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APPLICATION NUMBER:

125418Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	STN 125418
Priority or Standard	Priority
Submit Date(s)	February 3, 2012
Received Date(s)	February 3, 2012
PDUFA Goal Date	August 2, 2012
Division / Office	DOP2/OHOP
Reviewer Name(s)	Sandra J. Casak
Review Completion Date	July 3, 2012
Established Name	Aflibercept / AVE0005
(Proposed) Trade Name	Zaltrap
Therapeutic Class	Recombinant fusion protein
Applicant	Sanofi-aventis
Formulation(s)	(1) 100 mg / 4 mL in a 5 mL vial (2) 200 mg / 8 mL in a 10 mL vial
Dosing Regimen	4 mg/kg IV every 2 weeks.
Indication(s)	Aflibercept is indicated in combination a FOLFIRI chemotherapy regimen for patients with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.
Intended Population(s)	Previously treated patients with metastatic colorectal cancer.

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ..	19
1.4	Recommendations for Postmarket Requirements and Commitments	19
2	INTRODUCTION AND REGULATORY BACKGROUND	19
2.1	Product Information	19
2.2	Tables of Currently Available Treatments for Proposed Indications	20
2.3	Availability of Proposed Active Ingredient in the United States	23
2.4	Important Safety Issues With Consideration to Related Drugs.....	23
2.5	Summary of Presubmission Regulatory Activity Related to Submission	30
2.6	Other Relevant Background Information	32
2.6.3	Aflibercept development	38
3	ETHICS AND GOOD CLINICAL PRACTICES.....	39
3.1	Submission Quality and Integrity	39
3.2	Compliance with Good Clinical Practices	40
3.3	Financial Disclosures.....	41
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	42
4.1	Chemistry Manufacturing and Controls	42
4.2	Clinical Microbiology.....	43
4.3	Preclinical Pharmacology/Toxicology	43
4.4	Clinical Pharmacology	44
4.4.1	Mechanism of Action.....	45
4.4.2	Pharmacodynamics.....	45
4.4.3	Pharmacokinetics.....	46
5	SOURCES OF CLINICAL DATA.....	46
5.1	Tables of Studies/Clinical Trials	47
5.2	Review Strategy	47
5.3	Discussion of Individual Studies/Clinical Trials.....	47
6	REVIEW OF EFFICACY	57
	Efficacy Summary.....	57
6.1	Indication	60
6.1.1	Methods	61
6.1.2	Demographics	61
6.1.3	Subject Disposition.....	68
6.1.3	Protocol Violations.....	69

6.1.4	Analysis of Primary Endpoint(s)	71
6.1.5	Analysis of Secondary Endpoints(s)	76
6.1.6	Other Endpoints	81
6.1.7	Subpopulations	81
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	81
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	81
6.1.10	Additional Efficacy Issues/Analyses	81
7	REVIEW OF SAFETY.....	81
	Safety Summary	81
7.1	Methods.....	86
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	86
7.1.2	Categorization of Adverse Events.....	86
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	87
7.1.3.1	Safety data from EFC10261/VITAL	87
7.1.3.2	Safety data from EFC10547/VANILLA	90
7.1.3.3	Safety data from Phase 1-2 aflibercept single-agent studies	92
7.1.3.4	Sanofi's meta-analysis of the placebo-controlled Phase 3 studies (VELOUR/VITAL/VANILLA)	94
7.1.3.5	Safety data from NCI-sponsored trials and ongoing trials.	Error!
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7.2	Adequacy of Safety Assessments	103
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	103
7.2.2	Explorations for Dose Response.....	107
7.2.3	Special Animal and/or In Vitro Testing	107
7.2.4	Routine Clinical Testing	107
7.2.5	Metabolic, Clearance, and Interaction Workup	107
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	108
7.3	Major Safety Results	108
7.3.1	Deaths.....	112
7.3.2	Nonfatal Serious Adverse Events (SAEs)	114
7.3.3	Dropouts and/or Discontinuations	116
7.3.4	Significant Adverse Events (Non-Fatal Grade 3-4 Adverse Events)	118
7.3.5	Submission Specific Primary Safety Concerns	123
7.3.5.1	Cardiac Dysfunction	124
7.3.5.2	Acute Drug Reactions	126
7.3.5.3	Arterial Thrombotic Events (ATE) and Venous Thromboembolic Events (VTE).....	128
7.3.5.4	Hypertension	130
7.3.5.5	Hemorrhage.....	136
7.3.5.6	Proteinuria, Nephrotic Syndrome, and Renal Impairment.....	137
7.3.5.7	Other VEGF/R Inhibition Related Toxicities	139

