CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125418Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	July 25, 2012
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLA #	STN BL 125418/0
Applicant Name	sanofi-aventis U.S. LLC
Date of Submission	February 3, 2012
PDUFA Goal Date	August 4, 2012
Proprietary Name / Established (USAN) Name	Zaltrap Aflibercept Injection
Dosage Forms / Strength	solution for injection/ supplied in vials containing 100 mg (25 mg/mL) and 200 mg (25 mg/mL)
Proposed Indication(s)	For the treatment of metastatic colorectal cancer, in combination with the chemotherapy regimen 5-fluorouracil, irinotecan, and leucovorin (FOLFIRI)
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Reg. Project Manager Review	Melanie Pierce
Medical Officer Review	Sandra Casak
Statistical Review	Jenny Zhang/Kun He
Pharmacology Toxicology Review	Alexander Putman/Whitney Helms
OBP Review	Sarah Kennett/Chana Fuchs
Facilities Review	Suvarna Kalavati & Mahesh Ramanadham
Regulatory Project Manager (OBP)	Kimberly Rains
Clinical Pharmacology Review	Ruby Leong/Hong Zhou
Pharmaceutics	Anshu Marathe/Kevin Krudys/ Christine Garnett/
CDTL Review	Steven Lemery
OPDP/DPDP	Carole Broadnax
OSI	Lauren Iacono-Connor/Tejashri Purohit-Sheth
OSE/DMEPA	James Schlick/Todd Bridges

OND=Office of New Drugs
OBP=Office of Biotechnology Products
OPDP= Office of Prescription Drug Promotion
DPDP= Division of Drug Professional Drug Promotion
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations

Division Director Summary Review

1. Introduction

This original BLA seeks approval for ZALTRAP (xxx_aflibercept) Injection for the treatment of metastatic colorectal cancer, in combination with 5-fluorouracil, irinotecan, and leucovorin (FOLFIRI) chemotherapy. xxx-aflibercept is a fusion protein, derived from recombinant DNA technology in Chinese Hamster Ovary cell line expression system. The fusion protein consists of the vascular endothelial growth factor (VEGF) binding region from the extracellular domain of the VEGF Receptors 1 and 2 and the Fc portion of the human IgG1 immunoglobulin. The mechanism of action of ZALTRAP is postulated to be angiogenesis inhibition, as demonstrated in *in vitro* and *in vivo* models. This product is closely related to the product Eylea (aflibercept, Regeneron), which is approved for the treatment of macular degeneration, however the two products differ in route of administration, product strengths, product formulation, and product purity. In order to minimize medication errors and enhance tracking of post-marketing safety information, FDA required a distinct non-proprietary name for this product.

Substantial evidence for effectiveness was demonstrated in the results of a single, randomized, placebo-controlled, multicenter, multinational trial (Protocol EFC10262 or VELOUR) enrolling 1226 patients with metastatic colorectal cancer, whose tumors were no longer responsive to oxaliplatin-based chemotherapy. In this trial, patients were equally allocated through randomization to receive xxx_aflibercept 4 mg/kg by intravenous infusion every 2 weeks or matching placebo infusions in conjunction with a standard combination chemotherapy regimen consisting of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI). This clinical trial met its primary endpoint, demonstrating a statistically robust and clinically meaningful improvement in overall survival (HR 0.82, p=0.0032), with median survival times of 13.5 and 12.1 months in the xxx_aflibercept/FOLFIRI and FOLFIRI alone arms, respectively. These results are also supported by statistically significant improvements in progression-free survival (PFS) (HR 0.76, p=0.0007), with median PFS times of 6.9 and 4.8 months in the xxx_aflibercept/FOLFIRI and FOLFIRI alone arms, respectively, and a statistically significant increase in overall response rate among patients receiving xxx_aflibercept plus FOLFIRI compared to FOLFIRI alone. These findings were supported by consistent trends favoring the xxx_aflibercept/FOLFIRI arm for subsets based on age, gender, and prior bevacizumab treatment. Although these subsets are underpowered, the benefits of xxx_aflibercept were observed both in subsets of patients who had received and those who had not received prior bevacizumab as part of the first-line treatment for metastatic disease.

Evaluation of the safety of xxx-aflibercept was based primarily on data from three randomized trials (VELOUR, VITAL, and VANILLA) providing safety data on 1333 patients treated with xxx_aflibercept, supported by additional safety data from other Phase 1 and 2 trials for a total database of 2073 patients receiving xxx-aflibercept. The safety profile xxx_aflibercept is

similar to that observed with other angiogenesis-inhibiting products, consisting of hypertension, proteinuria, hemorrhage, impairment of wound healing, viscus perforation and fistula formation, and dysphonia as well as an increase in the incidence of chemotherapy-related toxicities of neutropenia, thrombocytopenia, diarrhea, stomatitis, and palmar-plantar erythrodysesthesia. Based on these risks, and consistent with labeling for other products in this class, the product labeling will contain a Boxed Warning denoting the risks of hemorrhage with this product.

All members of the review team have recommended approval. The application provides substantial evidence of efficacy on an important endpoint (survival) and demonstrated in an adequate safety database that the toxicity profile is acceptable and qualitatively similar to that observed with the other approved anti-angiogenic biologic product, bevacizumab (i.e., there are no novel or unusual safety signals). In light of the need for additional therapeutic options that may extend survival for this incurable stage of colon cancer, I have concluded that the risk: benefit profile is favorable and also recommend approval of the application.

