared to chemotherapy or targeted therapeutic agents alone.

Proposed Indication: Panitumumab is indicated for —

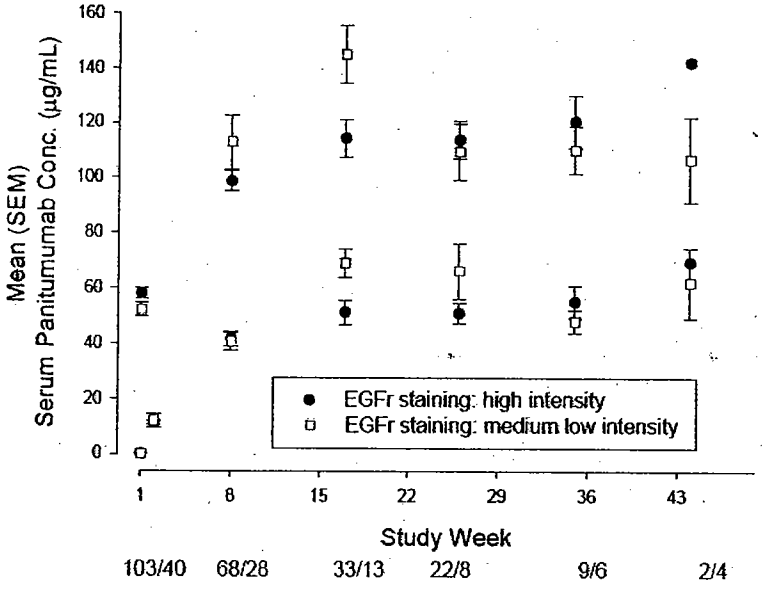
The effectiveness of Panitumumab is based on progression free survival (PFS). Currently, no data are available to demonstrate an improvement in disease-related symptoms or increased survival with Panitumumab.

2.1.3 What are the proposed dosage and route of administration?

Dosage and Route of Administration: The recommended dose of Vectibix is 6 mg/kg given once every 2 weeks (Q2W) as an IV infusion over 60 to 90 minutes. Vectibix should be diluted in 100 mL (for dose <1000 mg) or 150 mL (for dose >1000 mg) 0.9% sodium chloride injection USP for IV infusion.

2.1.4 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

Because Panitumumab is an EGFr inhibitor, the effect of EGFr expression on its PK was investigated. Membrane staining for EGFr expression was measured by immunohistochemistry (IHC) using DakoCytomation EGFR PharmDx®-kits. The EGFr staining data were from Study 20025405 (2.5 mg/kg QW). Subjects' tumors IHC staining of 2+ or 3+ in ≥10% evaluated tumor cells was defined as "high", and IHC staining with 1+ in ≥10% or the sum of 1+, 2+, and 3+ in ≥10% or 2+ or 3+ in < 10% evaluated tumor cells were defined as "medium low". The results suggested that the intensity of EGFr staining in evaluated tumor cells had no effect on the PK of Panitumumab at dose of 2.5 mg/kg QW (Figure 1).



Number of samples for high/medium low groups on study weeks 1, 8, 17, 26, 35, and 44

FIGURE 1: Serum Panitumumab Concentratiosn after IV Administration of Panitumumab at 2.5 mg/kg QW in Subjects with High or Medium Low Intensity of EGFr Staining in Evaluated Tumor Cells (Study 20025405)

Results from Phase 2 and 3 studies in metastatic colon or rectum carcinoma (mCRC) patients receiving 6 mg/kg Q2W showed that Panitumumab concentrations were similar although the EGFr expression intensity was different (Table 1 and Figure 2). The results also suggested that the intensity of EGFr membrane expression in tumor cells had no

effect on the PK of Panitumumab. In the pivotal study 20020408, no effect of EGFr membrane expression on the response rate was observed (Table 2).

TABLE 1. Summary of Serum Panitumumab Concentrations by EGFr Expression Intensity at Week 7 before and after IV Infusion of Panitumumab at 6 mg/kg Q2W

Study	EGFr Expression	C_{trough} (µg/mL)			C_{max} (µg/mL)		
		Mean	%CV	n	Mean	%CV	n
20030167	≥10%	33	51	46	152	29	45
20030250	(-) /<10%	33	54	48	175	23	42
20020408	≥1%	28	57	130	175	41	120
Total		30	55	224	170	36	207

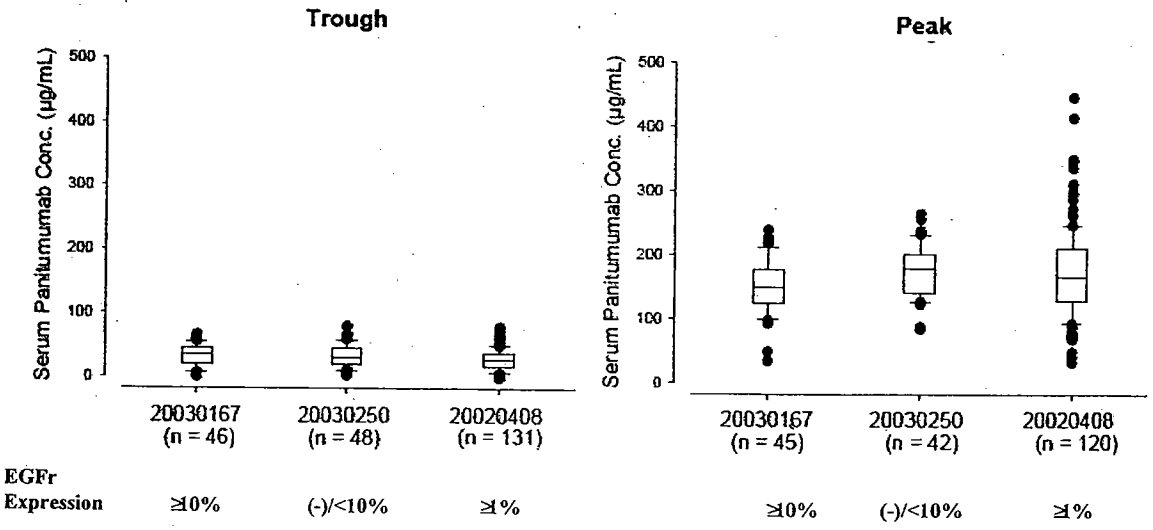


FIGURE 2: Serum Panitumumab Concentrations by EGFr Expression Intensity at Week 7 before and after IV of Panitumumab at 6 mg/kg Q2W

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TABLE 2. EGFr Expression in Responders and Non-responders (Study 20020408)

		Week 1 (n=434)			
		Panitumumab (n=222)		BSC (n=212)	
		Responders (n=18)	Non-responders (n=204)	Responders (n=1)	Non-responders (n=211)
EGFr	<1%		1		1
	1-9%	7	48		49
	10-20%	4	58	1	67
	>20 to 35%	1	13		27
	>35%	6	84		67
		Week 7 (n=246)			
		Panitumumab (n=175)		BSC (n=71)	
		Responders (n=18)	Non-responders (n=157)	Responders (n=1)	Non-responders (n=70)
EGFr	<1%		1		
	1-9%	7	35		20
	10-20%	4	48	1	24
	>20 to 35%	1	11		9
	>35%	6	62		17
		Follow-up Visit (n=194)			
		Panitumumab (n=72)		BSC (n=122)	
		Responders (n=18)	Non-responders (n=204)	Responders (n=0)	Non-responders (n=122)
EGFr	<1%				1
	1-9%	1	15		26
	10-20%	3	23		40
	>20 to 35%	1	3		15
	>35%	3	23		40

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?

Fifteen studies were conducted in cancer patients, of which 13 studies included PK information to support the clinical pharmacology and biopharmaceutics portion of the BLA. The list of studies is shown in Figure 3.

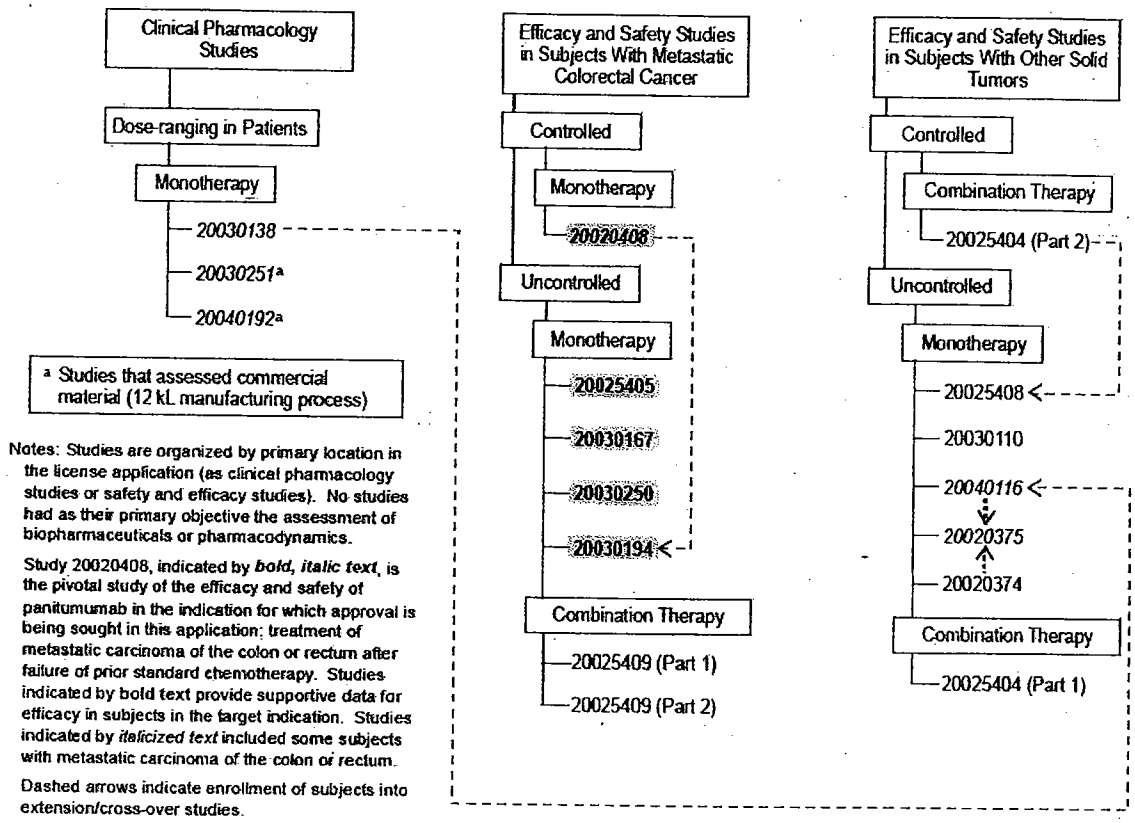


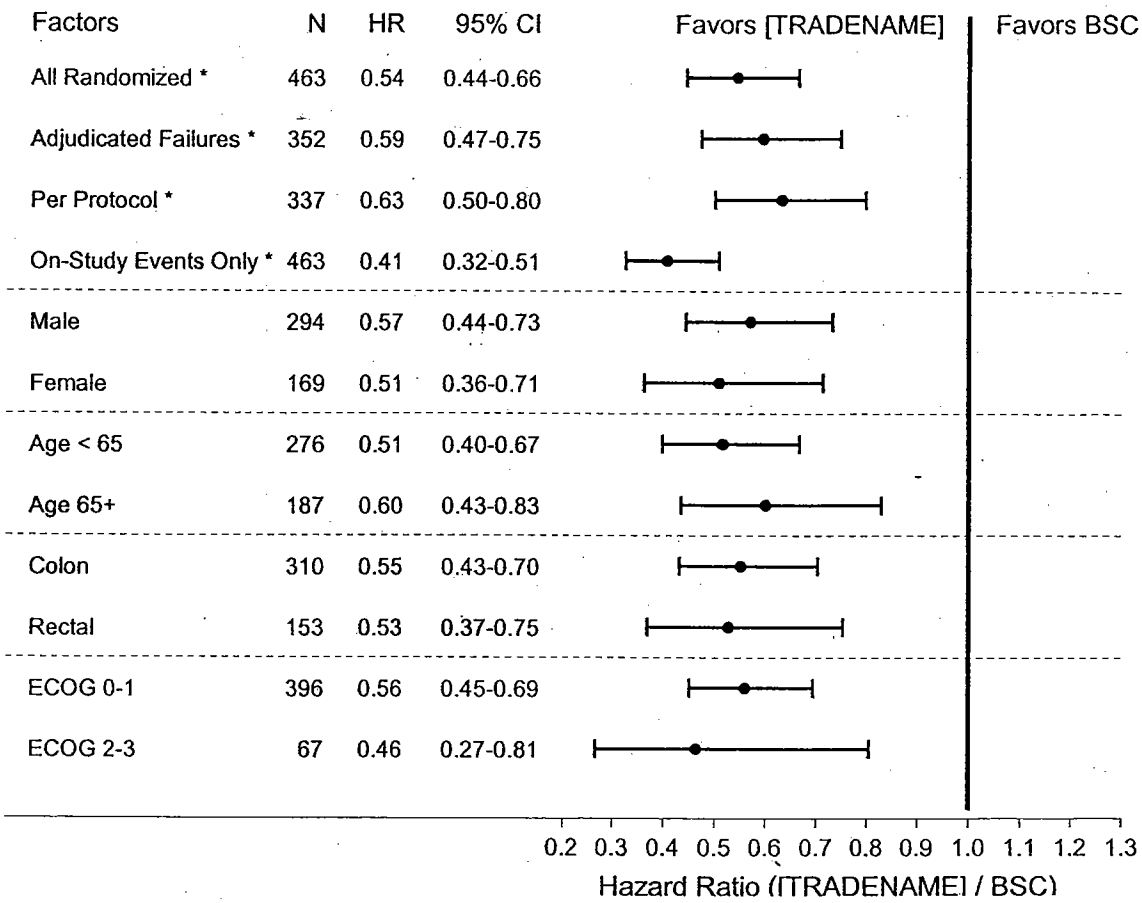
FIGURE 3: Panitumumab Clinical Studies

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Response Endpoints: In the clinical study in colorectal cancer patients, the efficacy of Panitumumab was evaluated with a primary endpoint of PFS and secondary endpoints including overall response rate (ORR) and overall survival (OS). These endpoints are acceptable for accelerated approval of oncology agents. PFS is defined as time from date of randomization to date of first observed progression or death (whichever comes first). Response rate assessment is based on a blinded central review of scans using modified Response Evaluation Criteria in Solid Tumors (RECIST). The use of the independent review committee (IRC) radiology assessment minimized the potential for the bias in interpretation of results.

For the primary endpoint of PFS, the analysis was based on IRC review of all patients. In patients who received Vectibix, the rate of disease progression or death was reduced by 46% [Hazard Ratio = 0.54, (95% CI: 0.44, 0.66), $p < 0.001$]. The tumor response rate were 8% [95% CI: 5.0, 12.6] for Vectibix arm and 0% [95% CI: 0.0, 1.6] for Best Supportive Care (BSC) arm, respectively. Currently, no difference in OS between Vectibix arm and BSC arm was observed in an interim analysis. Prospective sensitivity and univariate subset analyses of PFS (Figure 4) were consistent with the primary

analysis (all randomized).



* Cox model adjusted for ECOG performance score and geographic region.

The figure shows the hazard ratio (HR) for progression-free survival (PFS) for Vectibix plus BSC relative to BSC alone, the 95% CI for the HR, and the sample size (N) in each analysis. The circle on the horizontal bar represents the HR, and the length of the horizontal bar represents the 95% CI.

FIGURE 4: Progression-free Survival Sensitivity Analyses and Results by Baseline Characteristics

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2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to IV, F, Analytical Section; if no, describe the reasons)

Yes. Panitumumab is a recombinant, human IgG2 monoclonal antibody targeting EGFr. A validated immunoassay with electrochemiluminescence (ECL) detection was used to measure Panitumumab concentration in human serum samples. In addition, an ELISA assay was used for the determination of anti-Panitumumab antibodies (see Analytical Section).

2.2.4 Exposure-response

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

The relationship between PK and efficacy was not examined by the sponsor. In 3 studies supporting efficacy claims (Studies 20030167, 20030250, and 20020408), the blood samples were collected at pre-dose (C_{trough}) and at the end of infusion (C_{max}) at Weeks 7 and 23. The relationship between C_{trough} or C_{max} and tumor response at Weeks 7 and 23 was analyzed by the reviewer using logistic regression. No significant correlation was identified (Table 3). Approximately 27% (112/408) of the subjects in those trials discontinued treatment before Week 7, hence no PK data were available for these subjects. The sample size of the responders is too small to draw a conclusion on the relationship between Panitumumab concentration and clinical response.

TABLE 3. Logistic Regression of Response (Probability of Tumor Response) as a Function of C_{trough} and C_{max}

Endpoints	Parameters	Estimate	Pr> ChiSq
Response at Week 7	C_{trough}	0.000013	0.3177
	C_{max}	0.000002	0.6802
Response at Week 23	C_{trough}	-0.00001	0.7617
	C_{max}	-0.000005	0.1920

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

In the Phase 1 dose-escalation studies examining doses ranged from 0.75 to 5 mg/kg QW, 6 mg/kg Q2W and 9 mg/kg Q3W, an acceptable safety profile was seen in these dosing regimens and no MTD was reached.

In clinical studies, the skin toxicities were the most common toxicities observed in subjects treated with Panitumumab. Similar toxicities have been reported with the chimeric EGFr inhibitor (cetuximab) and with small molecule tyrosine kinase inhibitors (gefitinib and erlotinib). Skin-toxicities has been considered as an on-target pharmacodynamic effect for EGFr blockade (i.e., an anti-EGFr class effect), and has been used as a biological marker for dose selection purposes in treating subjects with anti-EGFr inhibitors. Toxicities related to nail, hair, and eye, in addition to skin toxicities,

have been reported to be associated with EGFr inhibitors. These toxicities together with skin toxicities were included in a composite adverse event category of "integument/eye toxicity" (I/E toxicity i.e. skin and mucosal toxicity).

In study 20030138, the incidence of moderate I/E toxicity reached a peak at the dose of 2.5 mg/kg QW. No severe I/E toxicity was observed at the dose ranged from 0.75 to 5 mg/kg QW. The percentage of subjects who exhibited a severe degree of I/E toxicity was higher at 9 mg/kg Q3W than that of 6 mg/kg Q2W (Figure 5).

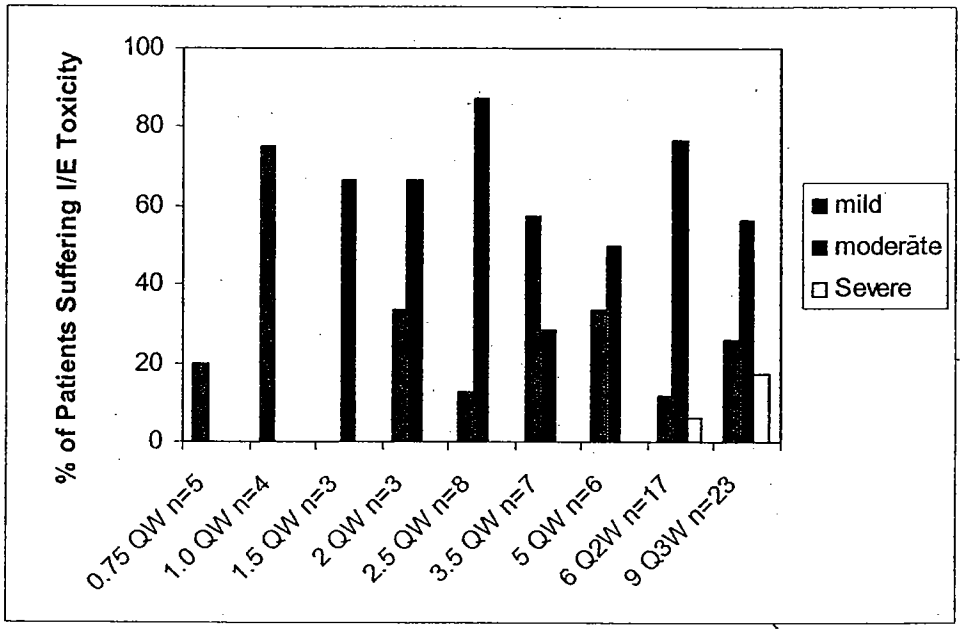

FIGURE 5: Incidence of I/E Toxicity (Study 20030138)

The relationship between Panitumumab dose and the incidence of I/E toxicity within 28 days of Panitumumab treatment was described using a 3-parameter logistic regression model as the following:

$$\text{Incidence of Toxicities} = P_{max} \cdot \frac{\exp(\alpha + \beta \cdot \text{dose})}{1 + \exp(\alpha + \beta \cdot \text{dose})}$$

where Pmax describes the maximum percentage of subjects that could have the adverse event, α describes the intercept of the logistic curve, and β describes the steepness of the curve. Using this model, the estimates for these parameters in study 20030138 and 2002374 are listed in Table 4.

TABLE 4. Parameter Estimates in Dose-Toxicity Logistic Model

Study	Dose (mg/kg, QW)	P_{max}	α	β
20030138	0.75 – 5	0.91	-6.96	4.68
20020374	1.0 – 2.5	0.94	-5.43	5.43

In Study 20020374, 92% of subjects who received Panitumumab at 2.5 mg/kg QW developed I/E toxicity, and 4% of subjects developed grade 3 or 4 I/E toxicity. A similar

relationship between Panitumumab doses and the incidence of I/E toxicity was observed in Study 20030138 (Figure 6). The dose at which 90% of subjects had the adverse event was estimated to be 1.7 mg/kg QW (95% CI: 1.0 to 2.4).

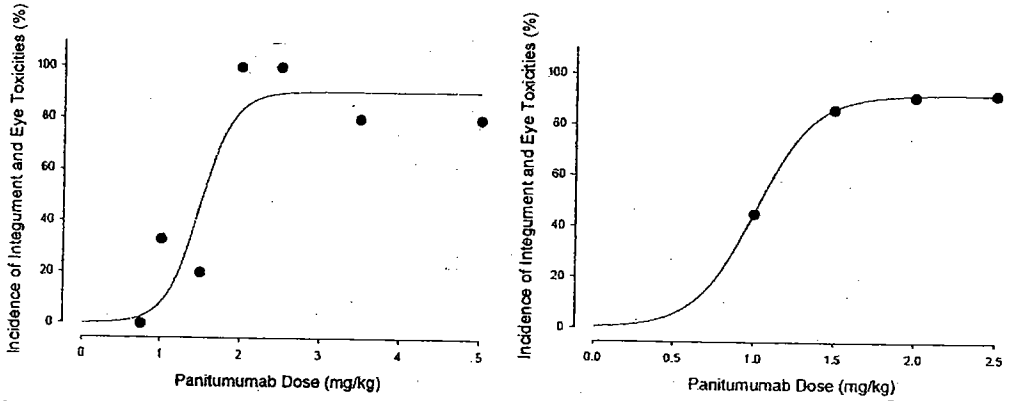

FIGURE 6: Observed and Modeled Incidence of Integument and Eye Toxicities Within 28 Days of Panitumumab Treatment in Study 20030138(L) and 20020374 (R)

As a plateau in the incidence of I/E toxicity was observed at 2.5 mg/kg QW, doses higher than 2.5 mg/kg QW would not be expected to result in further enhancement of biological activity, whereas doses below this level would produce partial EGFr blockade. As expected, I/E toxicity was a common toxicity among the mCRC patients receiving Panitumumab, occurring in 721 subjects (91%) in Phase 2 and 3 studies. Sixty four subjects (8%) required reduction of the Panitumumab dose as a result of adverse events associated with I/E toxicity. The incidence of I/E toxicity in responders and non-responders in the pivotal study 20020408 is listed in Table 5.

TABLE 5. Incidence of Intrgument/Eye Toxicities in Study 20020408

	Week 1 (n=434)			
	Panitumumab (n=222)		BSC (n=212)	
	Responders (n=18)	Non-responders (n=204)	Responders (n=1)	Non-responders (n=211)
Integument/Eye Toxicity	18	184	0	37
Grade 3/4 Integumen/EyeToxicity	6	34	0	4
	Week 7 (n=246)			
	Panitumumab (n=175)		BSC (n=71)	
	Responders (n=18)	Non-responders (n=157)	Responders (n=1)	Non-responders (n=70)
Integument/Eye Toxicity	18	151	0	11
Grade 3/4 Integumen/EyeToxicity	6	26	0	0
	Follow-up Visit (n=194)			
	Panitumumab (n=72)		BSC (n=122)	
	Responders (n=18)	Non-responders (n=204)	Responders (n=0)	Non-responders (n=122)
Integument/Eye Toxicity	8	61		22
Grade 3/4 Integumen/EyeToxicity	3	9		3

The median time to first I/E toxicity was 10 days (95% CI: 8, 12) (i.e, after 2 Panitumumab doses of 2.5 mg/kg QW or after 1 Panitumumab dose of 6.0 mg/kg Q2W). The median duration of I/E toxicity (any grade) was 149 days (95% CI: 133, 189). Among subjects who had ≥grade 3 I/E toxicity (n = 94), the median time to reach ≥grade 3 severity was 15 days (95% CI: 14, 26); the median duration of ≥grade 3 events was 28 days (95% CI: 21, 36). Incidence and duration of I/E toxicity were correlated with the duration of Panitumumab exposure. But the duration of severe I/E toxicity was not correlated with Panitumumab exposure (Figure 7). There is no correlation identified between the duration of I/E toxicity and C_{trough} of Panitumumab (Figure 8).

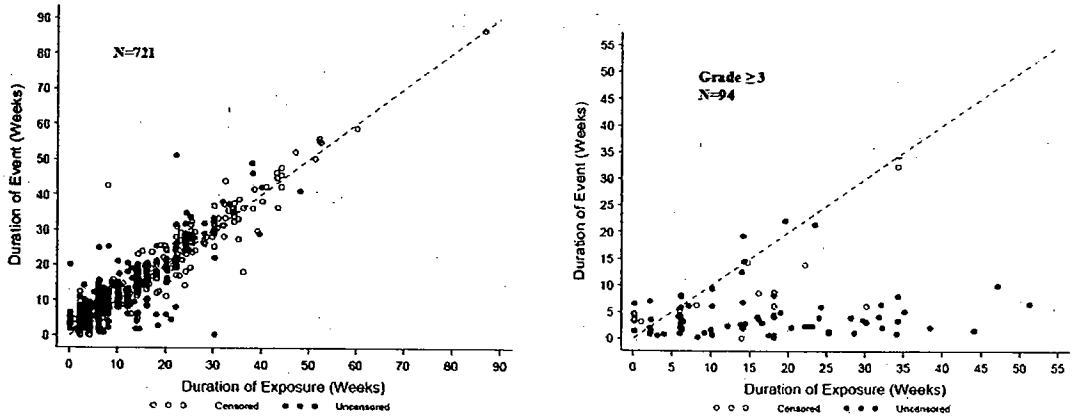

FIGURE 7: Duration of Integument/Eye Toxicities versus the Duration of Panitumumab Exposure

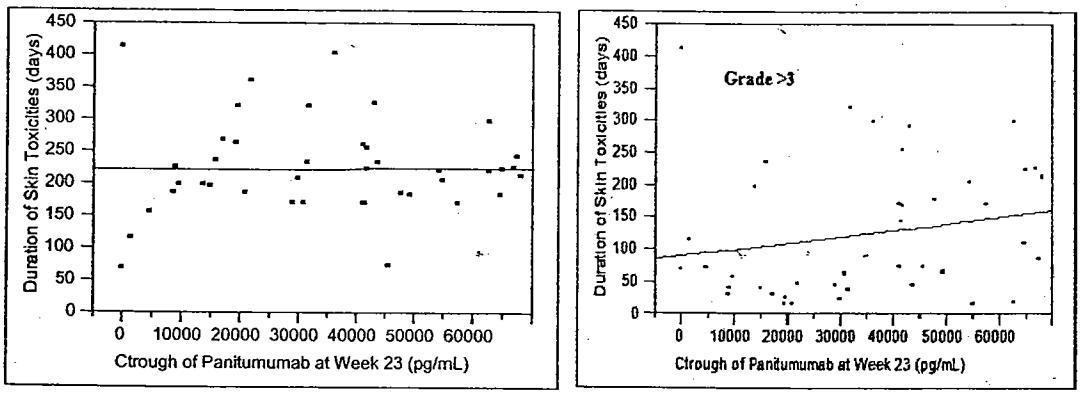

FIGURE 8: Duration of Integument/Eye Toxicities versus C_{trough} of Panitumumab at Week 23

2.2.4.3 Does this drug prolong the QT or QTc interval?

No. There was a cardiac safety pharmacology study in cynomolgus monkeys conducted for Panitumumab, which included electrocardiograms in the repeat-dose toxicity study for up to 6 months. In this study, there was no evidence of QT prolongation and no cardiac effects were observed. Cardiac monitoring of patients was conducted in Phase 1 and 2 studies. The conclusion based upon experience in over 300 patients and preclinical investigations is that Panitumumab is not associated with cardiac toxicity. Therefore, continued monitoring was not conducted in Phase 3 study.

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

There is no unresolved dose or dosing regimen issue. In the Phase 1 dose-escalation studies examining doses ranging from 0.75 to 5.0 mg/kg QW, 6 mg/kg Q2W and 9 mg/kg Q3W, an acceptable safety profile was seen in these dosing regimens. No MTD was reached. A plateau in the incidence and severity of I/E toxicity was observed at 2.5 mg/kg QW. Additionally, C_{trough} achieved at 2.5 mg/kg QW exceeded the IC_{90} (represents the serum Panitumumab concentration at which the nonlinear pathway is saturated by 90%) established in animal xenograft models and appeared to saturate the nonlinear clearance pathway mediated by EGFr. Therefore, 2.5 mg/kg was considered an optimal QW dose.

PK simulations demonstrated that less-frequent dosing schedules of 6 mg/kg Q2W and 9 mg/kg Q3W could result in similar C_{trough} as 2.5 mg/kg QW (Figure 9). The $C_{troughs}$ of Panitumumab (mean ± SD) at steady-state for 6 mg/kg Q2W (47 ± 19 μg/mL) and at 9 mg/kg Q3W (49 ± 29 μg/mL) were comparable to those at 2.5 mg/kg QW (56 ± 22 μg/mL). The selected dose of Panitumumab in the pivotal clinical study is 6 mg/kg given once every 2 weeks by IV infusion over 60 minutes.

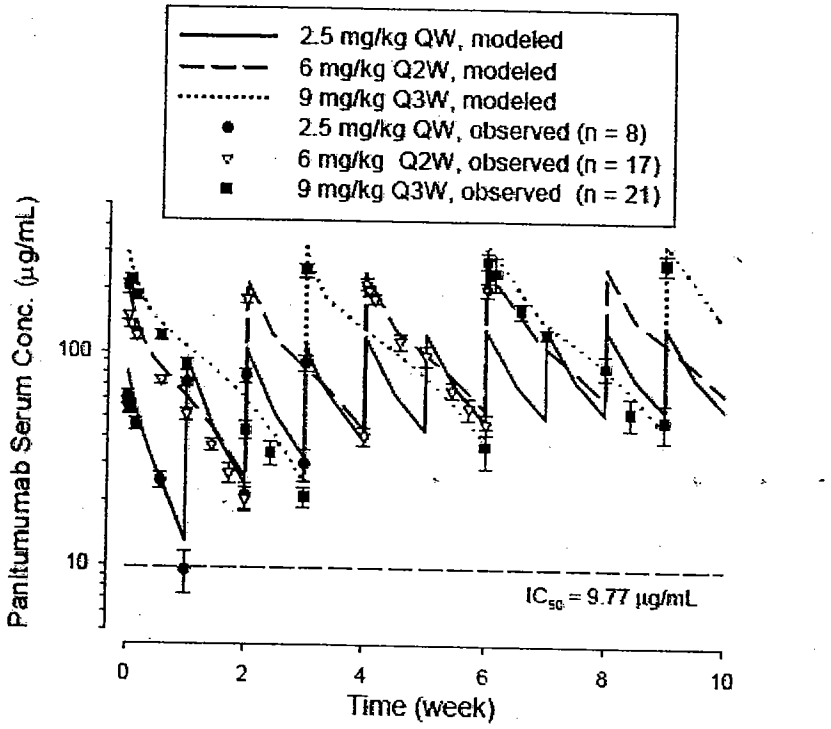

FIGURE 9: Modeled and Observed Mean (SE) Panitumumab Concentrations (Study 20030138) for Different Dosing Regimens

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites.

2.2.5.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Panitumumab administered as monotherapy or in combination with chemotherapy exhibits nonlinear PK (Figure 10). The area under the concentration-time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 0.75 to 9.0 mg/kg due to saturation of EGFr clearance pathway. Meanwhile, Panitumumab clearance (CL) decreased from 30.6 to 4.6 mL/day/kg. However, at doses above 2.0 mg/kg, the AUC of Panitumumab increased in an approximately dose propotional manner. Because of the large molecular size of Panitumumab (147 kDa), the volume of distribution is limited, which is 40 mL/kg for the central compartment and 26 mL/kg for the peripheral compartment.

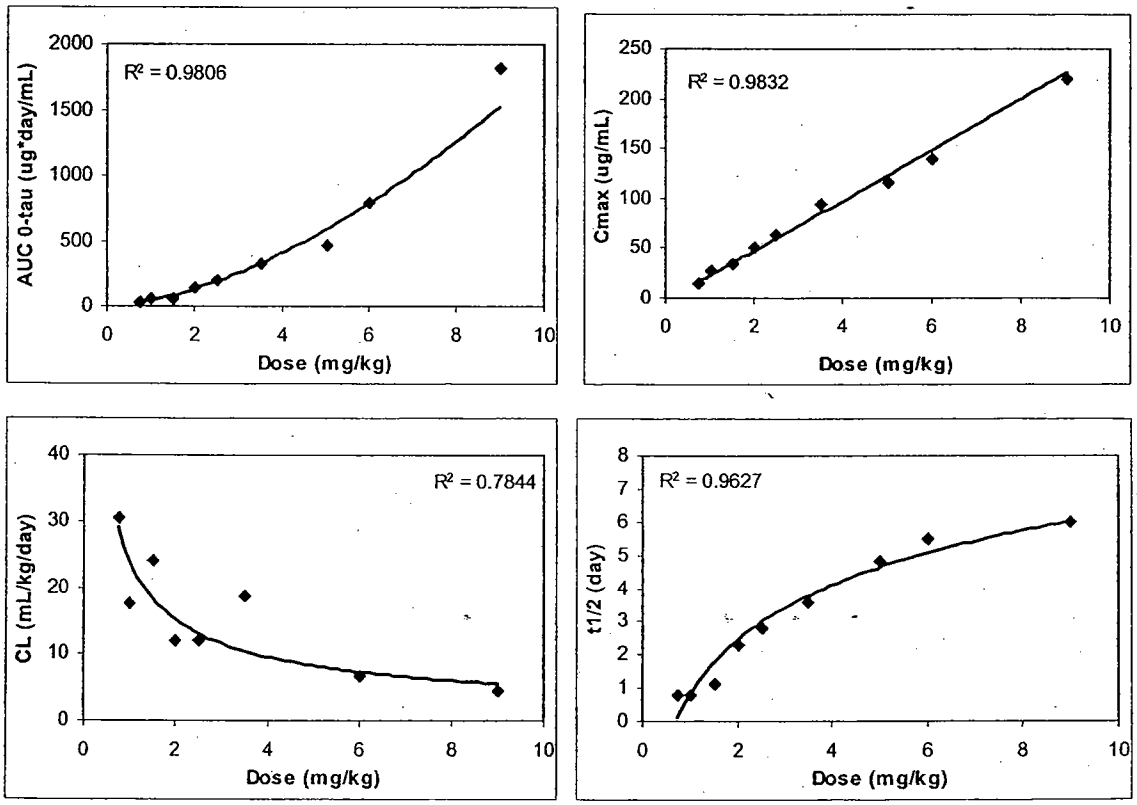

FIGURE 10: Plots of $AUC_{0\text{-}tau}$, C_{max}, CL and $T_{1/2}$ vs. Panitumumab Doses

2.2.5.2 Do PK parameters change with time following chronic dosing?

Yes. PK parameters of Panitumumab did change with time following chronic 6 mg/kg Q2W dosing as demonstrated in Figure 11. Values of CL obtained after the third dose were lower than those obtained after the first dose, while the half-life increased from 5.6 days to 7.5 days. The steady state was observed after 3 doses of 6 mg/kg Q2W. Three materials namely hybridoma, CHO, and CHO were used in clinical trials. The PK comparability results between hybridoma and CHO and between and

CHO are discussed in Section 4.5.

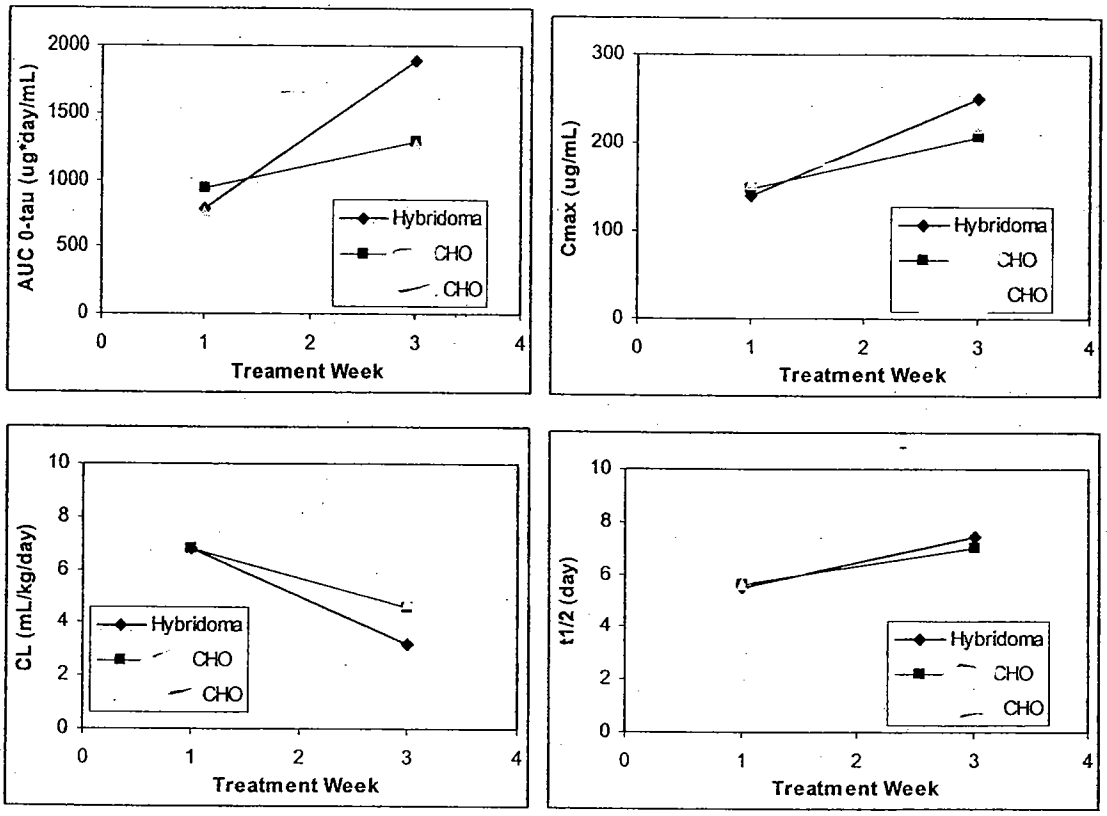

FIGURE 11: Plot of Panitumumab PK Parameters vs. Treatment Week

2.2.5.3 **How long is the time to the onset and offset of the pharmacological response or clinical endpoint?**

The overall response rates (ORR) were 8% and 0% in the Panitumumab and BSC alone arms, respectively. A statistically significant prolongation ($p < 0.001$; stratified log-rank test) in PFS was observed in patients receiving Panitumumab compared to those receiving BSC alone (Figure 12). Median PFS was 56 days and 51 days and mean PFS were 96 days and 60 days in the Panitumumab and BSC alone arms, respectively. However, there was no difference observed in OS between these two arms.