7.4	Supportive Safety Results	141
7.4.1	Common Adverse Events	141
7.4.2	Laboratory Findings	144
7.4.3	Vital Signs	149
7.4.4	Electrocardiograms (ECGs)	149
7.4.5	Special Safety Studies/Clinical Trials	150
7.4.6	Immunogenicity	151
7.5	Other Safety Explorations.....	151
7.5.1	Dose Dependency for Adverse Events	152
7.5.2	Time Dependency for Adverse Events.....	152
7.5.3	Drug-Demographic Interactions	154
7.5.4	Drug-Disease Interactions.....	161
7.5.5	Drug-Drug Interactions.....	164
7.6	Additional Safety Evaluations	164
7.6.1	Human Carcinogenicity	164
7.6.2	Human Reproduction and Pregnancy Data.....	164
7.6.3	Pediatrics and Assessment of Effects on Growth	164
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	164
7.7	Additional Submissions / Safety Issues	165
8	POSTMARKET EXPERIENCE.....	166
9	APPENDICES	167
9.1	Literature Review/References	167
9.2	Labeling Recommendations	168
9.3	Advisory Committee Meeting	170
9.4	Additional Tables and Figures	170

Table of Tables

Table 1 - Chemotherapy for metastatic disease	21
Table 2 - NCCN guidelines for the treatment of patients with metastatic colorectal carcinoma.....	22
Table 3 - Hypertension associated with bevacizumab therapy (Chen, 2009).....	24
Table 4 - Incidence and RR of high grade hypertension with bevacizumab among patients with various tumor types (copied from Rampura, 2010)	25
Table 5 - RPLS and anticancer drugs: Empirica search.....	26
Table 6 - Incidence of proteinuria in bevacizumab Phase 2-3 controlled randomized trials.....	27
Table 7 - Estimated new cancer cases and deaths by sex, US 2011.....	34
Table 8 - VELOUR: OS analysis excluding site 036007	41
Table 9 - Financial disclosable interests.....	41
Table 10 - Aflibercept dose modifications for hypertension	51
Table 11 - Aflibercept Dose Modifications for Anti-VEGFR Inhibition-Related AEs	52
Table 12 - Proteinuria management.....	53
Table 13 - FOLFIRI dose reduction levels.....	53
Table 14 - FOLFIRI dose modifications for hematologic toxicity	53
Table 15 - FOLFIRI dose modifications for non-hematologic toxicity	54
Table 16 - VELOUR Amendments	56
Table 17 - VELOUR: Geographic region of precedence.	61
Table 18 - VELOUR: Demographics (ITT population)	62
Table 19 - VELOUR: Disease characteristics at baseline (ITT population)	62
Table 20 - VELOUR: Prior treatments (ITT population).....	63
Table 21 - VELOUR: Prior response to advanced treatment (patients who received treatment only for metastatic/advanced disease)	64
Table 22 - VELOUR: ITT population by stratification factors (IVRS)	64
Table 23 - VELOUR: Stratification errors at randomization and actual composition of the ITT population (by CRF).....	64
Table 24 - VELOUR: Baseline medical/surgical co-morbidities observed in > 5% of patients (by PT, ITT population)	65
Table 25 - VELOUR: Baseline cardiovascular risk factors or thromboembolic events (ITT population).....	66
Table 26 - VELOUR: Baseline non-cancer concomitant medication (in ≥10% of the ITT population)	66
Table 27 - VELOUR: Antihypertensive treatment at baseline.....	67
Table 28 - VELOUR: Anticoagulant treatment at baseline	67
Table 29 - VELOUR: Patient population.....	68
Table 30 - VELOUR: Patients disposition.....	68
Table 31 - VELOUR: Eligibility criteria violations	70
Table 32 - VELOUR: Overall survival analysis	72
Table 33 - VELOUR: Censored patients for IRC PFS assessment	77
Table 34 - VELOUR: FDA PFS analysis	77