2. Background

ZALTRAP is the second biologic product for treatment of cancer which mediates its effects through anti-angiogenesis. The other product, Avastin (bevacizumab, Genentech), was first approved in February 2004, for the first-line treatment of colorectal cancer in combination with an infusional 5-fluorouracil-containing combination chemotherapy regimen, based on an improvement in overall survival supported by improvements in progression-free survival.

Indicated Population and Available Therapy
Based on recent data, the National Cancer Institute projects that there will be an estimated 103,170 new cases of colon cancer and 40, 290 new cases of rectal cancer in 2012; NCI also projects that there will be an estimated 51,690 deaths due to colorectal cancer in the United States in 2012. Based on data collected between 2002 through 2008, 20% of colorectal cancers are metastatic at the time of diagnosis, with a 5-year survival rate of 11.9%, thus the need for additional drugs which may extend life is clear.

The backbone chemotherapy regimen (FOLFIRI) administered in the VELOUR trial is consistent with the current standard of care in the U.S. for this patient population. Per the NCCN guidelines, acceptable treatment for this patient population includes irinotecan-based chemotherapy, either as a single agent or in combination with fluoropyrimidines or, for frail and elderly patients, single agent capecitabine or a fluoropyrimidines plus leucovorin. In addition, any of these regimens may be combined with bevacizumab. For patients with EGFR-expressing metastatic colorectal cancers without activating mutations in *KRAS*, the addition of cetuximab or panitumumab is also considered acceptable treatment. However, the majority of patients in VELOUR trial (approximately two-thirds) had not received bevacizumab as a component of first-line treatment for metastatic colorectal cancer. The use of bevacizumab in combination with combination chemotherapy (irinotecan- or oxaliplatin-based) for the initial treatment of metastatic colorectal cancer represents the current standard of care for most patients in the U.S. Bevacizumab labeling was expanded on June 20, 2006, to include a new indication as an adjunct to chemotherapy for the second-line treatment of

patients with metastatic colorectal cancer, in combination with an oxaliplatin-containing regimen (FOLFOX4). Patients in this trial (E3200) had received a prior irinotecan-based regimen but not prior bevacizumab for initial treatment of metastatic colorectal cancer. The basis for this approval was demonstration of an improvement in overall survival [HR 0.75 (95% CI: 0.63, 0.89), p=0.001 stratified log rank test] with median survival times of 13.0 months and 10.8 months for patients receiving bevacizumab plus FOLFOX4 and FOLFOX4 alone, respectively.

Regulatory History

- IND 9948 was submitted by Regeneron Pharmaceuticals on August 2, 2001 for the clinical development program of xxx_aflibercept for the treatment of patients with solid tumors or lymphoma. May 3, 2007, Regeneron requested a Pre-Phase 3 meeting to discuss development and registration plans for use of aflibercept in combination with FOLFIRI for the treatment of second-line metastatic colorectal cancer (mCRC). This study is intended as the basis for registration for aflibercept to be used in combination with 5FU-based therapy for second line treatment of patients with mCRC. This trial contained a planned interim analysis of survival at 65% of the total events, at which time a final analysis of progression-free survival would be conducted.
- July 13, 2007: FDA provided draft comments in preparation for an end-of-phase 2 meeting on the VELOUR trial; Regeneron cancelled the meeting based on the draft responses. In the draft responses, FDA noted that based on Regeneron's analysis plan for progression-free survival, a hazard ratio of (b) (4) or better is needed for statistical significance, which translates into an (b) (4) difference in median PFS times. FDA noted that this treatment effect would not be reasonably likely to predict an effect on survival (b) (4) FDA also noted that in the US, patients typically receive bevacizumab in combination with first-line chemotherapy. In order for results of this trial to be generalized to the US population, a sufficient number of patients in the proposed study should be enrolled who have received prior bevacizumab in combination with chemotherapy. FDA regards subgroup analysis between study arms in patients who have received bevacizumab to be of particular importance.
- On October 11, 2007, Regeneron requested a Type C-CMC meeting to discuss their response to CMC issues raised during a May 16, 2006, CMC meeting. Regeneron also requested feedback from FDA on other development activities such as (b) (4) validation plans, potency, immunogenicity assay development/validation, and immunogenicity sampling plans.
- November 19, 2007: first patient enrolled in VELOUR trial
- On March 13, 2009, FDA's letter responding to questions posed by Regeneron regarding concepts for definitive studies of xxx_aflibercept as an adjunct to chemotherapy for the treatment of mCRC, FDA noted that use of bevacizumab in the first-line treatment of mCRC was part of the U.S. standard of care and Regeneron's proposed trial should enroll such patients.
- July 30, 2010, FDA's letter responding to Regeneron's queries (b) (4)
    - The proposed pre-specified statistical significance boundary for PFS in protocol EFC10262 is a hazard ratio of (b) (4) that translates in (b) (4) median PFS prolongation. It is unlikely that such a finding will predict a statistically significant

result in overall survival (OS) for the final analysis. However, if the magnitude of the effect is overwhelming and supported by a strong trend in improved overall survival, we would be open to further discussion. We may also require the final high level OS results prior to making an approval decision based on one study to ensure the primary endpoint is met, justifying approval based on the results of a secondary endpoint (PFS).