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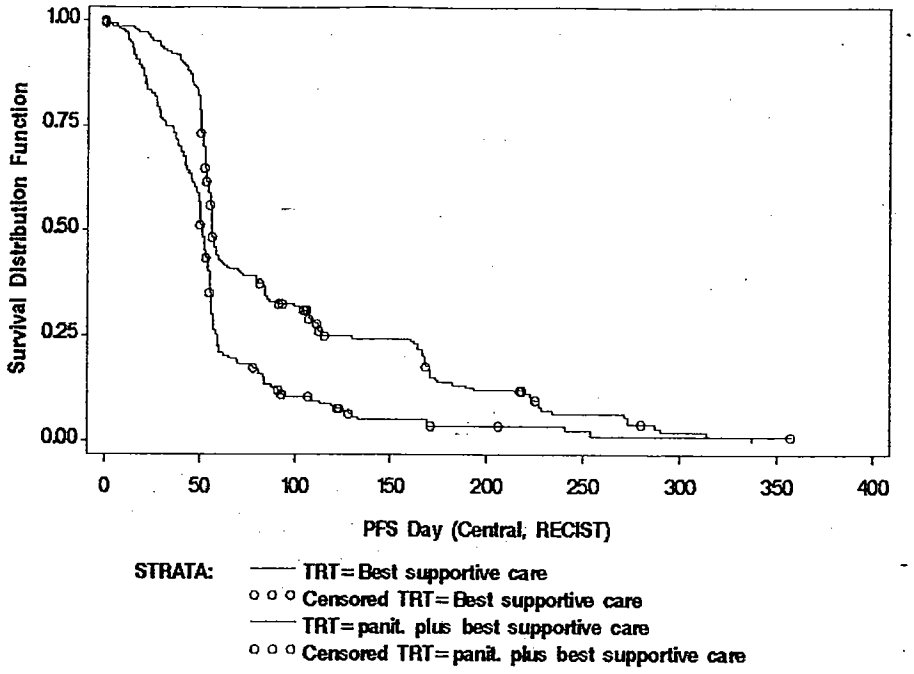

FIGURE 12: Progressive-Free Survival Kaplan-Meier Estimates (Study 20020408)

2.2.5.4 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetic information for intravenously administered Vectibix submitted in this application was obtained from cancer patients in a total of 15 studies. No PK studies were conducted in healthy volunteers.

2.2.5.5 What are the basic PK parameters?

The investigated Panitumumab dose levels in the clinical studies ranged from 0.01 to 5 mg/kg QW, 6 mg/kg Q2W, and 9 mg/kg Q3W. PK parameters for Panitumumab after first and third dose cross studies are listed in Tables 6 and 7. After intravenous (IV) infusion, serum Panitumumab concentrations declined bi-exponentially. The concentration-time profile was best described by a 2-compartmental PK model with linear and nonlinear clearance pathways, likely to be mediated by the reticuloendothelial system (RES) and EGFr, respectively. The time-averaged clearance decreased with increasing dose and approached the clearance value for endogenous immunoglobulin G1 (IgG1) and IgG2, suggesting saturation of EGFr at doses > 2 mg/kg QW.

TABLE 6. PK Parameters for Panitumumab after First Dose in all Studies [median (range)]

Study	Dose (mg/kg)	Dose Freq.	N	Material	$AUC_{0\text{-}tau}$ (µg*day/mL)	C_{max} (µg/mL)	CL (mL/kg/day)	T1/2 (day)
20030138 Phase 1, monotherapy ,subjects with advanced solid tumors	0.75	QW	5	hybridoma	25 (10-28)	14 (9-20)	30.6 (26.3-73.0)	0.8 (0.2-2.0)
	1	QW	4	hybridoma	58 (34-83)	28 (24-31)	17.7 (11.9-29.3)	0.8 (0.7-0.9)
	1.5	QW	6	hybridoma	60 (51-88)	34 (26-40)	24 (17-27)	1.1 (0.8-2.3)
	2	QW	3	hybridoma	147 (122-176)	50 (40-53)	12.0 (9.6-14.9)	2.3 (2.1-2.6)
	2.5	QW	8	hybridoma	194 (133-265)	63 (50-86)	11.9 (8.4-17.6)	2.8 (0.7-3.7)
	3.5	QW	7	hybridoma	328 (174-387)	94 (65-112)	18.7 (16.3-18.9)	3.6 (1.8-5.8)
	5	QW	5	hybridoma	468 (339-570)	116 (78-132)	NC	4.8 (3.3-5.8)
	6	Q2W	7	hybridoma	787 (641-1071)	140 (101-194)	6.8 (5.1-8.7)	5.5 (3.9-9.2)
	6	Q2W	10	— CHO	931 (554-1092)	148 (109-183)	6.8 (4.5-10.4)	5.6 (3.4-7.3)
	9	Q3W	5	hybridoma	1813 (968-2912)	220 (177-380)	4.6 (2.5-9.1)	6.0 (3.7-8.8)
	9	Q3W	16	— CHO	1622 (1038-2068)	211 (158-320)	4.8 (4.0-7.9)	6.5 (4.9-13.6)
20030251 Phase 1, monotherapy ,subjects with advanced solid tumors	6	Q2W	29	— CHO	757 (307-1096)	154 (97-204)	7.4 (4.4-19.5)	5.6 (1.1-11.1)
20040192 Phase 1, monotherapy , Japanese with advanced solid tumors	2.5	QW	6	— CHO	121 (109-205)	41 (35-57)	17.7 (14.7-19.8)	3.1 (2.4-3.9)
	6	Q2W	6	— CHO	705 (539-843)	107 (93-179)	8.5 (8.5-8.5)	6.9 (5.5-10.5)

TABLE 7. PK Parameters for Panitumumab after Third Dose in all Studies (median (range))

Study	Dose (mg/kg)	Dose Freq.	N	Material	$AUC_{0\text{-}tau}$ (µg*day/mL)	C_{max} (µg/mL)	CL (mL/kg/day)	T1/2 (day)
20030138	6	Q2W	4	hybridoma	1890 (1217-1981)	251 (170-266)	3.2 (3.0-4.9)	7.4 (6.8-8.2)
	6	Q2W	10	– CHO	1292 (823-1911)	207 (122-324)	4.6 (3.1-7.3)	7.0 (3.6-10.9)
	9	Q3W	2	hybridoma	2593 (2415-2771)	292 (281-303)	3.5 (3.3-3.7)	8.8 (8.1-9.6)
	9	Q3W	6	– CHO	2220 (1528-2639)	256 (169-282)	4.1 (3.4-5.9)	8.3 (6.8-10.6)
20030251	6	Q2W	22	– CHO	1259 (701-2002)	219 (134-397)	4.8 (3.0-8.6)	8.4 (4.8-21.7)
20040192	2.5	QW	6	– CHO	246 (197-384)	69 (53-89)	NC	4.2 (3.4-5.8)
	6	Q2W	4	– CHO	1059 (950-1195)	162 (140-177)	NC	7.4 (6.2-8.8)

PK parameters for – CHO Panitumumab after 3rd dose in Study 20030138 are listed in Table 8.

TABLE 8: PK Parameters (mean ± SD) for – CHO-derived Panitumumab after Third Dose (Studies 20030138, n=10)

Parameters	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}tau}$ (µg*day/mL)	$AUC_{0\text{-}\infty}$ (µg*day/mL)	CL (mL/kg/day)	$T_{1/2}$ (day)
Values	38.8 (13.7)	213.3 (59.1)	1305.7 (374.3)	1804.4 (598.3)	3.7 (1.4)	7.5 (2.1)

2.2.5.6 **Is this a high extraction ratio or a low extraction ratio drug?**

Not applicable because Panitumumab is a monoclonal antibody protein.

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

No mass balance study has been conducted for Panitumumab. Panitumumab is a monoclonal antibody. Mass balance studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that then recycled into other proteins.

2.2.5.8 **What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

A population PK analysis investigated the inter-individual variability associated with the PK data using nonlinear mixed-effect modeling (NONMEM, version V, level 1.1, GlobeMax Inc., Hanover, MA). The inter-subject variability of PK parameters is listed in Table 9. The estimated inter-subject variability is 53% and 25% for CL and volume of distribution, respectively. The population PK analysis identified the actual body weight to be a potentially influential covariate. Data from PK simulations suggest that a weight-based dose would result in less variability in Panitumumab exposure across body weights than a fixed dose, supporting the current use of body weight-based doses (mg/kg).

TABLE 9. PK Parameter Estimates in Population PK Analysis

	Fixed Effect: PK Parameter Estimates (%RSE)					
Model	V_1 (L)	V_2 (L)	K_m (µg/mL)	V_{max} (mg/day)	CL (L/day)	Q (L/day)
Base	3.50 (2.01%)	2.68 (3.19%)	0.371 (2.94%)	9.48 (1.08%)	0.269 (2.66%)	0.401 (2.97%)
Final	3.22 (1.32%)	2.49 (6.14%)	0.501 (21.2%)	10.1 (4.47%)	0.208 (5.63%)	0.380 (7.50%)

	Random Effects		
Model	Inter-subject variability on V_1 (%CV)	Inter-subject variability on CL (%CV)	Residual variability (%CV)
Base	29.2	62.8	29.6
Final	24.9	53.3	28.8

2.3 INTRINSIC FACTORS

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

A population PK analysis was performed to explore the potential effects of selected covariates on Panitumumab PK. Results suggest that age (26-85 years old), gender, tumor type (mCRC, Lung Cancer or Renal Cancer), race, mild to moderate renal function, mild to moderate hepatic function, chemotherapeutic agents, and EGFr expression intensity in tumor cells (1+, 2+ or 3+) had no apparent impact on the PK of Panitumumab. These results suggest that dose adjustments would not be necessary based on chemotherapy status, age, sex, or tumor type.

2.3.1.1 Age

Of the 225 subjects with PK and age information available from Studies 20030167, 20030250, and 20020408, 87 subjects (39%) were ≥65 years and 21 (9%) subjects were ≥ 75 years. No differences in Panitumumab concentrations were observed between subjects who were ≥65 years and who were < 65 years. No relationship was observed between Panitumumab concentration and age (Figure 13). Dose modification based on age is not necessary.

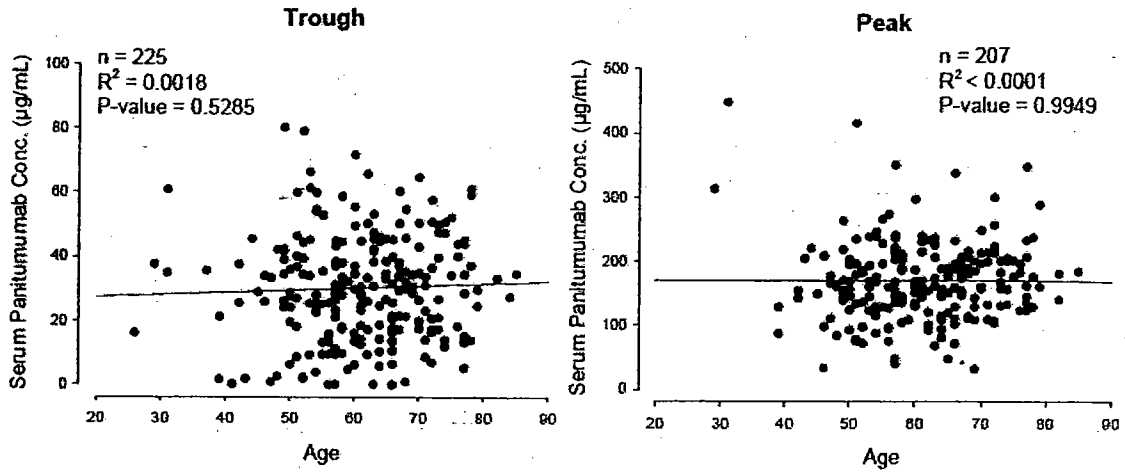

FIGURE 13: Panitumumab Concentrations vs. Age

2.3.1.2 Gender

Of the 225 subjects with PK and sex information available from Studies 20030167, 20030250, and 20020408, 83 subjects (37%) were women. The mean peak Panitumumab concentration values were similar between men and women (Figure 14). The mean C_{trough} of Panitumumab was 15% higher in women than in men (Table 10); however, the concentration ranges were similar between women and men.

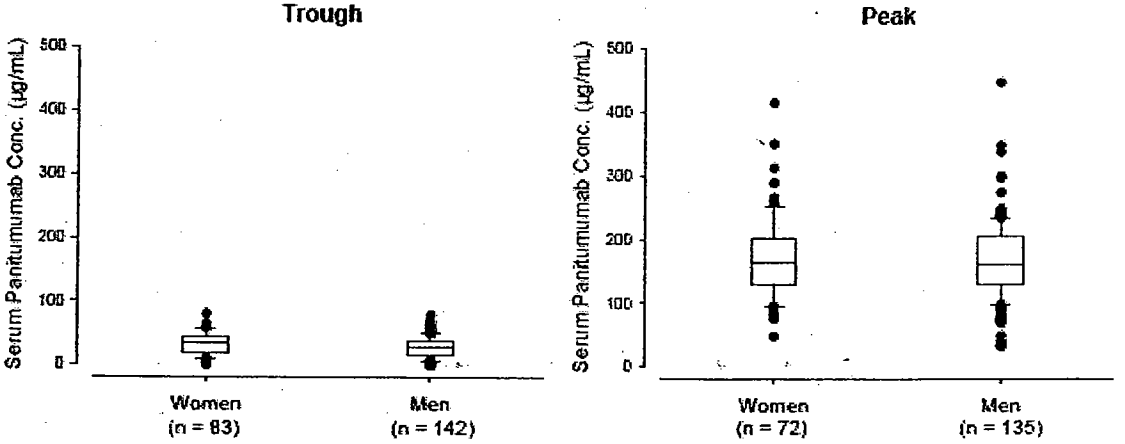

FIGURE 14: Serum Panitumumab Concentrations in Men and Women at Week 7 Before and After IV Infusion of Panitumumab at 6 mg/kg Q2W

TABLE 10. Summary of Serum Panitumumab Concentrations in Men and Women at Week 7 Before and After IV Infusion of Panitumumab at 6 mg/kg Q2W

Concentration	Woman			Man			Ratio	
(µg/mL)	Mean	%CV	n	Mean	%CV	n	(Woman/Man)	90% CI
Trough	33	51	83	29	57	142	115	102 to 129
Peak	172	37	72	168	36	135	102	93 to 111

Gender appeared to have no impact on the PK of Panitumumab. Similar efficacy and safety were observed for men and women patients in the clinical trials; therefore, dose modification based on gender is not necessary.

2.3.1.3 Race

Of the 225 subjects with PK and race information available from Studies 20030167, 20030250, and 20020408, only 17 subjects (8%) were non-White. The mean peak and trough Panitumumab concentrations were approximately 10% to 20% lower for non-White subjects than those for White subjects (Table 11).

TABLE 11. Serum Panitumumab Concentrations in White and Non-White Subjects at Week 7 before and after IV Infusion of Panitumumab at 6 mg/kg Q2W

Concentration (µg/mL)	non-White			White (reference)			Ratio	90% CI
	Mean	%CV	n	Mean	%CV	n		
Trough	24	77	17	31	53	208	79	56-101
Peak	150	30	16	171	37	191	88	72-103

Further analysis of the PK of Panitumumab for different ethnic subgroups that were included in the "non-White" category was conducted. No apparent differences in AUC values were observed among different ethnic groups (p-value = 0.46, Figure 15). It was noted that the mean value of AUC for Asian patients was lower (12%) than that for the White patients (Table 12). This difference was not statistically significant, and could be due to the effect of body weight on the PK of Panitumumab because serum Panitumumab concentrations were generally higher for heavier subjects than for lighter subjects. Based on the mean body weight data, the Asian patients (61.7 kg) were 25% lighter than White patients (82.8 kg).

TABLE 12. Summary of Simulated AUC Values and Observed Body Weights for Different Ethnic Groups

Race Category		n	Simulated AUC (µg·day/mL)	Body Weight (kg)
White	White	600	1250 ± 445	82.8 ± 20.3
Other	Black	45	1228 ± 436	83.7 ± 22.8
	Hispanic	30	1214 ± 448	82.0 ± 16.0
	Asian	29	1097 ± 329	61.7 ± 14.2
	Other	2	1326	78.2 – 85.6

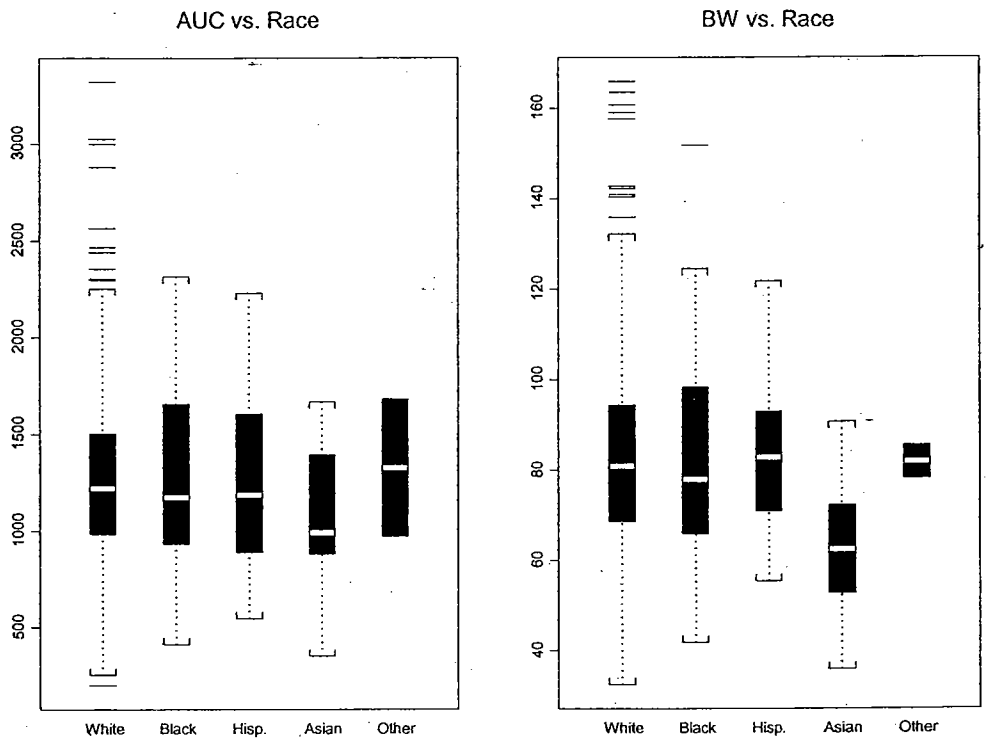

FIGURE 15: Distribution of Individual AUC Values and Body Weights among Different Ethnic Groups

An open-label, multicenter, phase 1 study is ongoing in Japanese patients with advanced solid tumors. Patients were enrolled to receive Panitumumab at 2.5 mg/kg QW, 6 mg/kg Q2W, or 9 mg/kg Q3W until disease progression. At the cut-off time, PK data were available from patients who received Panitumumab at 2.5 mg/kg QW (n = 6) and 6 mg/kg Q2W (n = 6). The overall serum Panitumumab concentrations were lower in this study than those observed in non-Japanese patients in Studies 20030138 and 20030251 (Figure 16 and Table 13). Because this study is ongoing, the conclusion on whether Japanese patients have different PK of Panitumumab compared with that in non-Japanese can not be drawn.

TABLE 13. Panitumumab PK Parameters after the First Dose of Panitumumab at 2.5 mg/kg and 6 mg/kg between Non-Japanese (Studies 20030138 and 20030251) and Japanese (Study 20040192) Subjects

Dose	2.5 mg/kg QW			6 mg/kg Q2W		
Parameters	$AUC_{0\text{-}tau}$ (μg*day/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)	$AUC_{0\text{-}tau}$ (μg*day/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)
Japanese	135	44	8	684	118	20
Non-Japanese (ref.)	199	64	12	740	152	18
Ratio	0.68	0.68	0.72	0.92	0.78	1.09

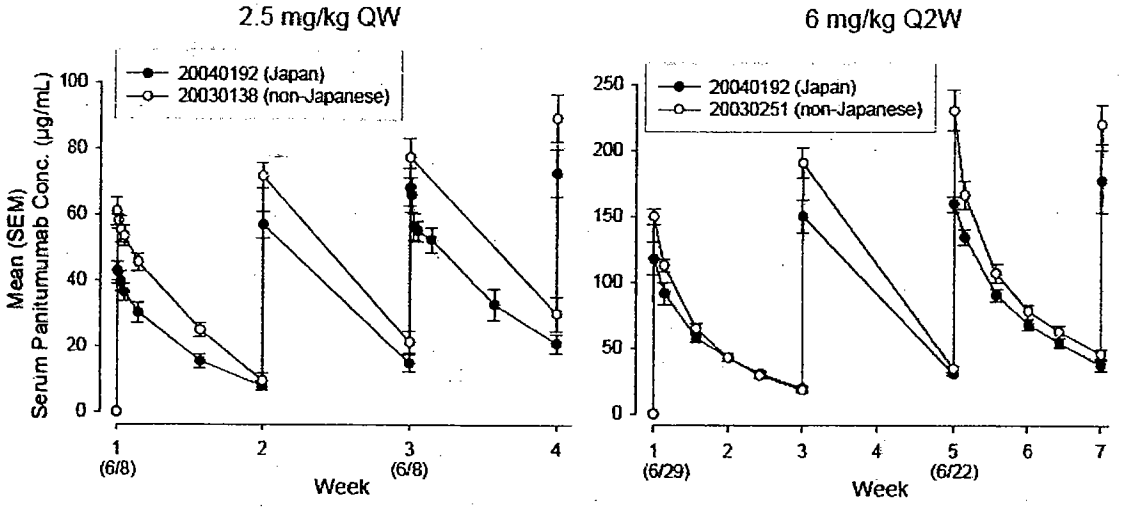

FIGURE 16: Comparison of Mean (SE) PK Profiles between Non-Japanese (Studies 20030138 and 20030251) and Japanese Subjects (Study 20040192)

2.3.1.4 **Body Weight**

As body weight increased, the AUC showed a trend of decreasing for the fixed-dose regimen (Figure 17, right panel), whereas it showed a trend of increasing for the weight-based regimen (Figure 17, left panel). Furthermore, a ratio in AUCs across weight of 1.46 for a weight-based and 2.52 for a fixed dose suggests that the weight-based dosing regimen is expected to result in lower variability in Panitumumab exposure.

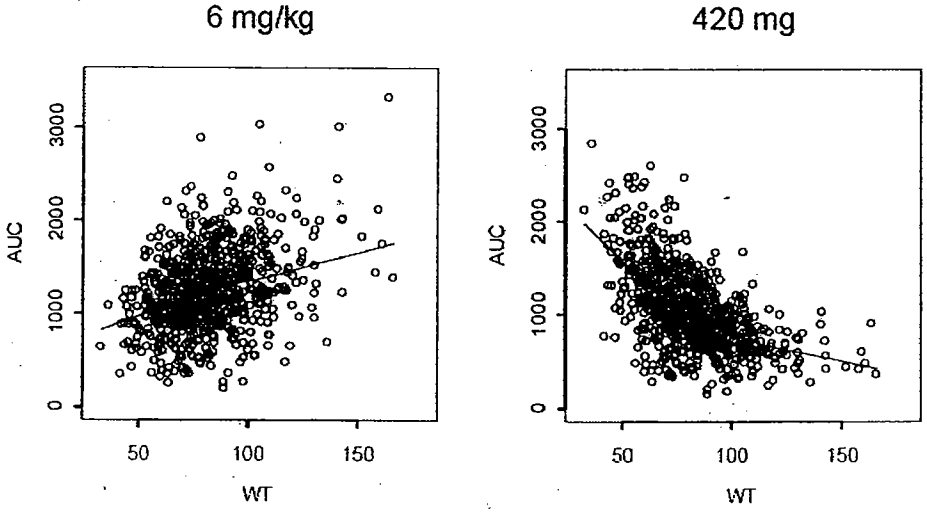

FIGURE 17: **Relationship between Body Weight and Simulated Steady State Exposure for Panitumumab Administered Once Every 2 Weeks (per sponsor's report # 104311)**

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 **Pediatric Patients**

The safety and effectiveness of Vectibix in pediatric patients have not been established. A Phase 1 pediatric study has been proposed as a PMC to be conducted in —

2.3.2.2 **Renal Impairment**

Two hundred and twenty five (225) patients had both PK and serum creatinine levels available in Studies 20030167, 20030250, and 20020408. The renal function was classified as normal (creatinine clearance CLcr > 80 mL/min), mildly impaired (CLcr = 50 to 80 mL/min), moderately impaired (CLcr = 30 to 49 mL/min), and severely impaired (CLcr < 30 mL/min). No patient in the dataset had severely impaired renal function. Although the mean peak and trough Panitumumab concentrations were higher in patients with mild or moderate renal impairment than in patients with normal renal function, the concentration ranges were similar among these subgroups (Table 14 and Figure 18). Renal function was used as a covariate in the population PK analysis and it appeared to have no impact on Panitumumab PK.

TABLE 14: Summary of Serum Panitumumab Concentrations in Patientss with Normal or Mildly-impaired Renal Function at Week 7 before and After IV Infusion of Panitumumab at 6 mg/kg Q2W

Concentration (µg/mL)	Mildly Impaired		Moderately Impaired		Normal	
	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N
C_{trough}	32 (42)	84	38 (54)	10	29 (62)	131
C_{max}	183 (28)	70	183 (30)	10	161 (41)	127

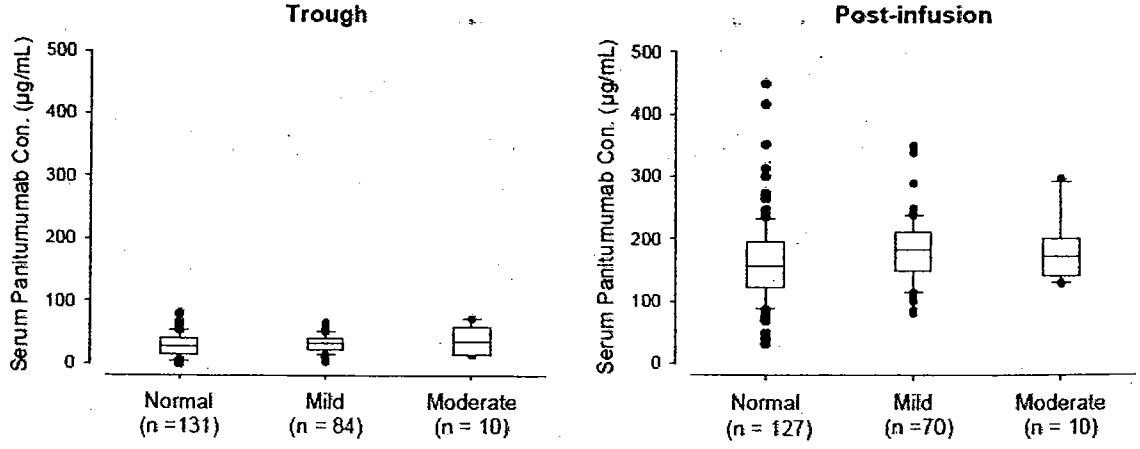

FIGURE 18: Relationship Between Renal Function and Serum Panitumumab Concentrations at Week 7 before and after IV Infusion of Panitumumab at 6 mg/kg Q2W

2.3.2.3 Hepatic impairment

A total of 225 patients had both PK and laboratory results associated with hepatic function available in studies 20030167, 20030250, and 20020408. Patients were considered to have "impaired" hepatic function if their serum aspartate aminotransferase or alanine aminotransferase was > 3 times the laboratory upper limit of normal or if their serum bilirubin was > 2 times the laboratory upper limit of normal at baseline. The mean C_{trough} of Panitumumab was approximately 10% higher in patients with hepatic impairment than in patients with normal hepatic function. However, the concentration ranges were similar between these two populations (Table 15). Hepatic function was used as a covariate in population PK analysis and it appeared to have no impact on Panitumumab PK.

TABLE 15: Serum Panitumumab Concentrations in Subjects with Normal or Impaired Hepatic Function at Week 7 before and after IV Infusion of Panitumumab at 6 mg/kg Q2W

Concentration (µg/mL)	Impairment			Normal			Ratio (Impairment/ Normal)	90% CI
	Mean	%CV	n	Mean	%CV	n		
Trough	34	51	9	30	55	216	113	82 to 144
Peak	177	37	8	169	36	199	104	83 to 126

An additional analysis was performed to evaluate the PK of Panitumumab in patients with different degrees of hepatic impairment as defined by the National Institutes of Health (NIH) criteria (Table 16).

Table 16. NIH Liver Function Classification

Liver Function Test	Normal (706)	Mild_1 (197)	Mild_2 (19)	Moderate (4)	Severe (1)
Total Bilirubin	≤ULN	≤ULN	> 1.0 – 1.5 x ULN	> 1.5-3 x ULN	> 3-10 x ULN
AST	≤ULN	> ULN	Any	Any	Any

ULN = upper limit of normal for the study participating institution
Numbers within parentheses correspond to the number of subjects included in the different hepatic impairment groups (derived using NIH classification criteria)

This analysis was performed using peak and trough Panitumumab concentrations collected from Studies 20030167, 20030250, and 20020408 conducted in Patients with metastatic colorectal cancer who had failed prior standard chemotherapy. Majority of patients had either normal or mildly impaired hepatic function per the NIH criteria. Only three and one patient had moderately and severly impaired hepatic function, respectively. Mean values for peak and trough panitumumab concentrations were similar among the different liver function groups (Table 17 and Figure 19). Results from this analysis

suggest that normal to mildly impaired hepatic function had no apparent impact on the PK of Panitumumab.

Table 17. Serum Concentrations of Panitumumab for Subjects with Varying Degrees of Hepatic Impairment

	Trough		Peak	
Liver function	n	Mean ± SD	n	Mean ± SD
Normal	144	32 ± 16	128	178 ± 62
Mild_1	64	30 ± 17	61	160 ± 60
Mild_2	11	22 ± 17	11	140 ± 60
Moderate	3	28 ± 14	3	152 ± 4

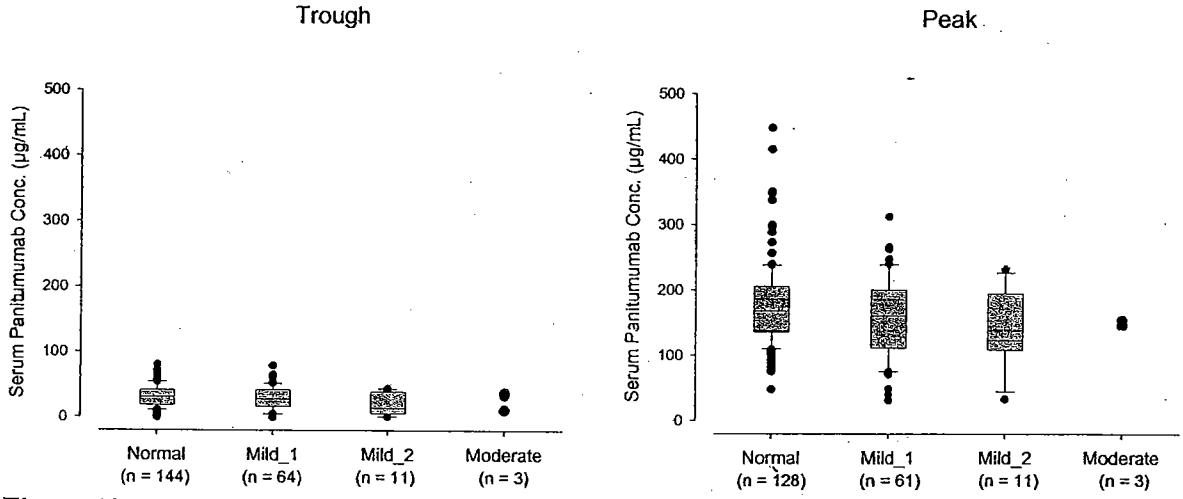

Figure 19. Relationship between Serum Panitumumab Concentrations and Hepatic Function at Week 7 before and after IV Administration of Panitumumab at 6 mg/kg Q2W

2.3.2.4 **What pregnancy and lactation use information is there in the application?**

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. However, EGFr has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Therefore, Panitumumab has the potential to cause fetal harm when administered to pregnant women and has been shown to be an abortifacient in cynomolgus monkeys when administered during the period of organogenesis at doses up to 6-fold the exposure of the recommended human dose on a mg/kg basis.

Human IgG is known to cross the placental barrier, therefore Panitumumab may be transmitted from the mother to the developing fetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with Panitumumab, and for 6 months following the last dose of Panitumumab. If Panitumumab is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential risk for loss of the pregnancy or potential hazard to the fetus.

Nursing Mothers: Studies have not been conducted to assess the secretion of

Panitumumab in human milk. Because human IgG is secreted into human milk, Panitumumab might also be secreted. The potential for absorption and harm to the infant after ingestion is unknown. Women must be advised to discontinue nursing during treatment with Panitumumab and for 2 months after the last dose of Panitumumab.

2.3.2.5 **Other factors that are important to understand the drug's efficacy and safety**

Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. The immunogenicity of Panitumumab has been evaluated using two different screening immunoassays for the detection of anti-Panitumumab antibodies, an acid dissociation bridging enzyme linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and Biacore® biosensor immunoassay (detecting both high and low-affinity antibodies). The results are shown in Table 18.

TABLE 18: Incidence of Non-Transient Anti-Panitumumab Antibodies

Assays	Pre-dose Positive N=636	Post-dose Positive N=447	Follow-up on Day 21 Positive N=197
Acid Dissolution ELISA	5 (<1%)	3 (<1%)	2 (1%)
Biacore	16 (2.5%)	19 (4.3%)	4 (2%)

For those patients whose sera tested positive in the screening immunoassays, an *in vitro* biological assay was performed to detect neutralizing antibodies. Seven of 447 (1.6%) of the patients with post-dose samples and 1/197 (< 1%) of the patients with follow-up samples were tested positive for neutralizing antibodies. There were no observed differences in PK profiles (Figure 20 and 21) between patients who developed antibodies to Panitumumab and those who did not. In the pivotal trial, all responders were negative for the anti-Panitumumab antibodies (Table 19).

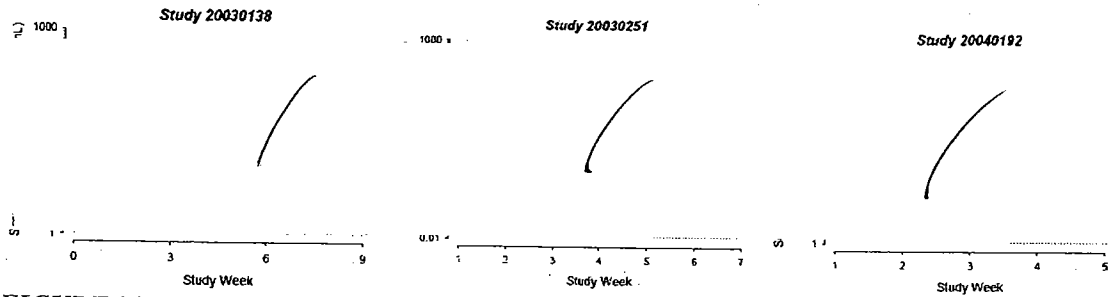

FIGURE 20: Effect of Anti-Panitumumab Antibodies on the PK Profiles (Phase 1 Monotherapy Studies with Intensive PK Sampling)

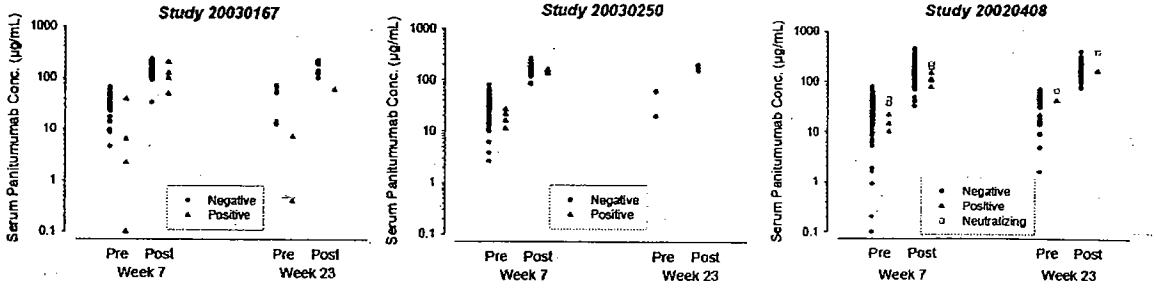

FIGURE 21: Effect of Anti-Panitumumab Antibodies on the PK Profiles (Phase 2/3 Monotherapy Studies with Sparse Sampling)

TABLE 19: Incidence of Immunogenecity for Responders and Non-responders in the Pivotal Trial

	Panitumumab		BSC	
Week 1 (n=434)				
	Responders (n=18)	**Non-responders (n=204)**	**Responders (n=1)**	**Non-responders (n=211)**
BiaCore Antibody (+)	**0**	**6**	**0**	**7**
Week 7 (n=246)				
	Panitumumab (n=175)		**BSC (n=71)**	
	Responders (n=18)	**Non-responders (n=157)**	**Responders (n=1)**	**Non-responders (n=70)**
BiaCore Antibody (+)	**0**	**11**	**0**	**1**
Follow-up Visit (n=194)				
	Panitumumab (n=72)		**BSC (n=122)**	
	Responders (n=18)	**Non-responders (n=204)**	**Responders (n=0)**	**Non-responders (n=122)**
BiaCore Antibody (+)	**0**	**5**		**0**

Infusion Reactions: In the randomized, controlled clinical trial of Vectibix monotherapy, 4% of patients experienced infusion reactions (defined as any reported allergic reaction, anaphylactoid reaction, chills, fever, or dyspnea, occurring within 24 hours of the first dose that were not otherwise designated as either anaphylactoid or allergic reaction). Severe infusion reactions (NCI CTC Grade 3-4) occurred with the administration of Vectibix in approximately 1% of all patients receiving Vectibix in clinical trials. Severe infusion reactions were identified by reports of anaphylactic reaction, bronchospasm, fever, chills, and hypotension. Although fatal infusion reactions have not been reported with Vectibix, fatalities have occurred with products in this pharmacologic class. Stop infusion for severe infusion reaction. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix.

Dermatologic Toxicity and Dose Modification: Dermatologic toxicities, including but not limited to dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures, were reported in 88% of patients and were severe (NCI-CTC grade 3 and higher) in 11% of patients receiving Vectibix monotherapy. Severe dermatologic toxicities were complicated by infection including sepsis, septic death, and abscesses requiring incisions and drainage. Withhold or discontinue Vectibix and monitor for inflammatory or infectious sequelae in patients with severe dermatologic toxicities.

Dose modification is recommended for the following clinical settings. If a patient develops dermatologic toxicities related to Panitumumab that are grade 3 or higher or are considered intolerable, temporarily withhold Panitumumab administration until the toxicities have improved. Once improved, reinstate Panitumumab administration at 50% of the original dose. If toxicities do not recur, escalate each additional dose of Panitumumab by 25% increments of the original dose until the recommended starting dose is reached. If toxicity does not resolve after withholding 1 or 2 doses of Panitumumab or if toxicity recurs or becomes intolerable at 50% of the original dose level, the use of Panitumumab should be permanently discontinued.

2.4 EXTRINSIC FACTORS

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

Except for concomitant medications, other factors have not been studied.

2.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.4.3 Drug-Drug interactions

2.4.3.1 **Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?**

No.

2.4.3.2 **Is the drug a substrate of CYP enzymes?**

No.

2.4.3.3 **Is the drug an inhibitor and/or an inducer of CYP enzymes?**

No.

2.4.3.4 **Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

No.

2.4.3.5 **Are there other metabolic/transporter pathways that may be important?**

No studies on the metabolism of Panitumumab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. This fact has been recognized in ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, "the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids". Therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P450 enzyme system is not expected to play any role in Panitumumab biotransformation.

2.4.3.6 **Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?**

No. Vectibix is used as monotherapy.

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

The most frequently reported concomitant medications for the Panitumumab plus BSC group were consistent with the known effects and complications of cancer and its treatment (ie, analgesics and gastrointestinal therapy). These included paracetamol (33%), omeprazole (20%), fentanyl (17%), morphine sulfate (17%), and tramadol hydrochloride (15%). Erythromycin use also was frequently reported in the Panitumumab plus BSC group (16%), but not in the BSC alone group (< 1%), and was generally used to treat skin-related conditions.

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

No formal drug-drug interaction studies have been conducted for Panitumumab with drugs that may be used in the intended patient population. Potential effects of drug-drug interactions on the PK between Panitumumab and chemotherapy agents were evaluated through cross-study comparisons.

1) In Study 20025404, Panitumumab was administered concurrently with Carboplatin/ Paclitaxel-containing chemotherapy: Panitumumab 1, 2, or 2.5 mg/kg QW 1-hour IV infusion + Paclitaxel 200 mg/m^2 Q3W 3-hour IV infusion + Carboplatin: target AUC of 6 mg·min/mL Q3W 30-minute IV infusion.

In this study, there was no cohort received Panitumumab alone. In order to evaluate the PK of Panitumumab with or without Paclitaxel/Carboplatin-containing chemotherapy regimen, Panitumumab PK data from Study 20025405 were used as a comparator. In

Study 20025405, patients received Panitumumab as monotherapy at 2.5 mg/kg QW after failure of prior standard Irinotecan and/or oxaliplatin-containing chemotherapy regimen (left panel, Figure 22). PK modelling using the peak and trough Panitumumab concentrations from Study 20025405 was conducted, and the modeled curve at 2.5 mg/kg QW was overlaid with the observed mean values at 2.5 mg/kg QW from Study 20025404 (right panel, Figure 22). The observed mean values from Study 20025404 were in agreement with the modelled curve from study 20025405, suggesting that Paclitaxel/Carboplatin-containing chemotherapy had no meaningful effect on the PK of Panitumumab.

