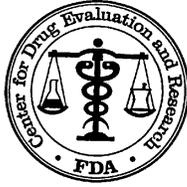


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125418Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: BLA 125-418
Drug Name: ZALTRAP[®] (aflibercept)
Indication(s): 2nd line metastatic colorectal cancer (MCRC)
Applicant: Sanofi-Aventis
Submission Date: February 3, 2012
PDUFA Date: August 4, 2012
Review Priority: Priority

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Keywords: Log-rank test, Cox model, MCRC, Overall survival

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1. EXECUTIVE SUMMARY

The Applicant is seeking approval for ZALTRAP[®] (aflibercept) in combination with irinotecan-fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer (MCRC) previously treated with oxaliplatin-based chemotherapy.

The primary support for efficacy comes from a single randomized, double-blind, placebo-controlled, multi-center phase III study (Study EFC10262 [VELOUR]) in 1226 patients with colorectal cancer treated with FOLFIRI as second line treatment for metastatic disease. The primary efficacy endpoint was overall survival (OS). The primary analysis was a log-rank test stratified by prior therapy with bevacizumab (yes vs. no) and ECOG performance status (0 vs. 1 vs. 2). Secondary endpoints included progression-free survival (PFS) and overall response rate (ORR).

Patients were randomized 1:1 to receive aflibercept 4 mg/kg or matching placebo intravenously (IV) on day 1 plus FOLFIRI every 2 weeks. Treatment was administered until progressive disease (PD), unacceptable toxicity, patient refusal, or discontinuation at investigator's discretion. Key inclusion criteria included: (a) patients must have progressed while on or after one prior oxaliplatin-based regimen for metastatic disease; (b) patients who relapsed while on or within 6 months of completion of adjuvant chemotherapy were eligible; (c) no prior treatment with irinotecan was permitted; prior treatment with bevacizumab was allowed.

Median OS was 13.5 months in the aflibercept arm and 12.1 months in the placebo arm. The hazard ratio (HR) was 0.82 with 95% confidence interval (CI) (0.71, 0.93) and log-rank p-value of 0.0032. Median PFS by independent review committee (IRC) was 6.9 months in the aflibercept arm and 4.7 months in the placebo arm. The HR was 0.76 with 95% CI (0.66, 0.87) and log-rank p-value of 0.00007.

The results of the study (VELOUR) demonstrated that patients treated with aflibercept plus FOLFIRI had longer median OS than those treated with placebo plus FOLFIRI. Whether the results provide an overall favorable benefit to risk ratio will be determined by the clinical team.

2. INTRODUCTION

2.1 Overview

ZALTRAP[®] (aflibercept) is an anti-angiogenic agent targeting VEGF pathways, including VEGF-A, VEGF-B, and PlGF. Aflibercept is a new molecular entity (NME) with no current approved indications. The purpose of this submission is to obtain approval for aflibercept 4 mg/kg IV for the treatment of patients with metastatic colorectal cancer (MCRC) previously treated with oxaliplatin-based chemotherapy.

The efficacy and safety of aflibercept in patients with MCRC have been evaluated in a single randomized, double-blind, placebo-controlled, multi-center phase III study (Study EFC10262

[VELOUR]) in 1226 patients. The primary efficacy endpoint was overall survival (OS). Key secondary endpoints included progression-free survival (PFS) and overall response rate (ORR).

2.2 Data Sources

The data sources, including Applicant study reports, data sets analyzed, and literature referenced, are in the Electronic Document Room (EDR) at \\cbsap58\M\CTD_Submissions\STN125418\0000.

3. STATISTICAL EVALUATION

The purpose of this submission is to obtain approval for aflibercept for the treatment of patients with metastatic colorectal cancer (MCRC) previously treated with oxaliplatin-based chemotherapy. Study EFC10262 (VELOUR) is the pivotal study in support of this indication.

3.1 Data and Analysis Quality

The data submitted for this application are of high quality and well-documented. The reviewer was able to reproduce the applicant's results with reasonable effort.