Regeneron will need to demonstrate that these results translate into clinical benefit, and if so, that the risk-benefit ratio clearly favors the use of aflibercept in the proposed setting. (b) (4)

FDA restated recommendations made in the July 13, 2007 communication, to split the alpha between the co-primary endpoints, noting that FDA would not consider the results of secondary endpoints (i.e., PFS) for regulatory approval if the type I error is not properly controlled.

- On August 25, 2010, Regeneron submitted an amended SAP based on FDA comments from the July 30, 2010 letter. FDA responded with additional comments in a letter issued on September 20, 2010.
- On May 12, 2011, a meeting between Regeneron Pharmaceuticals, Inc. and FDA was held to summarize product development since the type C pre-Phase II meeting held on October 11, 2007, inform FDA how the outstanding CMC issues from the type C pre- Phase 3 meeting will be addressed in the BLA, and obtain feedback on the proposed table of contents of the module 3 quality section.
- On July 7, 2011, Regeneron met with FDA to discuss the contents and format of the proposed BLA
- On February 3, 2012, sanofi-aventis, Regeneron's corporate partner, submitted the BLA for xxx_aflibercept.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. The active pharmaceutical ingredient, xxx-aflibercept, is a fusion protein consisting of the human VEGF receptor 1, human VEGF receptor 2, and Fc portion of the IgG1, produced by recombinant DNA technology in a CHO cell expression system. The final product is intended for intravenous infusion and is formulated as a solution at a concentration of 25 mg/mL in strengths of 100 mg and 200 mg. (b) (4) A pre-approval inspection for the xxx_aflibercept drug substance production (b) (4) was conducted (b) (4) by BMAB reviewers Kalavati Suvarna and Lakshmi Narasimhan and product reviewer Sarah Kennett under BLA 125387 in support of the approval of Eylea. Based on this inspection, the requirement for inspection of this contract manufacturer was waived. Inspections of drug product manufacturing sites were also waived based on based on the compliance history, current GMP status, and previous inspections (b) (4) Stability

testing supports an expiry of 36 months when stored at 2-8 °C. Dr. Kennett has concluded "that the data provided in the application support the conclusion that the manufacture of Zaltrap™ (aflibercept) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented." There are no outstanding issues which preclude approval from a facilities or CMC perspective. Several requests for post-marketing commitments (PMCs) to further characterize or improve the manufacturing process have been conveyed to sanofi-aventis and agreement reached on final PMC language and timelines.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. Dr. Putman has determined that no post-marketing commitments (PMCs) or post-marketing requirements (PMRs) are requested or required for approval.

Many of the nonclinical studies provided in this NDA were previously submitted to and reviewed under STN BL 125387 in support of marketing approval of Eylea (aflibercept, Regeneron). These included *in vitro* and *in vivo* pharmacodynamic studies assessing binding activity to VEGF, anti-angiogenic and antineoplastic activity and impairment of wound healing in rabbit models. Additionally, the application contained pharmacokinetic studies in two species (rats and cynomolgus monkeys), 3- and 6-month toxicology studies in cynomolgus monkeys, reproductive toxicology studies, and local tolerance studies. No studies were conducted to evaluate carcinogenicity or mutagenicity of aflibercept; this is consistent with FDA's current practice not to require such studies for the intended patient population (metastatic colorectal cancer).

In chronic toxicology trials, weekly/every two weeks intravenous administration of xxx_aflibercept to growing young adult (sexually mature) cynomolgus monkeys resulted in changes in the bone (effects on growth plate and the axial and appendicular skeleton), nasal cavity (atrophy/loss of the septum and/or turbinates), kidney (glomerulopathy with inflammation), ovary (decreased number of maturing follicles, granulosa cells, and/or theca cells), and adrenal gland (decreased vacuolation with inflammation). Most of these findings were noted from the lowest dose tested (3 mg per kg per dose) correlating to systemic exposure (AUC) approximately equivalent to those at the human recommended dose. Skeletal and nasal cavity effects were not reversible after a post-dosing recovery period.

Repeated administration of xxx_aflibercept (4 doses administered over 2-3 weeks) resulted in a delay in wound healing in rabbits at dosages ranging from 0.3 mg/kg to 30 mg/kg. In full-thickness excisional and incisional skin wound models, xxx_aflibercept administration reduced fibrous response, neovascularization, epidermal hyperplasia/re-epithelialization, and tensile strength.

xxx-aflibercept impaired reproductive function and fertility in monkeys in the 6-month repeat-dose toxicology study, where xxx_aflibercept inhibited ovarian function and follicular development, as evidenced by decreased ovary weight, decreased amount of luteal tissue, decreased number of maturing follicles, atrophy of uterine endometrium and myometrium, vaginal atrophy, abrogation of progesterone peaks and menstrual bleeding. Alterations in sperm morphology and decreased sperm motility were noted in male monkeys. These effects were observed at all doses tested including the lowest dose tested, 3 mg per kg. Reversibility was observed within 18 weeks after cessation of treatment. Systemic exposure (AUC) with a 3 mg per kg per dose in monkeys was approximately equivalent to AUC in patients at the recommended dose.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Pharmacokinetic data were provided from 19 trials, including two pharmacodynamic trials in healthy volunteers, trials of both monotherapy and xxx-aflibercept in combination with chemotherapy in patients with various cancers, and a QT/QTc assessment study.