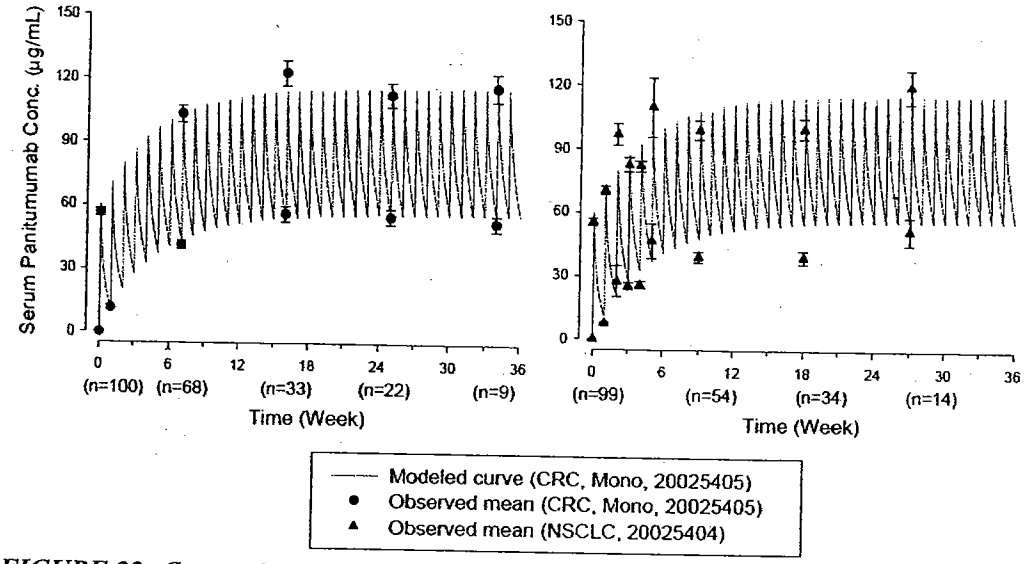

FIGURE 22: Comparison of Panitumumab Mean (SE) PK Profiles at 2.5 mg/kg QW after Monotherapy (Studyh 20025405) and in Combination with Paclitaxel/Carboplatin-containing Chemotherapy (Study 20025404)

Mean plasma Paclitaxel concentration-time profiles at Weeks 0 and 3 following the co-administration of Panitumumab and Paclitaxel are shown in Figure 23. Comparing with the PK paramters of Paclitaxel in the labeling, Panitumumab had no effect on the PK of Paclitaxel (Figure 23 and Table 20). The PK of Carboplatin was not evaluated because it is primarily eliminated through the kidney.

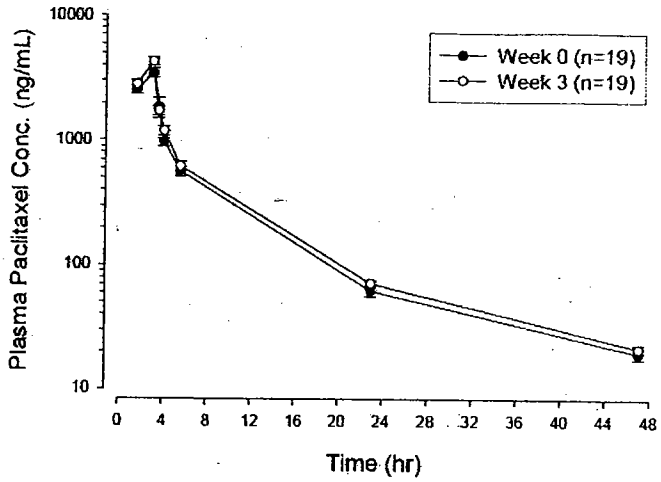

FIGURE 23. Mean Plasma Paclitaxel Concentration-time Profiles at Weeks 0 and 3 Given Concomitantly with Panitumumab at 2.5 mg/kg QW

TABLE 20. Paclitaxel Pharmacokinetic Parameters [Mean (SD)] after IV Infusions of Paclitaxel at 200 mg/m^2 Concurrently with Panitumumab at 2.5 mg/kg QW

Parameter	Week 0 (n = 19)	Week 3 (n = 17)	PI[a] (n = 5)	Schiller[b] (n = 10)
C_{max} (ng/mL)	3858 (1300)	4207 (1250)	3650	5122
AUC_{0-24} (ng·hr/mL)	14522 (4190)	16262 (3402)	15007	19121

[a]Taxol Prescribing Information 2003 (175 mg/m^2 given as a 3-hour IV infusion)
[b]Schiller et al, 1994 (210 mg/m^2 given as a 3-hour IV infusion)

2) In Study 20025409, 19 patients received IV infusions of Panitumumab at 2.5 mg/kg over 1 hour on day 1 of weeks 1 through 4 of the first 6-week cycle. Chemotherapy was administered on day 1 of weeks 1 to 4 according to the IFL regimen until disease progression, inability to tolerate Panitumumab, or other reasons for discontinuation. IFL dosing regimen is as the followings:

- Irinotecan at 125 mg/m^2, given IV infusion over 90 minutes (after completion of the Panitumumab infusion)
- Leucovorin at 20 mg/m^2, given IV bolus over 5 to 10 minutes (after completion of the Irinotecan infusion)
- 5-fluorouracil at 500 mg/m^2, given IV bolus over 5 to 10 minutes (after completion of the Leucovorin bolus)

Comparing the Panitumumab PK results obtained from Study 20025409 (Panitumumab + IFL) and Study 20030138, in which Panitumumab was administrated alone, Irinotecan had no effect on the PK of Panitumumab (Figure 24). Comparing the Irinotecan PK results obtained from this study to the PK information in the labeling, as well as results reported by Slatter[1], approximately a 30% decrease in C_{max} and AUC of Irinotecan, and its active metabolite, SN-38, was observed when Irinotecan-containing chemotherapy was administered concurrently with Panitumumab (Table 21). The clinical relevance of this finding is unknown. The sponsor has proposed to conduct a formal drug interaction study

between Panitumumab and Irinotecan as a PMC.

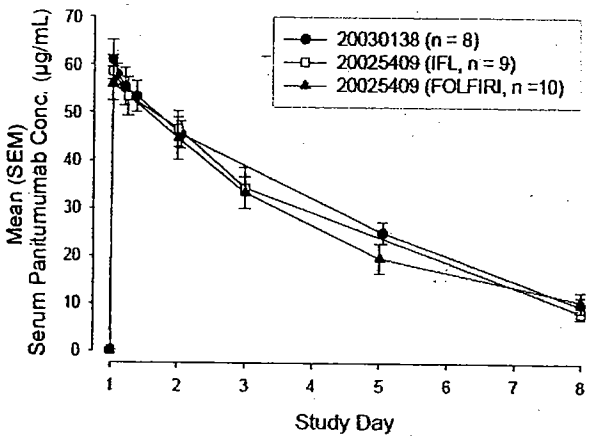

FIGURE 24: Mean (SE) Serum Panitumumab PK Profile after IV Administration of Panitumumab With or Without Irinotecan-based Chemotherapy (Studies 20025409 and 20030138)

TABLE 21. Summary of Irinotecan and SN-38 PK Parameter Values (Mean [SD]) after Weekly IV Administration of IFL Concurrently with Panitumumab at 2.5 mg/kg QW (Study 20025409)

Parameter	Week 1 (n = 10)	Week 3 (n = 9)	PI[a] (n = 64)	Slatter[b] (n = 8)
Irinotecan				
C_{max} (ng/mL)	1314 (300)	1199 (321)	1660 (797)	1534 (143)
AUC_{0-24} (ng·hr/mL)	7447 (2785)	7074 (2713)	10200 (3270)	7765 (1876)
SN-38				
C_{max} (ng/mL)	19.8 (5.2)	15.6(6.9)	26.3 (11.9)	27.1 (11.6)
AUC_{0-24} (ng·hr/mL)	168 (90)	159 (85)	229 (108)	228 (149)

[a]Camptosar Prescribing Information, 2005 (125 mg/m^2 given as a 90-minute IV infusion)
[b]Slatter J, 2000 (125 mg/m^2 given as a 90-minute IV infusion)

Panitumumab treatment can cause diarrhea as a single agent. When Panitumumab used in combination with Irinotecan, it appears to increase the severity and incidence of diarrhea. In clinical studies with Panitumumab as a single agent, diarrhea was reported as an adverse reaction in 106/789 (13%) of the treated patients. Most of these cases of diarrhea were mild or moderate in severity; < 2% had treatment-related grade 3 or higher diarrhea. In Study 20025409, 19 patients received Panitumumab in combination with Irinotecan, bolus 5-fluorouracil, and Leucovorin, the incidence of NCI-CTC grade 3-5 diarrhea was 58%. In the same study, 24 patients received Panitumumab plus FOLFIRI, the incidence of NCI-CTC grade 3-5 diarrhea was 25%. Therefore, the combination of Panitumumab with bolus IFL is not recommended.

2.4.3.9 **Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

None.

2.4.3.10 **Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?**

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The efficacy results from the pivotal trial, Study 20020408, were obtained using the — CHO material. The to-be-marketed — CHO Panitumumab was only used in Phase 1 studies. To support the manufacturing change between the —, CHO and the — expression system, the PK was assessed through a cross-study evaluation.

In Study 20030251, the PK profiles of Panitumumab were evaluated after administration of the —, CHO material at 6 mg/kg Q2W. The PK profiles after the first and third doses were similar to those from Study 20030138, in which —, CHO Panitumumab was administered (Figure 25). The 90% confidence intervals (CIs) of the parameter ratios (AUC $_{0-tau}$ after 1st dose and C_{max} after 3nd dose) were slightly outside the 80 to 125% bioequivalence criterion (Table 22). These PK differences between — and — CHO are likely due to the cross-study comparison with limited number of patients and they are not expected to affect clinical efficacy and safety.

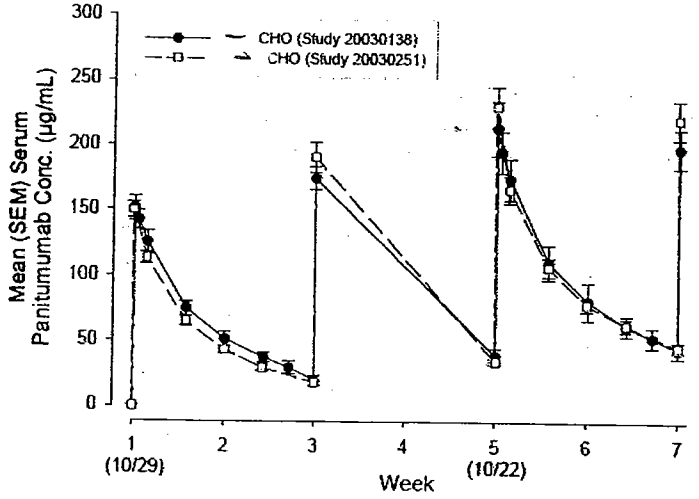

FIGURE 25: Mean (SEM) Serum Concentration-time Profiles of Panitumumab at 6 mg/kg Q2W from a — CHO Process (Study 20030138) and — CHO Process (Study 20030251)

TABLE 22. PK Parameters of Panitumumab after First and Third Dose of and CHO Panitumumab at 6 mg/kg (Study 20030138 and 20030251)

Parameters		After 1st dose		After 3rd dose	
		– CHO	— CHO	— CHO	– CHO
AUC_{0-tau} (µg*day/mL)	mean	841.3	744.2	1305.7	1310.5
	SD	177.3	195.5	374.3	372.5
	Geomean	823.5	714.9	1259.3	1259.3
	N	10	29	10	22
	Ratio 90%CI	87 73-104		100 83-121	
C_{max} (µg/mL)	mean	150.0	151.8	213.3	231.9
	SD	23.5	29.2	59.1	71.1
	Geomean	148.3	149.0	205.9	222.3
	N	10	29	10	22
	Ratio 90%CI	101 89-113		108 89-130	

During the drug development, hybridoma-derived Panitumumab was used in Phase 1 studies. The PK comparability between the hybridoma-derived and — CHO-derived Panitumumab at 6 mg/kg Q2W was assessed (Figure 26 and Table 23) in Study 20030138. After the first dose of 6 mg/kg Panitumumab, the difference in mean AUC_{0-tau} and C_{max} values for hybridoma-derived and CHO-derived Panitumumab were within 5% (Table 23). The 90% CIs for these two parameters were within the 80% to 125% interval (Bioequivalence Criterion) (Table 23). PK for hybridoma-derived and CHO-derived Panitumumab were comparable at dose of 6 mg/kg Q2W.

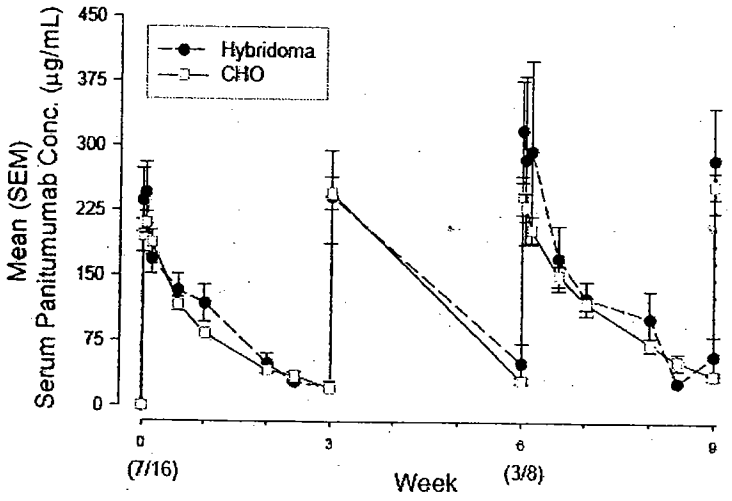

FIGURE 26: Mean (SE) Serum Panitumumab Concentration (Study 20030138)

TABLE 23. PK parameters of Panitumumab after the first dose of Hybridoma- and — CHO-derived Panitumumab at 6 mg/kg (Study 20030138)

Parameters		After 1st dose	
		— CHO	Hybridoma
AUC 0-tau (µg*day/mL)	mean	841.3	808.8
	SD	177.3	158.7
	Geomean	823.5	796.2
	N	10	7
	Ratio 90%CI	103 86-124	
C_{max} (µg/mL)	mean	150.0	143.6
	SD	23.5	29.0
	Geomean	148.3	141.1
	N	10	7
	Ratio 90%CI	105 90-123	

2.5.1.1 **What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

The PK differences observed between — and — CHO are likely due to cross-study comparison with limited number of patients and they are not expected to affect clinical efficacy and safety.

2.5.1.2 **If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?**

The sponsor submitted additional safety data in 61 patients treated with — CHO-derived Panitumumab. According to the clinical review, the safety profiles of the — CHO-derived Panitumumab appear to be similar to those with — CHO-derived Panitumumab.

2.5.1.3 **If the formulations are not BE, what dosing recommendations should be made that would allow approval of the to-be-marketed formulation? (e.g., dosage adjustments may be made for injectables)**

Not applicable.

2.5.2 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 because Vectibix is given via intravenous infusion.

2.5.3 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moiety identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

An immunoassay with electrochemiluminescence (ECL) detection was used to determine the active moiety, Panitumumab, in serum.

2.6.2 Which metabolites have been selected for analysis and why?

There is no metabolite selected for analysis because Panitumumab is a protein.

2.6.3 For all moiety measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Not applicable because Panitumumab is a protein.

2.6.4 What bioanalytical methods are used to assess concentrations?

An immunoassay with electrochemiluminescence (ECL) detection was used to measure Panitumumab concentration in human serum samples. A biotinylated anti-idiotypic antibody to Panitumumab was immobilized on streptavidin-coated magnetic beads and was used to capture Panitumumab in serum samples. A ruthenium-labeled Panitumumab anti-idiotypic antibody was used to detect Panitumumab. ECL counts were obtained by — analyzer (—) for standards, quality controls, and samples containing Panitumumab. The ECL counts produced by the analyzer were directly proportional to the amount of Panitumumab concentration.

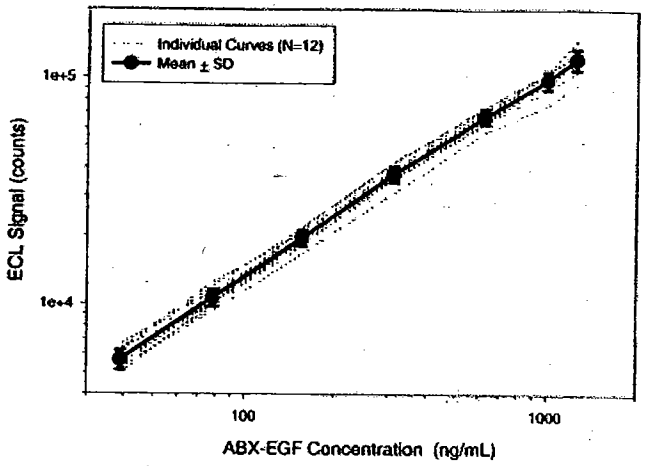

FIGURE 27: Panitumumab Calibration Curve

The calibration curve was log-linear over the entire range (Figure 27), and data were fit using a log-log model: Log(y) = A + B *Log(x)

- Calibration range: 39 ng/mL to 1250 ng/mL
  - The lowest calibration level, 39 ng/mL, had an inter-day mean recovery of 98 % and an inter-day precision of 4 .0% and was established as the lower limit of quantification (LLOQ) for the assay.
  - The highest calibration level, 1250 ng/mL, had an inter-day mean recovery of 98 .7% and an inter-day precision of 3.2% and was established as the upper limit of quantification (ULOQ) for the assay.
- Sensitivity: limit of quantification(LOQ) was 78 ng/mL.
- Accuracy and Precision:
  - Across all QC levels (50 (low), 100 (low-mid), 500 (mid), and 1000 (high) ng/mL) of analysts, intra-assay accuracy ranged from 86 .6% to 113% with precision ranging from 3 .3% to 8 .5%.
  - Inter-assay accuracy ranged from 71.6 to 113% with pooled variance of 15%.
- Back-calculated recovery across all assays ranged from 87.6 to 110%. The interday precision was between 2 .2 and 5 .0% over the calibration range of 39 to 1250 ng/mL.

2.6.5 Antibody Measurements

2.6.5.1 Acid Dissociation Bridging Enzyme Linked Immunosorbent assay (ELISA)

The double-antigen bridging ELISA was used for detecting antibodies to Panitumumab in serum samples. Anti-Panitumumab antibodies, if present, would form a "bridge" between the Panitumumab on the plate and the biotinylated Panitumumab added. The captured biotinylated Panitumumab was detected through the addition of

A subject was considered to be positive for a Panitumumab-induced human anti-human antibody (HAHA) response if the mean optical density of the postdose sample was at least 2 times higher than the mean optical density of the subject baseline (Week 0) sample.

2.6.5.2 Biacore Assay

The Biacore 3000 is a biosensor-based instrument that uses surface plasmon resonance (SPR) as the detection principle to monitor biomolecular binding events.

Two different Biacore immunoassays were developed and validated to detect antibody binding to Panitumumab and the premonomer. The assay was developed to be run as a single or dual flow cell assay enabling simultaneous or singular detection of antibody binding to Panitumumab and/or the premonomer respectively. Changes in refractive index due to mass accumulation at the sensor surface occur upon anti-Panitumumab antibody binding to the surface. This binding interaction is monitored and recorded in real-time on a sensorgram as a plot of the SPR signal (recorded in response units; RUs) over time (recorded in seconds). The change in RUs is directly proportional to the mass accumulation on the surface.

The threshold of the Panitumumab surface assay was validated at 168 response units (RU) for the Panitumumab surface and 196 RU for the premonomer surface. The assay sensitivity at the threshold is approximately 1 μg/mL based on titration of the anti-Panitumumab positive control antibody. For the purpose of identifying subjects with developing antibody responses, cutpoints were established using a concentration of 1.8 μg/mL control antibody. The cutpoints were set at 183 RU for the Panitumumab surface and 236 RU for the premonomer surface.

The specificity of binding to Panitumumab or the premonomer observed in serum samples was confirmed by competition through the addition of 1 mg/mL Panitumumab to the serum sample prior to testing. Only samples that tested above the assay threshold and were competed with the addition of free Panitumumab were considered positive for anti-Panitumumab antibodies.

2.6.5.3 Bioassay for Neutralizing Antibodies

Positive serum samples identified in either the acid-dissociation bridging ELISA or the Biacore immunoassays and confirmed by competition were further evaluated in a bioassay for neutralizing antibody activity. Briefly, the bioassay used the adherent human epidermoid carcinoma cell line A431, which expresses EGFr. Upon binding to the receptor, recombinant human EGF (rhEGF) induced the phosphorylation of tyrosine residues on the intracellular portion of EGFr. After stimulation, the EGFr was immunoadsorbed from A431 cell lysates onto streptavidincoated 96-well plates using a biotinylated monoclonal antibody that binds to the extracellular portion of the receptor. The intracellular phosphorylated portion of the captured EGFr was detected using a mouse monoclonal anti-phosphotyrosine antibody that is further detected using a ruthenium-labeled anti-mouse IgG antibody. Using an plate reader, an electrical current was placed across the plate-associated electrodes in the presence of a

tripropylamine (TPA)-containing buffer. The result was a series of electrically induced oxidation-reduction reactions involving ruthenium (from the captured complex) and TPA, leading to a luminescent signal. The consequent electrochemiluminescent (ECL) signal was measured by photodiodes and was quantified as counts per second (CPS). The validated limit of detection of the screening bioassay at the 95% confidence interval above background was 62.5ng/mL in neat human serum. The validated limit of quantitation for the screening bioassay was 125 ng/mL in neat human serum.

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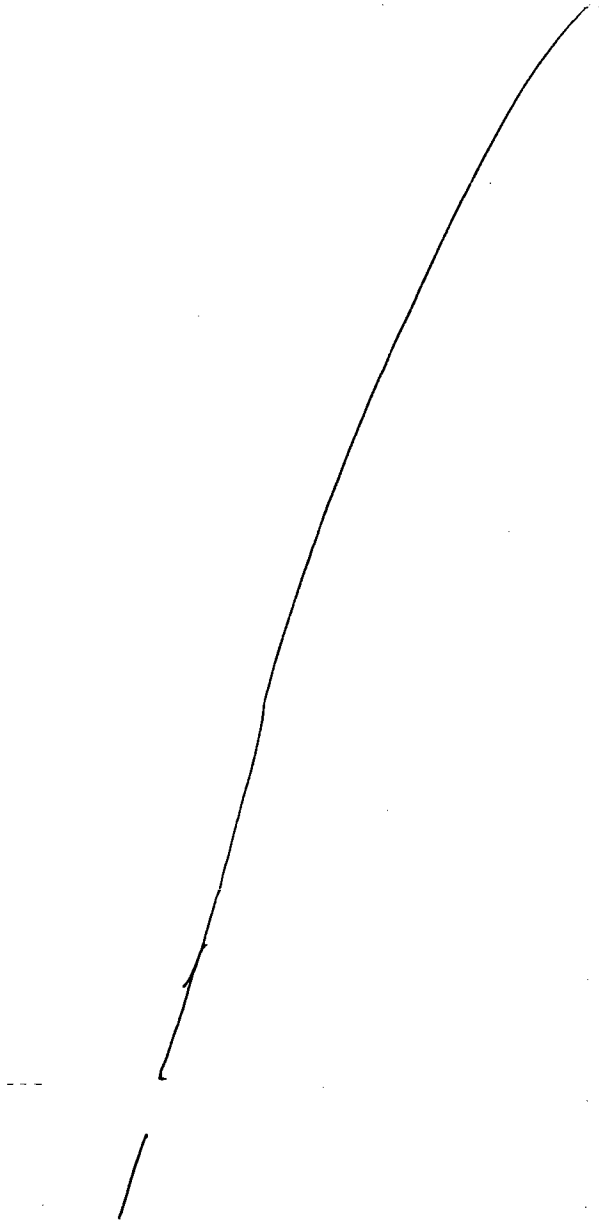
_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling



4 APPENDICES

4.1 APPENDIX 1 - INDIVIDUAL STUDY REVIEWS

Clinical Studies that Include Intensive PK Sample Collection

Study	Phase	Material	Dose (mg/kg)	Tumor Type
20030318	1	Hybridoma — CHO	0.75 – 5.0 QW; 6 Q2W; 9 Q3W	Solid tumors
20030251	1	— CHO	6 Q2W	Solid tumors
20040192	1	— CHO	2.5 QW; 6 Q2W	Solid tumors (Japanese)
20025404 (+paclitaxel+Carboplatin)	2	Hybridoma	1, 2, 2.5 QW	NSCLC
20025409 (+IFL)	2	Hybriodma	2.5 QW	mCRC

Clinical Studies that Include Sparse PK Sample Collection

Study	Phase	Material	Dose (mg/kg)	Tumor Type
20020408	3	— CHO	6 Q2W	mCRC
20025405	2	Hybridoma	2.5 QW	mCRC
20030167	2	CHO	6 Q2W	mCRC
20030250	2	— CHO	6 Q2W	mCRC
20025408	2	Hybridoma	2.5 QW	NSCLC
20030110	2	Hybridoma	2.5 QW	Prostate
20020374	2	Hybridoma	1, 1.5, 2, 2.5 QW	Renal
20040116	1	— CHO	0.1, 1.5, 2.5, 3.5, 5, 6 Q2W; 9 Q3W	Solid tumors

EGFR Exp.	20030250		20030167		20020408	
	Responders	Total N	Responders	Total N	Responders	Total N
<1%	2	36			0	1
1-10%	5	52	0	3	7	55
>10-20%			5	59	4	62
>20-35%			0	7	1	14
>35%			6	22	6	90
Total	7 (8%)	88	11 (12%)	91	18 (8%)	222

1. **Study 20030138 (Abgenix Study No.ABX-EG-9901):**

Title: An Open Label, Multiple Dose, Dose-rising Clinical Trial of the Safety of ABX-EGF in Patients With Renal, Prostate, Pancreatic, Nonsmall-cell Lung, Colorectal, or Esophageal Cancer

2. **Study 20040116 (Abgenix Study No.ABX-EG-9902):**

Title: An Open Label, Maintenance Dosing, Clinical Trial of ABX-EGF in Patients With Renal, Prostate, Pancreatic, Nonsmall-cell Lung, Colorectal, or Esophageal Cancer; to Follow Clinical Trial ABX-EG-9901

Indication: —

Brief Description:

Study 20030138 was a multicenter study to evaluate the safety and PK (PK) of multiple

escalating doses of Panitumumab administered intravenously to subjects with advanced solid tumors.

Study 20040116 assessed the safety of continued Panitumumab treatment in subjects who benefited from and tolerated Panitumumab treatment in Study 20030138.

Methodology:

In Study 20030138, subjects were to receive 4 intravenous infusions of Panitumumab, administered over a period of 4 weeks (1 infusion every week [QW]), 8 weeks (1 infusion every 2 weeks [Q2W]), or 12 weeks (1 infusion every 3 weeks [Q3W]). In dose cohorts 1 to 5 and 6b, subjects received a loading dose (twice the assigned dose) followed by 3 additional doses at the assigned dose level. All other dose cohorts (6a; 7 to 16) received 4 infusions at the same dose level. Dose cohorts 1 to 14 received Panitumumab produced by a manufacturing process using hybridoma cells; dose cohorts 15 and 16 received Panitumumab produced by a manufacturing process using Chinese hamster ovary (CHO) cells — scale process). Subjects were enrolled into dose cohorts in a sequential, ascending-dose fashion as shown in the following table.

Dose Cohorts and Regimens in Study 20030138

Dose Cohort	Assigned Dose (mg/kg)	Frequency	Loading Dose [a]	Infusion Duration (hr)	Manufacturing Cell Expression System
1	0.01	QW	Yes	2	Hybridoma
2	0.03	QW	Yes	2	Hybridoma
3	0.1	QW	Yes	2	Hybridoma
4 [b]	0.3	QW	Yes	2	Hybridoma
5	1.0	QW	Yes	2	Hybridoma
6a [b]	0.75	QW	No	2	Hybridoma
6b [c]	0.75	QW	Yes	2	Hybridoma
7	1.0	QW	No	2	Hybridoma
8	1.5	QW	No	1	Hybridoma
9	2.0	QW	No	1	Hybridoma
10	2.5	QW	No	1	Hybridoma
11	3.5	QW	No	1	Hybridoma
12	5.0	QW	No	1	Hybridoma
13	6.0	Q2W	No	1	Hybridoma
14	9.0	Q3W	No	1	Hybridoma
15	6.0	Q2W	No	1	CHO
16	9.0	Q3W	No	1	CHO

[a] In cohorts administered loading doses, the first dose was twice the assigned dose (eg, for Dose Cohort 1, subjects were administered a loading dose of 0.02 mg/kg followed by 3 weekly doses of 0.01 mg/kg).

[b] Selected subjects in these dose cohorts received 4 infusions of panitumumab at weeks 0, 3, 4, and 5 to allow for a complete assessment of PK after the first dose ("PK dosing schedule")

[c] Enrolled in conjunction with Cohort 6a.

Source: Source: Table 15-1.2.1 and Study 20030138 protocol (Appendix 1)

Subjects whose disease was considered "stable" or "responding" at the last visit in Study 20030138 were screened for eligibility and, if eligible, allowed to participate in the follow-up

study, 20040116.
In Study 20040116, subjects originally assigned to a QW regimen in Study 20030138 received the same Panitumumab dose Q2W; those originally assigned to a Q2W or Q3W regimen continued to receive the same dose and schedule as originally assigned.
In Study 20040116, subjects were scheduled to receive 8 doses (Q3W) or 12 doses (Q2W) of Panitumumab over 6 months; the duration of the safety follow-up was 4 weeks, starting the day after the last dose of Panitumumab.

Subjects:
Ninety-seven subjects were enrolled in Study 20030138; 96 received at least 1 dose of Panitumumab:
Sex: 72 (75%) men, 24 (25%) women **Mean (SD) Age:** 60.4 □11.0 years
Ethnicity (Race): 84 (88%) White or Caucasian, 8 (8%) Black or African American, 2 (2%) Hispanic or Latino, 1 (1%) Asian, 1 (1%) Other (East Indian)
Twenty subjects continued Panitumumab treatment in Study 20040116:
Sex: 13 (65%) men, 7 (35%) women **Mean (SD) Age:** 54.1 □11.1 years
Ethnicity (Race): 19 (95%) White or Caucasian, (5%) Asian

A tumor sample showing EGFr-positive staining by immunohistochemistry (IHC) in ≥10% of tumor cells was required.

Product:
Panitumumab manufactured using the hybridoma expression system was supplied at 10 mg/mL in 5-mL vials. Fill lot numbers were 1708/TFP-99015, 2090/TFP-99027, 2439/TFP-99028, 3737/TFP-99059A, 5940/TFP-00072, 7096/TFP-00093, 7334/TFP-00098, 8084/TFP-01023, 9204/TFP-01046, 9974/TFP-01075, TFP-02066, N10004F, and P01007F.
Panitumumab manufactured using the CHO expression system (— , scale manufacturing process) was supplied at 20 mg/mL in 10-mL vials. Fill lot numbers were A021929 and A023479.

Duration of Treatment:
Subjects were scheduled to receive 4 intravenous infusions of Panitumumab, given QW for 4 weeks; Q2W for 8 weeks, or Q3W for 12 weeks. Subjects who continued treatment in Study 20040116 were scheduled to receive up to 8 additional doses (Q3W) or 12 additional doses (Q3W) of Panitumumab over 6 months. Subjects who benefited from treatment in Study 20040116 could continue to receive Panitumumab treatment in extended-treatment Study 20020375.

Efficacy Endpoints (for both studies except as noted):
Primary : tumor response rate
Study 20030138: after the treatment period (week 7 for the QW and Q2W schedules; week 15 for the Q3W schedule)
o Study 20040116: best response throughout treatment

Pharmacokinetic Endpoints (for both studies except as noted):
- predose and postdose serum concentrations of Panitumumab for all subjects after each administration (for Study 20030138; at selected infusions for Study 20040116)
- PK parameters after the first dose for dose cohorts 6 to 16 (≥0.75 mg/kg QW) and after the third dose for dose cohorts 13 to 16 (6 mg/kg Q2W and 9 mg/kg Q3W): observed

maximum serum concentration (Cmax), area under the serum concentration-time curve (AUC), clearance (CL), half-life (t1/2) (for Study 20030138)

Table 7-10. Sampling Time Points for Serum Samples for Panitumumab Concentration in Study 20030138

	Sampling Time Points				
Regimen	Infusion 1	Infusion 2	Infusion 3	Infusion 4	Safety Follow-up
QW	Pre-infusion Postinfusion: 0.5, 1, 4, 8, 24, and 96 hours	Pre-infusion Postinfusion: 0.5 hours	Pre-infusion Postinfusion: 0.5 hours	Pre-infusion Postinfusion: 0.5 hours	2, 4, and 6 weeks after last infusion
Q2W	Pre-infusion Postinfusion: 0.5, 8, 24, 96, 168, 240, and 288 hours	Pre-infusion Postinfusion: 0.5 hours	Pre-infusion Postinfusion: 0.5, 8, 24, 96, 168, 240, and 288 hours	Pre-infusion Postinfusion: 0.5 hours	2, 4, and 6 weeks after last infusion
Q3W	Pre-infusion Postinfusion: 0.5, 8, 24, 96, 168, 336, and 408 hours	Pre-infusion Postinfusion: 0.5 hours	Pre-infusion Postinfusion: 0.5, 8, 24, 96, 168, 336, 408 hours	Pre-infusion Postinfusion: 0.5 hours	4, 6, and 8 weeks after last infusion
PK Dosing	Pre-infusion Postinfusion: immediately, 0.25, 0.5, 1, 4, 8, and 24 hours; Week 1 visit; and Week 2 visit	Pre-infusion Postinfusion: immediately	Pre-infusion Postinfusion: immediately	Pre-infusion Postinfusion: immediately	2, 4, and 6 weeks after last infusion

In Study 20040116, serum samples were collected before and 30 minutes after all infusions on weeks 0, 6, 14, and 22 for subjects on the Q2W regimen, and on weeks 0, 9, and 21 for subjects on the Q3W regimen.

Serum samples were stored at approximately –70°C until assayed using a validated electrochemiluminescence (ECL) detection method at Abgenix.

Efficacy Results:

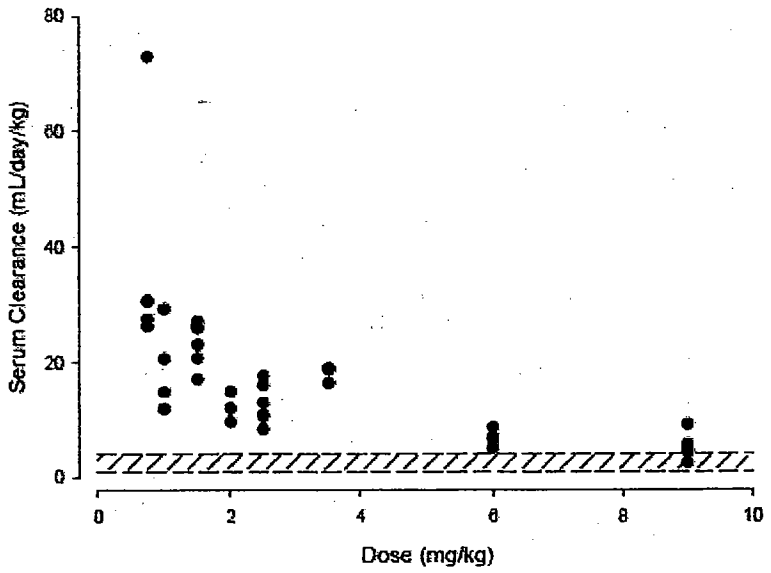
PK Results:

Panitumumab exhibited nonlinear PK in a dose range of 0.75 to 9 mg/kg. Clearance decreased with increasing dose and approached the clearance value for endogenous IgG2; the nonlinear clearance is consistent with progressive saturation of EGFr. Based on the exposure (Cmax and AUC0-tau) after the first dose, the PK of Panitumumab derived from the hybridoma and CHO expression systems were comparable.

PK Parameters for Panitumumab after First Dose Cross all Studies (median (range))-study 20030138

Study	Dose (mg/kg)	Dose Freq.	N	Material	$AUC_{0\text{-}tau}$ (µg*day/mL)	C_{max} (µg/mL)	CL (mL/kg/day)	T1/2 (day)
20030138 Phase 1, monotherapy ,subjects with advanced solid tumors	0.75	QW	5	hybridoma	25 (10-28)	14 (9-20)	30.6 (26.3-73.0)	0.8 (0.2-2.0)
	1	QW	4	hybridoma	58 (34-83)	28 (24-31)	17.7 (11.9-29.3)	0.8 (0.7-0.9)
	1.5	QW	6	hybridoma	60 (51-88)	34 (26-40)	24 (17-27)	1.1 (0.8-2.3)
	2	QW	3	hybridoma	147 (122-176)	50 (40-53)	12.0 (9.6-14.9)	2.3 (2.1-2.6)
	2.5	QW	8	hybridoma	194 (133-265)	63 (50-86)	11.9 (8.4-17.6)	2.8 (0.7-3.7)
	3.5	QW	7	hybridoma	328 (174-387)	94 (65-112)	18.7 (16.3-18.9)	3.6 (1.8-5.8)
	5	QW	5	hybridoma	468 (339-570)	116 (78-132)	NC	4.8 (3.3-5.8)
	6	Q2W	7	hybridoma	787 (641-1071)	140 (101-194)	6.8 (5.1-8.7)	5.5 (3.9-9.2)
	6	Q2W	10	[redacted] CHO	931 (554-1092)	148 (109-183)	6.8 (4.5-10.4)	5.6 (3.4-7.3)
	9	Q3W	5	hybridoma	1813 (968-2912)	220 (177-380)	4.6 (2.5-9.1)	6.0 (3.7-8.8)
	9	Q3W	16	[redacted] CHO	1622 (1038-2068)	211 (158-320)	4.8 (4.0-7.9)	6.5 (4.9-13.6)

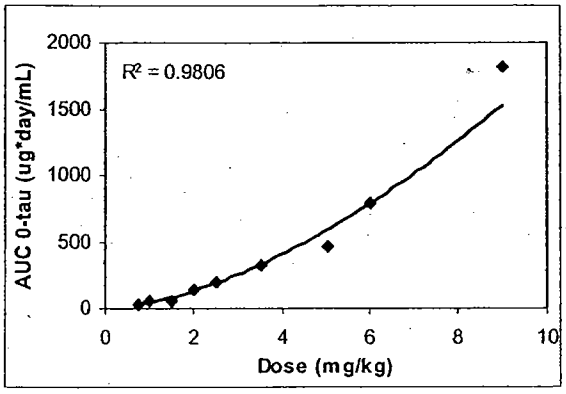
Figure 10-1. Individual Panitumumab Clearance After the First Dose (Study 20030138)

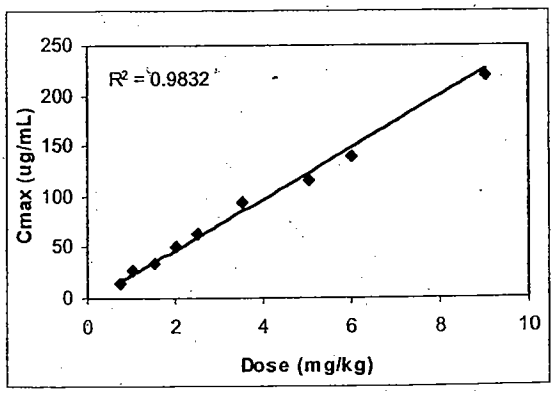


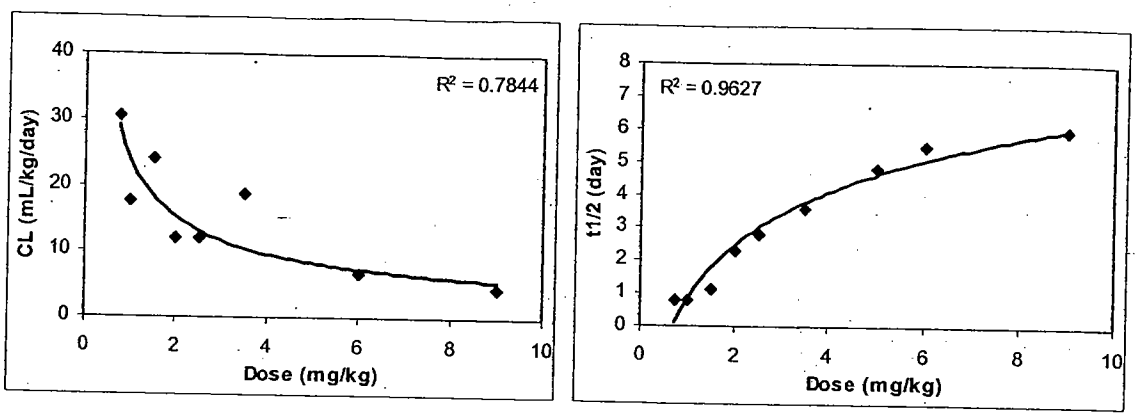
Shaded area represents the typical human IgG_1 and IgG_2 clearance values expected when antigen-mediated clearance is absent (Humira®, 2002; ABX-IL8, Abgenix data on file).