Table 35 - VELOUR: PFS discrepancies between IRC and investigator assessments	78
Table 36 – VELOUR: PFS sensitivity analyses	79
Table 37 - VELOUR: Evaluable population for IRC ORR analysis	79
Table 38 - VELOUR: Response rates (IRC assessment)	80
Table 39 - VELOUR: Post-study treatments	80
Table 40- Summary of studies used to evaluate safety	86
Table 41 - VITAL: AEs by SOC (safety population)	88
Table 42 - VITAL: AEs with $\geq 10\%$ incidence by PT (safety population)	89
Table 43 - VANILLA: AEs by SOC (safety population)	90
Table 44 - VANILLA: AEs (PT) with an incidence of $\geq 10\%$ (safety population)	91
Table 45 - Single-agent aflibercept Phase 1-2 studies: AEs by SOC (safety population, 4 mg/kg every 2 weeks cohorts)	92
Table 46 - Single agent aflibercept Phase 1 and 2 studies: AEs (PT) with an incidence of $\geq 5\%$ (safety population)	93
Table 47 - Phase 3 trials: Most frequent AEs in the aflibercept arms (by PT)	94
Table 48 - Phase 3 trials: AEs of special interest	95
Table 49 - Hypertension in Phase 3 placebo-controlled studies, FDA analysis	96
Table 50 – Hemorrhagic events in Phase 3 placebo-controlled studies, FDA analysis	97
Table 51 - Venous thromboembolic events in Phase 3 placebo-controlled trials, FDA analysis	98
Table 52 - VELOUR: Overall exposure (safety population)	103
Table 53 - VELOUR: Aflibercept/placebo exposure	104
Table 54 - VELOUR: Irinotecan exposure	105
Table 55 - VELOUR: 5-FU exposure	105
Table 56 - VELOUR: Exposure by age groups	106
Table 57 - VELOUR: Major safety results summary	108
Table 58 - VELOUR: AEs by SOC	109
Table 59 - VELOUR: AEs by PTs that occurred in $\geq 5\%$ of patients (all Grades)	110
Table 60 - VELOUR: AEs by PTs, Grades 3-4 (incidence $\geq 2\%$)	111
Table 61 - VELOUR: AEs by HLT with an incidence $\geq 10\%$	112
Table 62 - VELOUR: Deaths during treatment and up to 30-days after last study treatment drugs	113
Table 63 - VELOUR: Non-fatal SAEs (by SOC)	115
Table 64 - VELOUR: Non-fatal SAEs with incidences $\geq 2\%$ (by PT)	115
Table 65 - VELOUR: Non-fatal SAEs with incidences $\geq 3\%$ (by HLT)	116
Table 66 - VELOUR: AEs (by SOC) leading to treatment withdrawals	117
Table 67 - VELOUR: More frequent AEs (PT) leading to treatment discontinuation	117
Table 68 - VELOUR: Grade 3-4 non-fatal AEs by SOC	118
Table 69 - VELOUR: Non-fatal Grade 3-4 AEs by PT (incidence $\geq 2\%$)	119
Table 70 - VELOUR: Neutropenia and neutropenic complications (regardless of outcome)	120
Table 71 – VELOUR: Grade 3-4 non-fatal infections by HLT	122
Table 72 - VELOUR: Non-fatal Grade 3-4 AEs (by PTs) in other SOC	123
Table 73 - VELOUR: Cardiac dysfunction list of terms	124