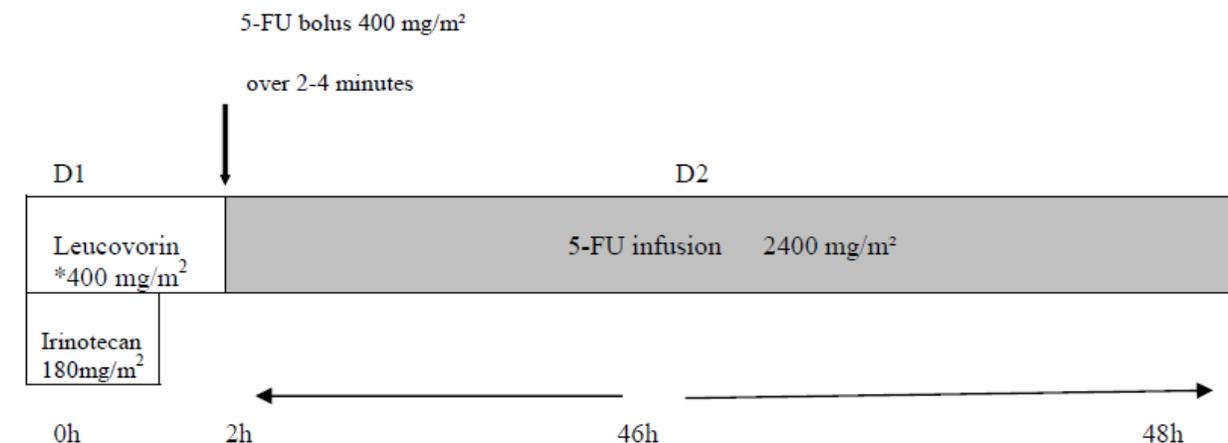
3.2 Evaluation of Efficacy

Study Design and Endpoints

Study VELOUR is a single randomized, double-blind, placebo-controlled, multi-center phase III in 1226 patients with colorectal cancer treated with FOLFIRI as second line treatment for metastatic disease. The FOLFIRI regimen was chosen as the control backbone for VELOUR due to its worldwide recognition as a standard regimen for the treatment of patients with MCRC by the medical oncology community. At the time that VELOUR was initiated, no data were available in the second-line setting after an oxaliplatin-based therapy for the combination of FOLFIRI and bevacizumab, which precluded conducting the trial with bevacizumab as an active comparator.

Study eligibility criteria included: age \geq 18 years; histologically or cytologically proven adenocarcinoma of the colon or rectum; metastatic disease that was not amenable to potentially curative treatment (ie, inoperable); measurable or non-measurable disease (as per RECIST criteria); only one prior oxaliplatin-containing chemotherapeutic regimen for metastatic disease. Patients who relapsed within 6 month of completion of oxaliplatin-based adjuvant chemotherapy were eligible. Patients meeting the eligibility criteria were randomized in a 1:1 ratio to either aflibercept 4 mg/kg administered over 1 hour on Day 1 of the 2-week cycle or matching placebo followed immediately by the FOLFIRI regimen. The FOLFIRI regimen was administered as illustrated in Figure 1.

Figure 1: FOLFIRI Regimen



*400 mg /m² of leucovorin expressed in dl racemic
Source: Applicant's CSR

Treatment assignment was performed via IVRS using permuted-block randomization stratified by prior therapy with bevacizumab (yes vs. no) and ECOG performance status (0 vs. 1 vs. 2). Patients who, at the time of randomization, were on the follow-up phase of a double-blind controlled study with bevacizumab while that study was still blinded, could still be randomized into VELOUR. In such cases, stratification for prior bevacizumab was to be “yes”.

The primary endpoint of the study is overall survival (OS), defined as the time from randomization to the date of death due to any cause. Once disease progression was documented, patients were followed every 2 months for survival status, until death or until the study cutoff date, whichever came first. Secondary endpoints included independent review committee (IRC)-determined progression-free survival (PFS) and objective response rate (ORR) according to RECIST criteria v1.0. Tumor assessments were conducted every 6 weeks.

Reviewer Comment:

An IRC was set up after study initiation following implementation of Amendment 2 in April 2008. For patients who died before implementation of Amendment 2 or who denied consent for IRC review, the investigators' assessment was used in the PFS analysis. Only patients who consented to IRC review were included in the analyses of ORR.

Sample Size Determination

For the primary endpoint of OS, the expected median survival time was 11 months in the control arm and 13.75 months in the treatment arm, corresponding to a hazard ratio (HR) of 0.80. Assuming exponential survival times, a total of 863 deaths were required to detect a 20% risk reduction in the aflibercept arm relative to the placebo arm with 90% power, using a two-sided log-rank test at a significance level of 0.0499. This calculation took into account two interim efficacy analyses for OS at 36.5% and 65% information and one futility analysis at the time of the first interim efficacy analysis. Assuming an accrual period of 30 months followed by 9

months of follow-up after randomization of the last patient, a total of 1200 patients were required to observe the targeted number of events.

Interim Analyses

Two interim analyses were performed for OS at 36.5% (315 deaths) and 65% (561 deaths) information. Using a group sequential approach with an O'Brien-Fleming alpha-spending function and an overall two-sided significance level of 0.0499, the two-sided nominal α allocated to the first and second interim and final analysis was 0.00042, 0.0107, and 0.0466, respectively.

A futility boundary was also planned at the time of the first interim analysis based on a Gamma(-5) β -spending function; the futility boundary would be crossed if $HR \geq 1.084$. The corresponding conditional power under the alternative hypothesis at that time was 0.327.

The final PFS analysis was performed at the time of the second interim OS analysis.