Source: Figure 7.4 of the PK report (Appendix 12)

VECTIBIX™ administered as monotherapy or in combination with concomitant chemotherapy exhibits nonlinear PK (Figure 6). The area under the concentration-time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 0.75 to 9.0 mg/kg. Meanwhile, VECTIBIX™ clearance (CL) decreased from 30.6 to 4.6 mL/day/kg. Because of the large molecular size of Panitumumab (147 kDa), the volume of distribution is limited. The volume of distribution approximated the plasma volume, 40 mL/kg, for the central compartment and was approximately 26 mL/kg for the peripheral compartment.



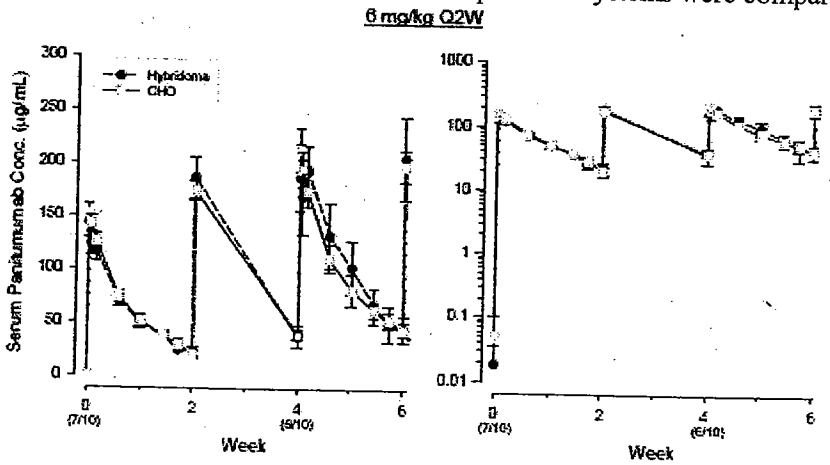




Plots of $AUC_{0\text{-}tau}$, C_{max}, CL and $T_{1/2}$ vs. Panitumumab Doses (Study 20030138)

PK Comparability:

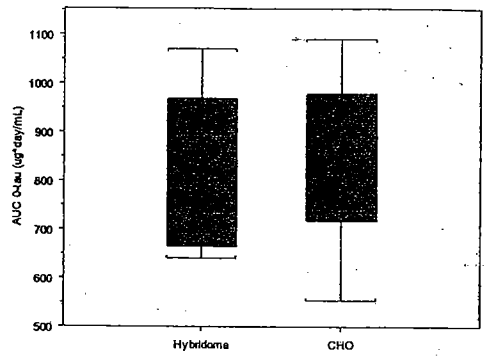
Based on the exposure (Cmax and AUC0-tau) after the first dose, the PK of Panitumumab derived from the hybridoma and CHO expression systems were comparable.

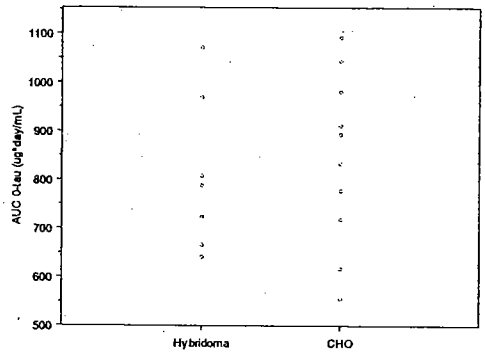


Parameters		After 1st dose		After 3rd dose	
		CHO	Hybridoma	CHO	Hybridoma
AUC 0-tau (µg*day/mL)	mean	841.3	808.8	1305.7	1744.3
	SD	177.3	158.7	374.3	361.5
	Geomean	823.5	796.2	1259.3	1711.9
	N	10	7	10	4
	Ratio 90%CI	103 86-124		74 55-98	
C_{max} (µg/mL)	mean	150.0	143.6	213.3	234.2
	SD	23.5	29.0	59.1	43.9
	Geomean	148.3	141.1	205.9	230.7
	N	10	7	10 (9*)	4
	Ratio 90%CI	105 90-123		89 (85) 67-118 (66-110)	

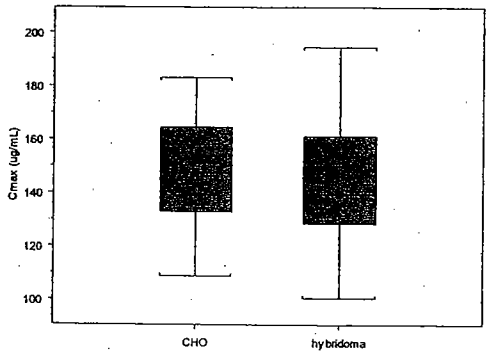
After 1st dose: CHO vs. Hybridoma

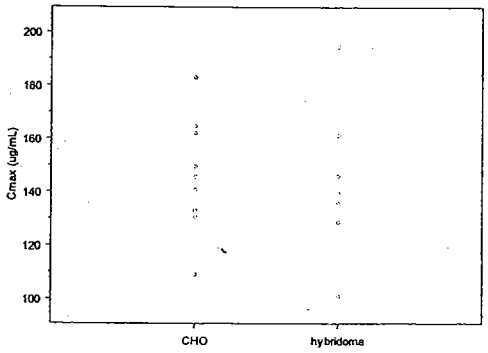
AUC 0-tau:



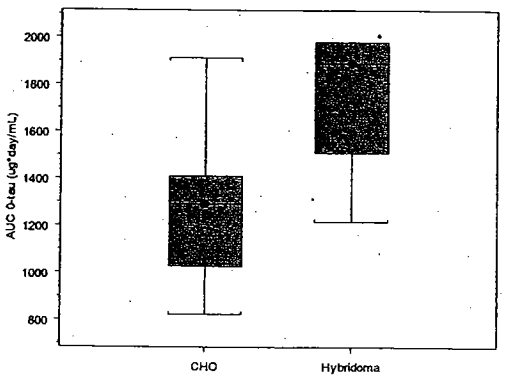


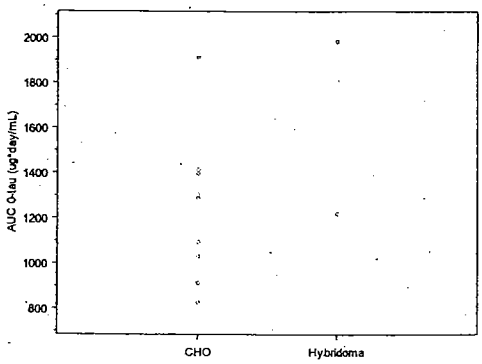
Cmax after 1st dose:



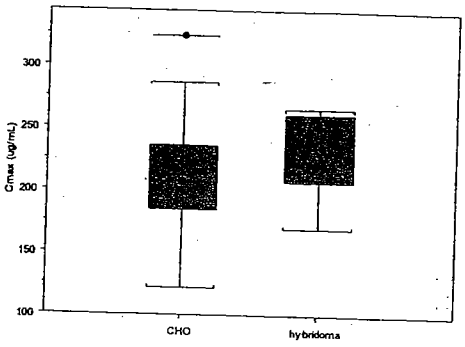


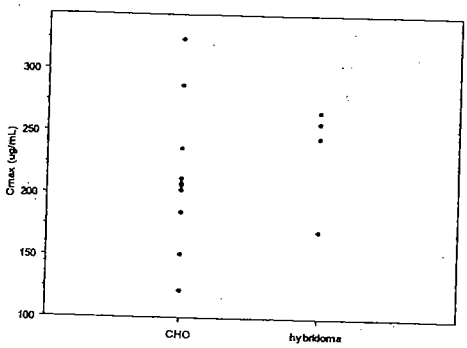
AUC0-tau after 3rd dose:





Cmax after 3rd dose:





The most frequent treatment-related adverse events (incidence ≥10%) were rash (60%), dry skin (19%), fatigue (16%), diarrhea (14%), nausea (13%), and stomatitis (10%). Most subjects (79%) experienced treatment-related adverse events that were mild or moderate in severity; 8% of subjects experienced grade 3 treatment-related adverse events, and 1% experienced a grade 4 treatment-related adverse event.

This study did not reach a maximum tolerated dose (MTD).

The most frequent skin toxicities (incidence ≥10%) were rash (61%) and dry skin (19%); these occurred more frequently in the dose cohorts receiving ≥2.5 mg/kg Panitumumab than in the dose cohorts receiving < 2.5 mg/kg Panitumumab. The median duration of skin toxicity tended to be longer in the 6 mg/kg Q2W and 9 mg/kg Q3W dose cohorts (range of medians: about 15 to 17 weeks) as compared with lower dose cohorts (range of medians: about 4 to 10 weeks); however, the duration of exposure was longer on the Q2W and Q3W schedules (8 and 12 weeks, respectively) than on the QW schedule (4 weeks).

Antibodies to Panitumumab were not detected among subjects who had a baseline sample and ≥1 postbaseline sample for assessment of HAHA (80 subjects [83%] in Study 20030138; 16 subjects [80%] in Study 20040116). No evidence of cardiotoxicity was observed.

Conclusions:

This large phase 1 study (20030138) and its extension trial (20040116) in subjects with advanced solid tumors provide the following critical information for the Panitumumab monotherapy program.

- Overall, Panitumumab demonstrated a favorable safety profile. As described for other EGFr inhibitors, treatment-related events were primarily skin-related and were generally mild-to-moderate and manageable, consisting predominantly of rash and dry skin.
- The safety profile of Panitumumab monotherapy was similar when administered at different doses and schedules, ie, 2.5 mg/kg QW, 6.0 mg/kg Q2W, and 9 mg/kg Q3W. As well, PK data showed that similar trough concentrations canbe achieved with 2.5 mg/kg QW, 6.0 mg/kg Q2W, and 9.0 mg/kg Q3W dosing schedules
- No MTD was reached.

- A loading dose of Panitumumab was not required since the time for Panitumumab to accumulate to a steady state level was not as long as expected based on the estimated half-life (< 5 days at doses ≤5 mg/kg, and 6 to 8 days for doses of 6 and 9 mg/kg).
- Panitumumab was safely infused over 60 minutes or 120 minutes.
- As expected for this fully human monoclonal antibody, no elicitation of antiPanitumumab antibodies in response to exposure to study drug was observed.
- No infusion reactions were reported as adverse events, despite the fact that premedications for infusion reactions were not required by the protocol.
- The PK and safety of Panitumumab derived from the hybridoma and CHO manufacturing processes were similar.
-

3. STUDY 20030251

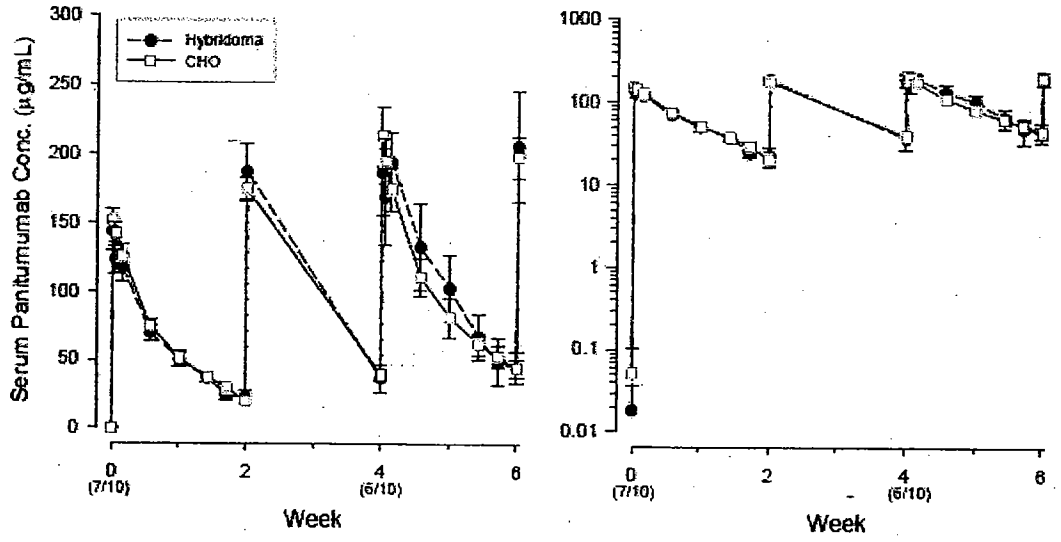
An Open-Label Clinical Trial Evaluating the Safety and PK of Two Dose Schedules of Panitumumab in Subjects With Advanced Solid Tumors

The primary objective of this study was to evaluate the safety and PK of 2 dose schedules of — CHO-derived Panitumumab (the scale and process intended for commercialization) in subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy was available.

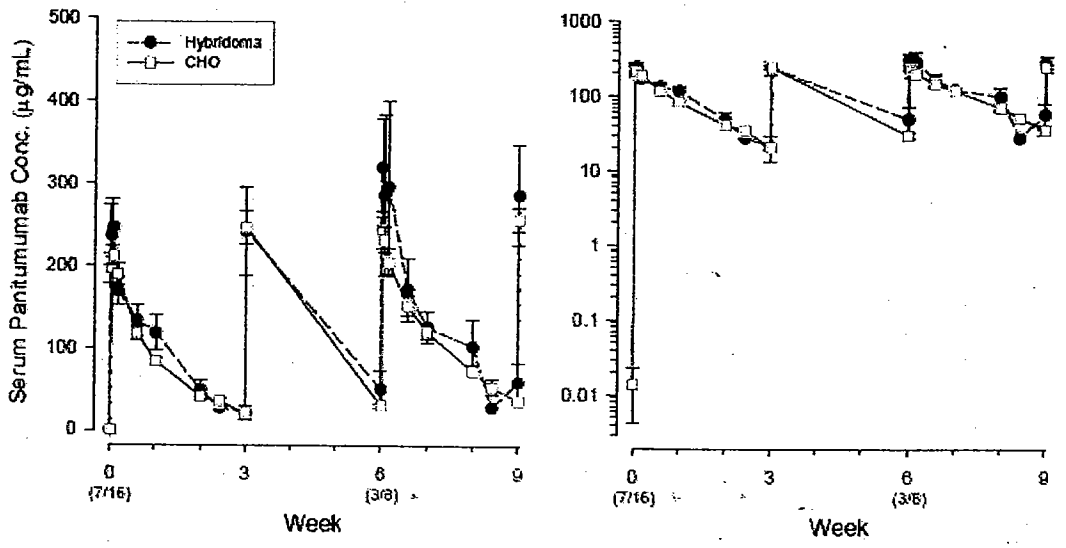
This is an ongoing, multicenter, open-label, sequentially enrolling study evaluating — CHO-derived Panitumumab administered as monotherapy in subjects with advanced solid tumors that were refractory to standard therapy or for which no standard therapy was available. Subjects receive Panitumumab at a dose of 6.0 mg/kg given once every 2 weeks (cohort 1) or 9.0 mg/kg given once every 3 weeks (cohort 2). Cohort 1 was divided into 2 subcohorts (cohorts 1A and 1B).

Results: Mean (SEM) serum Panitumumab concentration time profiles for cohorts receiving 6 and 9 mg/kg hybridoma- and CHO-derived Panitumumab are presented in the following plots.

6 mg/kg Q2W



9 mg/kg Q3W



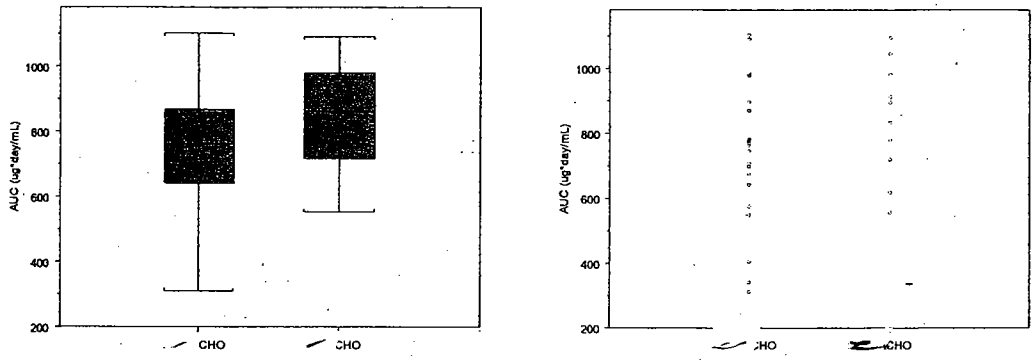
Study 20030138 and Study 20030251: Compare — vs. — CHO

Parameters		After 1st dose		After 3rd dose	
		— CHO	— CHO	— CHO	— CHO
AUC_{0-tau} (µg*day/mL)	mean	841.3	744.2	1305.7	1310.5
	SD	177.3	195.5	374.3	372.5
	Geomean	823.5	714.9	1259.3	1259.3
	N	10	29	10	22
	Ratio 90%CI	87 73-104		100 83-121	
C_{max} (µg/mL)	mean	150.0	151.8	213.3	231.9
	SD	23.5	29.2	59.1	71.1
	Geomean	148.3	149.0	205.9	222.3
	N	10	29	10 (9*)	22

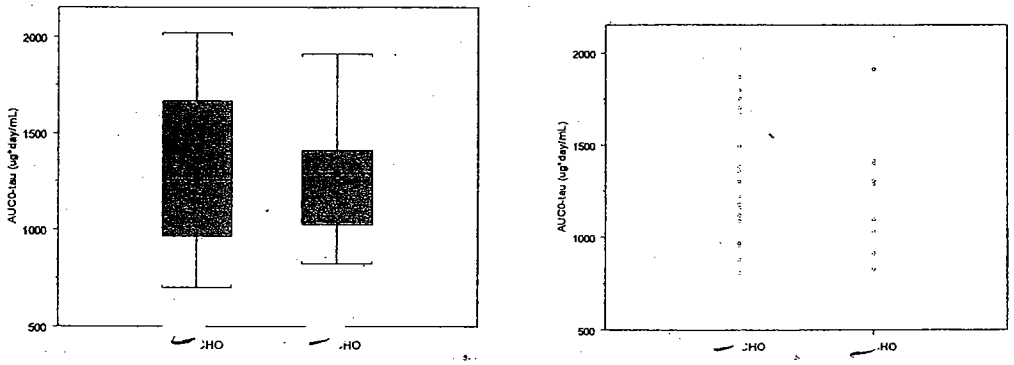
	Ratio 90%CI	101 89-113	108 (114) 89-130 (94-137)

*** Remove a NSCLC patient, who was treated as an outlier.**

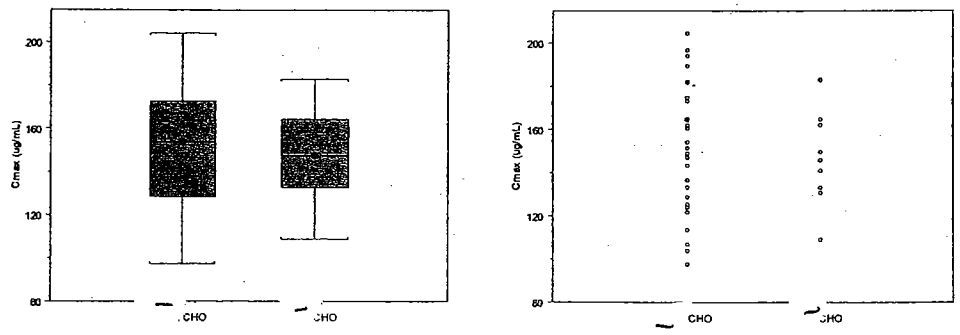
AUC 0-tau after 1st dose:



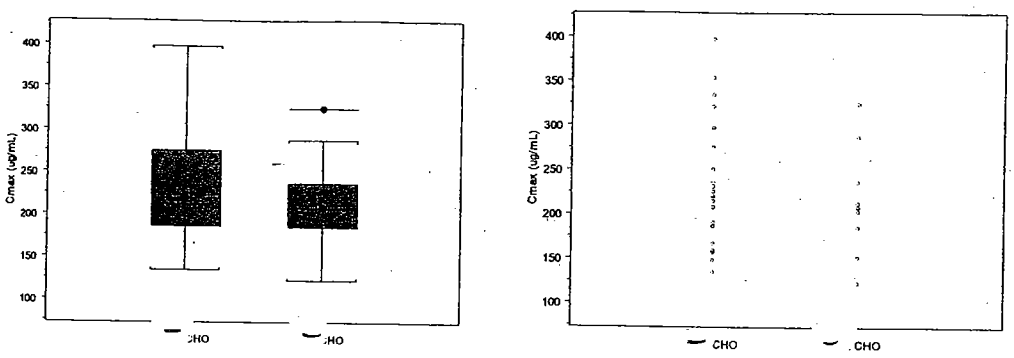
AUC 0-tau after 3nd dose:



Cmax after 1st dose:



Cmax after 3nd dose:



Conclusions: In this interim analysis of data from 55 subjects who had advanced solid tumors, the safety and pharmacokinetic profiles of — (ie, commercial-scale) CHO-derived Panitumumab at a dose of 6 mg/kg given once every 2 weeks appeared to be consistent with those observed in another study using — CHO-derived Panitumumab (Study 20030138). Although the overall incidence of discontinuations, serious adverse events, and deaths was higher than expected, likely reflecting the advanced disease status of the subject population and poor compliance with eligibility criteria, treatment-related adverse events were consistent with previous experience and with the known effects of EGFr inhibitors. No subject developed de novo antibodies to Panitumumab; however, 1 subject had pre-existing anti-Panitumumab antibodies that increased in titer after Panitumumab administration. All potential infusion reactions occurred with 30-minute infusions; however, 30-minute infusions were generally well tolerated, with an incidence of potential infusion reactions (3% of all 30-minute infusions administered) similar to that observed with 60-minute infusions in other clinical studies of Panitumumab.

90%CI is slightly out of the range of 80%-125%, which could not demonstrate the comparability betweer — and — CHO. The sponsor is requested for more safety data using to-be-marketed material, — CHO in the ongoing clinical studies.

4. Study 20040192

A Phase 1 Clinical Study of ABX-EGF (Panitumumab) Evaluation of the Safety and PK of ABX-EGF in Japanese Subjects with Advanced Solid Tumors

In this ongoing, open-label, multicenter, phase 1 study, Japanese subjects with advanced solid tumors were enrolled to receive — CHO-derived Panitumumab at 2.5 mg/kg QW, 6 mg/kg Q2W, or 9 mg/kg Q3W until disease progression, inability to tolerate Panitumumab monotherapy, or other reasons for discontinuation.
At the time of the data cutoff for this license application (16 May 2005), study enrollment was still open and treatment was ongoing. PK data were available from all subjects who received Panitumumab at 2.5 mg/kg QW (n = 6) and 6 mg/kg Q2W (n = 6); no subjects were enrolled into the 9 mg/kg Q3W cohort. The overall serum Panitumumab concentrations were lower in this study than those observed in non-Japanese subjects in Study 20030138 and Study 20030251. This difference could be due to the effect of body weight on the PK of Panitumumab. The serum

Panitumumab concentrations were generally higher for heavier subjects than for lighter subjects. Based on the mean body weight data, the Japanese subjects (63.4 [16.8] kg, n = 12) in this study were 27% and 18% lighter than non-Japanese subjects enrolled in Study 20030138 (86.4 [17.1] kg, n = 8 at 2.5 mg/kg QW) and Study 20030251 (77.1 [18.2] kg, n = 29 at 6 mg/kg Q2W), respectively.

Panitumumab PK Parameters After the First Dose of Panitumumab at 2.5 mg/kg and 6 mg/kg Between Non-Japanese (Studies 20030138 and 20030251) and Japanese (Study 20040192) Subjects

Dose	2.5 mg/kg QW			6 mg/kg Q2W		
Parameters	AUC $_{0\text{-}tau}$ (µg*day/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC $_{0\text{-}tau}$ (µg*day/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)
Japanese	135	44	8	684	118	20
Non-Japanese (ref.)	199	64	12	740	152	18
Ratio	68	68	72	92	78	109

Summary of Statistical Evaluation of Panitumumab Pharmacokinetic Parameters After the First Dose of Panitumumab at 2.5 mg/kg and 6 mg/kg Between Non-Japanese (Studies 20030138 and 20030251) and Japanese (Study 20040192) Subjects

	Japanese (Test)			Non-Japanese (Reference)[a]			Ratio
Parameter	Mean	%CV	n	Mean	%CV	n	(Test/reference)
2.5 mg/kg							
$AUC_{0\text{-}tau}$ (µg·day/mL)	135	27	6	199	24	8	68
C_{max} (µg/mL)	44	18	6	64	17	8	68
C_{min} (µg/mL)	8	38	6	12	33	7	72
6 mg/kg							
$AUC_{0\text{-}tau}$ (µg·day/mL)	684	17	6	740	26	29	92
C_{max} (µg/mL)	118	26	6	152	19	29	78
C_{min} (µg/mL)	20	20	6	18	50	28	109

$AUC_{0\text{-}tau}$ = area under the serum concentration-time during the dosing interval; C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; mean = arithmetic mean; ratio = ratio of arithmetic mean values expressed as a percentage

[a]Study 20030138 for the 2.5 mg/kg group and Study 20030251 for the 6 mg/kg group.

Source: \\documentum\Docbases\usddms\R&D Candidates\Development\AMG 954 - ABX-EGF\Preclinical Non-Study Specific\PKDM\Submission\BLA\Clinical\Supporting data\winnonlinus vs jap 2.5 output.pwo

Conclusions:

Results for the 12 subjects enrolled in this study indicate that commercial scale, — CHO-derived Panitumumab at 2.5 mg/kg QW and 6.0 mg/kg Q2W was well tolerated as monotherapy in Japanese subjects with advanced solid tumors. No DLT(s) was observed in either 2.5 mg/kg QW or 6.0 mg/kg Q2W dosing cohorts up to 4 weeks after the first Panitumumab infusion. Adverse events consisted primarily of mild or moderate events in the skin and gastrointestinal body systems.

Because limited data were available after week 4, time to PK steady-state could not be assessed for either cohort. The overall Panitumumab PK profiles are slightly lower than those observed in

non-Japanese subjects; however, based on the limited sample size in these 2 dose cohorts (6 subjects in each cohort), conclusions on the comparison of the PK between non-Japanese and Japanese subjects cannot be made at this time. Additional PK data in the Japanese population will be collected from the 9 mg/kg Q3W. No postdose blood samples tested seropositive for human antibodies to Panitumumab in either cohort as of data cutoff.

Study 20025404

A Two Part, Multiple Dose Clinical Trial of the Safety and Efficacy of ABX-EGF in Combination with Paclitaxel and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer

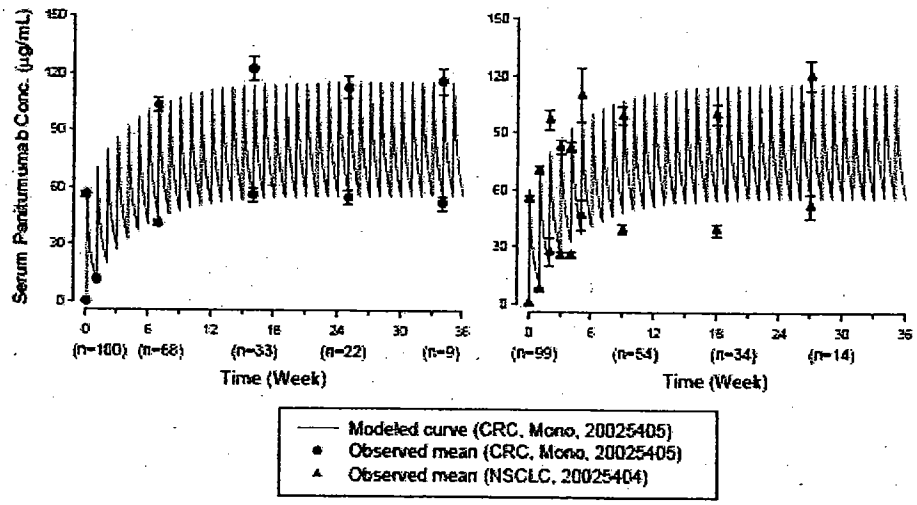
Methodology:
Open-label, multicenter, sequential dose escalation of Panitumumab with paclitaxel and carboplatin chemotherapy in subjects with advanced NSCLC. Subjects received up to 6 cycles of chemotherapy given every 3 weeks with Panitumumab doses of 1.0, 2.0, or 2.5 mg/kg IV once weekly. After 18 weeks of chemotherapy and Panitumumab, subjects with an objective tumor response or stable disease could receive up to 18 additional weeks of Panitumumab monotherapy (36 weeks total).
Number of Subjects Planned: 5 to 10 per dose cohort, or a maximum of 30 subjects total
Number of Subjects Enrolled: 19
Sex: 14 women, 5 men **Age:** Mean (SD) 52 (12) years **Ethnicity (Race):** 19 white

Panitumumab was administered concurrently with carboplatin/ paclitaxel-containing chemotherapy: Panitumumab 1, 2, or 2.5 mg/kg QW IV 1-hour + Paclitaxel 200 mg/m2 Q3W IV 3-hour + Carboplatin: target AUC of 6 mg·min/mL Q3W IV 30-minute;
VECTIBIX had no effect on the PK of paclitaxel (Table 11). And paclitaxel did not have effect on the PK of VECTIBIX (Figure 15). The PK of carboplatin was not evaluated because it is primarily eliminated through the kidney.

Paclitaxel Pharmacokinetic Parameter Values (Mean [SD]) After IV Infusions of Paclitaxel at 200 mg/m2 Concurrently with Panitumumab at 2.5 mg/kg QW

Parameter	Week 0 (n = 19)	Week 3 (n = 17)	PI[a] (n = 5)	Schiller[b] (n = 10)
C_{max} (ng/mL)	3858 (1300)	4207 (1250)	3650	5122
AUC_{0-24} (ng·hr/mL)	14522 (4190)	16262 (3402)	15007	19121

[a]Taxol Prescribing Information 2003 (175 mg/m2 given as a 3-hour IV infusion)
[b]Schiller et al, 1994 (210 mg/m2 given as a 3-hour IV infusion)



Comparison of Panitumumab Mean (SE) PK Profiles at 2.5 mg/kg QW After Monotherapy (Studyh 20025405) and in Combination With Paclitaxel/Carboplatin-containing Chemotherapy (Study 20025404)

Study	Dose (mg/kg)	Dose Frequency	Material	n	AUC_{0-tau} (µg·day/mL)	C_{max} (µg/mL)	CL (mL/day/kg)	$t_{1/2}$ (day)
20025404	(First Dose)							
(part 1)	1	QW	hybridoma	6	36 (25-43)	19 (15-23)	28.0 (23.1-40.0)	0.5 (0.5-0.6)
	2	QW	hybridoma	7	121 (96-194)	41 (35-52)	16.5 (9.0-19.6)	1.6 (0.9-2.8)
Phase 2, in combination paclitaxel and carboplatin in subjects with non-small cell lung cancer	2.5	QW	hybridoma	4	185 (173-267)	72 (61-86)	11.6 (10.7-12.6)	3.1 (2.0-4.8)
	(Fourth Dose)							
	1	QW	hybridoma	6	37 (32-46)	21 (15-23)	NC	0.6 (0.5-1.4)
	2	QW	hybridoma	7	208 (196-377)	60 (44-92)	NC	4.5 (2.8-9.4)
	2.5	QW	hybridoma	4	365 (328-654)	99 (96-133)	NC	5.2 (4.5-6.0)

Conclusions:

Panitumumab in combination with paclitaxel and carboplatin chemotherapy was well tolerated at all dose levels studied. Based on the incidence of dose-limiting toxicity, the Panitumumab dose of 2.5 mg/kg once weekly was determined to be safe and appropriate for use in Part 2 of the study. Panitumumab displayed nonlinear PK in the dose range studied and did not appear to influence the clearance or metabolism of paclitaxel.

Study 20025409

A Clinical Trial of the Safety and Efficacy of ABX-EGF in Combination with Irinotecan, Leucovorin, and 5-Fluorouracil in Subjects with Metastatic Colorectal Cancer

The overall objective of this study was to explore the safety and efficacy of Panitumumab in combination with standard 5-FU-based chemotherapy as first-line treatment of subjects with metastatic colorectal cancer, complementing previous and

ongoing studies using Panitumumab as monotherapy. Because both 5-FU and irinotecan share diarrhea as a major side effect, it was of interest to explore the possible potentiation by Panitumumab of the incidence or severity of diarrhea in this clinical setting.

Methodology:

Open-label, multicenter, noncomparative study of Panitumumab in combination with irinotecan, 5-fluorouracil, and leucovorin (IFL regimen) for untreated metastatic colorectal carcinoma. Subjects received irinotecan, 5-FU, and leucovorin in 6-week cycles, together with Panitumumab 2.5 mg/kg once weekly for up to 48 weeks or until disease progression, intolerable adverse event, or other reason for discontinuation.

Number of Subjects Planned: 84

Number of Subjects Enrolled: 19

Sex: 16 men (84%), 3 women (16%) **Age:** Mean (SD) 57 (12) years

Ethnicity (Race): 13 white (68%), 4 black (21%), 1 Asian (5%), 1 Hispanic (5%)

Nineteen subjects received IV infusions of Panitumumab at 2.5 mg/kg over 1 hour on day 1 of weeks 1 through 4 of the first 6-week cycle. Chemotherapy was administered as follows on day 1 of weeks 1 to 4 according to the IFL regimen until disease progression, inability to tolerate Panitumumab, or other reasons for discontinuation:

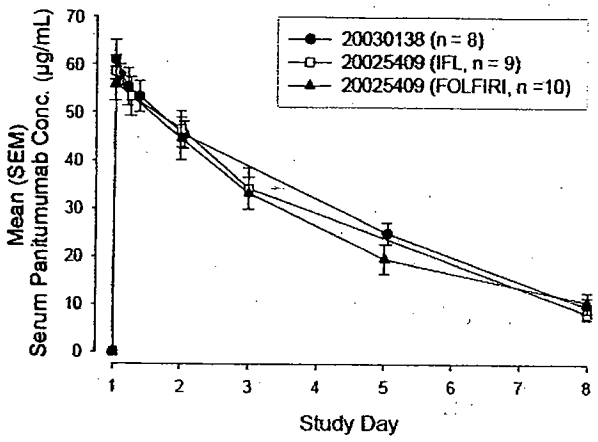
- Irinotecan at 125 mg/m2, given IV over 90 minutes (after completion of the Panitumumab infusion)
- Leucovorin at 20 mg/m2, given IV bolus over 5 to 10 minutes (after completion of the irinotecan infusion)
- 5-fluorouracil at 500 mg/m2, given IV bolus over 5 to 10 minutes (after completion of the leucovorin bolus)

Irinotecan did not have effect on the PK of VECTIBIX (Figure). Approximately a 30% decrease on C_{max} and AUC of irinotecan, and its active metabolite, SN-38, was observed when irinotecan-containing chemotherapy was administered concurrently with VECTIBIX (Table). Administration of VECTIBIX in combination with irinotecan–containing chemotherapy should be avoided.

Summary of Irinotecan and SN-38 Pharmacokinetic Parameter Values (Mean [SD]) After Weekly IV Administration of IFL Concurrently with Panitumumab at 2.5 mg/kg QW (Study 20025409)

Parameter	Week 1 (n = 10)	Week 3 (n = 9)	PI[a] (n = 64)	Slatter[b] (n = 8)
Irinotecan				
C_{max} (ng/mL)	1314 (300)	1199 (321)	1660 (797)	1534 (143)
AUC_{0-24} (ng·hr/mL)	7447 (2785)	7074 (2713)	10200 (3270)	7765 (1876)
SN-38				
C_{max} (ng/mL)	19.8 (5.2)	15.6(6.9)	26.3 (11.9)	27.1 (11.6)
AUC_{0-24} (ng·hr/mL)	168 (90)	159 (85)	229 (108)	228 (149)

[a]Camptosar□ Prescribing Information, 2005 (125 mg/m2 given as a 90-minute IV infusion)
[b]Slatter J, 2000 (125 mg/m2 given as a 90-minute IV infusion)



Mean (SE) Serum Panitumumab PK Profile After IV Administration of

Panitumumab With or Without Irinotecan-based Chemotherapy (Studies 20025409 and 20030138)

20025409	(First Dose)							
Phase 2, in combination with irinotecan, leucovorin, and 5-fluorouracil in subjects with metastatic colorectal cancer	2.5	QW	hybridoma	10	171 (119-301)	56 (36-76)	15.8 (10.6-19.5)	2.9 (1.3-4.2)
	(Sixth Dose)							
	2.5	QW	hybridoma	8	347 (234-689)	92 (58-152)	NC	5.7 (3.4-7.2)

Conclusions:
IFL chemotherapy in combination with once-weekly Panitumumab at a dose of 2.5 mg/kg administered as first-line therapy to subjects with metastatic colorectal cancer was associated with a higher-than-expected incidence of severe diarrhea (based on historical data), necessitating a change in the chemotherapy regimen from IFL to the FOLFIRI regimen in Part 2 of study 20025409.

4 Study 20020408 – Pivotal Study

An Open-label, Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects with Metastatic Colorectal Cancer

This phase 3 study was conducted to provide a controlled, 1:1 comparison of the efficacy and safety of Panitumumab plus best supportive care (BSC) versus BSC alone in subjects with EGFr-expressing metastatic colorectal cancer who had documented disease progression during or after prior standard treatment with fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy.

The primary objective of this study was to assess whether Panitumumab plus BSC improves progression-free survival compared with BSC alone in this subject population. Secondary objectives were to evaluate survival time, objective response, duration of response, time to response, time to disease progression, time to treatment failure, duration of stable disease, patient-reported outcomes, and the safety profile of Panitumumab plus BSC compared with BSC alone in this subject population.

Methodology:
This is an ongoing, multicenter, randomized, open-label, comparative study of Panitumumab plus BSC versus BSC alone in subjects with metastatic colorectal cancer who had disease progression

during or after treatment with prior, standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy. Subjects were randomly assigned in a 1:1 ratio to receive Panitumumab plus BSC or BSC alone.
Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and geographic region (Western Europe versus Central and Eastern Europe versus rest of world). Panitumumab was administered as an intravenous (IV) infusion at a dose of 6 mg/kg given once every 2 weeks until disease progression, inability to tolerate investigational product, or other reason for discontinuation. BSC was defined as the best palliative care available as judged appropriate by the investigator (excluding antineoplastic chemotherapy). Subjects were to be evaluated for tumor response according to modified Response Evaluation Criteria in Solid Tumors (RECIST) at weeks 8, 12, 16, 24, 32, 40, and 48 and every 3 months thereafter until disease progression. Tumor responses were to be confirmed no less than 4 weeks after the criteria for response were first met. In addition to the investigator's assessments, scans of all subjects evaluated for tumor response were evaluated by a blinded Independent Review Committee. Subjects determined to have progressive disease by investigator assessment were discontinued from the treatment phase of the study. All subjects were to complete a safety follow-up visit at least 4 weeks after the last assigned treatment (for the Panitumumab plus BSC group) or at any time within 4 weeks after the decision to withdraw from the treatment phase (for the BSC group). Subjects in the BSC alone group who had disease progression at any time were eligible to receive Panitumumab 6 mg/kg administered once every 2 weeks as part of a separate protocol (Study 20030194). All subjects are being followed-up for survival approximately every 3 months for up to 2 years after their randomization into the study. Enrollment is complete, but 32 subjects were still ongoing at the time of data cutoff. Although the study is ongoing, this clinical study report presents final data for the primary endpoint of progression-free survival and the co-secondary endpoint of best tumor response during the study, and an interim analysis of the co-secondary endpoint of survival.

Number of Subjects Planned:
Approximately 430 randomized subjects were planned.

Number of Subjects Enrolled:
Four hundred sixty-three subjects were enrolled into the Panitumumab plus BSC group (n = 231) and BSC alone group (n = 232).

Sex:
146 (63%) men, 85 (37%) women (Panitumumab plus BSC)
148 (64%) men, 84 (36%) women (BSC alone)

Mean (SD) Age:
61.2 (10.3) years (Panitumumab plus BSC)
61.4 (10.8) years (BSC alone)
Ethnicity (Race):
229 (99%) white, 1 (< 1%) black, 1 (< 1%) Hispanic (Panitumumab plus BSC)
228 (98%) white, 1 (< 1%) Hispanic, 2 (1%) Asian, 1 (< 1%) Japanese (BSC alone)

Diagnosis and Main Criteria for Eligibility:
Eligible subjects were men and women 18 years of age or older, competent to comprehend and sign an informed consent form, who had a pathologic diagnosis of colorectal adenocarcinoma with documented evidence of disease progression during or after prior treatment with a fluoropyrimidine, irinotecan, and oxaliplatin at an adequate

prespecified overall exposure. Radiographic documentation of disease progression during or within 6 months after the most recent regimen was required for enrollment, and the time interval between documented tumor progression and study entry was not to exceed 6 months. Subjects also were required to have unidimensionally measurable disease (≥20 mm); an ECOG status of 0 to 2; EGFr expression in ≥1% of evaluated tumor cells; and adequate hematologic, renal, and hepatic function.