Table 74 - VELOUR: Acute drug reactions by PT, incidence $\geq 1\%$	127
Table 75 - VELOUR: Acute drug reactions by HLT, incidence $\geq 1\%$	127
Table 76 - VELOUR: Arterial thromboembolic events (ATE)	129
Table 77 - VELOUR: Venous thromboembolic events (VTE)	129
Table 78 - VELOUR: SMQs for ATEs and VTEs	130
Table 79 - VELOUR: Hypertension by baseline BP status	132
Table 80 - Hypertension in VELOUR and Bevacizumab-IFL	136
Table 81 - VELOUR: Hemorrhages with incidence $\geq 1\%$ (by PT)	136
Table 82 - VELOUR: Renal function laboratory analysis	138
Table 83 - VELOUR: Grade 1-2 AEs by PT (incidence $\geq 5\%$)	141
Table 84 - VELOUR: Grade 1-2 AEs by HLT (incidence $\geq 10\%$)	142
Table 85 - VELOUR: Grade 1-2 AEs by SOC	143
Table 86 - VELOUR: Hematologic toxicity (lab dataset)	144
Table 87 - VELOUR: WBC shift table	145
Table 88 - VELOUR: ANC shift table	146
Table 89 - VELOUR: Platelets shift table	147
Table 90 - VELOUR: Hepatic function laboratory analysis	147
Table 91 - VELOUR: Summary of Hy's law cases	148
Table 92 - VELOUR: Other lab parameters	149
Table 93 - VELOUR: Patients with AEs per cycle	152
Table 94 - VELOUR: Most frequent AEs ($\geq 5\%$) per cycle, Placebo/FOLFIRI arm	153
Table 95 - VELOUR: Most frequent AEs ($\geq 5\%$) per cycle, Aflibercept/FOLFIRI	153
Table 96 - VELOUR: AEs by SOC by gender (all Grades)	154
Table 97 - VELOUR: GI SOC most common AEs by gender	155
Table 98 - VELOUR: Non-fatal Grade 3-4 AEs (by PT) by gender (incidence $\geq 2\%$) ..	156
Table 99 - VELOUR: AEs by PTs in the geriatric group (incidence $\geq 2\%$)	157
Table 100 - VELOUR: Hematologic toxicity (lab data) by age group	158
Table 101 - VELOUR: AEs by PTs, patients ≥ 75 years old (in at least 3 subjects). ...	159
Table 102 - VELOUR: BMI demographics	159
Table 103 - VELOUR: Grade 3-4 AEs (by PT) by BMI status	160
Table 104 - VELOUR: Grade 3-4 AEs (by HLT) by BMI status	161
Table 105 - VELOUR: AEs (PT) by ECOG PS (incidence $\geq 20\%$)	162
Table 106 - VELOUR: AEs (incidence $\geq 2\%$) by prior bevacizumab exposure	163
Table 107 - Study Flow Chart	170
Table 108 - VELOUR: Sanofi OS analysis excluding site 036007	172
Table 109 - VELOUR: Sanofi PFS analysis excluding site 036007	172
Table 110 - VELOUR: Radiotherapy received before randomization (ITT population) ..	173
Table 111 - VELOUR: Listing of randomized patients with erroneous IVRS "prior bevacizumab" strata	174
Table 112 - VELOUR: Listing of randomized patients with erroneous IVRS "no prior bevacizumab" strata	174
Table 113 - VELOUR: Listing of randomized patients with erroneous IVRS ECOG status strata	175

Table 114 - VELOUR: Medical/Surgical pre-existing conditions (by SOC, ITT population)	175
Table 115 - VELOUR: Concomitant use of non-cancer drugs at baseline (by therapeutic drug class, ITT population)	176
Table 116 - VELOUR: AEs (all Grades) by PT with an incidence of 2-4%	178
Table 117 - VELOUR: Urinalysis abnormalities, safety population (copied from the submission)	180
Table 118 - VELOUR: SMQs	180