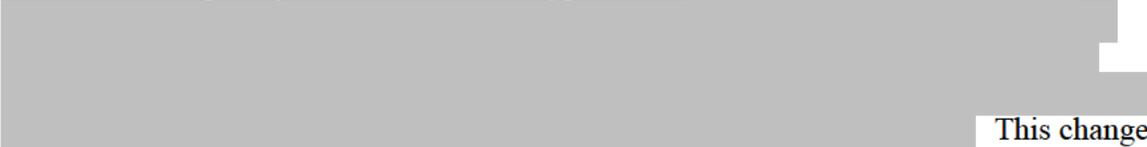
Reviewer Comments:

1. Note that the results of the interim analyses were reviewed by the DMC and the recommendation was to continue the study.
2. In the initial protocol, only one efficacy interim analysis for OS was planned at 65% information (561 deaths) with alpha allocation of 0.0107. On October 12, 2009, the DMC requested an earlier efficacy analysis to be performed at 36.5% information (315 deaths) for an early benefit-risk evaluation. This change was made before the blind was broken.

Multiplicity

The overall alpha level was split between OS and PFS. PFS was tested at a 2-sided 0.0001 level and the overall alpha level for OS was at a 2-sided 0.0499 level. Response rate was to be tested only after either OS or PFS was statistically significant.

Reviewer Comments:

1. In a letter dated August 30, 2010, the FDA requested to split the alpha level between OS and PFS to adequately control the overall type I error (b) (4)
 This change was made before the blind was broken, and had a negligible effect on the sample size and interim and final stopping boundaries for OS.
2. Given the alpha split and assuming a median PFS of 4 months in the control arm, it was considered that an improvement in median PFS of 2 to 2.5 months could reasonably reflect a clinically meaningful treatment benefit in OS. Based on this consideration and a predicted 845 PFS events, allocation of an alpha of 0.0001 to the final PFS analysis

would allow the statistical evaluation to be consistent with a meaningful clinical judgment.

Statistical Methodologies

The intent-to-treat (ITT) population was the primary analysis population and consists of all randomized patients with treatment as assigned at randomization. The primary analysis comparing OS between the two treatment arms was performed in the ITT population using the log-rank test stratified by the stratification factors specified at randomization (i.e., prior therapy with bevacizumab and ECOG PS). The hazard ratio (HR) and corresponding (1- α)% confidence interval (CI) were obtained from a stratified Cox proportional hazards model.

Similar analyses were performed for PFS at a significance level of 0.0001. PFS was defined as the time from randomization to disease progression (PD) or death due to any cause. If death or progression was not observed, the patient was censored at the date of last tumor assessment.

Two sensitivity analyses of PFS were performed:

Sensitivity analysis #1: PFS endpoint as assessed by the IRC, censoring for progression or death occurring more than 9 weeks (i.e., >1.5 times the assessment interval length) after the last valid tumor assessment and for other anti-tumor therapies in patients who did not have PD documented before such therapies.

Sensitivity analysis #2: PFS endpoint determined and analyzed using the investigator's assessment, and considering clinical disease progression (symptomatic deterioration) as an event.

ORR based on IRC evaluation was summarized using descriptive statistics and 95% CIs. The difference in ORR between treatment arms was compared using a stratified Cochran-Mantel-Haenszel (CMH) test. ORR was evaluated only in the evaluable patient (EP) population, which included all randomized patients with measurable disease at study entry (per IRC), and with at least one valid post-baseline tumor evaluation. Patients who died due to PD or had documented radiological PD before first having a protocol scheduled post-baseline imaging evaluation were not excluded. All analyses using the EP population were based on treatment assignment by IVRS. Only those patients who consented to IRC review were part of the EP analysis.

Reviewer Comment:

If an imbalance in adherence to the tumor assessment schedule was detected between the treatment arms, an additional sensitivity analysis of PFS based on tumor assessment by the IRC was to be performed by assigning fixed tumor assessment dates to time window. However, since no such imbalance was seen, this sensitivity analysis was not conducted.

Patient Disposition, Demographic and Baseline Characteristics

A total of 1226 patients (612 on aflibercept; 614 on placebo) were randomized into the study and constitutes the ITT population. Of these, five patients in each arm were not treated. A total of

138 patients (11.3%) were enrolled in North America. The data cutoff date for OS was February 7, 2011. The EP population included 1061 patients (531 on aflibercept; 530 on placebo) and was used for the analysis of ORR only.

Patient disposition and reasons for treatment discontinuation are summarized in Table 1.