Plasma concentrations of free and VEGF-bound aflibercept were measured using specific enzyme-linked immunosorbent assays (ELISAs). Free aflibercept concentrations appeared to exhibit linear pharmacokinetics in the dose range of 2-9 mg per kg. Following 4 mg per kg every two weeks intravenous administration of ZALTRAP, the elimination half-life of free aflibercept was approximately 6 days (range 4-7 days).

The clinical pharmacology and pharmacometrics reviewers (Drs. Leong and Krudis) concluded that there was sufficient data to support the proposed dosing regimen. The reviewers concluded that, based on population pharmacokinetic (PK) analyses, there were no clinically meaningful differences in exposure based on age, gender, or race. Based on clinical trial data, no clinically meaningful drug-drug interactions were observed with any of the components of the FOLFIRI or with several other commonly used chemotherapeutic agents; since xxx-aflibercept is a biologic (protein), *in vitro* testing for drug interactions were not performed. There was also no evidence of clinically important prolongation of QT.

The overall incidence of anti-product antibodies (APA) was determined in 15 trials conducted in patients with various cancers. The incidence of APA was 4.2% in patients receiving intravenous aflibercept (72/1706; of which 19 tested positive at baseline) and 3.5% in placebo-treated patients (41/1156; of which 22 tested positive at baseline). Among patients who tested positive in the APA assay and had sufficient samples for further testing, neutralizing

antibodies were detected in 17 of 48 aflibercept-treated patients and in 2 of 40 placebo-treated patients. Among the 17 xxx_aflibercept-treated patients with neutralizing antibodies, mean trough concentrations were lower than in the overall population; however there was insufficient data to determine whether these differences would alter product safety or efficacy.

6. Clinical Microbiology

As noted under section 3 above, I concur with the conclusions reached by the microbiology reviewer that there are no outstanding product sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The efficacy data supporting this application derives from a single, multinational, randomized, placebo-controlled, double-blind trial enrolling 1226 patients with metastatic colorectal cancer. FDA agreed that this single study was acceptable to support an approval provided the treatment effect on overall survival was clinically important, statistically robust, and consistent across relevant subgroups, and supported by other efficacy endpoints (progression-free survival and overall response rate). The results of EFC10262 (the VELOUR trial) met these criteria. The trial was well-conducted with the exception of deviation from Good Clinical Practices and applicable regulations of a single site, however as noted in Dr. Zhang's review, removal of data from this site did not alter the conclusions of the trial. Similarly, a small number of discrepancies were noted for stratification variables captured on case report forms as compared to the interactive voice randomization system (IVRS), which were similar in number across arms and did not alter the conclusions of the trial. The development program for xxx-aflibercept moved rapidly into multiple hypothesis-testing trials and determination of optimal dosing or of exposure-response relationships were limited.

In the VELOUR trial (Protocol EFC10262), patients were randomized (1:1) to receive xxx_aflibercept in combination with FOLFIRI chemotherapy. Key inclusion criteria were: age ≥ 18 years, histologically- or cytologically- documented adenocarcinoma of the colon or rectum, progression while receiving or following completion of a maximum of one prior oxaliplatin-containing regimen for the treatment of metastatic disease or relapsed while receiving or within 6 months of completion of an oxaliplatin-containing adjuvant chemotherapy regimen; no prior treatment with irinotecan. Randomization was stratified by ECOG status (0 vs. 1 vs. 2) and prior bevacizumab therapy (yes vs. no) in a permuted block design.

Patients were to receive xxx_aflibercept at a dose of 4 mg/kg or matching placebo by intravenous (IV) infusion over approximately 60 minutes every 2 weeks in combination with FOLFIRI chemotherapy. All doses of xxx_aflibercept or placebo were administered prior to any doses of chemotherapy on the day of treatment. FOLFIRI chemotherapy consisted of irinotecan 180 mg/m2 IV, leucovorin 400 mg/ m2 IV infusion over 2 hours, followed by 5-

fluorouracil (5-FU) 400 mg/ m2 over 2 to 4 minutes by intravenous bolus then 5-FU 2400 mg/ m2 by continuous IV infusion over 46 hours. Treatment was administered until progressive disease (PD), unacceptable toxicity, patient refusal, or discontinuation at investigator's discretion.

Patients were assessed for tumor status every 6 weeks until disease progression and for survival status every 2 months, thereafter.

The co-primary efficacy endpoints were overall survival (OS) and progression-free survival as determined by an independent radiologic review committee, using RECIST criteria v1.0. The co-primary analyses methods were a log-rank tests stratified by prior therapy with bevacizumab (yes vs. no) and ECOG performance status (0 vs. 1 vs. 2) for both overall survival and for progression-free survival. The key secondary endpoint was overall response rate (ORR) as determined by an independent radiologic review committee, using RECIST criteria v1.0.