Duration of Treatment:
Subjects received Panitumumab once every 2 weeks until disease progression, inability to tolerate investigational product, or other reason for discontinuation.

Efficacy Endpoints:

Primary

- progression-free survival

Secondary

- survival and best objective response over time (co-secondary)
- duration of response
- time to response
- time to disease progression
- time to treatment failure
- duration of stable disease

Summary - Results:

		Week 1 (n=434)			
		Panitumumab (n=222)		BSC (n=212)	
		Responders (n=18)	Non-responders (n=204)	Responders (n=1)	Non-responders (n=211)
Integument/Eye Toxicity		18	184	0	37
Grade 3/4 Toxicity		6	34	0	4
EGFr	<1%		1		1
	1-9%	7	48		49
	10-20%	4	58	1	67
	>20 to 35%	1	13		27
	>35%	6	84		67
BiaCore Antibody (+)		0	6	0	7
		Week 7 (n=246)			
		Panitumumab (n=175)		BSC (n=71)	
		Responders (n=18)	Non-responders (n=157)	Responders (n=1)	Non-responders (n=70)
Integument/Eye Toxicity		18	151	0	11
Grade 3/4 Toxicity		6	26	0	0
EGFr	<1%		1		
	1-9%	7	35		20
	10-20%	4	48	1	24
	>20 to 35%	1	11		9
	>35%	6	62		17
BiaCore Antibody (+)		0	11	0	1
		Follow-up Visit (n=194)			
		Panitumumab (n=72)		BSC (n=122)	
		Responders (n=18)	Non-responders (n=204)	Responders (n=0)	Non-responders (n=122)

Integument/Eye Toxicity		**8**	**61**		**22**
Grade 3/4 Toxicity		**3**	**9**		**3**
EGFr	**<1%**				**1**
	1-9%	**1**	**15**		**26**
	10-20%	**3**	**23**		**40**
	>20 to 35%	**1**	**3**		**15**
	>35%	**3**	**23**		**40**
BiaCore Antibody (+)		**0**	**5**		**0**

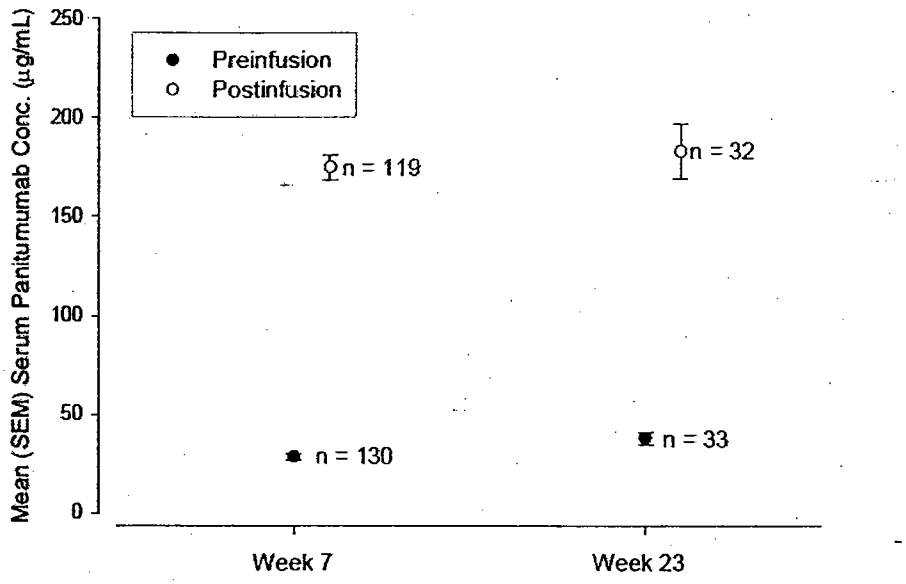
Subject Disposition:

A total of 463 subjects were randomized into this study (231 subjects in the Panitumumab plus BSC group and 232 subjects in the BSC alone group). Of the 231 subjects randomized to the Panitumumab plus BSC group, 229 subjects (99%) received Panitumumab at a dose of 6 mg/kg given once every 2 weeks during the study; 2 subjects died of disease progression within 1 day of randomization before receiving Panitumumab. In accordance with the protocol, no subject in the BSC group received Panitumumab during the treatment period of this study. At the time of the data cutoff (30 June 2005), enrollment was complete, and a higher percentage of subjects was still in the treatment period in the Panitumumab plus BSC group (29 subjects, 13%) compared with the BSC alone group (3 subjects, 1%). Most subjects in both groups discontinued the treatment period because of disease progression (by investigator assessment), although the percentage was lower in the Panitumumab plus BSC group (75%) than in the BSC alone group (85%). The median follow-up time was 20.0 weeks (range: 0 to 62.4) in the Panitumumab plus BSC group and 18.2 weeks (range: 0.1 to 71.1) in the BSC alone group. A total of 175 subjects (75%) in the BSC alone group who had radiographic disease progression (as determined by the investigator) were subsequently enrolled in Study 20030194.

PK Results:

Pharmacokinetic samples were only collected from subjects in the Panitumumab plus BSC group.

The mean trough and peak serum Panitumumab concentrations at weeks 7 and 23 are presented in Figure below. The Panitumumab concentrations at week 7 were similar to those at week 23, suggesting that the concentrations were at steady state at both weeks. The mean concentration of Panitumumab at steady state, calculated as the average of the week 7 and 23 concentrations, was approximately 30 mcg/mL before infusion (trough) and approximately 177 mcg/mL after infusion (peak).



Mean (±SE) Serum Panitumumab Concentration-Time Profiles After Q2W IV Infusion of 6 mg/kg Panitumumab

Efficacy Results:

A statistically significant improvement in the primary endpoint of progression-free was observed for the Panitumumab plus BSC group compared with the BSC alone group ($p < 0.0001$, stratified log-rank test, All Enrolled analysis set). Compared with BSC alone, the rate of disease progression or death was reduced by approximately 46% in the Panitumumab plus BSC group (hazard ratio = 0.542, 95% CI: 0.443, 0.663). The 95% CIs for the difference in Kaplan-Meier progression-free rates favored the Panitumumab plus BSC group at all protocol-specified assessment time points from week 8 to week 32. All prospectively defined and post-hoc sensitivity analyses confirmed the results of the primary analysis. Furthermore, 19 subjects (8%) in the Panitumumab plus BSC group and no subject in the BSC alone group had an objective response per modified RECIST criteria by central review (all partial responses). This difference was statistically significant at the 1% level ($p < 0.0001$, stratified exact test of common odds ratio, All Enrolled analysis set). The median duration of response was 17.0 weeks (95% CI: 16.4, 25.3; range: 4.0+, 40.4+, All Enrolled analysis set). An additional 64 subjects (28%) in the Panitumumab plus BSC group and 24 subjects (10%) in the BSC alone group had a best response of stable disease in the All Enrolled analysis set; the median duration of stable disease was 23.7 weeks (95% CI: 16.0, 24.3; range: 7.1+, 44.7) and 17.3 weeks (95% CI: 15.4, 24.1; range: 7.1+, 48.1), respectively, in these subjects. In a post-hoc analysis, the rate of progression-free survival and overall survival in the Panitumumab plus BSC group was favorable for subjects who had either a partial response or stable disease compared with subjects who did not. No difference in survival was observed between treatment groups at the 1% level in this interim analysis. The effects of Panitumumab on progression-free survival and objective response were consistent within subpopulations defined by age, sex, primary tumor type, ECOG performance status, and the quantity of tumor EGFr membrane staining (1% to 9% versus ≥10% of tumor cells) or highest tumor EGFr membrane staining intensity (0% 3+ staining versus > 0% 3+ staining); similar results also were observed in post-hoc analyses with alternative categories for the quantity of tumor EGFr membrane staining (1% to < 10%, 10% to 35%, or > 35%) and highest staining intensity (1+, 2+, or 3+).

Safety Results:

The Safety analysis set included the same 463 subjects as the All Enrolled analysis set. However, the 2 subjects in the Panitumumab plus BSC group who did not receive at least 1 dose of Panitumumab were analyzed in the BSC alone group (ie, according to actual treatment received). Due to the open-label design of the study, the potential existed for an over-reporting and attribution of adverse events to the "active" therapeutic agent in the Panitumumab plus BSC group compared with the control group receiving BSC alone. Two hundred twenty-nine subjects (100%) in the Panitumumab plus BSC group and 202 subjects (86%) in the BSC alone group had at least 1 adverse event during the study. A low percentage of subjects had an adverse event leading to discontinuation of treatment in the Panitumumab plus BSC (6%) and BSC alone (3%) groups. The percentage of subjects with severe (ie, grade 3) adverse events was higher in the Panitumumab plus BSC group (33%) than in the BSC alone group (18%), primarily as a result of adverse events associated with integument and eye toxicity.

Four subjects (2%) in each treatment group had a worst adverse event grade of life-threatening (ie, grade 4). The incidence of serious adverse events was higher in the Panitumumab plus BSC group (39%) than in the BSC alone group (24%); however, most of these events were associated with clinical disease progression (preferred terms corresponding to the primary tumor type such as "colorectal cancer" and "metastatic colorectal cancer" were to be reported as serious adverse events when the outcome was fatal). A higher incidence of these events was reported in the Panitumumab plus BSC group during the treatment period, likely because more subjects in the BSC alone group had radiographic disease progression by investigator assessment and withdrew from study or crossed over to the extension protocol (Study 20030194). When all deaths up to the time of data cutoff were included, the percentage of deaths was 51% in the Panitumumab plus BSC group, 48% in the BSC alone group for subjects who crossed over to Study 20030194, and 83% for subjects in the BSC alone group who did not cross over to Study 20030194.

Only 3% of deaths (2% in the Panitumumab plus BSC group and 1% in the BSC alone group) were not directly attributed to disease progression, and none were considered related to investigational product. Most subjects (90%) in the Panitumumab plus BSC group had treatment-related adverse events. Most of these treatment-related adverse events were mild or moderate and were integument-related toxicities consistent with the known effects of EGFr inhibitors. Eighteen percent of subjects in the Panitumumab plus BSC group had a severe (ie, grade 3) integument- and eye-related toxicity.

Integument-related toxicities leading to study discontinuation were reported for 1 subject in the Panitumumab plus BSC group (moderate dermatitis acneiform) and 1 subject in the BSC alone group (moderate jaundice). Even though jaundice would not typically be categorized as an integument toxicity (rather as a liver toxicity); it was conservatively included in this analysis because the preferred term of jaundice is included in the high-level and primary system organ class categories of "dermal and epidermal conditions NEC" and "skin and subcutaneous tissue disorders." In the Panitumumab plus BSC group, only 1 subject received a narcotic and 12 subjects (5%) received systemic steroids for integument-related toxicities.

Seventy-two subjects (31%) in the Panitumumab plus BSC group and 5 subjects (2%) in the BSC alone group had integument- and eye-related toxicities that were infectious in nature.

No subject had an adverse event that the investigator reported as an "infusion reaction" or "infusion-related reaction", although 1 subject had an infusion-associated event of moderate hypersensitivity. In a conservative, post hoc analysis of adverse event terms derived from Version 3.0 of the CTCAE (acute infusion reaction/cytokine release syndrome and allergic reaction/hypersensitivity occurring on the day of infusion and resolving the same day or the day after), potential infusion reactions occurred in 12 subjects, yielding a per-infusion incidence of 1.0% and a per-subject incidence of 5.2%. Only 4 subjects in the Panitumumab plus BSC group had clinically significant vital sign

changes (ie, ≥30%) in association with a potential infusion reaction.
Consistent with the known effects of other EGFr inhibitors, median magnesium levelsdecreased during the study for subjects in the Panitumumab plus BSC group compared with the BSC alone group. In the Panitumumab plus BSC group, 6 subjects (3%) had a reduction in magnesium levels to grade 3, and 2 subjects (1%) had a reduction in magnesium levels to grade 4. Four subjects (all in the Panitumumab plus BSC group) had adverse events of mild to severe hypomagnesemia or blood magnesium decreased. No subject withdrew from the study because of hypomagnesemia. No other clinically significant changes in laboratory values were observed in the Panitumumab plus BSC group compared with the BSC alone group. A total of 224 subjects in the Panitumumab plus BSC group were tested for anti-Panitumumab antibodies (221 subjects [99%] at baseline and 185 subjects [83%] postbaseline), and 61 subjects (27%) had a follow-up sample collected ≥21 days after the last dose of Panitumumab (ie, the duration of time considered appropriate for the evaluation of antibody formation). Three subjects tested positive for anti-Panitumumab antibodies in the screening ELISA at baseline (week 1). All serum samples from these 3 subjects were negative for neutralizing antibodies in the bioassay.

Conclusions:
Panitumumab at a dose of 6 mg/kg given once every 2 weeks plus BSC was associated with a clinically and statistically significant improvement ($p < 0.0001$) in progression-free survival compared with BSC alone in subjects with metastatic colorectal cancer who had disease progression during or after treatment with standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy. All prespecified and posthoc sensitivity analyses were consistent with the primary analysis. The tumor response rate in the Panitumumab plus BSC group (8%; 95% CI: 5, 13) was consistent with that observed in previous Panitumumab studies (5% to 10%). The effects of Panitumumab on progression-free survival and objective response were consistent within subpopulations defined by age, sex, primary tumor type, performance status, and the quantity or highest intensity of tumor EGFr membrane staining. Panitumumab was well tolerated in this study, with a low incidence of potential infusion reactions (approximately 5%) and low antigenicity. Most adverse events were integument-related toxicities consistent with the known effects of EGFr inhibitors.

Study 20025405
An Open Label Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of ABX-EGF in Subjects with Metastatic Colorectal Cancer

The objectives of this study were to assess the efficacy and safety of Panitumumab as monotherapy in subjects with metastatic colorectal cancer who had failed conventional fluoropyrimidine-based chemotherapy. Subjects whose tumors expressed both high and low levels of EGFr (defined below) were included to assess the possible effects of EGF expression on response to Panitumumab.

Methodology:
Open-label, multicenter, noncomparative study of Panitumumab as monotherapy for metastatic colorectal adenocarcinoma. Subjects were assigned to 1 of 2 cohorts based on tumor EGFr expression and received Panitumumab 2.5 mg/kg once weekly for 8 weeks (with 1 week rest) in multiple 9-week courses through disease progression, unacceptable toxicity, or other reason for discontinuation.

Number of Subjects Planned:
150: 100 in Cohort A and 50 in Cohort B ("high" vs "low" EGFr expression, respectively)

Number of Subjects Enrolled: 150 (106 in Cohort A and 44 in Cohort B); 148 were treated.

Sex: 56% men, 44% women **Age:** Median (range) 59 (21, 88) years

Ethnicity (Race): 81%-white, 9% black, 5% Asian, 3% Hispanic, 1% other

Diagnosis and Main Criteria for Eligibility:
Metastatic colorectal adenocarcinoma; bidimensionally measurable disease; previously failed treatment with a fluoropyrimidine (with or without leucovorin) and irinotecan, oxaliplatin, or both; the sum of 2+ and 3+ EGFr staining in □ 10% of evaluated tumor cells (Cohort A—high expression) or 1+ staining in □ 10% of tumor cells or the sum of
1+, 2+, and 3+ staining in □ 10% but 2+ plus 3+ in < 10% of tumor cells (Cohort B—low expression); adequate hematologic and organ function; signed informed consent

Efficacy Endpoints:
Objective tumor response rate at week 8 (primary), best overall response rate, progression-free survival, time to progression, overall survival

Safety Endpoints:
Incidence of adverse events; incidence, severity, and time to skin rash; laboratory and vital signs changes; left ventricular ejection fraction changes; incidence of anti-Panitumumab antibody formation

Efficacy Results:
Major efficacy variables are summarized in the following table:

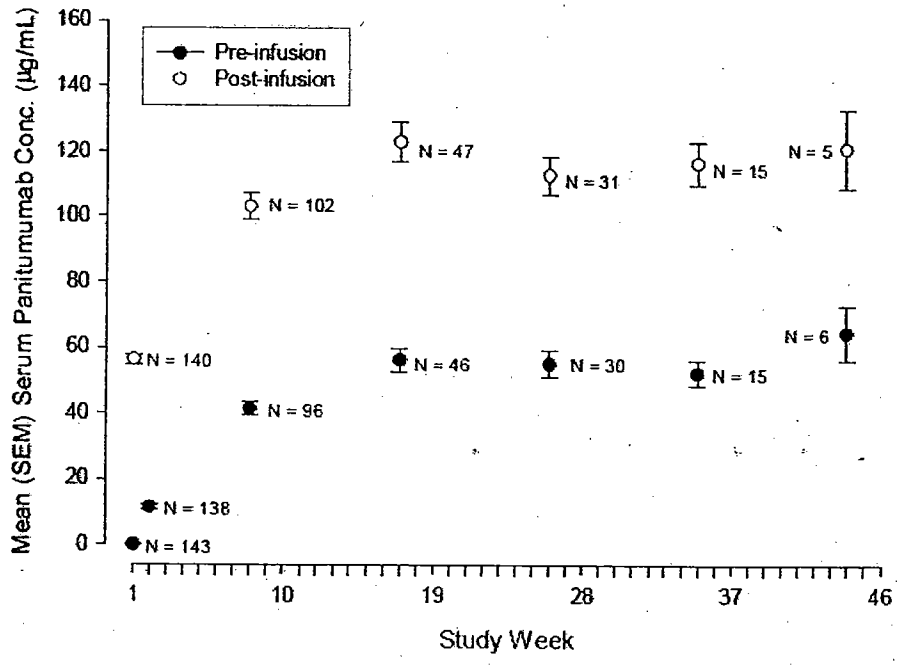
Variable	Cohort A (N=105)	Cohort B (N=43)	Exploratory Analysis (N=65)	Total (N=148)
8-week objective response rate [% (95% CI)]	4.8 (1.6, 10.8)	11.6 (3.9, 25.1)	6.2 (1.7, 15.0)	6.8 (3.3, 12.1)
Overall objective response rate [% (95% CI)]	6.7 (2.7, 13.3)	14.0 (5.3, 27.9)	10.8 (4.4, 20.9)	8.8 (4.8, 14.6)
Progression-free survival [median weeks (95% CI)]	16 (10, 16)	8 (8, 16)	12 (8, 16)	14 (8, 16)
Overall survival [median months (95% CI)]	9 (5, 10)	9 (6, 11)	8 (4, 9)	9 (6, 10)

Although response rates tended to be slightly higher in cohort B, time-to-event variables were similar between cohorts. Response rates and survival in the exploratory analysis subset were similar to that of the entire population.

Pharmacokinetic Results:
There were no apparent differences in the Panitumumab pharmacokinetic profiles between Cohorts A and B. Steady state levels were attained between study weeks 8 and 17. Mean concentrations of Panitumumab at steady state were approximately 55 µg/mL at trough and 120 µg/mL at peak.

Summary of Panitumumab Concentrations

Course	Study Week	No. Panitumumab Infusions	N	Trough [Panitumumab] Mean (SEM) µg/mL	Peak [Panitumumab] Mean (SEM) µg/mL
1	1	1	139	-	56.3 (1.6)
	2	1	138	11.5 (0.9)	-
	8	7	95	41.3 (2.0)	-
	8	8	100	-	103.2 (3.9)
2	17	15	48	56.3 (3.7)	-
	17	16	48	-	122.9 (6.0)
3	26	23	29	55.1 (4.0)	-
	26	24	30	-	112.7 (5.8)
4	35	31	15	52.3 (3.8)	-
	35	32	15	-	116.4 (6.7)
5	44	39	6	64.6 (8.3)	-
	44	40	6	-	121.0 (12.1)



Serum Panitumumab Concentration for Cohorts A and B Combined

Safety Results:

All 148 subjects experienced at least 1 adverse event while on study, 72 of whom (48%) had an event that was □ grade 3. Fifty subjects (34%) had an adverse event considered serious. Four subjects (3%) died during the treatment period. Treatmentrelated adverse events were seen in 142 subjects (96%); these were generally mild-tomoderate and consisted mainly of skin disorders such as rash, pruritus, dry skin, and acneiform dermatitis. No subject had an adverse event that the investigator described as an infusion reaction. Using a conservative post-hoc approach, possible infusion reactions were identified in 17% of subjects and in 2% of

infusions; these included nausea/vomiting, pyrexia, dizziness, dyspnea, fatigue, and rigors. Transient fluctuations were seen in vital signs during and postinfusion, particularly in diastolic blood pressure and pulse rate (both increases and decreases). However, in only 5 infusions did a clinically significant vital sign change coincide with clinical symptoms of an infusion reaction. No treatment-related laboratory changes were apparent and, of those subjects who had available postexposure samples, none tested seropositive for human antibodies to Panitumumab.

Conclusions:
Panitumumab given as monotherapy at a dose of 2.5 mg/kg once weekly was well tolerated in subjects with metastatic colorectal cancer who had failed prior standard chemotherapy regimens, and showed antitumor activity in subjects with both high and low EGFr-expressing tumors, as well as in subjects who had previously failed treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Study 20030167
A Phase 2, Multicenter, Single-arm Clinical Trial of ABX-EGF Monotherapy in Subjects with Metastatic Colorectal Cancer Following Treatment with Fluoropyrimidine, Irinotecan, and Oxaliplatin Chemotherapy

This study is ongoing.

Introduction and Objectives:
Data from an interim analysis of a phase 2 study (20025405) of Panitumumab monotherapy in subjects with metastatic colorectal cancer who had failed prior standard chemotherapy (fluoropyrimidine and either irinotecan, oxaliplatin, or both) have shown that inhibition of the epidermal growth factor receptor (EGFr) pathway by Panitumumab can result in objective tumor responses (Meropol et al, 2003; Hecht et al, 2004). The primary objective of this study was to assess the objective response rate through week 16 (responses needed to be confirmed no less than 4 weeks after the criteria for response were first met) and the duration of response in subjects with metastatic colorectal cancer who were receiving Panitumumab at the dose schedule of 6 mg/kg once every 2 weeks.

Methodology:
This is an ongoing, multicenter, open-label, single-arm, phase 2 clinical study examining the efficacy and safety of Panitumumab administered as monotherapy in subjects with EGFr-expressing (membrane staining in ≥10% of evaluated tumor cells) metastatic colorectal cancer who had developed progressive disease or relapsed during or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy (see Diagnosis and Criteria for Eligibility for details on the number of previous lines of chemotherapy and the overall exposure eligible subjects must have received). Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg given once every 2 weeks until subjects developed progressive disease, were unable to tolerate Panitumumab, or discontinued for other reasons (eg, administrative decision, consent withdrawn). Subjects were evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40, and 48 and every 3 months thereafter until disease progression. Subjects with symptoms suggestive of disease progression were to be evaluated for tumor response at the time these symptoms occurred. Four weeks after the last Panitumumab infusion received (regardless of the reason for discontinuation), subjects were to attend a safety follow-up visit. In addition, subjects were contacted to assess disease status and survival every 3 months through 24 months (the 24-month time period was calculated from the first day of Panitumumab

administration).

Number of Subjects Planned:
The planned sample size was 300 subjects who were confirmed to be eligible by an Independent Eligibility Review Committee (IERC) for the purpose of the primary analysis. Subjects were enrolled on the basis of investigator assessment only, then were retrospectively confirmed eligible by the IERC. To allow for an estimated IERC-determined ineligibility rate of 20%, the planned enrollment was set to approximately 375 subjects.

Number of Subjects Enrolled:
At the time of the data cutoff for this report, 93 subjects had enrolled in this study.
Sex: 51 (55%) men, 42 (45%) women **Age:** mean (SD) 58.5 (9.4) years
Ethnicity (Race): 74 (80%) white, 8 (9%) black, 7 (8%) Hispanic, 3 (3%) Asian, 1 (1%) other

Summary - Results:
This report provides interim efficacy, safety, and pharmacokinetic data using a data cutoff date of 20 May 2005.

Subject Disposition:
At the time of the data cutoff, 93 subjects had been enrolled into this study, and 91 subjects had received at least 1 dose of Panitumumab (the 2 subjects who did not receive Panitumumab were determined to be ineligible after enrollment). Eighteen subjects (19%) were still in the treatment period. Of the 73 subjects (78%) who ended treatment, 53 subjects (57% of all subjects enrolled) ended treatment because of radiographically documented disease progression. Other reasons for treatment discontinuation were protocol-specified criteria (ie, symptomatic integument-related toxicity) (4%), other reasons (ie, clinical disease progression not radiographically documented, which may have led to the subject not returning to the clinic for the follow-up visit) (3%), adverse event (2%), consent withdrawn (2%), subject request (1%), ineligibility determined (1%), and administrative decision (1%). Twenty-three subjects (25%) were still in the safety follow-up period at the time of the data cutoff, and 45 subjects (48%) had completed the safety follow-up period. The median follow-up time (from enrollment to the last on-study safety follow-up or long-term follow-up visit) was 15 weeks (range: 1 to 64 weeks). Fifty-nine subjects (63%) had ≥20 weeks of potential follow-up.

Among 91 patients, 11 are responders

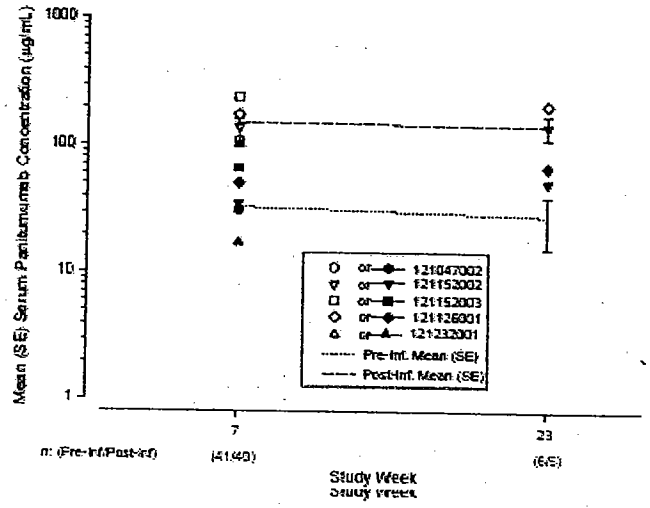
EGFr	N	Responders	Response rate
10%	3	0	0%
>10-20%	59	5	8%
>20 – 35%	7	0	0%
>35%	22	6	27%
Total	91	11	12%

PK Results:
An overlay of the individual Panitumumab concentrations of the other 5 subjects with the mean trough and peak concentrations of the other subjects in this study (ie, subjects who met the protocol-specified enrollment criteria) showed that the pharmacokinetic data from these subjects was similar to those of the eligible subjects. Therefore, as these subjects met other inclusion criteria, these subjects were included in the pharmacokinetic analyses.
According to previous studies (Studies 20020408 and 20030251), Panitumumab concentrations

are at steady state at week 7 after a dose of 6 mg/kg given once every 2 weeks. The mean (± SD) concentrations of Panitumumab at week 7 were 33.4 ± 17.0 µg/mL before infusion (trough) and 151.7 ± 43.4 mcg/mL after infusion (peak). Although the data were limited (n = 8 or 7 at week 23), the peak (151.4 ± 60.9 mcg/mL) and trough (35.7 ± 29.9 mcg/mL) concentrations at week 23 were similar to those observed at week 7.

These results were consistent with those from Study 20030250, which had the same study design as the current study, with the exception that enrolled subjects had tumors with low or negative EGFr expression (negative or positive membrane staining in < 10% of evaluated tumor cells), as measured by the DakoCytomation EGFR pharmDxTM kit. This similarity between the results of these studies suggests that differences in EGFr expression in tumor cells (as determined by membrane immunohistochemistry staining) do not result in noticeable differences in the steady-state concentrations of Panitumumab.

Appendix Figure 12-1. Overlay of Panitumumab Individual Concentrations (µg/mL) in Subjects that Received Prior Avastin or Small Molecule Treatment with Mean (±SE) Serum Panitumumab Concentration-Time Profiles From the Rest of the Subjects



Efficacy Results:

As described above, the primary analyses of efficacy were conducted using the Evaluable Adjudicated Prior Failures Set, consisting of all consented and enrolled subjects determined to be eligible by an IERC who had ≥20 weeks potential follow-up (n = 39).

After 16 weeks of treatment, 3 of the 39 subjects in the Evaluable Adjudicated Prior Failures Set had a partial response based on central assessment using modified WHO criteria (subsequently confirmed no less than 4 weeks after the criteria for response were met), resulting in an objective response rate of 7.7% (95% CI: 1.6, 20.9). No additional subjects in this analysis set had a response after 16 weeks; thus, the response rate over the entire treatment period also was 7.7%. For the 3 responders, the times to first objective response were 7.7, 11.0, and 11.1 weeks. The durations of response for the 3 responders were 14.0, 4.1+ (by central assessment, the response for this subject was ongoing at the time of treatment discontinuation; thus, the duration of response was censored at the time of treatment discontinuation), and 12.4 weeks, respectively. Across all subjects in the Evaluable Adjudicated Prior Failures Set, median progression-free survival time (defined for this interim report as the time from the date of enrollment to the date of first observed disease progression or death) was 7.6 weeks (95% CI: 7.1, 8.6). Time to disease progression (defined as the time from the date of enrollment

to the date of first observed disease progression or death if the death was due to disease progression) was 7.6 weeks (95% CI: 7.1, 11.4). Median time to treatment failure was 8.0 weeks (95% CI: 7.1, 15.4).
Scans collected for the purpose of disease assessment were assessed by the investigator for the purpose of treatment-related decisions and also assessed in a blinded fashion at a central imaging facility. Sensitivity analyses for primary and secondary efficacy endpoints were conducted based on investigators' disease assessments. Investigator and central assessments did not differ with respect to the number of responders with a best response of partial response at week 16. However, only 1 subject (identified above as having a time to response of 11.0 weeks) of the 3 subjects identified as responders through central assessment was categorized by investigator assessment as having a response. The other 2 responders identified by central assessment were categorized by the investigator as having a best response of stable disease.

Safety Results:
Safety analyses were conducted using the Safety Set, consisting of all consented subjects who received ≥1 dose of Panitumumab (91 subjects), and the 20-week Evaluable Safety Set, consisting of subjects in the Safety Set with ≥20 weeks potential follow-up (57 subjects). The Safety Set is the focus of the data discussed below.
All subjects in the Safety Set had an adverse event while on treatment or in safety follow-up. Thirty-eight subjects (42%) had a severe (grade 3) event, and 4 subjects (4%) had a life-threatening (grade 4) adverse event. Twenty-four subjects (26%) had serious adverse events. Eleven subjects (12%) had fatal (grade 5) adverse events.
Overall, adverse events affecting the skin and subcutaneous disorders system organ class were most common, occurring in 96% of subjects in the Safety Set. Almost all subjects (87/91; 96%) had at least 1 adverse event that was considered by the investigator to be at least possibly related to treatment with Panitumumab. These events included primarily skin and subcutaneous disorders (93%), gastrointestinal disorders (34%), and infections and infestations (29%).
The 5 most frequently occurring treatment-related adverse events were dermatitis acneiform (75%), erythema (57%), pruritus (53%), skin exfoliation (26%), and paronychia (22%). The incidence of mild (grade 1) treatment-related adverse events was 15%, and the incidence of moderate (grade 2) events was 54%. Severe (grade 3) treatment-related adverse events occurred in 22 subjects (24%).
One life-threatening (grade 4, not reported as serious) treatment-related adverse event (hypomagnesemia) occurred in 1 subject. Two subjects had adverse events reported as both serious treatment-related (an investigator-reported severe hypersensitivity reaction in 1 subject, described below, and severe vocal cord paralysis and fatal pulmonary embolism in the other subject).
Eighteen subjects (20%) in the Safety Set had adverse events that resulted in removal from treatment or removal from the study. Thirteen of these events were serious, and 3 events in 2 subjects were reported as serious and treatment-related; of these, 1 event was fatal (pulmonary embolism in subject 121124006).
As noted, 1 subject had an investigator-reported serious treatment-related hypersensitivity reaction (ie, infusion reaction) that was graded severe (dyspnea, chest pressure, tachycardia, tachypnea, hypertension, and hypoxia) 10 minutes after receiving the first Panitumumab infusion. The infusion was not interrupted, and symptoms resolved with treatment within 1 hour. The subject received 14 subsequent Panitumumab infusions with premedication, all of which were well-tolerated.
In an analysis of event terms derived from CTCAE version 3.0 (using terms in the categories of allergic reaction/hypersensitivity and cytokine release syndrome/acute infusion reaction occurring on the day of the infusion and resolving the same day or the day after onset), potential

infusion reactions were identified in 13% of subjects and in 2% of infusions. No subject had a vital sign change ≥30% in temporal association with an infusion reaction.
Grade 3 or 4 blood chemistry laboratory toxicities occurred in 28 subjects (31%) in the Safety Set (23 subjects [25%] had a grade 3 laboratory toxicity as their worst grade on study, and 5 subjects [5%] had a grade 4 laboratory toxicity as the worst grade on study). The grade 3/4 laboratory toxicity with the highest subject incidence was hypomagnesemia: 4 subjects (4%) had grade 3 hypomagnesemia, and 4 subjects (4%) had grade 4 hypomagnesemia.
No subject tested seropositive for anti-Panitumumab antibodies, either before or after exposure.

Conclusions:
In this interim analysis of data from 91 subjects with EGFr-expressing (membrane staining in ≥ 10% of evaluated tumor cells) metastatic colorectal cancer who had documented disease progression after receiving standard prior chemotherapy, Panitumumab was associated with a partial response (confirmed by independent central review) in 3 of 39 subjects who had ≥20 weeks of potential follow-up time and were confirmed to have failed prior standard chemotherapy by central review, resulting in an objective response rate of 7.7% (95% CI: 1.6, 20.9). The durations of response for the 3 responders were 4.1+ (this subject's response was ongoing at the time of treatment discontinuation), 12.4, and 14.0 weeks. Panitumumab was well tolerated, with a 2% per-infusion incidence of potential infusion reactions and no antiPanitumumab antibody formation.

Study 20030250
A Phase 2 Multicenter Single Arm Clinical Trial of ABX-EGF Monotherapy in Subjects with Metastatic Colorectal Cancer Whose Tumors Express Low or Negative EGFr Levels by Immunohistochemistry Following Treatment with Fluoropyrimidine, Irinotecan, and Oxaliplatin Chemotherapy

Introduction and Objectives:
Data from a previous phase 2 study (200205405) of Panitumumab monotherapy in subjects with metastatic colorectal cancer who had failed prior standard chemotherapy (fluoropyrimidine and either irinotecan, oxaliplatin, or both) have shown that inhibition of the epidermal growth factor receptor (EGFr) pathway by Panitumumab can result in objective tumor responses (Meropol et al, 2003; Hecht et al, 2004). Preliminary analysis in that study also suggested that EGFr levels did not correlate with response to Panitumumab treatment. The current phase 2 study was designed to test the efficacy and safety of Panitumumab as treatment in subjects with metastatic colorectal cancer who had documented disease progression during or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy and whose tumors expressed low or negative EGFr levels by immunohistochemistry.

The primary objective of the study was to assess the effect of treatment with Panitumumab monotherapy (at a dose of 6 mg/kg given once every 2 weeks) on the objective tumor response rate (based on a blinded review of scans at a central imaging laboratory per a modification of the World Health Organization [WHO] criteria) through week 16 (including a confirmatory scan no less than 4 weeks after the criteria for response were first met) and on the duration of response in subjects with metastatic colorectal cancer whose tumors express low or negative EGFr levels by immunohistochemistry. Secondary objectives included assessment of the effect of treatment with Panitumumab on objective response rate throughout the study, time to response, progression-free survival time, time to disease progression, time to treatment failure, duration of stable disease, survival time, change in patient-reported outcomes (PRO), and safety

in this subject population.

Methodology:
This is an ongoing multicenter, open-label, single-arm, phase 2 clinical study examining the efficacy and safety of Panitumumab administered as monotherapy in subjects with metastatic colorectal cancer whose tumors expressed low or negative EGFr levels by immunohistochemistry and who had developed progressive disease or relapsed while on or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy. Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg once every 2 weeks until subjects developed progressive disease, were unable to tolerate investigational product, or discontinued for other reasons (eg, administrative decision, consent withdrawn, etc).
Subjects were evaluated for tumor response at weeks 8, 12, 16, 24, 32, 40, 48, and every 3 months thereafter, until disease progression. Subjects with symptoms suggestive of disease progression were to be evaluated for tumor response at the time these symptoms occurred. Four weeks after the last Panitumumab infusion was received (regardless of the reason for discontinuation), subjects were to undergo a safety follow-up visit. After this initial safety follow-up visit, subjects were contacted to assess disease status and survival every 3 months after the last Panitumumab infusion was administered through month 24 (the 24-month time period was counted from the first Panitumumab infusion).

Number of Subjects Planned:
The planned sample size was 150 subjects confirmed to be eligible by an Independent Eligibility Review Committee (IERC) for the purpose of the primary efficacy analysis. Subjects were enrolled on the basis of investigator decision only, then were retrospectively confirmed to be eligible by the IERC. To allow for an expected IERC-determined ineligibility rate of 20% (a rate considered likely based on reports from studies with similar designs conducted in this subject population), the planned enrollment was set to approximately 190 subjects.

Number of Subjects Enrolled:
At the time of the data cutoff for this report, 88 subjects were enrolled, all of whom received $\geq$1 dose of Panitumumab. 36 are <1% and 52 have 1-9% of EGFr expression. 2 out of 36 and 9 of 52 are responders.

Sex: 51 (58%) men, 37 (42%) women **Age (mean [SD]):** 62.3 (11.5) years
Ethnicity (Race): 71 (81%) white, 12 (14%) black, 3 (3%) Hispanic, 1 (1%) Asian, 1 (1%) American Indian or Alaska native

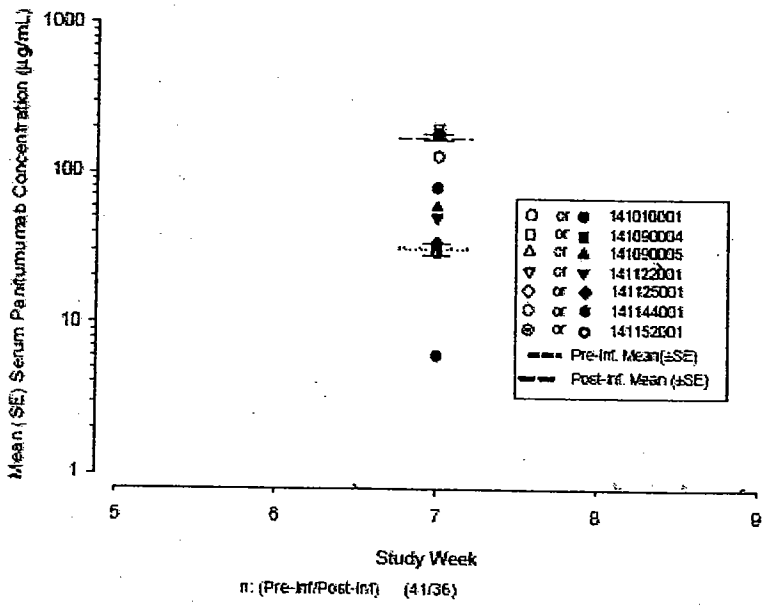
PK Results:
Ten subjects (141009001, 141010001, 141090004, 141090005, 141100001, 141122001, 141125001, 141144001, 141152001, 141275002) did not undergo the protocol-required 6-week wash-out of bevacizumab prior to treatment with Panitumumab.
At the time of the data cut-off for this report, 2 of these subjects (141100001 and 141275002) had not yet had their first scheduled pharmacokinetic sample collection at week 7; thus, they were not included in the pharmacokinetic analyses. Another of the 10 subjects (Subject 141009001) was excluded from pharmacokinetic analysis because he did not receive the full week 7 dose of Panitumumab. An overlay of the individual Panitumumab concentrations of the other 7 subjects with the mean trough and peak concentrations of the rest of the subjects in the study (who met all the enrollment criteria and were included in pharmacokinetic analyses) demonstrated that the concentrations were similar. Therefore, these 7

subjects were included in the Panitumumab pharmacokinetic data analyses, as they met all other inclusion criteria.