Table 1: Patient disposition

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Randomized but not treated	5 (0.8%)	5 (0.8%)
Randomized and treated	609 (99.2%)	607 (99.2%)
Discontinued study treatment	598 (97.4%)	593 (96.9%)
Reasons for treatment discontinuation		
Adverse event	74 (12.1%)	163 (26.6%)
Disease progression	437 (71.2%)	305 (49.8%)
Poor compliance to protocol	4 (0.7%)	4 (0.7%)
Subject lost to follow-up	2 (0.3%)	0
Other reason ^a	81 (13.2%)	121 (19.8%)
Investigator decision	21 (3.4%)	20 (3.3%)
Consent withdrawn	2 (0.3%)	6 (1.0%)
Subject request	43 (7.0%)	77 (12.6%)
Metastatic surgery	10 (1.6%)	12 (2.0%)
Other	5 (0.8%)	6 (1.0%)
Ongoing treatment	11 (1.8%)	14 (2.3%)
Status at last study contact		
Alive	149 (24.3%)	207 (33.8%)
Dead	460 (74.9%)	403 (65.8%)
Lost to follow-up	5 (0.8%)	2 (0.3%)

Source: Applicant's CSR

The main reasons for treatment discontinuation were disease progression (49.8% on aflibercept and 71.2% on placebo) and adverse events (26.6% on aflibercept and 12.1% on placebo). Ten patients (5 on each arm) did not receive any study treatment. The median study follow-up was 22.3 months.

Table 2 summarizes the number of patients in each stratum for both IVRS- and CRF-based stratification factors. Per IVRS, 30.4% of patients had prior bevacizumab therapy and most patients had ECOG PS 0 or 1 (97.8%).

Table 2: IVRS vs. CRF stratification

Stratification factor	IVRS		CRF	
	Placebo (N=614)	Aflibercept (N=612)	Placebo (N=614)	Aflibercept (N=612)
ECOG PS 0	350 (57.0%)	349 (57.0%)	354 (57.7%)	350 (57.2%)
ECOG PS 1	250 (40.7%)	250 (40.8%)	248 (40.4%)	249 (40.7%)
ECOG PS 2	14 (2.3%)	13 (2.1%)	12 (2.0%)	13 (2.1%)
Prior bevacizumab	187 (30.5%)	186 (30.4%)	177 (28.8%)	169 (27.7%)
No prior bevacizumab	427 (69.5%)	426 (69.6%)	437 (71.2%)	443 (72.4%)

Source: Created by Reviewer

Tables 3 and 4 summarize the discrepancies between IVRS and CRF stratification for ECOG PS and Prior bevacizumab, respectively. The discrepancy counts are on the off-diagonals (*italicized*) and are fairly balanced across treatment arms.

Table 3: Stratification discrepancies - ECOG PS

CRF	IVRS					
	Placebo			Aflibercept		
	0	1	2	0	1	2
0	346	<i>7</i>	<i>1</i>	341	<i>9</i>	<i>0</i>
1	<i>4</i>	243	<i>1</i>	<i>8</i>	241	<i>0</i>
2	<i>0</i>	<i>0</i>	12	<i>0</i>	<i>0</i>	13

Source: Created by Reviewer

Table 4: Stratification discrepancies - Prior Bevacizumab

CRF	IVRS			
	Placebo		Aflibercept	
	No	Yes	No	Yes
No	418	<i>19</i>	419	<i>24</i>
Yes	<i>9</i>	168	<i>7</i>	162

Source: Created by Reviewer

Reviewer Comment:

Patients who, at the time of randomization, were in the follow-up phase of a double-blind controlled study with bevacizumab while that study was still blinded, could still be randomized into VELOUR and were instructed to be stratified for prior bevacizumab as “yes”. If later, after unblinding, such patients were found to have been on the control (no bevacizumab) arm, their stratum was updated accordingly. Such patients would create discrepancies between IVRS and CRF stratification, but they should not be viewed as stratification errors as investigators were in compliance of protocol instructions. Thirty-one (31) of the 59 total discrepancies in prior bevacizumab stratification shown in Table 4 fit into this scenario.

Patient demographics were well-balanced between treatment arms and are summarized in Table 5.

Table 5: Patient demographics

	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%)

Other countries: Australia, New Zealand, South Africa, and Korea

Source: Applicant's CSR

Results and Conclusions

The following efficacy results and conclusions were verified by the reviewer.

Reviewer Comment:

Technically, the CI percentages for OS and PFS should be 95.34% and 99.99%, respectively. However, for labeling and ease-of-interpretation, all CIs reported herein are 95%.

Overall Survival (OS)

Table 6 summarizes the OS results, including the primary analysis based on IVRS stratification. Median OS was 12.1 months on placebo and 13.5 months on aflibercept with corresponding stratified HR of 0.82 (95% CI: 0.71, 0.93). The two-sided p-value for the stratified log-rank test was 0.0032, which is < 0.0466 and supports that OS is statistically significantly longer for patients on aflibercept as compared to placebo.