The sample size determination of 1200 patients was based on the following assumptions: median survival time of 11 months in the FOLFIRI alone arm and 13.75 months in the xxx_aflibercept/FOLFIRI arm, providing 90% power to detect a hazard ratio (HR) of 0.80 at an overall two-sided significance level of 0.0499, with adjustments for multiplicity to include two interim analyses of overall survival at 36.5% (315 deaths) and 65% (561 deaths) of the planned final survival analysis (863 deaths). The two-sided nominal significance level allocated to the first interim, second interim, and final analyses of overall survival were 0.00042, 0.0107, and 0.0466, respectively. Based on a request from the IND sponsor (Regeneron), the overall alpha level was split between overall survival and the PFS analyses, in order permit a definitive analysis of PFS to be tested at a 2-sided 0.0001 level. The assumptions regarding progression free survival assumed a 2 to 2.5 month improvement in median PFS times at approximately 845 PFS events. The final analysis of PFS was to occur at the time of the second interim analysis of overall survival. Response rate was to be tested only after either OS or PFS was statistically significant.

Results

A total of 1226 patients were enrolled in the VELOUR trial between November 19, 2007 and March 16, 2010. The data cut-off date for the final analysis of survival occurred after 863 deaths; median patient follow-up was 22.3 months however 97% of patients were no longer on treatment, primarily due to disease progression.

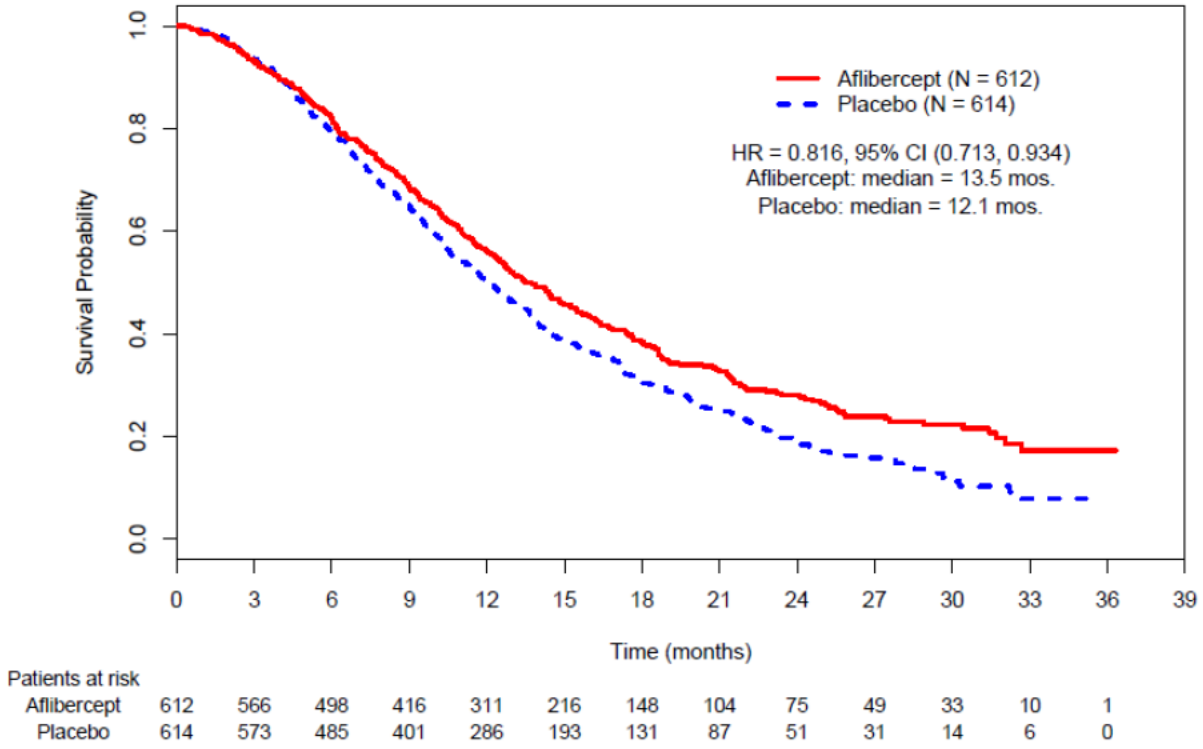
The following demographic information, by study arm and for the trial overall, is abstracted from Dr. Zhang's review (Table 5)