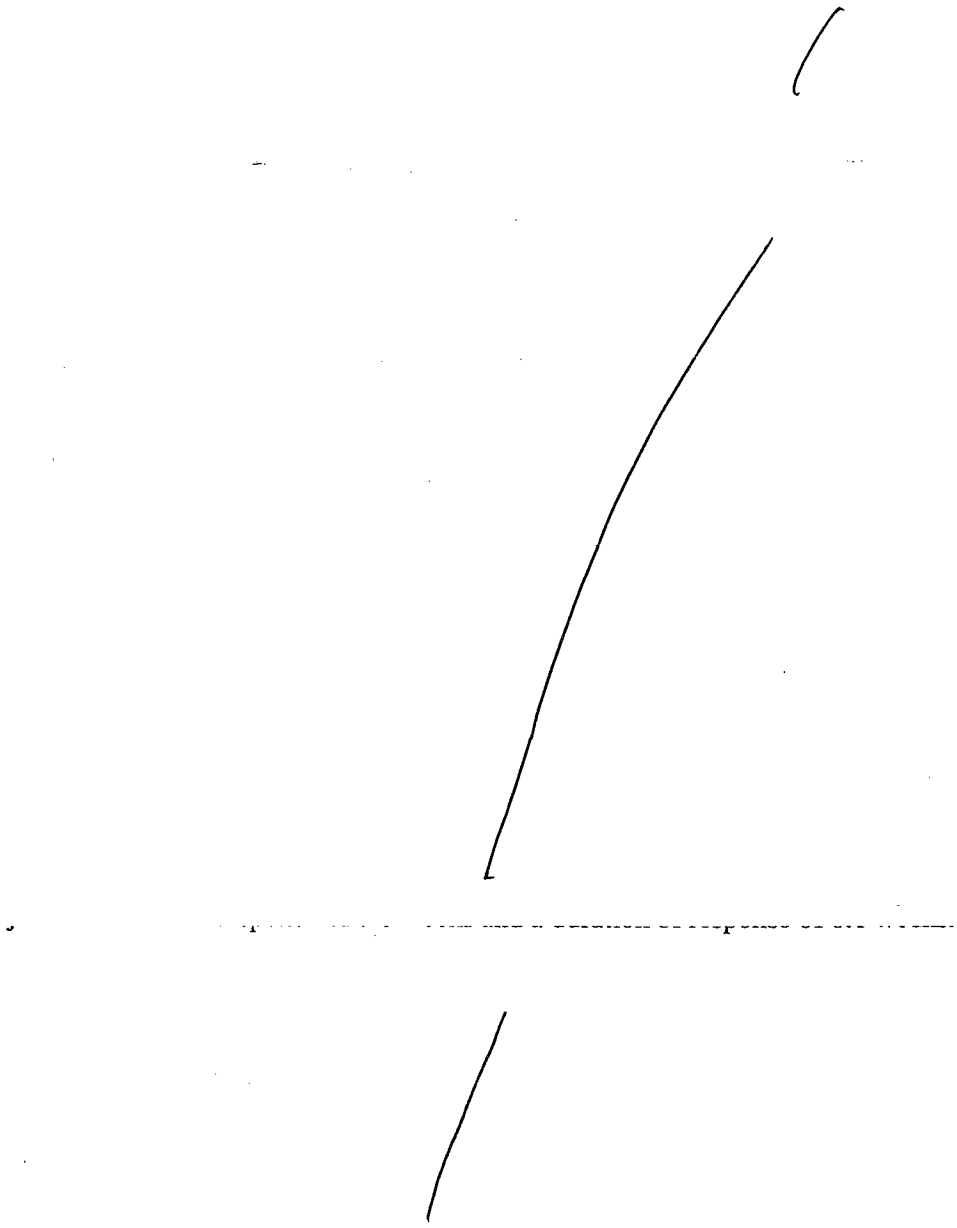
According to previous studies (Studies 20020408 and 20030251), Panitumumab concentrations are at steady state at week 7 after dosing with 6 mg/kg once every 2 weeks. The mean ± SD concentration of Panitumumab at week 7 was 32.6 ± 17.5 mcg/mL before infusion (trough) and 175.0 ± 40.7 mcg/mL after infusion (peak). Although the data were limited (n=3) at week 23, the peak (176.6 ± 24.6 mcg/mL) and trough (47.1 ± 23.7 mcg/mL) concentrations at week 23 were similar to those at week 7.

These results were consistent with those from Study 20030167, a phase 2 study with the same design as this study, with the exception that subjects enrolled had EGFr membrane staining in ≥ 10% of evaluated tumor cells, as measured by the DakoCytomation EGFR pharmDx kit. This similarity between the results of each study suggests that differences in EGFr expression by tumor cells do not result in noticeable differences in the steady-state concentrations of Panitumumab.

Appendix Figure 12-1. Overlay of Panitumumab Individual Concentrations (µg/mL) in Subjects that Received Prior Avastin with Mean (±SE) Serum Panitumumab Concentration-Time Profiles From the Rest of the Subjects



Efficacy Results:



Safety Results:
Safety analyses were conducted on the Safety Analysis Set, consisting of all consented subjects who received ≥1 dose of Panitumumab (88 subjects), and the 20-week Evaluable Safety Analysis Set, consisting of subjects in the Safety Analysis Set with ≥20 weeks potential follow-up (32 subjects). The Safety Analysis Set is the focus of the data presented below.

All 88 subjects in the Safety Analysis Set had an adverse event while on treatment or in safety follow-up. Thirty-one (35%) subjects had a severe (grade 3) event, and 4 (5%) subjects had a life-threatening (grade 4) adverse event. Five (6%) subjects had a fatal adverse event during treatment or during safety follow-up. Sixteen additional subjects had a fatal adverse event during long-term follow-up (ie, ≥31 days from the last dose of Panitumumab. Twenty-three (26%) subjects had a serious adverse event.

Overall, adverse events affecting the skin and subcutaneous disorders system organ class were most common, occurring in 91% of subjects. Most subjects (94%) had ≥1 adverse event that was reported by the investigator to be treatment-related. These events comprised primarily skin and subcutaneous disorders (91% of subjects), gastrointestinal disorders (33%), and general disorders and administration site conditions (28%). The 5 most frequently occurring treatment-related events were dermatitis acneiform (68% of subjects), erythema (60%), pruritus (59%), rash (26%), and skin exfoliation (26%). Most treatment-related adverse events were mild (grade 1) (28%) or moderate (grade 2) (43%) in severity. Seventeen (19%) subjects had severe (grade 3) treatment-related events, and 2 (2%) subjects had life-threatening (grade 4) treatment-related events. Seven (8%) subjects had serious treatment-related adverse events (hypomagnesemia [experienced by 2 subjects], hypocalcaemia [experienced by 1 of the subjects who had hypomagnesemia], acute myocardial infarction, adverse drug reaction, nausea/dehydration, hypersensitivity, and myocardial infarction/ cerebrovascular accident). For 1 (1%) of these subjects (Subject 140012003), the events (myocardial infarction and cerebrovascular accident) were fatal. Thirteen (15%) subjects had adverse events that led to permanent discontinuation of investigational product or removal from study. For seven (8%) of these subjects, the events were reported as treatment-related; 3 (3%) of these subjects had serious adverse events (acute myocardial infarction, adverse drug reaction, myocardial infarction/cerebrovascular accident) (the latter were fatal [see Subject 140012003 above]).

Four subjects had investigator-reported adverse events with preferred terms indicative of an infusion reaction or a reaction to Panitumumab (eg, "infusion-related reaction," "adverse drug reaction"). Two (2%) of these subjects had an adverse event that was reported as a mild infusion-related reaction; both events occurred during the third Panitumumab infusion. For 1 of the 2 subjects, the reaction was considered by the investigator to be related to Panitumumab. This subject had a transient temperature elevation to ≥38°C (to 38.1°C) in conjunction with the Panitumumab infusion; this was not associated with other clinically meaningful changes in vital signs (ie, change of ≥30% in blood pressure, respiration rate, pulse, or temperature). The other subject with a mild infusion related-reaction had a clinically meaningful decrease from preinfusion in diastolic blood pressure of 42% (not associated with notable changes in systolic blood pressure or other vital signs); 30 minutes later, her diastolic blood pressure had returned to baseline. Both subjects received 1 subsequent Panitumumab infusion without premedication and had no further infusion-related reactions. The third subject had an adverse event during the first Panitumumab infusion that was reported as a moderate hypersensitivity reaction (manifested by bronchospasm). The reaction was serious and was judged by the investigator to be related to Panitumumab. No clinically meaningful changes in vital signs were associated with the infusion. The subject continued in the study and received 1 additional infusion of Panitumumab with pretreatment that included dexamethasone, diphenhydramine, and ranitidine administered as prophylaxis, with no additional infusion reactions. The fourth subject had an adverse event during the second Panitumumab infusion that was reported as a severe adverse drug reaction, which included shaking and chills. The reaction was serious, judged by the investigator to be related to Panitumumab, and resulted in withdrawal of the subject from treatment. The infusion during which the reaction occurred was associated with ≥30% increases in blood pressure, respiration rate, and pulse.

In an analysis of adverse event terms derived from Version 3.0 of the Common Toxicity Criteria for Adverse Events (in the acute infusion reaction/cytokine release syndrome and allergic reaction/hypersensitivity categories) occurring the day of an infusion and resolving the same day or the next day, 16 infusions administered to 12 subjects (of 428 total infusions administered to 88 subjects) were associated with potential infusion reactions, yielding a per-infusion incidence

of 4% and a per-subject incidence of 14%. Changes in vital signs were observed in temporal association with Panitumumab administrations. However, only the subjects with the mild infusion-related reactions and severe adverse drug reaction described above had clinically meaningful vital sign changes in conjunction with a recorded or potential infusion reaction.

Overall, 14 (16%) subjects had 1 or more grade 3 or 4 laboratory toxicities as their worst grade on study (10 [11%] subjects had grade 3 laboratory toxicities, and 4 [5%] subjects had grade 4 laboratory toxicities). These most commonly were low magnesium levels. Five (6%) subjects had grade 3 low magnesium values, and 4 (5%) subjects had grade 4 low magnesium values.

No subjects in the Safety Analysis Set tested seropositive for antibodies to Panitumumab, either pre- or postexposure.

Results of safety analyses for the Evaluable Safety Analysis Set (all enrolled subjects with ≥20 weeks potential follow-up; 32 subjects) were generally similar to those for the Safety Analysis Set. One difference between the sets was that no subjects in the Evaluable Safety Analysis Set had a fatal adverse event while on study, while 5 subjects in the Safety Analysis set had an on-study fatal adverse event. Also, in comparison with the Safety Analysis Set, more subjects in the Evaluable Safety Analysis Set had grade 3 treatment-related adverse events (28% versus 19%), serious treatment-related adverse events (13% versus 8%), and treatment-related adverse events leading to withdrawal (13% versus 8%). Additional differences were that the incidence of grade 3 laboratory toxicities as the worst grade on study was greater in the Evaluable Safety Analysis Set than in the Safety Analysis Set (28% versus 11%) (including a greater incidence of grade 3 low magnesium values [13% versus 6%]), and the per-subject incidence of potential infusion reactions was greater in the Evaluable Safety Analysis Set (28%) than in the Safety Analysis Set (14%). Most of the differences that were observed between the 2 analysis sets may be explained by the unequal duration of safety follow-up and the cumulative nature of certain adverse events.

Conclusions:
In this interim analysis of data from 88 subjects with metastatic colorectal cancer whose tumors expressed low or negative EGFr levels by immunohistochemistry (ie, membrane staining was either negative or positive in < 10% of evaluated tumor cells) and who had documented disease progression during or after standard prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy, Panitumumab treatment [redacted]

[redacted]

Panitumumab was well tolerated, with a 4% per-infusion incidence and a 14% per-subject incidence of potential infusion reactions and no anti-Panitumumab antibody formation.

11. Study 20025408
A Clinical Trial of the Safety and Efficacy of ABX-EGF as Second Line Treatment for Advanced Non-small Cell Lung Cancer (crossover study for 20025404 Part 2 carboplatin plus paclitaxel chemotherapy control arm)

Introduction and Objectives: This study was designed to evaluate Panitumumab administered as monotherapy in the second-line treatment of non small-cell lung cancer (NSCLC) in subjects who developed progressive disease while receiving (or within 6 months of their last dose of) carboplatin plus paclitaxel chemotherapy on the control arm of Study 20025404 Part 2.

The study objectives were:

- **Primary:** To assess the response rate, [complete response (CR) or partial response (PR)], as measured by local assessment using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, in subjects with advanced NSCLC treated with Panitumumab following failure of paclitaxel and carboplatin therapy
- **Secondary:** To evaluate additional measures of Panitumumab clinical efficacy in subjects with advanced NSCLC treated with Panitumumab following failure of paclitaxel and carboplatin therapy
- To determine the safety of Panitumumab in subjects with advanced NSCLC following failure of paclitaxel and carboplatin therapy
- To determine the PK (PK) of Panitumumab in subjects with advanced NSCLC following failure of paclitaxel and carboplatin therapy

Methodology: This was an open-label, multicenter, single-arm study of Panitumumab monotherapy in subjects who developed progressive disease while receiving (or within 6 months of their last dose of) carboplatin plus paclitaxel chemotherapy on the control arm of the randomized (2:1 Panitumumab/carboplatin/paclitaxel: carboplatin/paclitaxel) Study 20025404 Part 2. Subjects received intravenous (IV) infusions of Panitumumab weekly over a 6-week treatment period, for up to eight 6-week treatment periods, until 1) disease progression, 2) discontinuation of treatment at the request of the subject or investigator, 3) unacceptable toxicity, or 4) death. Study drug at a weekly dose of 2.5 mg/kg was administered by an infusion pump over 1 hour using a 0.22-micron filter. During each 6-week treatment period, subjects visited the clinic weekly on the dosing day. Tumor response was assessed with appropriate radiographic studies at the end of each 6-week treatment period (computed tomography [CT] scan; cranial magnetic resonance imaging [MRI] if new central nervous system [CNS] symptoms or evidence of CNS disease at baseline; bone scan if the baseline scan was positive and CR or PR was documented on evaluation of non-bone lesion, or if clinical suspicion of new bone lesions). Tumor assessments were done using RECIST criteria and were based on local assessments. Subjects determined by the investigator to have a CR, a PR, or stable disease at the end of the first 6-week treatment period were eligible to receive up to 7 additional 6-week treatment periods (until disease progression, discontinuation of treatment at the request of the subject or investigator, unacceptable toxicity, or death).
Any objective response (CR or PR) required confirmation by repeat assessments no less than 6 weeks after the criteria for response were first met. Subjects with disease progression were discontinued from the treatment phase of the study. Any subject discontinuing study drug for any reason had to have a safety follow-up visit within
4 weeks after the last study drug infusion. After discontinuing or completing the study, all study subjects were to be contacted by either a clinic visit or telephone every 3 months until 24 months after the first dose of study drug to determine disease status and survival. Safety was monitored throughout the study by review of adverse events, including skin-related toxicities assessment; physical examinations; and laboratory studies, including hematology and serum chemistry panels and urinalyses. Cardiac function was monitored using CPK-MB, troponin T, and multiple gated acquisition (MUGA) scans (or echocardiograms) done at screening, every 3 (CPK-MB, troponin T) or 9 (MUGA) weeks through week 47, and at the safety follow-up visit. In addition, subjects

were monitored for human anti-human antibody (HAHA) formation using an enzyme-linked immunosorbent assay (ELISA). Samples for antibody testing were taken at weeks 0 (baseline), 18, and 36 and at the safety follow-up. Samples for PK analysis were collected within 30 minutes before infusion and within 30 minutes after completion of the infusion at weeks 0, 5, 18, and 36 and analyzed using an immunoassay with electrochemiluminescence (ECL) detection.

Number of Subjects Planned: Up to 75 subjects were planned to be enrolled in the control arm of Study 20025404 part 2; however, only 54 subjects were actually enrolled in that arm, of whom 30 developed progressive disease.
Number of Subjects Enrolled: This study was open to subjects who developed progressive disease while receiving (or within 6 months of their last dose of) carboplatin plus paclitaxel chemotherapy on the control arm of Study 20025404 part 2 (a total of 30 subjects). Nineteen of these 30 subjects were treated at study centers that had approved the 200245408 protocol. Of these 19 subjects, 9 were enrolled in this study.
Sex: 6 (67%) men, 3 (33%) women **Ethnicity (Race):** 100% white
Age: mean (standard deviation [SD]) 68.7 (9.8) years, range 52 - 81 years

Efficacy Endpoints:

Primary: The response rate (CR or PR), by local assessment using RECIST criteria, measured at the end of the initial 6-week treatment period (As stated in the protocol, each PR or CR was required to be confirmed by repeat assessments 6 weeks after the criteria for response were first met. As implemented, repeat assessments were made *no less than* 6 weeks after the criteria for response were first met).

Secondary: Progression-free survival time, survival time, best overall response rate, and time to disease progression

Safety Endpoints: Incidence of adverse events, laboratory abnormalities, and other safety parameters

Other Endpoints: The PK of Panitumumab in subjects with advanced NSCLC after failure of paclitaxel and carboplatin therapy

Efficacy Results:

PK Results: Peak and trough PK data were to be collected before and after infusion at weeks 0, 5, 18, and 36; however, PK data were available for evaluation only at weeks 0 and 5. One single PK datum was available at week 18, but it was collected from a subject who received > 20% Panitumumab dose reduction (Subject 4139, who skipped
4 infusions and also received several infusions at a reduced dose because of adverse events). No PK data were available at week 36. Since PK data were not available at weeks 18 and 36, the Panitumumab concentrations at steady state (reached after 5 weekly doses of 2.5 mg/kg in Study 20025404 Part 1) could not be estimated. The mean ± SEM concentrations at week 0

(postinfusion = 56.41 ± 3.04 mcg/mL) and at week 5 (preinfusion = 27.80 ± 2.79 mcg/mL, postinfusion = 94.09 ±14.70 mcg/mL) were similar to those observed in Study 20025404 (Parts 1 and 2).

Table 7-2. Descriptive Statistics for Serum Panitumumab Concentrations After Weekly IV Administration of 2.5 mg/kg Panitumumab

Summary Statistic	Week 0		Week 5	
	Pre-inf	Post-inf	Pre-inf	Post-inf
N	9	8	4	4
Mean	0.0	56.41	27.80	94.09
SD	0.0	8.59	5.58	29.39
SEM	0.0	3.04	2.79	14.70
Min				
Median	0.0	53.97	30.03	81.87
Max				
%CV	NA	15.2	20.1	31.2

Pre-inf: Pre-infusion
Post inf: Post-infusion
NA = Not applicable
Summary statistics are presented in µg/mL.
Source: documentum\Docbases\usddms\R&D Candidates\Development\AMG 954 - ABX-EGF\Study 20025408\PKDM\Final Analysis\Modified Data\5408 Working 072705

Safety Results: A total of 91 infusions of study drug were administered to the 9 subjects. All 9 subjects experienced at least 1 adverse event on study (through the safety follow-up). Adverse events most frequently occurred in the skin and subcutaneous tissue disorders body system (8 subjects). Most often this skin toxicity consisted of rashes (8 subjects), which were characterized as follicular (6 subjects), macular (5), papular (5), or pustular (3). Skin reactions were considered by the investigator to be related to study drug in 7 subjects. Rashes were generally grade 1 or 2 (according to the National Cancer Institute [NCI] common toxicity criteria [CTC] version 2.0); the most severe was grade 3 (1 subject), which was not infectious in nature. No subject discontinued treatment because of a rash, although 2 subjects skipped infusions because of rash (neither rash was infectious). These included Subject 4139, who skipped 4 infusions and also received several infusions at a reduced dose because of adverse events. This subject's course on study included prolonged, significant skin and eye toxicities that were likely the cause of both the skipped infusions and the reduced dosages.

Two of the 9 subjects experienced serious adverse events. In one case, approximately 5 weeks after initiation of study drug a subject experienced mental status changes, fell, and was unable to rise; MRI of the brain revealed brain metastases. A second subject experienced severe dyspnea approximately 7 weeks after initiation of study drug, with probable etiology reported as metastatic NSCLC. Neither event was considered related to study drug.

Four subjects experienced adverse events that led to discontinuation of study drug (disease progression in each case). No subject was reported to have an adverse event considered by the investigator to be an infusion reaction. Two Panitumumab infusions (of a total of 91 administered) in 2 subjects were identified, using the most conservative analysis methods, as being associated with a potential infusion reaction: mild nausea in one case and a moderate fever in another.

One subject died on study. The cause of death was progressive disease.

One subject had NCI CTC grade 3 changes in laboratory values (no subject had a grade 4 change): creatine kinase, alanine amino transferase, and aspartate amino transferase all increased to grade 3 in this subject. The grade 3 laboratory toxicities occurred within approximately the same timeframe as serious adverse events of mental status changes and a fall in this subject with brain metastases (approximately 7 weeks after the first dose of Panitumumab, 20 days after the last dose, 5 days after completion of study, and 5 days after administration of off-study

docetaxel).
No subject tested positive for anti-Panitumumab antibodies.

Conclusions: Results for the 9 subjects enrolled in this study indicate that Panitumumab was well tolerated as monotherapy in the second-line treatment of NSCLC after progression on standard chemotherapy (paclitaxel/carboplatin). Adverse events consisted primarily of mild or moderate skin rashes. The available PK data collected at weeks 0 and 5 were similar to those observed in Study 20025404 (Parts 1 and 2). Since PK data were not available at weeks 18 and 36, Panitumumab concentrations at steady state could not be estimated from this study. Efficacy data,

Study 20030110
A Clinical Trial Evaluating the Safety and Efficacy of ABX-EGF in Patients with Hormone-resistant Prostate Cancer with or without Metastases

Introduction and Objectives:
Prostate cancer is one of several adult solid tumors that express the epidermal growth factor receptor (EGFr) and thus may represent a promising therapeutic target for the human monoclonal antibody Panitumumab. The primary objective of this study was to assess the clinical effect (tumor and/or PSA response) of weekly 2.5-mg/kg doses of
Panitumumab in subjects with hormone-resistant prostate cancer (HRPC) with or without metastases. Secondary objectives included study of Panitumumab PK, safety profile (including immunogenicity), other efficacy endpoints (time to progression and overall survival).

Methodology:
This was a multicenter, single-arm study evaluating the efficacy and safety of Panitumumab in subjects with HRPC. Subjects received intravenous (IV) infusions of Panitumumab 2.5 mg/kg over 1 hour once weekly in 8-week courses. In the absence of disease progression, subjects continued Panitumumab treatment for up to 6 courses (48 doses). PSA levels were assessed every 4 weeks and other disease parameters every 8 weeks. At discontinuation of treatment, subjects entered a 4-week safety follow-up period, followed by a follow-up period of 2 years from the first dose of study drug.

Number of Subjects Planned:
Between 30 and 50 subjects

Number of Subjects Enrolled:
Thirty-three subjects were enrolled; all received at least 1 dose of Panitumumab.
Sex: 33 men **Mean (SD) Age:** 70.2 (8.6) years **Ethnicity (Race):** 27 white,
5 Hispanic, 1 black

Diagnosis and Main Criteria for Eligibility:
Hormone-resistant prostate cancer with or without metastases and with documented disease progression; tumor expressing EGFr in $\geq$10% of evaluated tumor cells; testosterone level < 50 ng/dL; failed front-line luteinizing hormone releasing hormone analog or orchiectomy; no prior chemotherapy; at least 18 years of age; adequate hematologic, hepatic, and renal function; ECOG performance score of 0 or 1.

Primary Efficacy Endpoint:
Disease response (PSA changes and/or tumor response) after initial 8-week course
Secondary Endpoints:
- tumor response after initial 8-week course
- PSA changes after initial 8-week course
- progression-free survival time and time to disease progression
- overall survival time
- time to PSA progression
- percent change in PSA after initial 8-week course
- peak and trough serum Panitumumab levels
- safety variables (including immunogenicity)

Efficacy Results:

PK Results:
After multiple weekly doses of Panitumumab 2.5 mg/kg, the mean (SEM) preinfusion serum concentration at week 8 was 60.2 (4.2) mcg/mL and the postinfusion concentration was 131.1 (5.7) mcg/mL. Panitumumab preinfusion accumulation was approximately 4-fold and postinfusion accumulation was approximately 2-fold.

All 33 treated subjects had preinfusion and postinfusion PK samples for week 1. Thirty-two subjects had postinfusion samples for week 2; due to subject attrition and/or missing samples, available data at weeks 7 and 8 were less (Table 10-1). Because only 1 subject had PK samples drawn at week 24 and no subject at week 48, these data are not discussed.

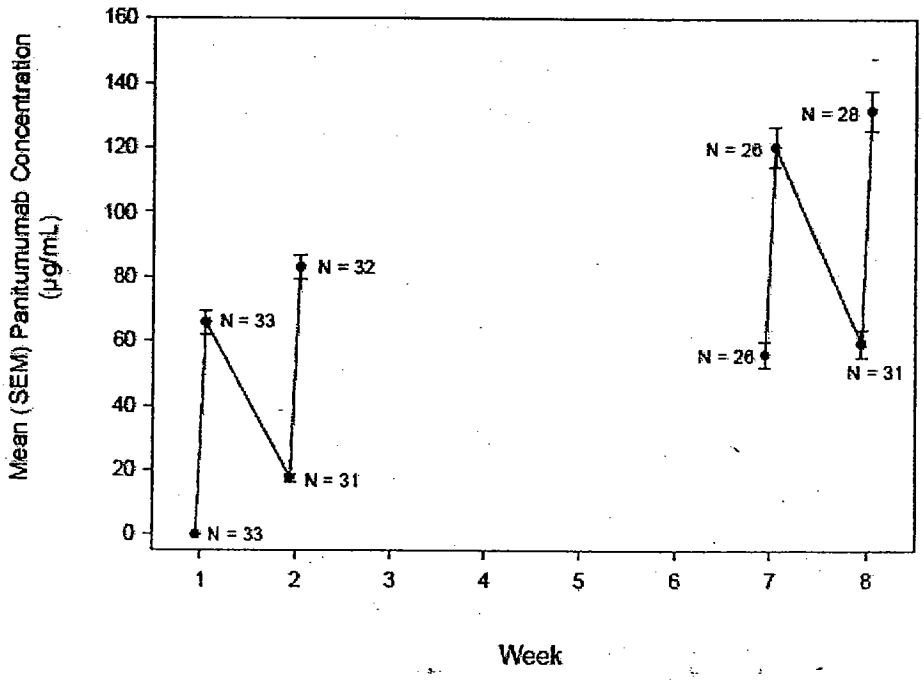
Mean (SEM) postdose Panitumumab concentration after the week 1 infusion increased over weeks 2, 7, and 8, indicative of Panitumumab accumulation over time (Table 10-1 and Figure 10-1). Week 8 postinfusion values for individual subjects ranged from 85.1 mcg/mL to 185.6 mcg/mL.

Preinfusion Panitumumab concentrations likewise showed accumulation of serum levels over time. Median accumulation ratios were 4.0 for preinfusion Panitumumab concentrations (week 8 vs week 2) and 2.0 for postinfusion concentrations (week 8 vs week 1). Overall, the intersubject variability of Panitumumab concentration was low, with CVs ranging from 37% to 45% for preinfusion data and from 23% to 30% for postinfusion data.

Table 10-1. Summary Statistics of Panitumumab Concentrations

	Week 1	Week 2		Week 7		Week 8	
	Post-inf	Pre-inf	Post-inf	Pre-inf	Post-inf	Pre-inf	Post-inf
N	33	31	32	26	26	31	28
Mean (µg/mL)	65.7	17.7	82.8	56.6	120.5	60.2	131.1
SD (µg/mL)	20.0	8.0	19.3	21.0	29.9	23.4	30.3
SEM (µg/mL)	3.5	1.4	3.4	4.1	5.9	4.2	5.7
Min (µg/mL)							
Median (µg/mL)	66.2	18.3	86.6	57.9	114.8	60.6	125.5
Max (µg/mL)							
CV (%)	30.4	45.1	23.3	37.1	24.8	38.8	23.1

Figure 10-1. Pre- and Postdose Concentrations of Panitumumab in First Course



Safety Results:

Thirty-two of 33 subjects (97%) experienced at least 1 adverse event while on study. Five subjects (15%) had a severe event and none had an event that was lifethreatening, fatal, or that led to discontinuation of treatment. Four subjects (12%) experienced an adverse event considered serious. No deaths occurred on study.

Thirty-two subjects (97%) had an event that was considered treatment-related, but these were generally mild or moderate, consisting mainly of rash and other skin disorders. These involved ≤ 50% of total body surface, did not require narcotics, and required systemic steroids in only 1 case. The skin reactions appeared after a median of 2 weeks from the first infusion, with a median total duration of 12 weeks.

Only 1 reaction was reported by the investigator as an "infusion reaction" (0.3% of total infusions or 3% of subjects). The most inclusive analysis of infusion-like reactions that occurred on the day of infusion identified 7 total events (2% of total infusions or 21% of subjects). These consisted of 1 case each of urticaria, lethargy, vomiting, hypotension, a multisymptom skin

reaction with dry cough, and 2 cases of flushing, all mild to moderate in severity. A low percent of Panitumumab infusions was associated with either increases (4% of infusions) or decreases (3% of infusions) in diastolic blood pressure of 30% or greater. No notable treatment-emergent laboratory trends or evidence of cardiotoxicity were seen. No subject developed antibodies to Panitumumab.

Conclusions:
Panitumumab is safe as a monotherapy in subjects with HRPC when administered weekly at a dose of 2.5 mg/kg. No disease responses were observed based on tumor remission or changes in PSA.

Study 20020374
A Two-part, Multiple Dose Clinical Trial Evaluating the Safety and Effectiveness of ABX-EGF in Patients With Renal Carcinoma

Introduction and Objectives:
Panitumumab is a high-affinity, fully human, IgG2 monoclonal antibody that targets the human epidermal growth factor receptor (EGFr). Renal cell carcinoma is one of several solid tumors that express the EGFr, thus representing a tumor type that might be sensitive to Panitumumab treatment.
The primary objective of part 1 of this study was to assess the safety and preliminary efficacy of weekly administration of Panitumumab at 4 different dose levels (1.0, 1.5, 2.0, and 2.5 mg/kg) in subjects with renal cell carcinoma. The secondary objective was to determine the PK of up to 4 dose levels of Panitumumab in these subjects.
The primary objective of part 2 of this study was to assess the safety of the administration of a 2.5 mg/kg weekly dose of Panitumumab in subjects with renal cell carcinoma, and to assess the clinical effect of this weekly dose over 8 weeks of treatment. The secondary objective was to determine the PK of this Panitumumab dose and schedule in these subjects.

Methodology:
This study was a multicenter, 2-part, multiple-dose study evaluating the safety and effectiveness of Panitumumab in subjects with renal cell carcinoma. Part 1 of the study had an open-label, dose-escalation design. Subjects were sequentially enrolled in 1 of 4 dose groups to receive once-weekly intravenous (IV) infusions of 1.0, 1.5, 2.0, or 2.5 mg/kg Panitumumab administered over 1 hour. In part 2, subjects with renal cancer who had a previous nephrectomy received 2.5 mg/kg Panitumumab administered once weekly by IV infusion over 1 hour. Two separate cohorts of subjects were enrolled in part 2. Cohort 1 was limited to subjects who had failed 1 biotherapy (interleukin-2 [IL-2] or interferon-α); in cohort 2 subjects had no prior therapy beyond nephrectomy and fell within the Motzer intermediate risk group criteria.

In part 1 and part 2, subjects first received once-weekly doses of Panitumumab during an initial 8-week treatment period (1 treatment cycle). Subjects who were considered to be stable or responding to treatment based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria were eligible to continue into an extended treatment period in which subjects received the same dose and schedule of Panitumumab for up to 10 months (4 additional 8-week cycles of Panitumumab treatment). Additionally, subjects in part 2 who previously received and tolerated Panitumumab treatment and were considered to be stable or responding to treatment based on RECIST criteria after the final Panitumumab infusion could continue receiving Panitumumab treatment, pending eligibility, on Study 20020375. Subjects from part 1 could not continue into Study 20020375.
If at any time during either part of the study, a subject exhibited evidence of disease progression,

withdrew consent, or was unable to tolerate study drug, treatment with Panitumumab was discontinued. All subjects, including those who discontinued treatment, were followed 4 weeks after the last infusion of Panitumumab for safety evaluation. Subjects were followed for 2 years (from the first dose of Panitumumab) to assess survival and to collect information on the use of any cancer medication or therapy.

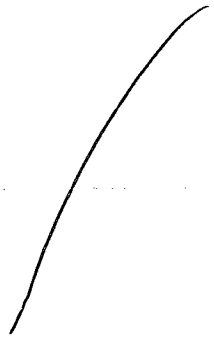
Number of Subjects Planned:
The planned sample size was 180 subjects, 80 in part 1 (20 per dose group) and 100 in part 2 (40 in part 2 cohort 1 and 60 in part 2 cohort 2).

Number of Subjects Enrolled:
Part 1:
Ninety-five subjects were enrolled in this part of the study and 88 received at least 1 dose of Panitumumab.
Sex: 64 men (73%), 24 women (27%) **Mean (SD) Age:** 57.3 (8.5) years
Ethnicity (Race): 83 white (94%), 3 Hispanic (3%), 1 black (1%), 1 Asian (1%)
Part 2:
One hundred and seven subjects were enrolled in this part of the study and all received at least 1 dose of Panitumumab.
Sex: 75 men (70%), 32 women (30%), **Mean (SD) Age:** 61.5 (10.3) years
Ethnicity (Race): 90 white (84%), 11 Hispanic (10%), 4 black (4%), 2 Asian (2%)

Primary Efficacy Endpoints
Part 1 and Part 2 Cohort 1:
• response rate (complete response or partial response based on assessments performed at the investigative site using RECIST criteria) at the end of the first 8-week treatment period; response was to be confirmed no less than 4 weeks after criteria for response were first met
Part 2, cohort 2:
• time to disease progression
Secondary Efficacy Endpoints
Parts 1 and 2:
• progression-free survival time
• survival time
• best overall response
Other Efficacy Endpoints
• duration of tumor response
• time to tumor response (complete response or partial response)
• duration of stable disease
Safety Endpoints
Parts 1 and 2:
• incidence and severity of adverse events
• exposure-adjusted incidence of adverse events
• on-study deaths
• change in laboratory values
• change in vital signs
• incidence of any anti-Panitumumab antibody formation
• Incidence, severity of, and time to skin rash
• change in MUGA scan results (% left ventricular ejection fraction [LVEF])
Pharmacokinetic Endpoints

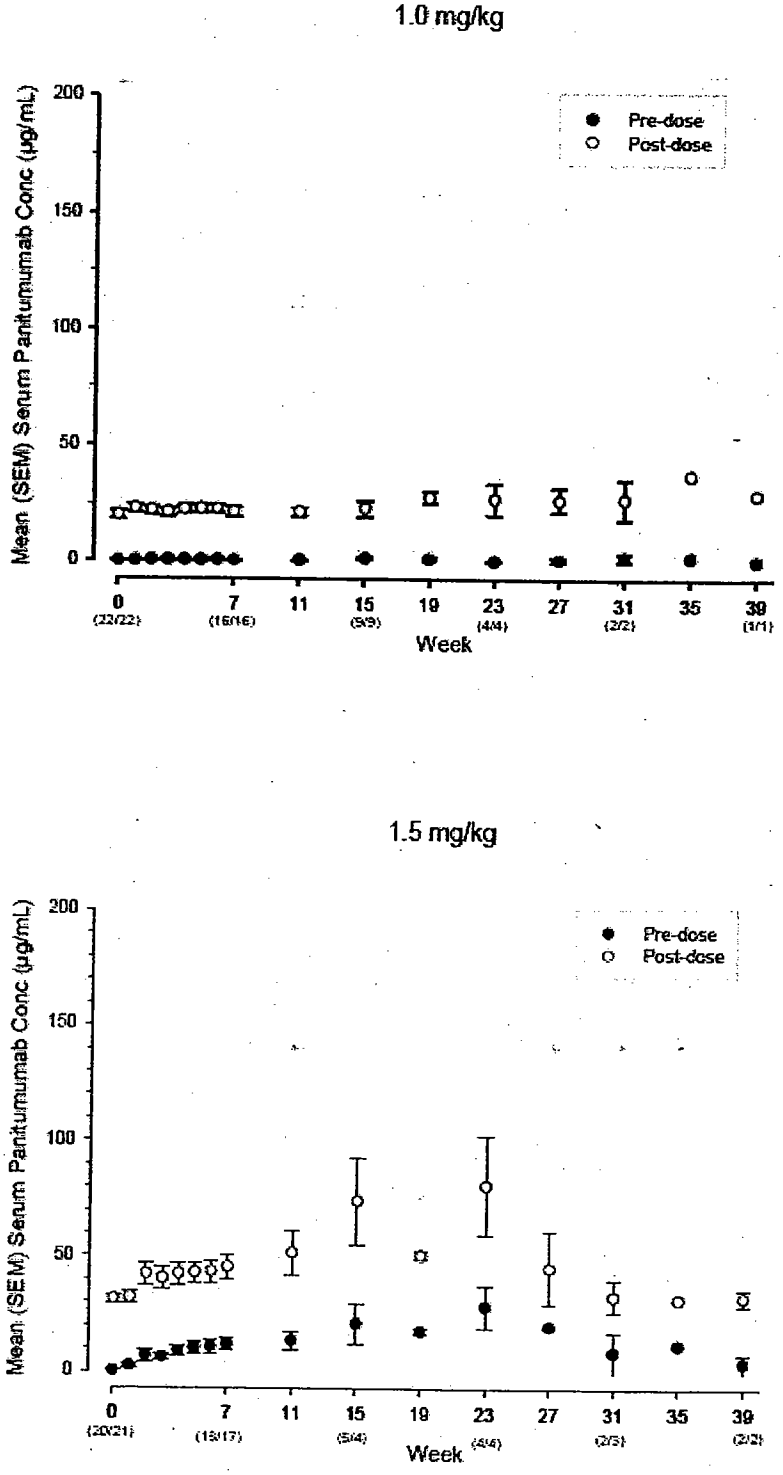
Part 1:
• concentration of Panitumumab before and after Panitumumab dosing weekly during the first 8 weeks and at study weeks 11, 15, 19, 23, 27, 31, 35, and 39
Part 2:
• concentration of Panitumumab before and after Panitumumab dosing at study weeks 0 (baseline), 7, 23, and 39

Efficacy Results:



PK Results:
In part 1, Panitumumab concentrations increased in a greater than dose-proportional manner, suggesting nonlinearity in the Panitumumab PK over the dose range of 1.0 to 2.5 mg/kg/week. Steady-state peak and trough concentrations were attained approximately after 8 and 7 weekly doses, respectively.
In part 2, no appreciable differences were observed in the pharmacokinetic (PK) profiles for Panitumumab administered at the dose of 2.5 mg/kg/week between cohorts 1 and 2. Because of the limited sampling schedule, the exact time that Panitumumab concentrations reached steady state could not be defined in this part of the study. Based on data collected from study week 23, the mean ± SD Panitumumab concentrations at steady state were 57.7 ±30.4 mcg/mL at trough and approximately 114 ± 38 mcg /mL at peak.

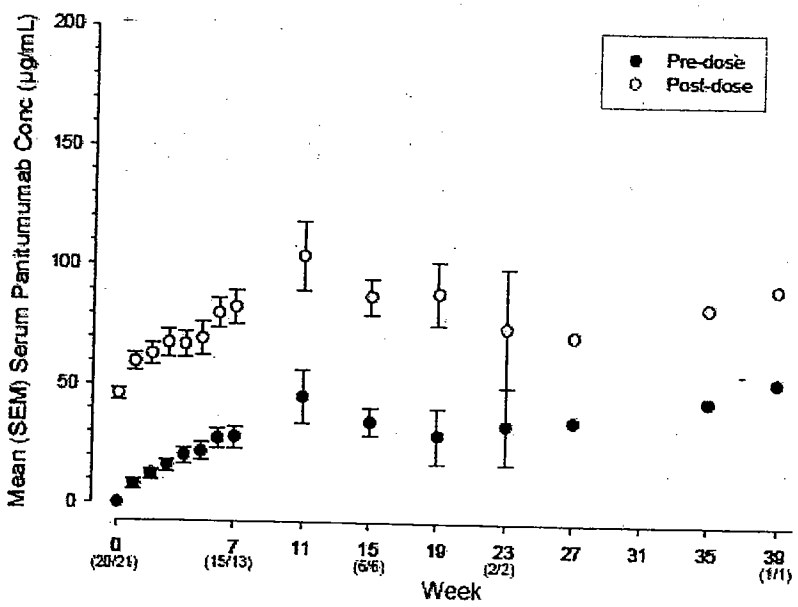
Figure 10-1. Serum Panitumumab Concentrations (Mean ± SEM) - Part 1



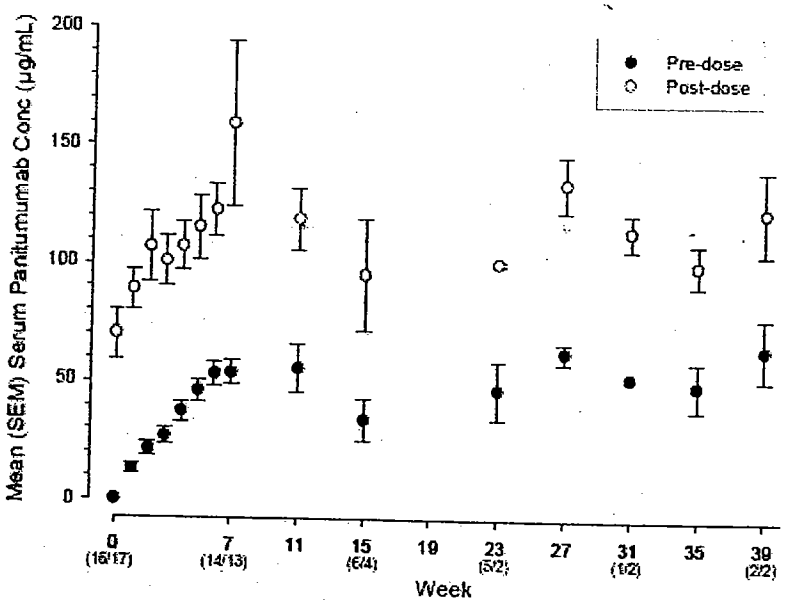
Number of subjects for each time point shown as pre-dose/post-dose.