Table 6: Overall Survival

	Placebo (N=614)	Aflibercept (N=612)
Primary analysis (IVRS)		
# of events	460	403
Median (in mos.)	12.1	13.5
Stratified HR (95% CI)	0.816 (0.713, 0.934)	
p-value	0.0032	
CRF Stratification		
Stratified HR (95% CI)	0.807 (0.705, 0.923)	
p-value	0.0018	
Unstratified analysis		
HR (95% CI)	0.809 (0.707, 0.924)	
p-value	0.0019	
Excluding site 036007 (N=606) (N=597)		
Stratified HR (95% CI)	0.822 (0.717, 0.941)	
p-value	0.0047	

Source: Created by Reviewer

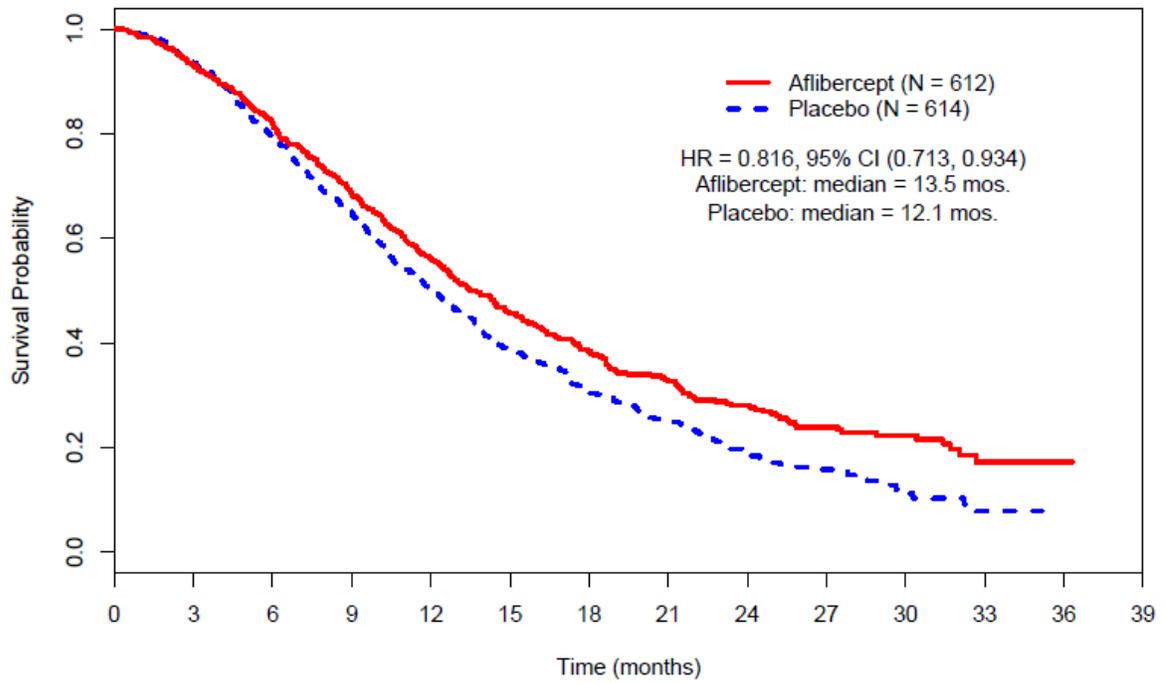
OS analyses based on CRF stratification and the unstratified analysis both gave similar results as the primary analysis.

Reviewer Comment:

Although the Australian site (036007, Dr. Van Hazel) was not inspected for logistical reasons, some evidence of non-compliance at the Australian site was found during the Sanofi New Jersey inspection. There were issues with protocol compliance, dosing, etc. Although the Applicant knew about these issues and actively corresponded with Dr. Van Hazel, they allowed enrollment to continue instead of shutting down the site. The unstratified HR for site 036007 was 0.457 (0.158, 1.317). A sensitivity analysis excluding the 23 patients from site 036007 was performed (Table 6). The results were consistent with those of the primary analysis, thus, it is reasonable to conclude that including site 036007 does not significantly affect the overall results.

The Kaplan-Meier curves for OS are presented in Figure 2.