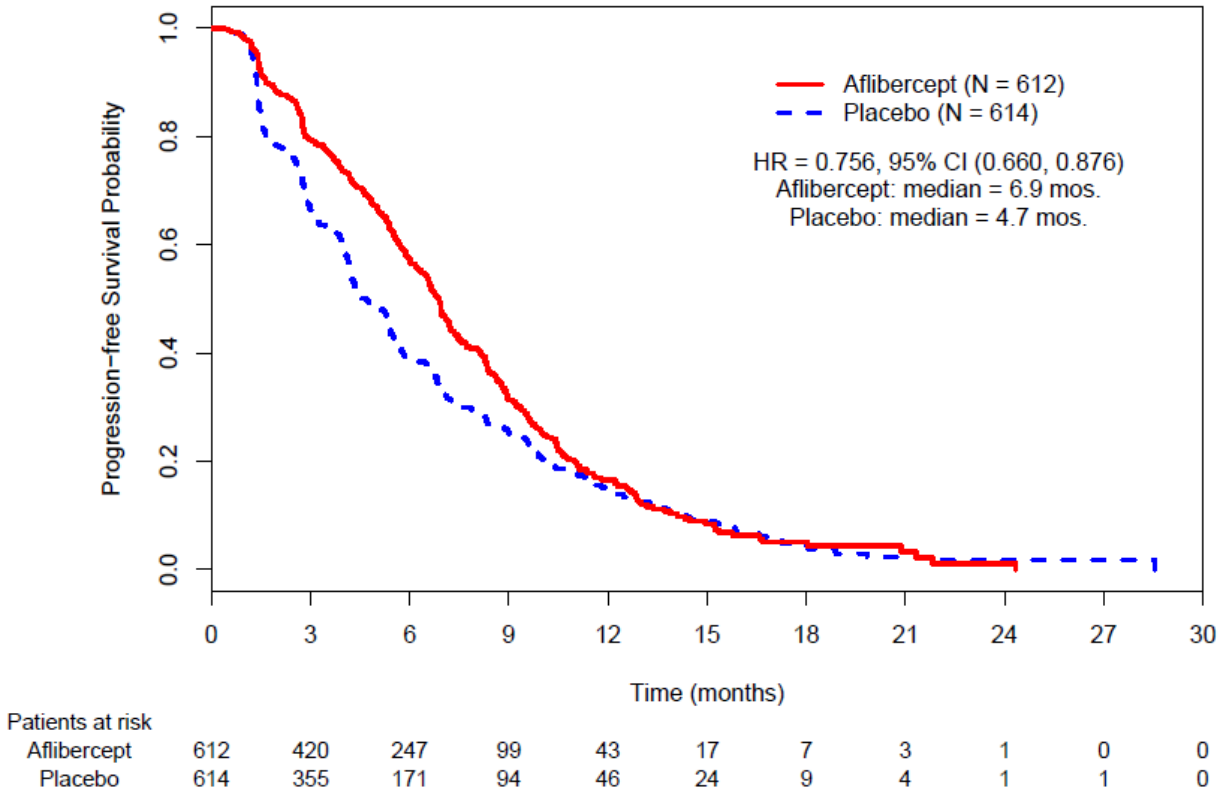
	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
Gender [n(%)]			
Number	614	612	1226
Male	353 (57.5%)	365 (59.6%)	718 (58.6%)
Female	261 (42.5%)	247 (40.4%)	508 (41.4%)
Age (Years)			
Number	614	612	1226
Median	61.0	61.0	61.0
Mean (SD)	60.2 (10.8)	59.5 (10.5)	59.8 (10.7)
Min : Max	19 : 86	21 : 82	19 : 86
Age class [n(%)]			
Number	614	612	1226
<65	376 (61.2%)	407 (66.5%)	783 (63.9%)
≥65 but <75	199 (32.4%)	172 (28.1%)	371 (30.3%)
≥75	39 (6.4%)	33 (5.4%)	72 (5.9%)
Race [n(%)]			
Number	614	612	1226
Caucasian/White	523 (85.2%)	548 (89.5%)	1071 (87.4%)
Black	27 (4.4%)	16 (2.6%)	43 (3.5%)
Asian/Oriental	51 (8.3%)	35 (5.7%)	86 (7.0%)
Other	13 (2.1%)	13 (2.1%)	26 (2.1%)
Region			
Number	614	612	1226
Western Europe	217 (35.3%)	208 (34.0%)	425 (34.7%)
Eastern Europe	136 (22.1%)	161 (26.3%)	297 (24.2%)
North America	75 (12.2%)	63 (10.3%)	138 (11.3%)
South America	56 (9.1%)	62 (10.1%)	118 (9.6%)
Other countries	130 (21.2%)	118 (19.3%)	248 (20.2%)

The VELOUR trial met its co-primary endpoints, demonstrating statistically significant and clinically meaningful increases in overall survival and progression-free survival. These results are summarized in the following table.

Efficacy Endpoints	Placebo/FOLFIRI (N=614)	ZALTRAP/FOLFIRI (N=612)
Overall Survival		
Number of deaths, n (%)	460 (74.9%)	403 (65.8%)
Median overall survival (95% CI) (months)	12.06 (11.07 to 13.08)	13.50 (12.52 to 14.95)
Stratified Hazard ratio (95% CI)	0.82 (0.71 to 0.94)	
Stratified Log-Rank test p-value	0.0032	
Progression Free Survival (PFS)[a]		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (95% CI) (months)	4.7 (4.2 to 5.4)	6.9 (6.5 to 7.2)
Stratified Hazard ratio (95% CI)	0.76 (0.66 to 0.87)	
Stratified Log-Rank test p-value [b]	0.00007	
Overall Response Rate (CR+PR) (95% CI) (%)[c]	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p-value	0.0001	

The Kaplan-Meier curves for overall survival and for progression-free survival abstracted from Dr. Zhang's review (Figures 2 and 4, respectively), are presented below





8. Safety

The size of the safety of the safety database is adequate to identify serious risks and to ensure an adequate risk: benefit assessment. Evaluation of the safety of xxx-aflibercept was based primarily on data from three randomized trials (VELOUR, VITAL, and VANILLA) providing safety data on 1333 patients treated with xxx_aflibercept, supported by additional safety data from other Phase 1 and 2 trials for a total database of 2073 patients receiving xxx-aflibercept. The safety profile is consistent with other angiogenesis-inhibiting products, consisting of hypertension, proteinuria, hemorrhage, impairment of wound healing, viscus perforation and fistula formation, and dysphonia as well as an increase in the incidence of chemotherapy-related toxicities of neutropenia, thrombocytopenia, diarrhea, stomatitis, and palmar-plantar erythrodysesthesia. The following table, abstracted from the proposed package insert, provides a comparison of adverse reactions occurring more frequently in, and thus attributed to, xxx_aflibercept.