Figure 10-1. Serum Panitumumab Concentrations (Mean ± SEM) - Part 1 (continued)

2.0 mg/kg



2.5 mg/kg



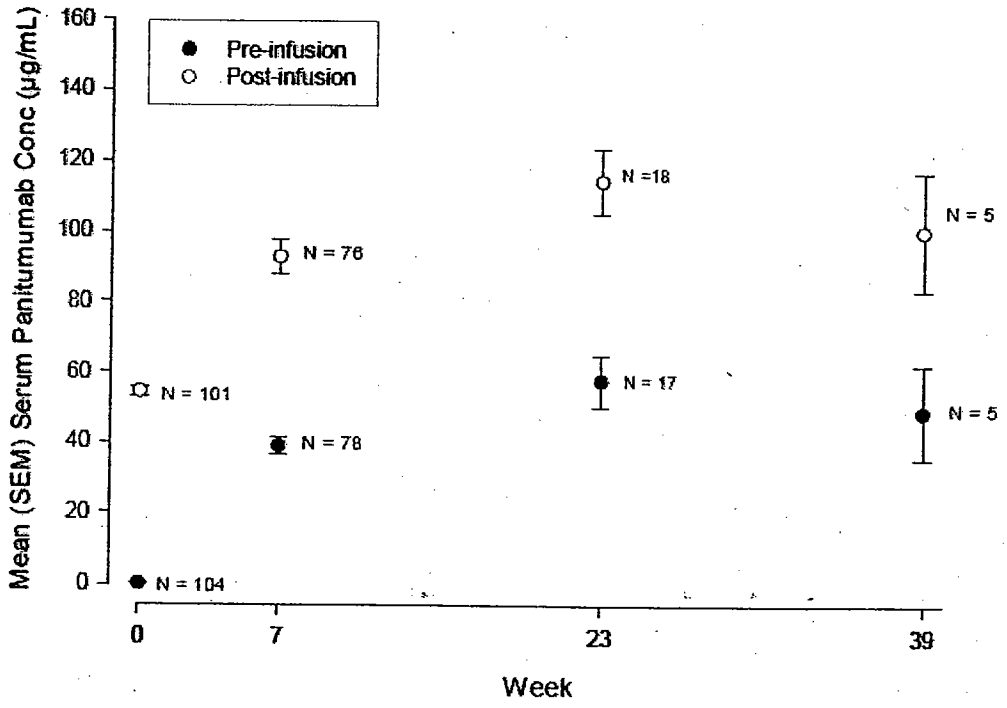
Number of subjects for each time point shown as pre-dose/post-dose.

Table 10-1. Summary Statistics of Post-infusion Serum Panitumumab Concentrations - Part 2, Cohorts 1 and 2 Combined

Subject	Week 0		Week 7		Week 23		Week 39	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
N	104	101	78	76	17	18	5	5
Mean	0.03	54.40	39.05	93.13	57.71	114.36	48.82	100.30
SD	0.09	12.07	19.93	43.29	30.38	38.32	29.90	37.46
SEM	0.01	1.20	2.26	4.97	7.37	9.03	13.37	16.75
Median	0.0	53.5	37.0	90.0	51.0	115.5	48.7	100.9
CV%	270.3	22.2	51.0	46.5	52.6	33.5	61.3	37.3

Pre-: pre-dose
Post-: Post-dose
Concentrations are presented in µg/mL

Figure 10-2. Post-infusion Serum Panitumumab Concentration (Mean ± SEM) - Part 2, Cohorts 1 and 2 Combined



Safety Results:

In part 1, all 88 subjects experienced at least 1 adverse event while on study, 30 (34%) of whom had an event that was ≥grade 3 per National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0. No clear dose-response relationship was observed between dose of Panitumumab administered and the incidence or severity of adverse events. The incidence, when adjusted for exposure, was lowest in the 1.0-mg/kg/week dose group (26.65 events per year) compared with the higher dose groups (38.03, 39.52, and 35.52 events per year in the 1.5, 2.0, and 2.5 mg/kg/week groups, respectively). Rash and fatigue were the 2 most common adverse events in all dose groups. When adjusted for exposure, the incidence of rash generally increased with increasing dose. The exposure-adjusted incidence was 3.22, 7.28, 6.46, and 9.22 events per year in the 1.0, 1.5, 2.0, and 2.5 mg/kg/week dose groups, respectively. In addition to rash, another integument adverse event, dry skin, also increased with exposure-adjusted dose (0, 0.27,

0.26, and 1.27 events per year in the 1.0, 1.5, 2.0, and 2.5 mg/kg/week dose groups, respectively. Most subjects (66%) experienced adverse events that were mild or moderate in severity; 28% experienced grade 3 adverse events, and 6% experienced grade 4 adverse events. The severity of adverse events had no obvious relationship to the dose of Panitumumab administered.

Twenty-five subjects (28 %) had an adverse event considered serious; the proportion of subjects with serious adverse events were 41%, 27%, 30%, and 14%, in the 1.0, 1.5, 2.0, and 2.5 mg/kg/week dose groups, respectively. Treatment-related adverse events were seen in 81 subjects (92 %); no dose relationship was observed and these events were generally mild-to-moderate, consisting mainly of rash, fatigue, nausea, diarrhea, dry skin, and dyspnea. Five subjects (6%) experienced a treatment-related serious adverse event; 3 subjects that received 1.0 mg/kg/week (events of diarrhea, dyspnea, or deep vein thrombosis) and 2 subjects that received 1.5 mg/kg/week (vomiting or rigors) Panitumumab. Eighteen subjects (20%) had adverse events that led to discontinuation of Panitumumab; 5 of these subjects had events that were considered related to treatment (mild skin rash, moderate fatigue, severe rash, and severe pain each in 1 subject, and moderate abdominal pain, severe nausea, and severe vomiting in the same subject). Four subjects (5%) died during the treatment period. No subject had an adverse event that the investigator described as an infusion reaction. An analysis of potential infusion reactions was conducted using prespecified preferred terms. Adverse events of interest were derived from Version 3.0 of the CTCAE, using terms in the following categories: allergic reaction/ hypersensitivity and cytokine release syndrome/acute infusion reaction. Potential infusion reactions were identified in 10 subjects (11%) and in 17 infusions (1%); these included nausea, dizziness, and vomiting. Transient fluctuations were seen in vital signs during and postinfusion, particularly in diastolic blood pressure (both increases and decreases). In only 6 of 1326 infusions did a clinically significant vital sign change coincide with clinical symptoms of a potential infusion reaction. In no case was the Panitumumab infusion interrupted or discontinued because of an adverse event. Sixteen subjects (18%) had a grade 3, and 2 subjects (2%) had a grade 4 laboratory toxicity. No effect of Panitumumab dose on LVEF was apparent. Eighty-six subjects (99%) had a postdose sample available for the assessment of antibodies; no postdose blood samples tested seropositive for human antibodies to Panitumumab.

In part 2, all 107 subjects experienced at least 1 adverse event while on study.
Thirty-six percent of subjects in part 2 had grade 3 adverse events (27% cohort 1, 41% cohort 2). The incidence of adverse events considered treatment-related was similar between the cohorts (23% cohort 1, 24% cohort 2). Rash was the most frequent adverse event in both cohort 1 and cohort 2 (86% and 87%). Fourteen percent (6) of subjects in cohort 1 and 5% (3) of subjects in cohort 2 had a grade 4 adverse event. Malignant neoplasm progression and pulmonary embolism were the only grade 4 events to occur in 2 subjects, 1 from each cohort. Treatment-related adverse events were reported in 98% of subjects in each cohort; these events were generally mild-to-moderate and consisted mainly of skin disorders (including rash, dry skin, and pruritus), fatigue, and diarrhea. Three subjects (7%) from cohort 1 and 6 subjects (10%) from cohort 2 died during the treatment period. No infusion reaction was reported as a treatment-related adverse event. Using a conservative post-hoc approach, potential infusion reactions were identified in 14 subjects (13%) and in 16 infusions (1%) overall; these included nausea and pyrexia. In no case was Panitumumab infusion interrupted or discontinued because of an adverse event.
Twenty-one subjects (21%) had a grade 3 and 1 subject (1%) had a grade 4 laboratory change. Ninety-three subjects (87%) had a postdose sample available for the assessment of antibodies; no postdose blood samples tested seropositive for human antibodies to Panitumumab.

Conclusions: Panitumumab was generally well-tolerated in subjects with renal cell carcinoma this 2-part study at doses up to 2.5 mg/kg/week. The most common treatment-related events were primarily skin-related and were generally mild-to-moderate and manageable, consisting predominantly of rash. No infusion reactions were reported as adverse events, despite the fact that premedications for infusion reactions were not required by the protocol.

4.2 APPENDIX 2 – PM REQUEST FORM

OFFICE OF CLINICAL PHARMACOLOGY

Pharmacometrics Consult Request Form

NDA:	**BLA 125147**	**Sponsor:**	**Amgen**
IND:			
Brand Name:	**To be determined**	**Priority Classification:**	**Priority**
Generic Name:	**PANITUMUMAB**	**Indication(s):**	
Dosage Form:	**20 mg/mL for IV infusion**	**Date of Submission:**	**3/29/06**
Dosing Regimen:	**6 mg/kg Q2W or 2.5 mg/kg QW**	**Due Date of PM Review:**	**July 31, 2006**
Division:	**DCP 5**	**Medical Division:**	**DBOP**
Reviewer:	**Angela Men Hong Zhao (TL)**	**Team Leader:**	**Hong Zhao**

Panitumumab is a recombinant, human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Binding of panitumumab to EGFR results in the internalization of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production. Panitumumab is indicated for

The effectiveness of panitumumab is based on progression free survival. Currently no data are available that demonstrate an improvement in disease-related symptoms or increased survival with panitumumab.

Tabular Listing of All Human Studies That Contain PK/PD information:

See attached Table below.

List the following for this compound (if known. The list will be confirmed by PM Scientist during the review):

Clinical endpoint(s):	Progression free survival, survival, time to disease progression, objective response, time to response, duration response, Growth Modulation Index (GMI) - exploratory endpoint
Surrogate endpoint(s):	No.
Biomarker(s):	No.
Any reported optimal dose based on PK/PD?:	No.
Any reported dose/concentrations associated with efficacy/ toxicity?:	Eye toxicity
Principal adverse event(s):	Integument and Eye toxicities

PHARMACOMETRICS REQUEST:

The sponsor has conducted population PK and PK/PD analyses. Please check their analyses and confirm the results

1) Population PK

The sponsor conducted "A Population Pharmacokinetic Analysis of Panitumumab in Subjects with Various Advanced Solid Tumors".

Associated clinical studies: 20020374, 20020408, 20025404; 20025405, 20025408, 20025409, 20030110, 20030138, 20030167, 20030250, 20030251, 20040116 and 20040192.

The number of subjects in each study ranged from 9 to 225, with each subject receiving intravenous infusions of panitumumab every one, two, or three weeks, depending on the dose, with or without concurrent administration of chemotherapy. Five of the studies (20030138, 20025404, 20025409, 20030251 and 20040192) were designed with intensive sampling schedules. Only peak and trough samples were taken for the other 8 studies.

Results suggest that age, gender, tumor type, race, hepatic function, renal function, chemotherapeutic agents, and EGFR expression in tumor cells had no apparent impact on the pharmacokinetics of panitumumab.

2) PK/PD

- The relationship between PK and efficacy was not examined because of lack of PK data in the efficacy studies
- Relationship Between PK and Toxicities
    - 2 safety endpoints selected for this analysis were:
        - reported integument or eye toxicity within the first 28 days after the first panitumumab dose;
        - reported grade 3 or 4 (per NCI CTC version 2.0 criteria) integument and eye toxicity within the first 28 days after the first panitumumab dose.
    - the primary finding of this analysis, that the amount of panitumumab administered is a predictor of the occurrence of integument and eye toxicity or grade 3 or 4 integument and eye toxicity.

3) Relationship Between PK and Anti-panitumumab Antibodies

- No clear trends were observed between the presence of anti-panitumumab antibodies (neutralizing and not neutralizing) and the PK of panitumumab.

Due Date to the Reviewer: July 31, 2006

The _X_ PM Scientist or the ____ Primary Reviewer (select one) will perform the PM Review

PM Briefing ____ or PM Peer Review ____ requested (for criteria see the PM Road Map of QA/QC process)

Primary Reviewer: Angela Men/Hong Zhao **Signature** _____ **Date:** 5/3/06

PM Scientist _____ **Signature** _____ **Date** _____

Appendix Table 1. Summary of Clinical Studies That Include PK Sample Collection

Study (Tumor Type)	Phase	Study Design	Material	Dose (mg/kg)	Sampling Schedule
20030251[a] (Solid Tumors)	1	Q2W until disease progression or unable to tolerate investigational product	— CHO	6	First 20 subjects[b] enrolled: Weeks 1 and 5: at 24, 96, 168, and 240 hours after the completion of infusion All subjects: Weeks 1, 3, 5, 7, and every 8 weeks thereafter: predose and at the end of infusion
20040192[a] (advanced solid tumors)	1	Cohort 1: QW dosing until disease progression or unable to tolerate investigational product	— CHO	2.5	Cohort 1: Week 1: Predose, 30 minutes, 1, 4, 8, 24 hrs (Day 2), 4 days (Day 5) after the completion of infusion Week 2: Predose, 30 minutes, 1, 4, 8 (Day 15), 24 hrs (Day 16), and 4 days (Day 19) after the completion of infusion Week 4 (Day 22) and Every 8 weeks: Predose and 30 minutes after the completion of infusion
		Cohort 2: Q2W dosing until disease progression or unable to tolerate investigational product	— CHO	6	Cohort 2: Week 1: Predose, 30 minutes, 24 hrs (Day 2), 4 (Day 5), 7 (Day 8), and 10 days (Day 11) after the completion of infusion Week 3: Predose and 30 minutes after the completion of infusion Week 5: Predose, 30 minutes (Day 29), 24 hr (Day 30), 4 (Day 33), 7 (Day 36) and 10 days (Day 39) after the completion of infusion Week 7 (Day 43) and Every 8 weeks: Predose and 30 minutes after the completion of infusion

mCRC = Metastatic colorectal cancer ; NSCLC = Non Small Cell Lung Cancer

[a]Study also contained a 9 mg/kg Q3W cohort; however, no subjects were enrolled in this cohort at the time of the data cutoff for this license application.

[b]Actual study included 28 subjects.

Source: Clinical Study Reports, Section 5.3 (Module 5).

Appendix Table 1. Summary of Clinical Studies That Include PK Sample Collection

Study (Tumor Type)	Phase	Study Design	Material	Dose (mg/kg)	Sampling Schedule
20030138 (solid tumors)	1	Loading dose + QW dosing for 3 doses Schedule 1: dosing on weeks 0-3	Hybridoma	0.01, 0.03, 0.1, 0.3, 0.75, 1.0 (including a 2x loading dose)	QW schedule 1: Week 0: predose and 0.5, 1, 4, 8, 24 and 96 hrs after the end of infusion Weeks 1-3: predose and at the end of infusion
		QW dosing for 4 doses Schedule 1: dosing on weeks 0-3 Schedule 2: dosing on week 0, 3-5	Hybridoma	0.75, 1.0, 1.5, 2.0, 2.5, 3.5, 5.0	QW schedule 2: Week 0: predose and at 0.5, 1, 4, 8, and 24 hrs after the end of infusion Weeks 3-5: predose and at the end of infusion
		Q2W dosing for 4 doses	Hybridoma and — CHO	6	Q2W schedule: Weeks 0, 4: predose and 0.5, 8, 24, 96, 168, 240, and 288 hrs after the end of infusion Weeks 2, 6: predose and at the end of infusion
		Q3W dosing for 4 doses	Hybridoma and — CHO	9	Q3W schedule: Weeks 0, 6: predose and 0.5, 8, 24, 96, 168, 336, and 408 hrs after the end of infusion Weeks 3, 9: predose and at the end of infusion
20040116 (20030138 extension, solid tumors)	1	Q2W dosing for 12 doses	— CHO	0.1, 1.5, 2.5, 3.5, 5, 6	Q2W schedule: Weeks 0, 6, 14, and 22: predose and at the end of infusion
		Q3W dosing for 8 doses	— CHO	9	Q3W schedule: Weeks 0, 9, and 21: predose and at the end of infusion

mCRC = Metastatic colorectal cancer ; NSCLC = Non Small Cell Lung Cancer

Appendix Table 1. Summary of Clinical Studies That Include PK Sample Collection

Study (Tumor Type)	Phase	Study Design	Material	Dose (mg/kg)	Panitumumab Sampling Schedule
20020408 (mCRC)	3	Q2W until disease progression or unable to tolerate investigational product	—CHO	6	Weeks 7 and 23:Predose and at the end of infusion
20025405 (mCRC)	2	QW dosing for 8 doses per cycle, and up to 6 cycles	Hybridoma	2.5	Cycle 1 (Week 0): Predose and at the end of infusion Cycle 1 (Week 1): End of infusion All cycles (Week 7): Predose and at the end of infusion
20030167 (mCRC)	2	Q2W dosing until disease progression or unable to tolerate investigational product	— CHO	6	Weeks 7 and 23: Predose and at the end of infusion
20030250 (mCRC)	2	Q2W dosing until disease progression or unable to tolerate investigational product	—CHO	6	Weeks 7 and 23: Predose and at the end of infusion

mCRC = Metastatic colorectal cancer ; NSCLC = Non Small Cell Lung Cancer

Appendix Table 1. Summary of Clinical Studies That Include PK Sample Collection

Study (Tumor Type)	Phase	Study Design	Material	Dose (mg/kg)	Panitumumab Sampling Schedule
20025404 (NSCLC)	2	Part 1: QW dosing for 6 doses in combination with paclitaxel and carboplatin	Hybridoma	1, 2, 2.5	Weeks 0 and 3: Predose, at the end of infusion, and 4, 24, 48, 72, and 144 (or 96) hr after the start of infusion. Weeks 1, 2, 4, and 5: Predose and at the end of infusion
		Part 2: QW dosing in combination with paclitaxel and carboplatin until disease progression, intolerability to study drug/chemotherapy or other reason for discontinuation	Hybridoma	2.5	Weeks 0, 1, 3, 4: Predose and at the end of infusion.
		Extended treatment: QW until disease progression, intolerability to study drug/ or other reason for discontinuation or a maximum of 4 additional 3-week cycles	Hybridoma		Extended treatment: Weeks 9, 18, 27, 36, and 45: predose and at the end of infusion
20025408 (20025404 Part 2 crossover, NSCLC)	2	QW dosing for 6 doses per cycle, and up to 8 cycles until disease progression, intolerability to study drug/ or other reason for discontinuation	Hybridoma	2.5	Weeks 0, 5, 18, and 36: Predose and at the end of infusion
20030110 (Prostate)	2	QW dosing for 6 doses per cycle, and up to 6 cycles	Hybridoma	2.5	Weeks 1, 2, 7, 8, 24, and 48: Predose and at the end of infusion

mCRC = Metastatic colorectal cancer ; NSCLC = Non Small Cell Lung Cancer

Appendix Table 1. Summary of Clinical Studies That Include PK Sample Collection

Study (Tumor Type)	Phase	Study Design	Material	Dose (mg/kg)	Sampling Schedule
20020374 (Renal)	2	Part 1: QW dosing for 8 doses	Hybridoma	1.0, 1.5, 2.0, 2.5	Part 1: Weeks 0-7: predose and at the end of infusion.
		Part 2: QW dosing for 8 doses	Hybridoma	2.5	Part 2: Weeks 0, 7, 23, and 39: predose and at the end of infusion
20025409 (mCRC)	2	QW dosing for 6 doses per course, and up to 8 courses in combination with IFL (Part 1) or FORFIRI (Part 2)	Hybridoma	2.5	First 10 subjects enrolled Course 1 (weeks 1 and 6): Predose, at the end of infusion, and 24, 48, 96, and 168 hrs after the start of infusion. All other subjects Courses 1, 3, 5, and 7 (week 1): Predose and at the end of infusion

mCRC = Metastatic colorectal cancer ; NSCLC = Non Small Cell Lung Cancer

4.3 APPENDIX 3 - PM CONSULT REVIEW

Pharmacometrics Review

BLA 125,147 Submission Date: July, 31 2005

PDUFA Date: September 28, 2006

Previous related submission: IND- 8382

Drug name: Vectibix (Panitumumab)

Formulation: 20 mg/mL for *intravenous* infusion

Sponsor: Amgen

Reviewer: Rajanikanth Madabushi, Ph.D.

Secondary Reviewer: Yaning Wang, Ph.D.

Type of Submission: New Drug Application, NME

TABLE OF CONTENTS

INTRODUCTION:

Panitumumab is a high-affinity (K_d = 5 x 10-11 M), fully human monoclonal antibody (IgG2) that targets the human epidermal growth factor receptor (EGFr or erbB1), leading to inhibition of EGFr activation. EGFr is a 170,000 dalton transmembrane glycoprotein that promotes cell growth in a variety of tissues. EGFr expression is frequently associated with malignant transformations in carcinomas of the prostate, breast, ovary, lung, kidney, and colon, and others (Gullick, 1991; Herbst and Shin, 2002). The high affinity interaction of Panitumumab with the active site of the EGFr blocks the binding of the various ligands, including EGF and transforming growth factor-alpha (TGFα). This blocking of receptor-ligand interaction may in turn arrest tumor proliferation, inhibit metastasis, and trigger apoptosis (programmed cell death).

POPULATION PHARMACOKINETIC ANALYSES:

OBJECTIVES:

The objectives of this analysis were to:
1) develop a population pharmacokinetic (PK) model that describes the disposition of Panitumumab in subjects with various advanced solid tumors and to estimate appropriate fixed effect and random effect parameters,
2) to estimate the effects of covariates on inter-subject variability in Panitumumab PK parameters in subjects with various advanced solid tumors, and
3) identify covariate-associated changes in PK of Panitumumab that may potentially lead to dose adjustment.

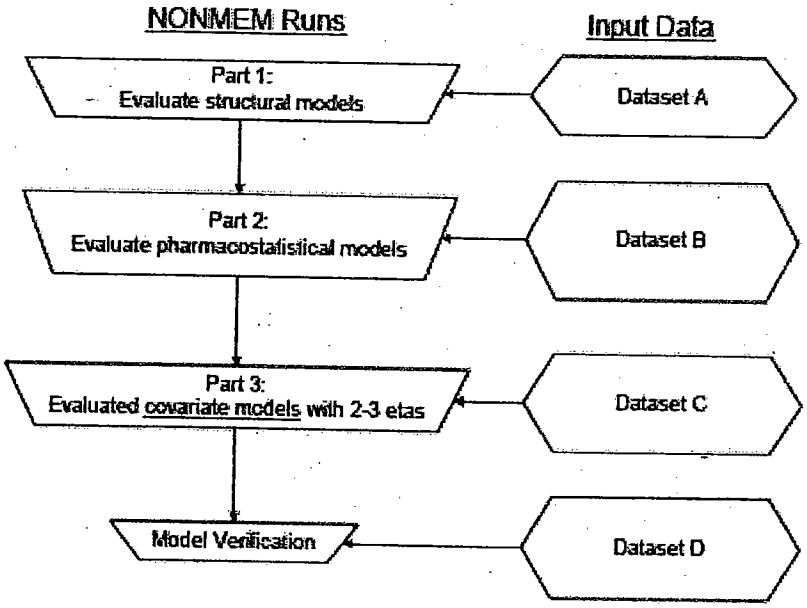
DATA:

The integrated data set for NONMEM analysis was generated from the clinical case report tabulations of the following 13 studies: 20020374, 20020408, 20025404, 20025405, 20025408, 20025409, 20030110, 20030138, 20030167, 20030250, 20030251, 20040116 and 20040192. The number of subjects in each study ranged from 9 to 225, with each subject receiving intravenous infusions of Panitumumab every one, two, or three weeks, depending on the dose, with or without concurrent administration of chemotherapy.
Five of the studies (20030138, 20025404, 20025409, 20030251 and 20040192) were designed with intensive sampling schedules. Only peak and trough samples were taken for the other 8 studies. The entire data were divided into four datasets. As the analysis progressed from the structural model to the final model, the amount of data available increased, and each subsequent dataset was built upon the previous version. The structural model determination was performed on a 2-study dataset (Dataset A – Studies 200303138, 20040116). Inter-subject variability was explored using a 4-study (Dataset B - 20030138, 20040116, 20025405, 20025408) and 10-study dataset (Dataset C - 20030138, 20040116, 20025405, 20025408, 20025404, 20025409, 20020374, 20030251, 20040192, and 20030110). The covariate model structure was built using the Dataset C, while the model verification was performed on a 3-study dataset (Dataset D - 20030167, 20020408, 20030250).

METHODS:

Panitumumab serum concentration-time data was analyzed using non-linear mixed-effects modeling with NONMEM (version V). Modeling was done using log-transformed data, exponential inter-subject error terms, and additive residual error. The PK model was implemented as differential equations with ADVAN 8 subroutine. The first-order conditional estimation (FOCE) was employed for all runs. Modeling proceeded in 4 steps as shown in Figure 1 below:

Figure 1: Model development and Verification (per sponsor's report # 104311)

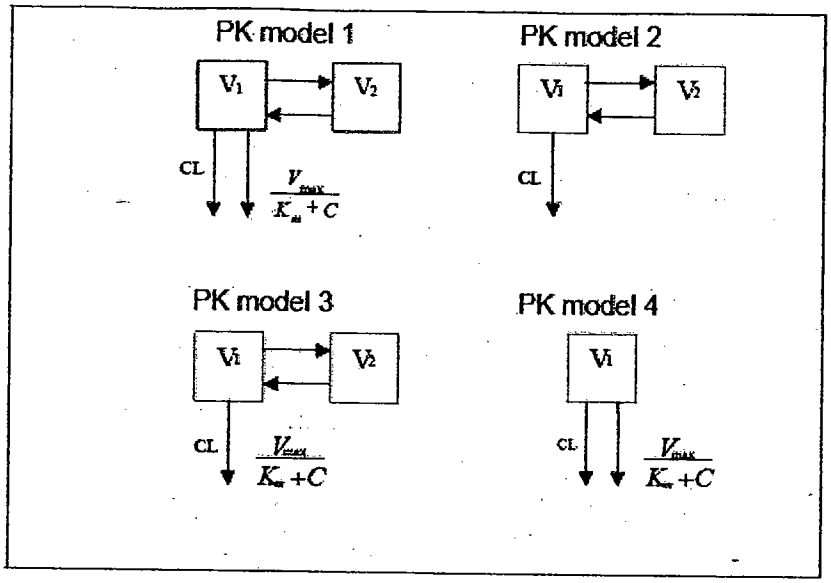


First, an adequate structural PK model was determined. Then, various combinations of pharmacostatistical models were investigated and the most appropriate was selected for use in development of a final model with covariates. The final model with the estimated parameters was then used for internal and external predictive checks to the dataset used to estimate the parameters and an independent model verification dataset, respectively.

The assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness of fit criteria including: (i) visual inspection of diagnostic scatter plots (predicted vs. observed concentration, residual/weighted residual vs. predicted concentration or time, and histograms of individual random effects); (ii) successful convergence of the minimization routine with at least 2 significant digits in parameter estimates; (iii) physiological responsibility of parameter estimates; and (iv) precision of parameter estimates.

A two-compartment open model with dual elimination, linear and Michaelis-Menten clearance, from the central compartment parameterized in terms of V1, V2, K_m, V_{max}, CL, and Q was the structural model to describe the concentration-time data. Three alternate structural models were evaluated: a two-compartment open model with only the linear elimination (PK model 2), a two-compartment open model with only the Michaelis-Menten elimination (PK model 3), and a one-compartment open model with dual elimination processes (PK model 4). A schematic of the structural models evaluated is shown in Figure 2 below:

Figure 2: Structural PK models evaluated during model development (per Sponsor's report # 104311)



All inter-subject error terms were modeled as log-normally distributed using an exponential structure.

$$\theta_i = \hat{\theta} \bullet exp(\eta_{\theta_i})$$

where:

θ_i is the estimated parameter value for individual i (e.g., $V_{1,i}$, $V_{2,i}$, $K_{m,i}$, $V_{max,i}$, CL_i, Q_i)

$\hat{\theta}$ is the typical population value of the parameter

η_{θ_i} is individual-specific inter-subject random effect for individual i and parameter $\hat{\theta}$ and is assumed to be ~$N(0, \omega^2)$ with covariances defined by the inter-subject covariance matrix Ω.

The residual error model was described by an additive error model for log-transformed Panitumumab concentration data.

$$ln(C_{ij}) = ln(\hat{C}_{ij}) + \varepsilon_{ij}$$

where:

ln is the natural log transformation

C_{ij} is the jth measured observation in individual i

$\hat{C}_{ij}$ is the jth model predicted value in individual i

ε_{ij} is the proportional residual random error of log-transformed concentration data for individual i and measurement j and is assumed to be distributed: $\varepsilon \sim NID(0, \sigma^2)$.

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented. This approach is a simplification of the global model approach described by Burnham and Anderson. Before modeling covariate effects, covariates within the population were explored and assessed by inspection of the frequencies of categorical variables and summary statistics for continuous variables (mean, SD, minimum, and maximum). Correlations between continuous covariates were examined graphically using matrix plots, whereas the relationship between continuous covariates and categorical covariates were evaluated using box plots. Covariate parameter relationships were identified based on these exploratory graphics, scientific interest, and mechanistic plausibility of prior knowledge. Next, the identified covariates of interest were added to the pharmacostatistical model. In cases of colinearity between covariates, one covariate was chosen for inclusion. The effects of continuous and categorical covariates were modeled using normalized power models and relative fraction power models, respectively

$$\hat{\theta}_n = \theta_n \cdot \prod_{1}^{m}\left(\frac{cov_{mi}}{ref_m}\right)^{\theta_{(m+n)}} \cdot \prod_{1}^{p}\theta_{(p+m+n)}^{cov_{pi}}$$

where the typical value of the nth model parameter ($\theta\hat{}_n$) was described as a function of m individual continuous covariates (cov_{mi}) and p individual categorical covariates (cov_{pi}), such that θ_n is an estimated parameter describing the typical pharmacokinetic parameter value for an individual with covariate values equal to the reference covariate values ($cov_{mi} = ref_m$, $cov_{pi} = 0$). $\theta_{(m+n)}$ and $\theta_{(p+m+n)}$ are estimated parameters describing the magnitude of variability for the mth continuous covariate and p^{th} categorical covariate that can explain the nth model parameter. Population parameters, including fixed-effect parameters (covariate coefficients and structural model parameters) and random-effect parameters, were then estimated.

An exploratory assessment of any remaining trends was conducted by graphical inspection of all covariate effects (i.e., plots of MAP Bayes estimates of individual random effects (η_i) and/or WRES from the full model vs. covariates). Inferences regarding impact of covariates in explaining inter-subject variability were based on the resulting parameter estimates and their precision. No hypothesis testing was conducted.

The final Panitumumab population PK model was verified by 3 methods. Specifically, a single prediction into an independent dataset (Maximum a posteriori (MAP) Bayesian estimation), a Monte Carlo simulation into the dataset used to estimate the final parameters (internal predictive check; dataset C) and a Monte Carlo simulation into the verification dataset (external predictive check; dataset D) were performed with the final model and parameters.

RESULTS:

The baseline subject characteristics were summarized (Table 1 and Table 1) for the datasets used in the model development (10-study dataset), in model verification (3- study dataset), and the combined dataset of 13 studies.

Table 1: Baseline Characteristics of Subjects Included in the Population PK Analysis: Categorical Variables

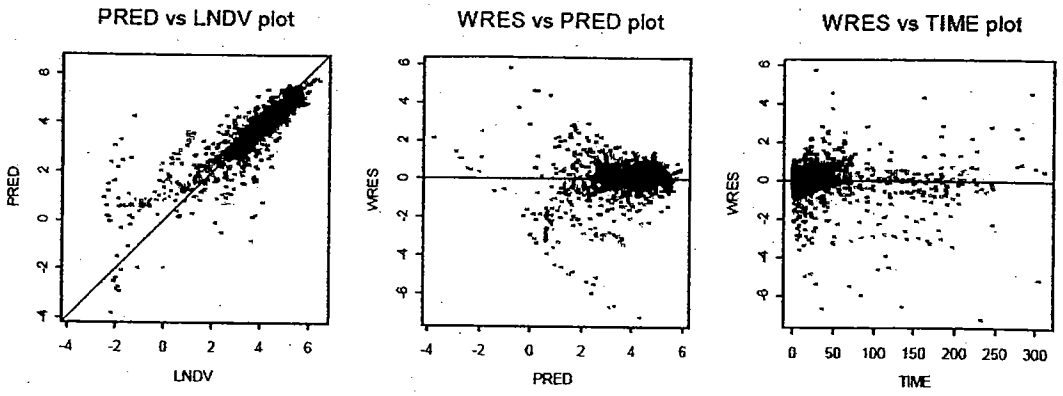
Categorical Variables	10 Studies N	(%)	3 Studies N	(%)	13 Studies N	(%)
Sex						
Man	463	(65.6)	162	(61.8)	625	(64.6)
Woman	243	(34.4)	100	(38.2)	343	(35.4)
Race						
White	600	(85.0)	240	(91.6)	840	(86.8)
Other	106	(15.0)	22	(8.4)	128	(13.2)
Tumor Type						
Colon/Colorectal/Rectal	247	(35.0)	262	(100)	509	(52.6)
Lung	162	(23.0)			162	(16.7)
Renal	210	(30.0)			210	(21.7)
Other	87	(12.0)			87	(9.0)
Expression System						
Hybridoma	613	(86.8)			613	(63.3)
CHO	93	(13.2)	262	(100)	355	(36.7)
Concurrent Chemotherapy						
No	539	(76.4)	262	(100)	801	(82.7)
Yes	167	(23.6)			167	(17.3)

Table 2: Baseline Characteristics of Subjects Included in the Population PK Analysis: Continuous Variables

Continuous Variables	10 Studies (N = 706) Mean	(SD)	Min – Max	3 Studies (N = 262) Mean	(SD)	Min – Max	13 Studies (N =968) Mean	(SD)	Min – Max
Age (year)	60	(11.6)	21 – 88	61	(10.1)	29 – 85	60	(11.2)	21 – 88
Weight (kg)	81	(20.4)	32 – 166	78	(18.5)	40 – 154	80	(20.0)	32 – 166
Height (cm)	172	(9.9)	131 – 198	172	(6.6)	122 – 196	172	(9.2)	122 – 198
Albumin Concentration (g/L)	38	(5.3)	16 – 49	39	(4.5)	19 – 50	38	(5.2)	16 – 50
Alanine Amino Transferase Concentration (U/L)	25	(17.6)	2 – 182	34	(28.0)	2 – 206	27	(21.3)	2 – 206
Aspartate Amino Transferase Concentration (U/L)	29	(17.9)	7 – 141	41	(28.2)	10 – 212	32	(21.9)	7 – 212
Creatinine Concentration (µmol/L)	83	(28.4)	18 – 194	71	(20.0)	35 – 150	80	(27.0)	18– 194
Creatinine Clearance (mL/min)	81	(32.8)	27 – 296	90	(26.4)	33 – 174	84	(31.4)	27 – 296
H-score	160	(75.6)	0 – 300	160	(0.0)	160 – 160	160	(64.5)	0 – 300
Sum of Percent of Cells with EGFr Staining (%)	81	(28.3)	0 – 100	25	(27.6)	0 – 100	66	(37.4)	0 – 100
EGFr Maximum Staining Intensity	2	(0.8)	0 – 3	2	(0.8)	0 – 3	2	(0.9)	0 – 3
BMI (kg/m^2)	26	(6.1)	14 – 57	26	(6.5)	14 - 62	27	(6.2)	14 – 62
BSA (m^2)	2	(0.3)	1 – 3	2	(0.2)	1 – 3	2	(0.2)	1 – 3

As Panitumumab is an antibody that targets the EGF receptor, EGFr-mediated clearance has been proposed for Panitumumab elimination in addition to the reticuloendothelial system, a common clearance mechanism for antibodies. Based on
diagnostic plots, objective functions, physiologic reasonability of parameters, and residual error, PK model 1, was chosen for further development. The diagnostic plots for the structural PK model are shown below in Figure 3.

Figure 3: Diagnostic plots for the structural PK model (per Sponsor's report # 104344)



A series of NONMEM analyses using the 4-study dataset (dataset B) were conducted to investigate the sensitivity and performance of PK model 1 to variations in the value of Km using fixed values at 1, 10, 50, or 200 mcg/mL and then estimated for Km. Since it was possible to obtain convergence and reasonable estimate (0.596 mcg/mL) without fixing Km, the modeling proceeded without Km fixed. Inter-subject variability on various PK parameters was explored using the 4-study dataset and the 10-study dataset. A model with inter-subject variability terms on V1 and CL would converge successfully and was taken forward.

Selection of covariates for inclusion in the model was assessed by visual inspection of scatter plots and box plots of covariates versus the inter-subject random effects. Body size was identified as a potential descriptor of inter-subject variability. Categorical covariates of interest included in the model were concurrent chemotherapy, tumor type, and race. Although an additional categorical covariate, sex, was of interest and the random effect on CL (Eta3) versus sex plot showed slight differences in median values between the sexes, it was excluded from the model because of a high correlation with body weight.

The equations that describe the final differential and covariate model structures are shown below.

$$\frac{dA_1}{dt} = \frac{Q}{V_2} \times A_2 - \frac{Q}{V_1} \times A_1 - \frac{CL}{V_1} \times A_1 - [(\frac{A_1}{V_1}) \times V_{max}]/[K_m + (\frac{A_1}{V_1})]$$

$$\frac{dA_2}{dt} = \frac{Q}{V_1} \times A_1 - \frac{Q}{V_2} \times A_2$$

$$V_{1,i} = V_{1,ref} \times (\frac{WT_i}{WT_{ref}})^{\theta_{V_1}^{WT}} \times exp(\eta_{1,i})$$

$$V_{max,i} = V_{max,ref} \times (\frac{WT_i}{WT_{ref}})^{\theta_{V_{max}}^{WT}} \times \theta_{Vmax}^{race} \times \theta_{Vmax}^{lung} \times \theta_{Vmax}^{renal} \times \theta_{Vmax}^{other} \times \theta_{Vmax}^{chemo} \times exp(\eta_{2,i})$$

$$CL_i = CL_{ref} \times (\frac{WT_i}{WT_{ref}})^{\theta_{CL}^{WT}} \times \theta_{CL}^{race} \times \theta_{CL}^{lung} \times \theta_{CL}^{renal} \times \theta_{CL}^{other} \times \theta_{CL}^{chemo} \times exp(\eta_{3,i})$$

$$V_{2,i} = V_{2,ref} \times (\frac{WT_i}{WT_{ref}})^{\theta_{V_2}^{WT}} \times exp(\eta_{4,i})$$

$$Q_i = Q_{ref} \times (\frac{WT_i}{WT_{ref}})^{\theta_5^{WT}} \times exp(\eta_{5,i})$$

$$Y_{i,j} = ln(F_{i,j}) + \varepsilon_{i,j}$$

where $Y_{i,j}$ and $F_{i,j}$ are the observed and predicted Panitumumab serum concentrations, respectively, for subject i at time j. The inter-subject random effects parameters $\eta 1$ and η_3 were modeled as exponential errors, the other parameters (η_2, η_4, η_5) were fixed to zero, and off

diagonally were not estimated. The covariate coefficients enter the model as fixed effects and are represented by θ's. The superscript of θ represents the covariate of subject i and the subscript of θ represents the PK parameter on which the covariate is evaluated for its effect. WT_i represents the body weight of subject i, and WT_{ref} represents the weight of a reference subject. Structural parameter estimates and inter-subject variability are presented for the base model and final models in Table 3 and Table 4, respectively.

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Figure 4: Eta versus covariate plots (per sponsor's report #: 104311).