Figure 2: Kaplan-Meier curves for OS

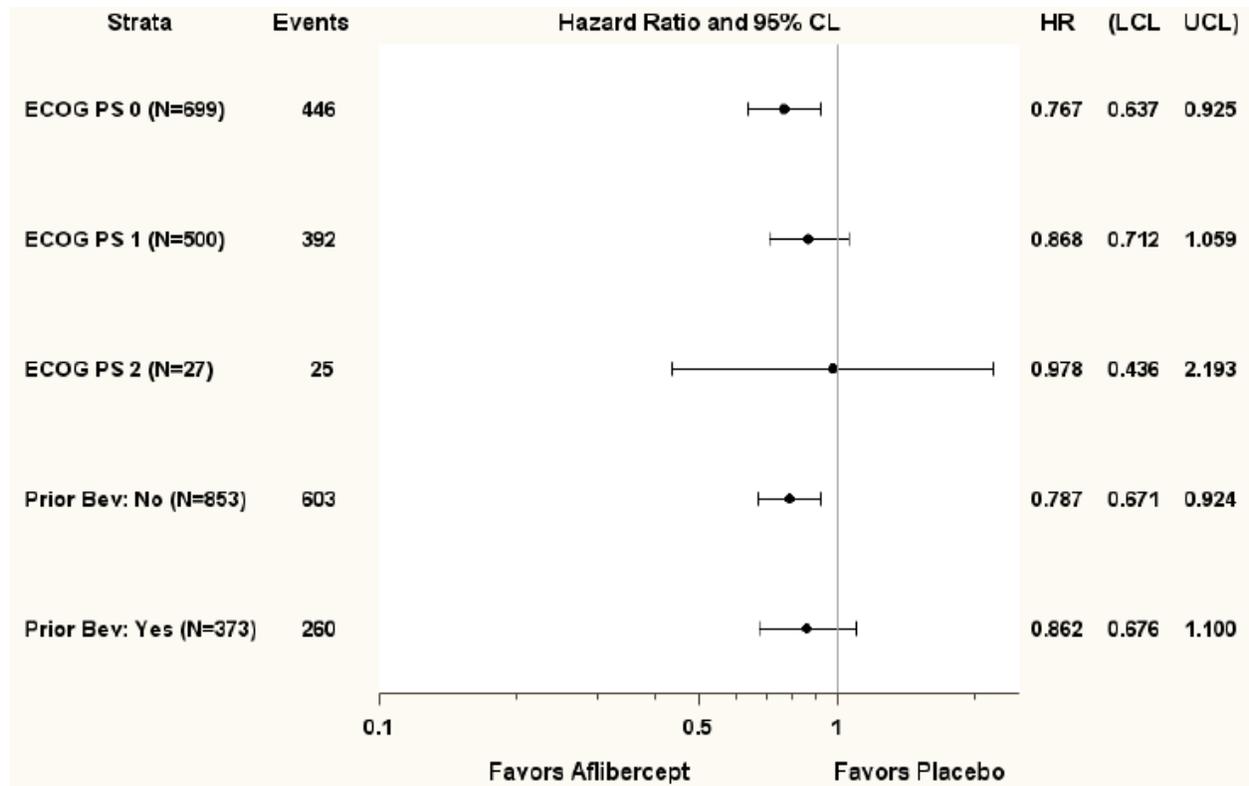


Patients at risk		Time (months)												
		0	3	6	9	12	15	18	21	24	27	30	33	36
Aflibercept	612	566	498	416	311	216	148	104	75	49	33	10	1	
Placebo	614	573	485	401	286	193	131	87	51	31	14	6	0	

Source: Created by Reviewer

Figure 3 is a forest plot summarizing the OS results by IVRS stratification. The results by strata are generally consistent and supportive of the primary OS results.

Figure 3: Forest plot of OS by IVRS Stratification



Source: Created by Reviewer

Progression-Free Survival (PFS)

Table 7 summarizes the PFS results, including the primary analysis based on IVRS stratification. Median PFS was 4.7 months on placebo and 6.9 months on aflibercept with corresponding stratified HR of 0.76 (95% CI: 0.66, 0.88). The two-sided p-value for the stratified log-rank test was 0.00007, which is < 0.0001 and supports that PFS is statistically significantly longer for patients on aflibercept as compared to placebo. PFS analyses based on CRF stratification and the unstratified analysis both gave similar results as the primary analysis.