	Placebo/ FOLFIRI (N=605)		**ZALTRAP/ FOLFIRI (N=611)**	
Primary System Organ Class Preferred Term (%)	**All grades**	**Grades 3-4**	**All grades**	**Grades 3-4**
Infections and infestations				
Urinary Tract Infection	6%	0.8%	9%	0.8%

Primary System Organ Class Preferred Term (%)	Placebo/ FOLFIRI (N=605)		ZALTRAP/ FOLFIRI (N=611)	
	All grades	Grades 3-4	All grades	Grades 3-4
Blood and lymphatic system disorders				
Leukopenia	72%	12%	78%	16%
Neutropenia	57%	30%	67%	37%
Thrombocytopenia	35%	2%	48%	3%
Metabolism and nutrition disorders				
Decreased Appetite	24%	2%	32%	3%
Dehydration	3%	1%	9%	4%
Nervous system disorders				
Headache	9%	0.3%	22%	2%
Vascular disorders				
Hypertension	11%	1.5%	41%	19%
Respiratory, thoracic and mediastinal disorders				
Epistaxis	7%	0	28%	0.2%
Dysphonia	3%	0	25%	0.5%
Dyspnea	9%	0.8%	12%	0.8%
Oropharyngeal Pain	3%	0	8%	0.2%
Rhinorrhea	2%	0	6%	0
Gastrointestinal disorders				
Diarrhea	57%	8%	69%	19%
Stomatitis	33%	5%	50%	13%
Abdominal Pain	24%	2%	27%	4%
Abdominal Pain Upper	8%	1%	11%	1%
Hemorrhoids	2%	0	6%	0
Rectal Hemorrhage	2%	0.5%	5%	0.7%
Proctalgia	2%	0.3%	5%	0.3%
Skin and subcutaneous tissue disorders				
Palmar-Plantar Erythrodysesthesia Syndrome	4%	0.5%	11%	3%
Skin Hyperpigmentation	3%	0	8%	0

Primary System Organ Class Preferred Term (%)	Placebo/ FOLFIRI (N=605)		ZALTRAP/ FOLFIRI (N=611)	
	All grades	Grades 3-4	All grades	Grades 3-4
Renal and urinary disorders				
Proteinuria*	41%	1%	62%	8%
Serum creatinine increased	19%	0.5%	23%	0
General disorders and administration site conditions				
Fatigue	39%	8%	48%	13%
Asthenia	13%	3%	18%	5%
Investigations				
AST increased	54%	2%	62%	3%
ALT increased	39%	2%	50%	3%
Weight decreased	14%	0.8%	32%	3%

Note: Adverse Reactions are reported using MedDRA version MEDDRA13.1 and graded using NCI CTC version 3.0

* Compilation of clinical and laboratory data

Based on these risks, and consistent with labeling for other products in this class, the product labeling will contain a Boxed Warning denoting the risks of hemorrhage with this product, however, I concur with the recommendations of the clinical review team that a REMS is not required to ensure safe us of xxx_aflibercept. I also concur that the risks of xxx_aflibercept are acceptable in light of its benefits, the life-threatening nature of metastatic colorectal cancer, and the lack of satisfactory therapy for this population.

9. Advisory Committee Meeting

This application was not referred to an advisory committee. The review team concurred that the trial design and conduct were adequate, the primary efficacy endpoint was clinically important and relevant in this patient population and the treatment effect was robust, internally consistent across relevant subgroups and supported by demonstration of treatment effects on related efficacy endpoints, and that the safety profile was acceptable for this indication (treatment of metastatic colorectal cancer). Based on these determinations, the review team agreed that the application did not raise significant efficacy issues or safety issues or expose patients to risks that were unacceptable for the intended population; therefore, outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

The Division and the PeRC agreed that sanofi-aventis' proposed waiver from the requirement to conduct pediatric studies under PREA should be granted because the disease (colorectal cancer) does not occur in children, therefore necessary studies are impossible or highly impracticable to perform.

11. Other Relevant Regulatory Issues

The only unresolved relevant regulatory issue is the assignment of an acceptable non-proprietary name, as discussed in section 12 of this review.

12. Labeling

- Proprietary name: The proposed proprietary name of Zaltrap was determined to be acceptable by DMEPA in their February 13, 2012 review. The clinical review staff had no objections to the proposed tradename.

- Non-proprietary name: FDA determined that a unique nonproprietary name will be required for sanofi-aventis' (sanofi) Zaltrap ([xxx]_aflibercept), a biological product submitted in a 351(a) biologics license application (BLA) to distinguish the product from Eylea (aflibercept), a previously licensed biological product submitted in a different 351(a) BLA by Regeneron Pharmaceuticals Inc. (Regeneron) that contains similar drug substance. A distinct nonproprietary name was required to minimize medication errors by (1) preventing patients from receiving a product different than what was intended to be prescribed, (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint, and to facilitate postmarketing safety monitoring by providing a clear means of determining which "aflibercept" product is dispensed to patients. sanofi-aventis proposed three non-proprietary names without the requested underscoring between the prefix and aflibercept. This proposal is currently under review and the final non-proprietary name has not been assigned.