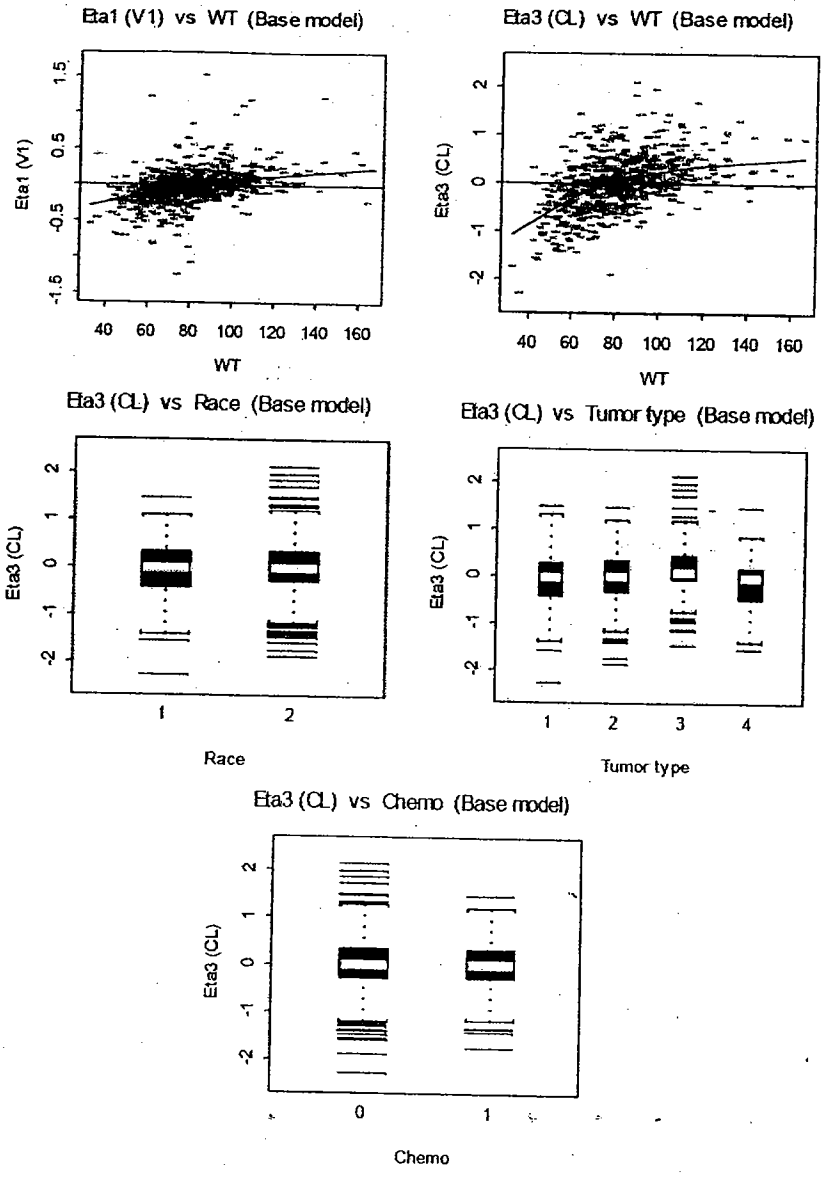

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Table 3: Population model based parameter estimates for the base model.

Parameter	Units	Fixed effects – Population mean PK parameter		Random effects – Inter-subject/Residual variance	
		Estimate	SE (%RSE)	Estimate (~ CV%)	SE (%RSE)
V_1- volume of central compartment	L	3.50	0.0705 (2.01)	0.0852 (29.2)	0.0119 (14.0)
V_2- volume of peripheral compartment	L	2.68	0.0855 (3.19)	0.00[a]	—
K_m – Michaelis-Menten constant	µg/mL	0.371	0.0109 (2.94)	—	—
V_{max} – Michaelis-Menten maximum elimination rate	mg/day	9.48	0.102 (1.08)	0.00[a]	—
CL – Linear clearance from central compartment	L/day	0.269	0.00715 (2.66)	0.394 (62.8)	0.0288 (7.31)
Q – Inter-compartmental distribution clearance	L/day	0.401	0.0119 (2.97)	0.00[a]	—
σ^2	—	—[b]	—	0.0879 (29.6)	0.00633 (7.20)
Minimum objective function value	—	-5434			
AIC	—	-5422			

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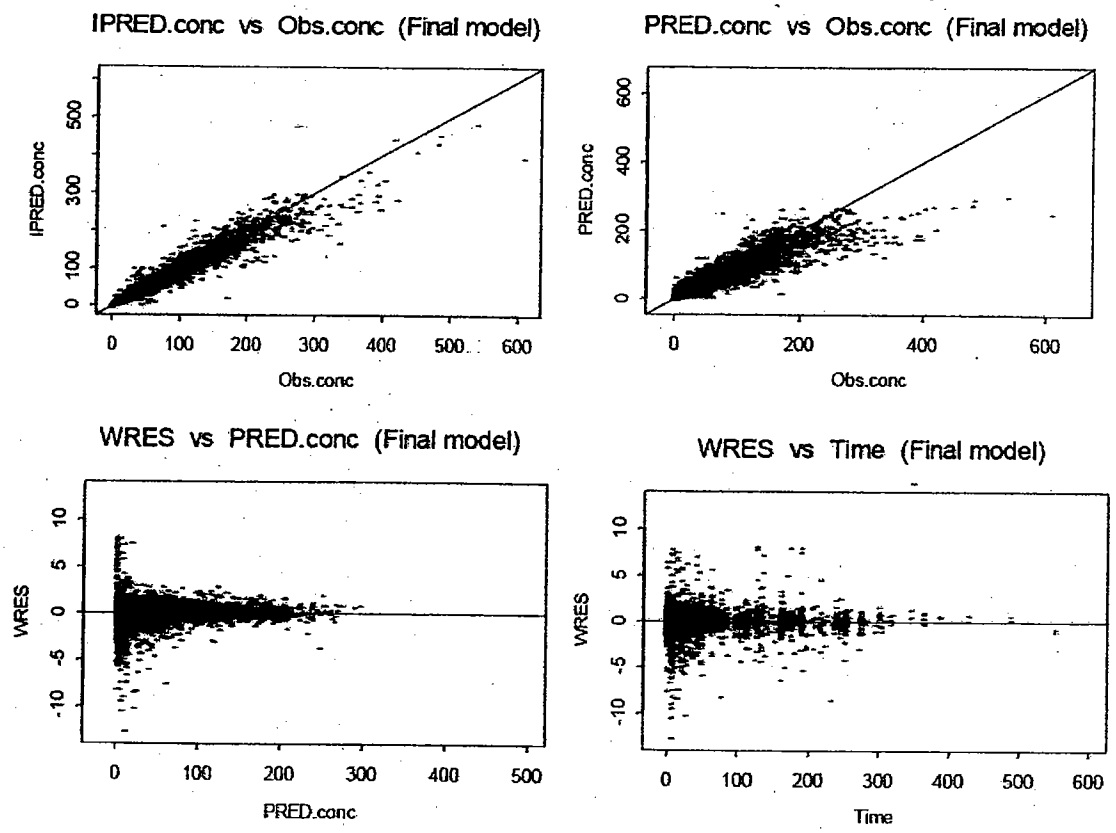
Table 4: Population model based parameter estimates for the Final model.

Parameter	Units	Fixed effects – Population mean PK parameter		Random effects – Inter-subject/Residual variance	
		Estimate	SE (%RSE)	Estimate (~ CV%)	SE (%RSE)
V_1- volume of central compartment	L	3.22	0.0426 (1.32)	0.0620 (24.9)	0.00996 (16.1)
V_2- volume of peripheral compartment	L	2.49	0.153 (6.14)	0.00[a]	—
K_m – Michaelis-Menten constant	µg/mL	0.501	0.106 (21.2)	—	—
V_{max} – Michaelis-Menten maximum elimination rate	mg/day	10.1	0.451 (4.47)	0.00[a]	—
CL – Linear clearance from central compartment	L/day	0.208	0.0117 (5.63)	0.284 (53.3)	0.0238 (8.38)
Q – Inter-compartmental distribution clearance	L/day	0.380	0.0285 (7.50)	0.00[a]	—
σ^2	—	—[b]	—	0.0830 (28.8)	0.00691 (8.33)
Minimum objective function value	—	-6103			
AIC	—	-6061			

Compared with the base model, the final model resulted in an improved overall goodness-of-fit, including a decrease in minimum objective function (Δ=669; df=15) and Akaike's Information Criterion (AIC, Akaike, 1978). Figure 5 presents the diagnostic plots for the final model. The final model provided reasonably precise estimates (<22% RSE) of all fixed and random pharmacostatistical parameters with residual variability of 28.8%. The unexplained inter-subject variability (%CV) for V1 and CL was reduced from 29.2% to 24.9% and 62.8% to 53.3%, respectively, when comparing the base with the final models.

Figure 5: Diagnostic plots of the final population pharmacokinetic model.
The current covariate model explained a portion of the inter-subject variability in the base model;



however, substantial variability remained. Parameter estimates for covariates are summarized in Table 5 along with the relative standard errors of estimates, the %RSE, and the symmetric, asymptotic normal 95% CI (point estimate ± 2*SE).

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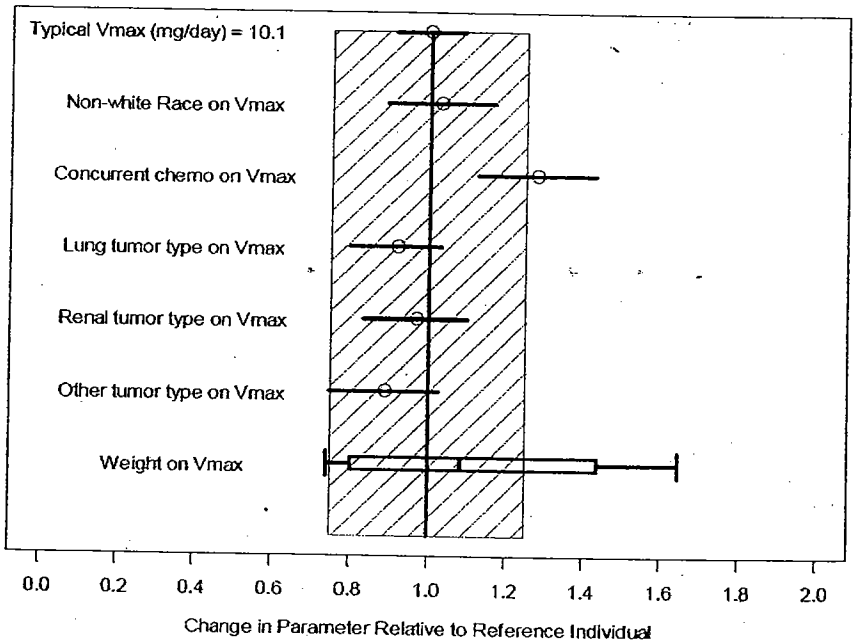
Table 5: Final estimated covariate coefficients for the population covariate (per sponsor's report # 104311).

Continuous Covariate				
Parameter	Covariate	Covariate Coefficient		95% CI of Estimate
		Estimate	SE (%RSE)	
V_1	WT	0.633	0.0477 (7.54)	0.540, 0.726
V_2	WT	0.386	0.235 (60.9)	-0.0746, 0.847
V_{max}	WT	0.588	0.112 (19.0)	0.368, 0.808
CL	WT	0.715	0.163 (22.8)	0.396, 1.03
Q	WT	0.554	0.337 (60.8)	-0.107, 1.21
Categorical Covariates				
Parameter	Covariate	Covariate Coefficient		95% CI of Estimate
		Estimate	SE (%RSE)	
V_{max}	Race	1.03	0.0701 (6.81)	0.893, 1.17
	Concurrent Chemo	1.28	0.0790 (6.17)	1.13, 1.43
	Lung tumor	0.915	0.0595 (6.50)	0.802, 1.04
	Renal tumor	0.867	0.0680 (7.03)	0.833, 1.11
	Other tumor	0.887	0.0706 (7.96)	0.753, 1.03
CL	Race	1.02	0.119 (11.7)	0.787, 1.25
	Concurrent Chemo	0.812	0.139 (17.1)	0.540, 1.08
	Lung tumor	1.08	0.169 (15.6)	0.747, 1.41
	Renal tumor	1.24	0.126 (10.2)	0.985, 1.49
	Other tumor	0.938	0.101 (10.8)	0.744, 1.14

The magnitude of covariate effects on PK parameters and uncertainty in the effects are presented in Figure 6.

Figure 6: Covariate effects for Base model vs. Final Model (per sponsor's report # 104311). (a): Covariate effects on V_{max}; (b): covariate effects on CL, (c): Covariate effects on V1, V2 and Q.

(a)



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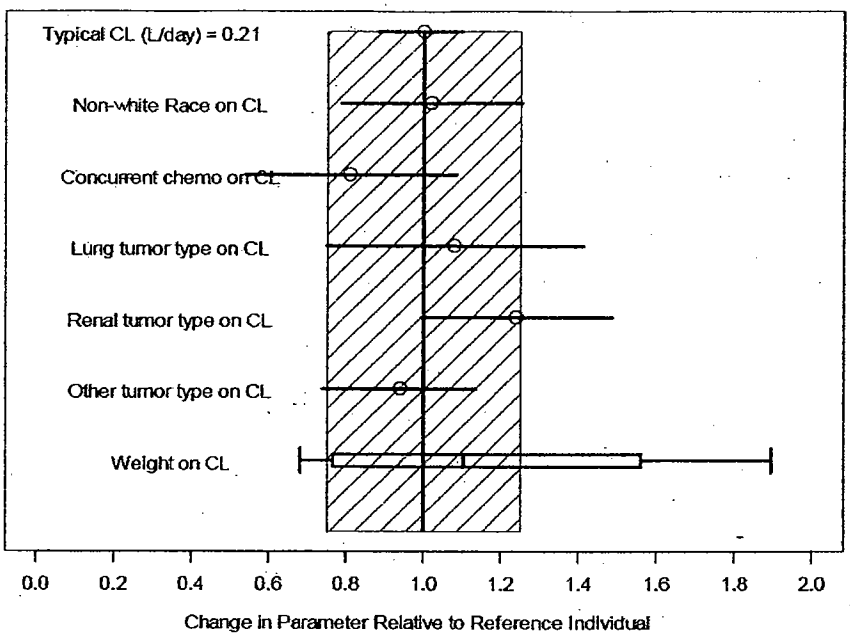
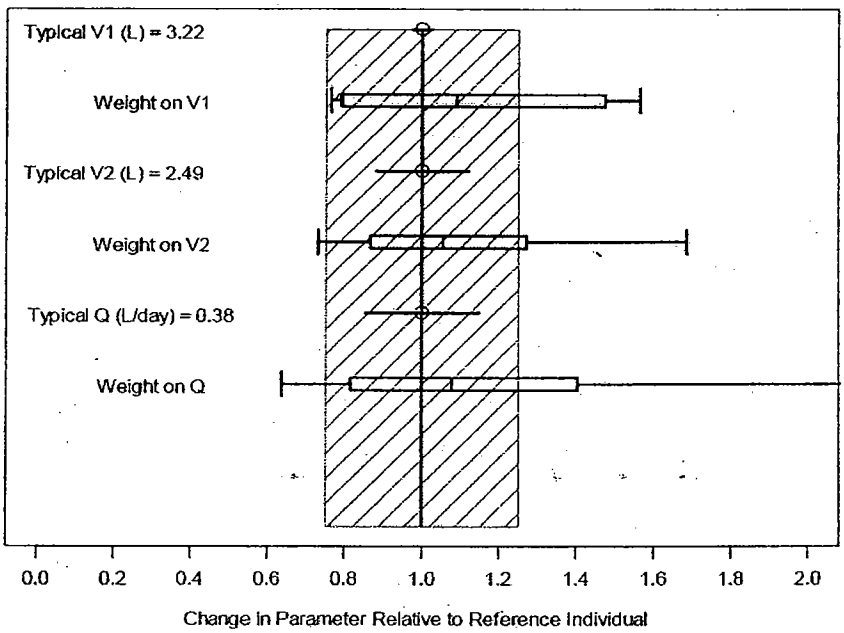
(b)



(c)



The effects of body weight variation given the uncertainty of the point estimates (95% CI) were outside the 25% range, suggesting body weight potentially was an influential covariate on Panitumumab disposition.

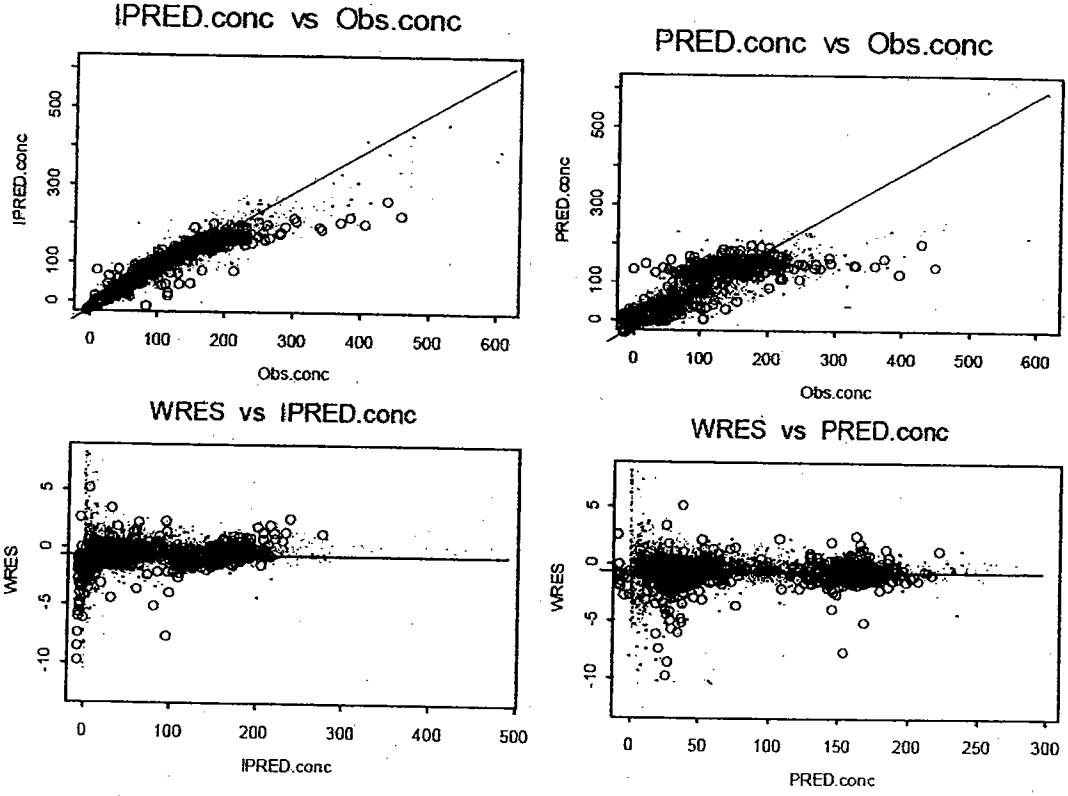
MODEL VERIFICATION:

In the MAP Bayesian estimation, diagnostic plots were overlaid with the diagnostic plots from the final model run to assess the predictive capability of the model (Figure 7). In general, trends in the data were similar between the verification and 10-study datasets.

In the external predictive check, the average concentration across all time points (C_{avg}) within each individual was calculated for the observed and predicted data, and used as the metric for assessment of predictive performance. The quantile-quantile plot showed that the model provided

small but consistent bias when compared with the observed concentrations. A similar simulation conducted with fixed effects only did not demonstrate this pattern. Therefore, the overestimation observed was believed to arise from either bias in random variance parameters and/or differing characteristics of the verification dataset as compared with the 10-study dataset.

Figure 7: Diagnostic plots for MAP Bayesian estimates (per sponsor's report #104311). Small solid circles represent data values for the model development dataset and large open circles represent the data values from the verification dataset.



SIMULATIONS:

Simulations were conducted using individual predicted PK parameters to evaluate the effects of concurrent chemotherapy, tumor type on the systemic exposure to Panitumumab. Intravenous infusions of Panitumumab 6 mg/kg Q2W to all subjects in the final dataset and the exposure over one dosing interval (AUC0-τ) were simulated for the steady state condition (week 7). Results showed similar exposures in subjects regardless of concurrent chemotherapy or sex or tumor type. Although the median exposure in subjects with "other" tumors (code = 4) was higher than that of subjects with colorectal, lung, or renal tumors, the range was similar.

Figure 8: Simulated Panitumumab Exposure (AUC0-τ) vs. Three Covariates: Status of Concurrent Chemotherapy, Sex and Tumor Type (per sponsor's report # 104311).

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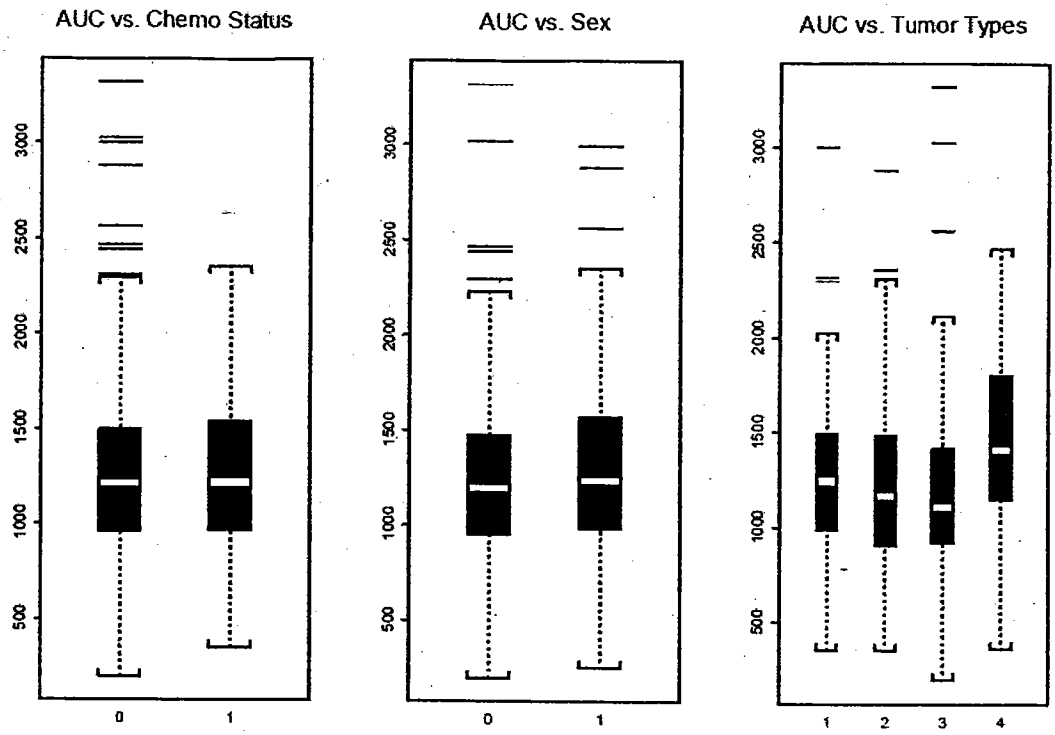

These results suggest that dose adjustments would not be necessary based on chemotherapy status, sex, or differing tumor type. As body weight increased, the AUC showed a decreasing trend for the fixed-dose regimen (Figure 9, right panel), whereas it showed an increasing trend for the weight-adjusted regimen (Figure 9, left panel). Further, a ratio in AUCs across weight of 1.46 for a weight-adjusted and 2.52 for a fixed dose suggests that the weight-adjusted dose regimen will be expected to result in lower variability in exposure.

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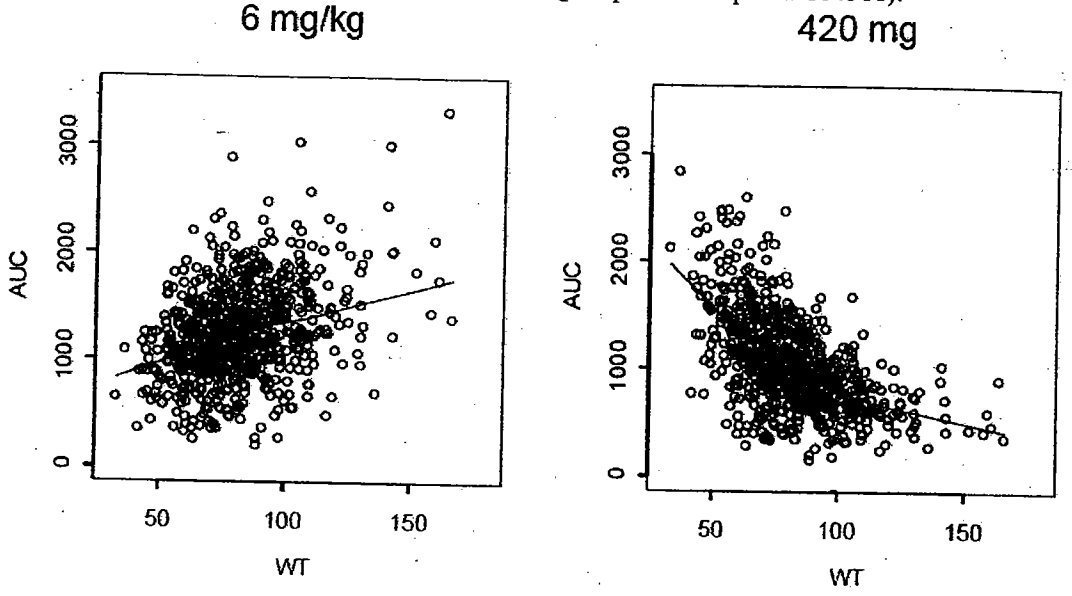
Figure 9: Relationship between Body Weight and Simulated Steady State Exposure for Panitumumab Administered Once Every 2 Weeks (per sponsor's report # 104311).



CONCLUSION:

A two-compartment open model with a linear and a Michaelis-Menten elimination pathway adequately described the population PK of Panitumumab. Of the available covariates, age, hepatic function, renal function, EGFr membrane expression in tumor cells, and protein expression system graphically did not correlate with changes in intersubject variability and were excluded from the PK model. Body weight, chemotherapy, and tumor type were able to decrease inter-subject variability in CL and V1. The final model provided precise estimates for all structural PK parameters (%RSE < 22%) with inter-subject variability of 53.3% and 24.9% (CV %) for CL and V1, respectively, with residual variability of 28.8%.

Simulations indicated that dose adjustments would not be necessary for concurrent chemotherapy or tumor type, as changes in these covariates were not correlated with notable variations in Panitumumab exposure. Also, the covariate analysis showed that, compared with a fixed-dosing scheme, the current weight-adjusted dosing scheme would result in smaller overall inter-subject variability in Panitumumab exposure.

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RELATIONSHIP BETWEEN PK AND INTEGUMENT AND EYE TOXICITIES

In the 13 studies with any PK data included in this license application, 1304 subjects received at least one dose of Panitumumab. An occurrence of integument and eye toxicity was reported for 87.9% of the subjects; grade 3 and grade 4 integument and eye toxicity was reported for 11.6% of the subjects. As integument and eye toxicities are known toxicities for EGFr inhibitors (Segaert and Van Cutsem, 2005, Shah et al, 2005), an exploratory analysis was performed to assess the relationship between PK parameters and this specific toxicity.

OBJECTIVE

To asses a potential PK/safety relationship, using only studies designed to collect first dose PK data. Two primary questions were considered:

1) Are any of the PK parameters related to this toxicity?

2) Do the PK parameters add predictive value beyond that of dose and various demographic and baseline disease status variables?

ENDPOINTS

The 2 safety endpoints selected for this analysis were:

- reported integument or eye toxicity within the first 28 days after the first Panitumumab dose;
- reported grade 3 or 4 (per NCI CTC version 2.0 criteria) integument and eye toxicity within the first 28 days after the first Panitumumab dose.

Twenty-eight days was chosen as the period of observation because the treatment of some subjects in Study 20030138 was limited to 4 weekly doses. Adoption of this 28-day observation window was thought to be acceptable since the majority (95%) of integument and eye toxicity and 58% of grade 3 or 4 integument and eye toxicity occurred during the 28 days after the first dose.

EXPLORATORY VARIABLES

PK Variables

- First Dose
  - maximum concentration, minimum concentration and AUC normalized to a 2-week period;
- Steady-state
  - post-hoc estimate of the maximum concentration, minimum concentration and AUC normalized to a 2-week period

For studies with intensive sampling after the first first-dose AUC was calculated using only the concentrations during the first dosing interval. For studies with sparse sampling a post-hoc estimate of the first dose AUC was used. All post-hoc estimates were generated from the population pharmacokinetic model.

Dosing variables

- First scheduled dose (mg, mg/kg and mg/m2), and
- Scheduled dose (mg, mg/kg and mg/ m2) over the first 4 weeks of dosing.

Demographic and Baseline Disease Status Variables

- actual body weight (kg)
- sex (m, f)
- age, age category (<65, between 65 and 74, and ≥75 years of age)
- race (white, other)
- primary tumor type (colorectal, other)
- EGFr IHC tumor membrane staining category: 0% - <10%, 10% - 20%, >20% - 35%, and >35%
- prior radiotherapy (yes, no)
- prior surgery (yes, no)

MISSING DATA

Some of the 717 subjects included in the analysis had pharmacokinetic measures missing. There were 199 subjects missing first dose minimum; 131 of those were in protocols where PK samples were not collected before the second scheduled dose. There were 42 subjects missing first dose maximum. The first dose AUC could not be estimated for 26 subjects using the first dose concentrations and post hoc steady state parameters could not be estimated for 6 subjects.

METHODS

Logistic regression was used to evaluate the relationship between the pharmacokinetic parameters and the reported incidence of any integument and eye toxicity and grade 3 or 4 integument and eye toxicity within the first 28 days after the first Panitumumab dose. Initially, the 6 pharmacokinetic variables and 6 dose variables were individually examined for a relationship with each of the 2 toxicity endpoints. If none of the models demonstrated a significant relationship ($p \leq 0.05$) the process stopped. If one or more of the variables demonstrated a statistically significant relationship, the Bayesian Information Criterion (BIC) was used to rank those one variable models. Each of these one variable models was taken as a "starting model" for the next stage of the model selection process.

For each starting model all other variables were candidates for consideration using a forward-selection process. Each step selected the variable which, when added to the current model, yielded the smallest BIC. If the smallest BIC value at the current step was no smaller than the BIC for the previous step, then the process was stopped and the model from the previous step was considered the best for that endpoint and starting model.

When a variable was entered into the model, higher order terms and 2 factor interactions (including the newly selected variable) were included as exploratory variables in the next step of the process. Finally, any demographic or baseline disease status factor that entered into the model was examined for the studies not included in this PK/safety analysis. If the factor did not appear significant in the other studies (p-value > 0.1), then it was removed from the screening process for that starting model. When a significant higher order effect was observed, a 3-parameter logistic model was considered for incorporation of a maximum risk less than one rather than allowing decreasing risk with higher values of the explanatory variables.

RESULTS:

A summary of the modeling results is present in Table 6.

Table 6: Summary of the Modeling results based on BIC criterion (per sponsor's report of Summary of Clinical Pharmacology).

	Any Integument and Eye (IE) Toxicity in first 28 days	Grade 3 or 4 IE Toxicity in first 28 days
Best single PK or dose parameter model	Scheduled 4 week dosing (mg) BIC = 615.5 p-value < 0.0001 Area Under ROC = 0.705	Scheduled first dose (mg) BIC = 298.1 p-value = 0.0014 Area Under ROC = 0.631
Best single PK parameter model	First Dose AUC Normalized Over 2 Weeks BIC = 657.3 p-value <0.0001 Area Under ROC = 0.684	First Dose C_{max} BIC = 306.2 p-value = 0.030 Area Under ROC = 0.619
Selected model:	Scheduled 4 week dosing (mg), Tumor Type, Tumor by Dose Interaction BIC = 590.5 p-value < 0.0001 Area Under ROC = 0.750*	Scheduled first dose (mg) BIC = 298.1 p-value = 0.0014 Area Under ROC = 0.631

*3-Parameter Logistic, Separate Maximum Incidence for colorectal and other)

These results indicate that

1) For incidence of any integument and eye toxicity, the Panitumumab dose (expressed in total mg) over the first 4 weeks is the best single predictor, although other dose and PK variables predict well too;

2) For grade 3 and 4 integument and eye toxicity the first Panitumumab dose is the best predictor, although AUC and Cmax are also predictive; and

3) Subjects with a diagnosis of colorectal carcinoma are more likely to experience integument and eye toxicity.

Results for the selected model for occurrence of any integument and eye toxicity can be found in Table 7 and results for the selected model for occurrence of grade 3 or 4 integument and eye toxicity can be found in Table 8. These tables display the selected model, the observed responses and the resultant predicted responses for selected doses. Additionally, for studies not included in the analysis, a logistic model with dose in mg provides a reasonably good fit of the data (any integument or eye toxicity: p-value < 0.0001, Area Under ROC = 0.635; grade 3 or 4 integument or eye toxicity: p-value < 0.0001, Area Under ROC = 0.679.).

Table 7: Predicted probabilities of integument and eye toxicity during the 28 Days after the first dose for selected dosing regimens using the selected model (per sponsor's report of Summary of Clinical Pharmacology).

Dosing Regimen	Dosing in Model	Estimate (95% CI) for Weight = 62.1 kg	Estimate (95% CI) for Weight = 84.4 kg	Estimate (95% CI) for Weight = 107.3 kg	Model Predicted Proportion in Dosing Regimen	Observed Outcome
0.1 QW loading[a]	No	0.060 (-0.013 - 0.133)	0.066 (-0.011 - 0.142)	0.073 (-0.009 - 0.155)	0.069	0/4 (0.000)
1 QW[a]	No	0.256 (0.125 - 0.387)	0.418 (0.295 - 0.532)	0.601 (0.502 - 0.701)	0.403	14/31 (0.469)
2.5 QW	No	0.768 (0.705 - 0.832)	0.945 (0.909 - 0.984)	0.850 (0.815 - 0.905)	0.829	241/292 (0.825)
2.5 QW	Yes	0.877 (0.811 - 0.944)	0.938 (0.905 - 0.970)	0.974 (0.946 - 1.002)	0.927	181/197 (0.919)
6 Q2W	No	0.824 (0.784 - 0.865)	0.853 (0.815 - 0.890)	0.861 (0.815 - 0.909)	0.842	39/52 (0.750)
6 Q2W	Yes	0.913 (0.873 - 0.953)	0.953 (0.932 - 0.993)	0.987 (0.966 - 1.009)	0.947	26/26 (1.000)
9 Q3W	No	0.824 (0.784 - 0.865)	0.853 (0.815 - 0.890)	0.861 (0.815 - 0.909)	0.860	2/3 (0.667)
9 Q3W	Yes	0.913 (0.873 - 0.953)	0.953 (0.932 - 0.993)	0.987 (0.966 - 1.009)	0.960	19/20 (0.950)

Table 8: Predicted probabilities of Grade 3 or 4 integument and eye toxicity during the 28 Days after the first dose for selected dosing regimens using the selected model (per sponsor's report of Summary of Clinical Pharmacology).

0.1 Q/W loading	0.024 (0.010 - 0.039)	0.025 (0.010 - 0.039)	0.026 (0.010 - 0.040)	0.025	0/4 (0.000)
1 Q/W	0.027 (0.013 - 0.042)	0.029 (0.014 - 0.044)	0.031 (0.016 - 0.045)	0.029	0/32 (0.000)
2.5 Q/W	0.034 (0.019 - 0.050)	0.040 (0.024 - 0.056)	0.047 (0.030 - 0.064)	0.040	22/498 (0.045)
6 Q2W	0.058 (0.038 - 0.077)	0.080 (0.049 - 0.112)	0.119 (0.066 - 0.182)	0.079	6/79 (0.077)
9 Q3W	0.080 (0.053 - 0.128)	0.139 (0.055 - 0.222)	0.226 (0.045 - 0.406)	0.171	3/23 (0.130)

DISCUSSION AND CONCLUSION:

This analysis should be interpreted cautiously because PK data obtained after the first dose were not available for 3 studies accounting for the majority of the subjects receiving the higher Panitumumab doses in this license application. In addition the demographics for the subjects included in this analysis had notable differences from those not included.

The primary finding of this analysis, that the amount of Panitumumab administered is a predictor of the occurrence of integument and eye toxicity or grade 3 or 4 integument and eye toxicity, appears consistent in the studies not included in this analysis. The other finding of this analysis, that amount of drug administered is a better predictor than PK parameters of exposure, has a useful clinical application as dosage offers a greater clinical convenience for patient management.

REVIEWER'S COMMENTS:

POPULATION PHARMACOKINETIC ANALYSIS

- The conduct and results of the population pharmacokinetic analyses are acceptable.
- The following statement under Special Populations section of the Clinical Pharmacology Section

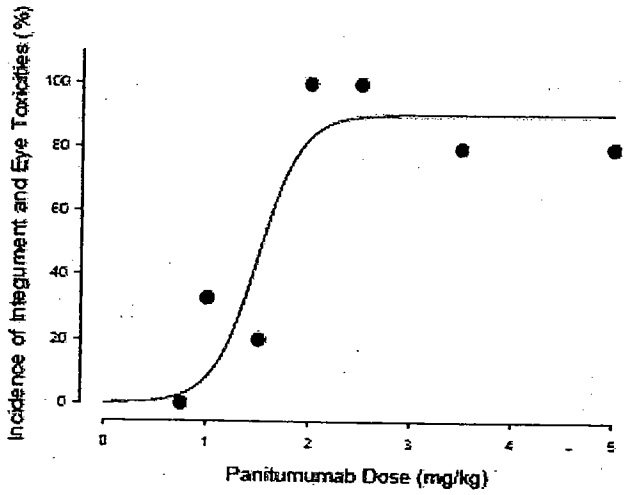
" Results suggested that age, gender, — race —

cells had no apparent impact on the pharmacokinetics of [TRADENAME™] ."

RELATIONSHIP BETWEEN PK AND INTEGUMENT AND EYE TOXICITIES

- The conduct and the results of the exposure – integument and eye toxicity analysis is acceptable.
- Skin toxicity and toxicities related to nail, hair, and eye have been reported to be associated with EGFr inhibitors (Segaert and Van Cutsem, 2005; Shah et al, 2005). These toxicities together with skin toxicities were included in a composite adverse event category of "integument and eye toxicities." Mechanistically one would expect better correlation between exposure expressed as concentration or AUC of Panitumumab and the integument and eye toxicity compared to dose (mg) as an exposure metric. However, in the present analysis, amount of drug administered is reported to be a better predictor of the eye and integument toxicity than PK parameters of exposure. The reason for better correlation with the amount of drug administered to be a better correlated to eye and integument toxicity could be because of the low IC_{90} (9.77 μg/mL) of Panitumumab. Concentration levels beyond 9.77 μg/mL might result in a plateau of incidence of the integument and the eye toxicities. At 2.5 mg/kg QW and higher doses a complete blockade of the EGFR pathway occurs shown in Figure 10.

Figure 10: Observed and Modeled Incidence of Integument and Eye Toxicities Within 28 Days of Panitumumab Treatment in Subjects With Advanced Solid Tumors (Study 20030138). (per sponsor's report – Summary of Clinical Pharmacology).



4.4 APPENDIX 4 - OCP FILING REVIEW FORM

4.4.1 Office of Clinical Pharmacology

5 *NEW DRUG APPLICATION FILING AND REVIEW FORM*

5.1.1.1.1 General Information About the Submission

	Information		Information
BLA Number	125147	Brand Name	TBD
OCP Division	V	Generic Name	*Panitumumab*
Medical Division	Biologics	Drug Class	human IgG2 monoclonal antibody directed against the EGFr
OCPB Reviewer	Hong Zhao, Ph.D. Angela Yuxin Men, M.D., Ph.D.	Indication(s)	
OCPB Team Leader	Hong Zhao, Ph.D.	Dosage Form	ng/mL
		Dosing Regimen	infusion over 1 hour every 2 wk
Date of Submission	March 29, 2006	Route of Administration	IV infusion
Estimated Due Date of OCP Review	August, 2006	Sponsor	
PDUFA Due Date		Priority Classification	Standard
5.1.1.2 Division Due Date	August, 2006		

5.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			

Labeling	x			
Reference Bioanalytical and Analytical Methods	x	7	7	
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	NA			
Blood/plasma ratio:				
Plasma protein binding:	x	1	1	
Pharmacokinetics (e.g., Phase I) -				
5.2 HEALTHY VOLUNTEERS-	NA			
single dose:				
multiple dose:				
5.2.1 Patients-				
single dose:	x	1	1	
multiple dose:	x	5	5	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	ref			
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x	1	1	
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	3	3	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1	1	
Phase 3 clinical trial:				
Population Analyses -	NA			
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	NA			
In-Vitro Release BE	X	6	6	
(IVIVC):	NA			
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	NA			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies		27	27	

5.2.1.1.1.1 Filability and QBR comments		
5.2.1.2	"X" if yes	5.2.1.2.1.1.1.1.1 Comments
5.2.1.3 Application filable?	Yes	
5.2.1.4 Comments sent to firm?		
QBR questions (key issues to be considered)	Hepatic impairment patient	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-660, HFD-850(Electronic Entry or Lee), HFD-150(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

5 Page(s) Withheld

_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_✓§ 552(b)(4) Draft Labeling