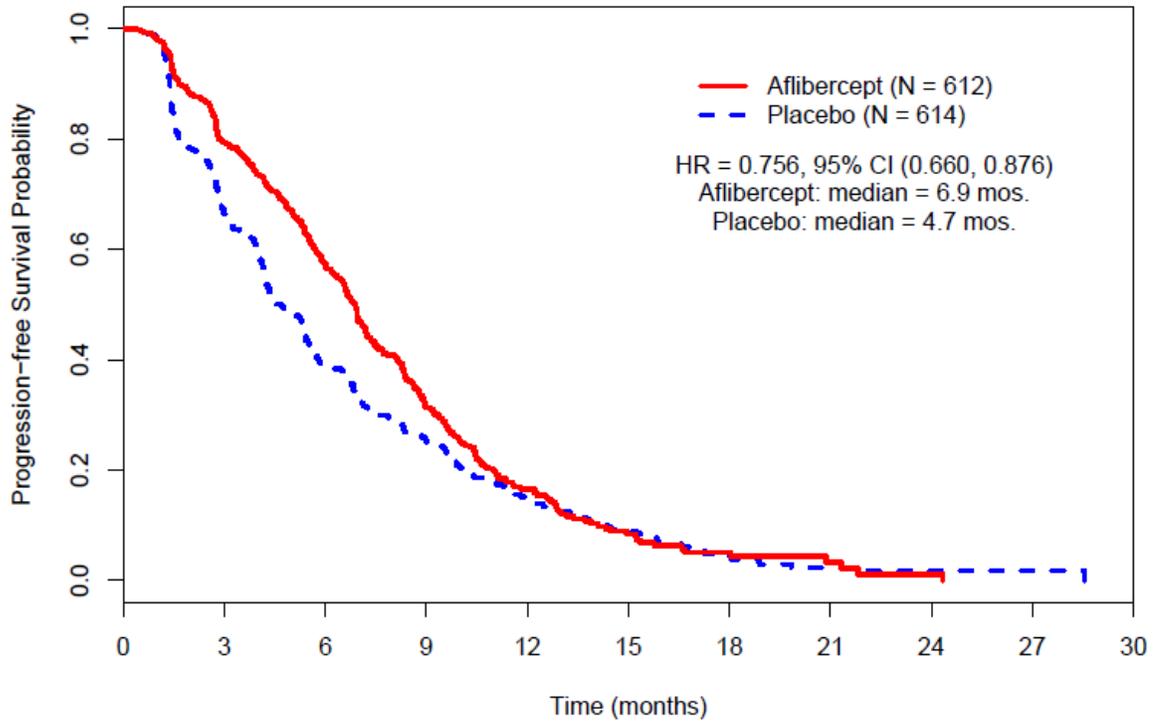
Table 7: Progression-free survival

	Placebo (N=614)	Afibercept (N=612)
Primary analysis (IVRS)		
# of events	454	393
Median (in mos.)	4.7	6.9
Stratified HR (95% CI)	0.756 (0.660, 0.876)	
p-value	0.00007	
CRF Stratification		
Stratified HR (95% CI)	0.745 (0.650, 0.855)	
p-value	0.00003	
Unstratified analysis		
HR (95% CI)	0.756 (0.660, 0.866)	
p-value	0.00005	

Source: Created by Reviewer

The Kaplan-Meier curves for PFS are presented in Figure 4.

Figure 4: Kaplan-Meier curves for PFS



Patients at risk	Time (months)										
	0	3	6	9	12	15	18	21	24	27	30
Afibercept	612	420	247	99	43	17	7	3	1	0	0
Placebo	614	355	171	94	46	24	9	4	1	1	0

Source: Created by Reviewer

Table 8 summarizes the PFS sensitivity analysis results, which are both supportive of the primary analysis.

Table 8: PFS sensitivity analyses

	Placebo (N=614)	Aflibercept (N=612)
Sensitivity 1: (IRC) censoring late progressions and deaths; censoring for new anti-cancer therapy		
# of events	353	281
Median (in mos.)	4.5	7.0
Stratified HR (95% CI)	0.652 (0.556, 0.764)	
p-value	<0.00001	
Sensitivity 2: (INV) including clinical progression (symptomatic deterioration)		
# of events	485	452
Median (in mos.)	4.5	6.2
Stratified HR (95% CI)	0.813 (0.714, 0.925)	
p-value	0.0017	

Source: Created by Reviewer

Objective Response Rate (ORR)

ORR was only assessed in the evaluable patient (EP) population. Overall, 165 patients were excluded from the EP population (84 on placebo; 81 on aflibercept). Table 9 gives a summary of the reasons for exclusion; the most common reason for exclusion was the absence of target lesions at baseline (57 on placebo; 41 on aflibercept). Since the primary endpoint was OS, patients with only non-target lesion(s) at baseline were still eligible for randomization.

Table 9: Reasons for exclusion from EP population for ORR

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Any reason	84 (13.7%)	81 (13.2%)
Reason for exclusion from evaluable population		
No IRC reading	18 (2.9%)	24 (3.9%)
Only non target lesions at baseline*	57 (9.3%)	41 (6.7%)
No post baseline TA except for early death or PD*	9 (1.5%)	16 (2.6%)

*among patients read by the IRC

Source: Applicant's CSR

Table 10 summarizes the ORR results based on IRC assessment in the EP population. The ORR was 11.1% on placebo and 19.8% on aflibercept. The p-value from a stratified Cochran-Mantel-Haenszel (CMH) test was 0.0001, which demonstrates a statistically significant difference in ORR between treatment arms.

Table 10: Objective response rate (ORR)

	Placebo (N=530)	Afibercept (N=531)
CR	2 (0.4%)	0
PR	57 (10.8%)	105 (19.8%)
SD	344 (64.9%)	350 (65.9%)
PD	114 (21.5%)	55 (10.4%)
NE	13 (2.5%)	21 (4.0%)
ORR	11.1%	19.8%
(95% CI)	(8.5, 13.8)	(16.4, 23.2)
p-value	0.0001	

Source: Created by Reviewer

3.3 Evaluation of Safety

Please refer to the Clinical Review of this application for the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Figure 5 and 6 present the forest plots of OS analyses by demographics and baseline characteristics subgroups, respectively. All subgroup analyses are generally consistent and support the primary OS analysis.