- Physician labeling: With the exception of the assignment of a non-proprietary name, all major issues regarding the physician labeling have been resolved. Additional modifications to the proposed labeling include the following
  - Boxed Warning:
  - Indications and Usage – revised to indicate the specific chemotherapy regimen used in the VELOUR trial and to indicate that patients should have cancer that is no longer responsive to oxaliplatin-based chemotherapy
  - Dosage and Administration: (b) (4) edited for brevity and

command language; created separate subsections for preparation for administration (2.3) and for administration (2.4), with relocation of information on recommended administration to section 2.4. Deleted redundant statements (b) (4) Deleted unsupported statements (b) (4)

- Dosage Forms and Strengths: editorial changes
- Contraindications: Removed (b) (4) in accordance with applicable FDA Guidance.
- Warnings and Precautions: (b) (4) edited to change from passive to active voice (e.g., "monitor patients" rather than "patients should be monitored"); modified incidence of GI perforation based pooled risk across three randomized trials, since VELOUR trial appears to show a lower than expected differential risk of GI perforation between arms; added information to section 5.4 to note that the safety of xxx_aflibercept has not been evaluated in a patient population with NYHA class III or IV heart failure; updated incidence data for thrombotic microangiopathy and provided denominator; (b) (4) added a statement to section 5.8, noting that the risk of diarrhea/dehydration appears to be greater in elderly patients compared to younger patients. (b) (4)
- Adverse Reactions: (b) (4) modified incidence figures to reflect studies with adequate exposure, ascertainment of samples, and testing in assay with acceptable performance characteristics.
- Drug Interactions: edited for brevity and relevance to approved indication.
- Use in Specific Populations: In section 8.1, added subsections for "risk summary" and "animal data" as recommended by MHT consultant; data on potential impairment of fertility based on findings in animals moved to new subsection 8.8 on males and females of reproductive potential as recommended by MHT consultant; section 8.3 edited for brevity; sections 8.6 and 8.7 revised to characterize the number of patients with hepatic impairment or renal impairment evaluated in the pop PK analysis; database.
- Overdosage: edited for brevity and available data; recommendations for management removed as these are based on theory rather than clinical experience.

- Description: (b) (4)
- Clinical Pharmacology: (b) (4) retained results of *in vivo* and *in vitro* test results (b) (4) ; added new subsection (12.6) on cardiac electrophysiology to note that minor effects have been identified and the effects of xxx_aflibercept on QTc have not been adequately studied,
- Nonclinical Toxicology: Sections 13.1 and 13.2 edited for brevit (b) (4)
- Clinical Studies: Information on subgroup analyses limited to subgroups defined by prior bevacizumab use, as important information for prescribers.
- How Supplied: edited for brevity and to limit redundancy (e.g., information on storage of product prepared for administration is contained in section 2).

- Carton and immediate container labels: sanofi-aventis incorporated all FDA-requested carton and container labeling changes. As noted above, the non-proprietary name has not been assigned; therefore, final carton/container labeling is pending.

- Patient labeling/Medication guide: The clinical and safety reviewers agree that a Medication Guide is not required to ensure safe and effective use of ZALTRAP. sanofi-aventis proposed patient labeling, however FDA considered this labeling unnecessary to enhance safe use and at FDA's request, the patient labeling was withdrawn. FDA's request was based on the determination that the product would be infused under the direct supervision of a healthcare provider in an office, clinic, or hospital-based setting, where patient counseling would be conveyed verbally and, potentially in writing, to the patient. In addition, it is unlikely that patient labeling would be provided to the patient, given that the product is not directly dispensed to the patient, but instead is prepared in a pharmacy that may be off-site.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that this application approved.

- Risk Benefit Assessment

  Regular approval is sought for the ZALTRAP (xxx_aflibercept) for use in combination with irinotecan- and fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer, a condition treated with cytotoxic chemotherapy for which 5 year survival is approximately 10% with standard treatment. This BLA relies primarily on the results a single, large, multicenter, placebo-controlled trial which provides substantial evidence of effectiveness based on demonstration of a clinically meaningful and robust improvement in overall survival, supported by statistically

significant improvements in progression-free survival and objective tumor responses. The safety profile is consistent with other angiogenesis-inhibiting products, consisting of hypertension, proteinuria, hemorrhage, impairment of wound healing, viscus perforation and fistula formation, and dysphonia as well as an increase in the incidence of chemotherapy-related toxicities of neutropenia, thrombocytopenia, diarrhea, stomatitis, and palmar-plantar erythrodysesthesia. The risks of xxx_aflibercept are acceptable in light of its benefits, the life-threatening nature of metastatic colorectal cancer, and the lack of satisfactory therapy for this population.

All review disciplines have recommended approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the conclusion of the review team that a REMS is not required to ensure safe use of this product

- Recommendation for other Postmarketing Requirements and Commitments

  The Quality review team requested several post-marketing commitments to improve and further characterize the product and agreement has been reached with sanofi-aventis on these commitments.

  No review team member has identified the need for a post-marketing requirement under FDAAA. I concur with that such post-marketing requirements are not needed to ensure safe use of this product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
07/26/2012