Figure 5: OS analyses by demographic subgroups

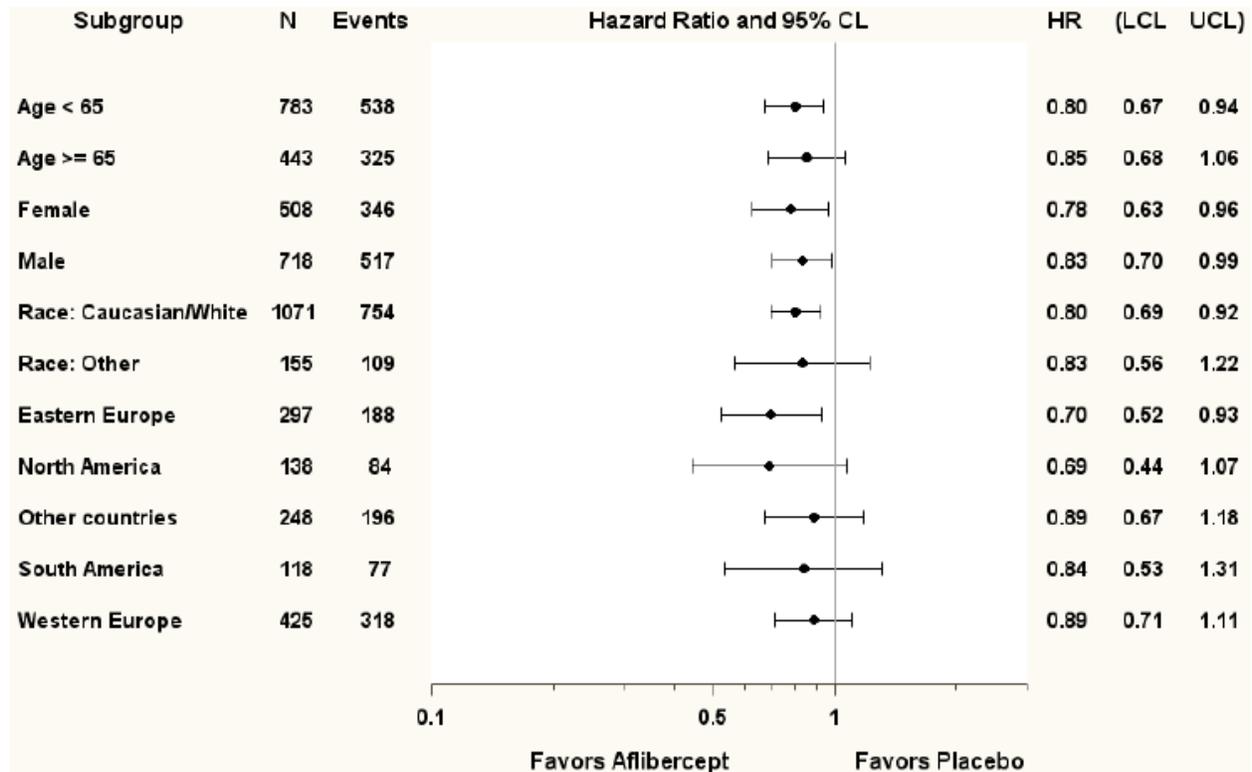


Table 11: Summary of key efficacy results

	Placebo (N=614)	Aflibercept (N=612)
OS		
# of events	460	403
Median (in mos.)	12.1	13.5
Stratified HR (95% CI)	0.816 (0.713, 0.934)	
p-value	0.0032	
PFS		
# of events	454	
Median (in mos.)	4.7	
Stratified HR (95% CI)	0.756 (0.660, 0.876)	
p-value	0.00007	
ORR		
	(N=530)	(N=531)
ORR	11.1%	19.8%
(95% CI)	(8.5, 13.8)	(16.4, 23.2)
p-value	0.0001	

Source: Created by reviewer

Major Statistical Issues

There were no major statistical issues with this application. The following is a list of statistical concerns that were evaluated and resolved by the reviewer:

- There were some discrepancies in stratification by IVRS (interactive voice response system) versus CRF (case report form). Thus, a sensitivity analysis using the CRF stratification was conducted. The results were similar to the primary analysis using IVRS stratification.
- Some evidence of non-compliance at the Australian site (036007) was found during the Sanofi New Jersey inspection. There were issues with protocol compliance, dosing, etc. A sensitivity OS analysis excluding the 23 patients from site 036007 was performed. The results were similar to the primary analysis.

5.2 Conclusions and Recommendations

The results of the study (VELOUR) demonstrated that patients treated with aflibercept plus FOLFIRI had longer median OS than those treated with placebo plus FOLFIRI. Whether the results provide an overall favorable benefit to risk ratio will be determined by the clinical team.

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/s/

JING J ZHANG
07/05/2012

KUN HE
07/05/2012

RAJESHWARI SRIDHARA
07/10/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125-418

Applicant: Sanofi-Aventis

Stamp Date: Feb 3, 2012

Drug Name: Afibercept

NDA/BLA Type: Priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: BLA125418 Filing - Statistics

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/s/

JING J ZHANG
03/28/2012

KUN HE
03/28/2012