Table of Figures

Figure 1 - Aflibercept structure	20
Figure 2 - VEGF Pathway	33
Figure 3 - Study design	48
Figure 4 - VELOUR: OS Kaplan Meier curves	72
Figure 5- VELOUR: OS analysis by stratification factors.....	73
Figure 6 - VELOUR: OS Kaplan Meier plot by prior bevacizumab use.....	74
Figure 7 – VELOUR: OS subgroup analysis by demographic factors	75
Figure 8 - VELOUR: OS subgroup analysis by baseline characteristics	76
Figure 9 - VELOUR: PFS Kaplan Meier analysis	78
Figure 10 - VELOUR: Edema by visit (in absolute number of patients/visit).....	128
Figure 11 - VELOUR: VTEs by Cycle.....	130
Figure 12 - VELOUR: Hypertension by Cycle	131
Figure 13 - VELOUR: Blood pressure means by cycle.....	133
Figure 14 - VELOUR: Systolic blood pressure by cycle by prior hypertensive status (copied from the submission)	134
Figure 15 - VELOUR: Diastolic blood pressure by cycle by prior hypertensive status (copied from the submission)	135
Figure 16 - VELOUR: Proteinuria by Cycle (Cycles 1-10), worst Grade.....	137
Figure 17 - VELOUR: Median hemoglobin (g/dL) Cycles 1-20.....	145
Figure 18 - VELOUR: Median ANC ($10^9/L$) Cycles 1-20	146
Figure 19 - VELOUR: Median platelet count ($10^9/L$) per cycle (Cycles 1-20)	147
Figure 20 - VELOUR: Incidence of subjects (%) with AEs per cycle	152

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for the use of aflibercept in combination with the FOLFIRI regimen for the treatment of patients with metastatic colorectal carcinoma that is resistant to or has progressed after an oxaliplatin-containing regimen.

The Applicant provided data establishing the safety and effectiveness of the product for the proposed indication as described under 21 CFR 314.70 and 21 CFR 601.2.

1.2 Risk Benefit Assessment

Analysis of condition
<p>Summary of evidence</p> <p>Aflibercept is proposed as a treatment for patients with metastatic colorectal carcinoma whose disease progressed after or during first line treatment with an oxaliplatin-based regimen. With the exception of selected patients with oligometastatic disease, metastatic colorectal carcinoma is generally considered incurable and the aim of therapy is to prolong survival and improve quality of life. The standard of care is to administer chemotherapy until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to the quality of life. In the U.S., treatment of metastatic disease is a continuum of care, and once the first line of chemotherapy is no longer useful in preventing the progression of the disease, treatment continues with a different chemotherapy regimen that has not been used before in that particular patient.</p> <p>In the U.S., an estimated 101,340 cases of colon and 39,870 cases of rectal cancer were expected to occur in 2011, with an estimated 49,380 deaths (http://seer.cancer.gov/statfacts/html/colorect.html#incidence-mortality).</p>
<p>Conclusion</p> <p>Metastatic colorectal carcinoma is a progressive disease with a fatal outcome. Median survival after diagnosis of the disease is approximately 22 months.</p>
Unmet medical need
<p>Summary of evidence</p> <p>First-line therapy of advanced or metastatic colorectal carcinoma usually consists of the administration of oxaliplatin or irinotecan in combination with leucovorin and a fluoropyrimidine. In the first or second-line settings, monoclonal antibodies can be added to chemotherapy. Bevacizumab (anti-VEGFR2 monoclonal antibody) is approved in combination with oxaliplatin and irinotecan containing regimens, and cetuximab is approved in combination</p>

with irinotecan in patients who are refractory to irinotecan-containing therapy (in patients who have KRAS wild-type tumors). Once the first line of chemotherapy is not longer useful in preventing the progression of the disease, the treatment continues with a different chemotherapy regimen that has not been used before in that particular patient (i.e., if a patient received an oxaliplatin-based regimen for first line, an irinotecan-based regimen may be used for the second line treatment).

There are no current approved treatments for patients who received bevacizumab in combination with chemotherapy in the first line setting. Bevacizumab has been approved in combination with irinotecan used in the IFL regimen (first-line treatment), a regimen that is not longer used in clinical practice. FOLFIRI is a regimen that delivers 76% more 5-FU, 93% more leucovorin, and 8% more irinotecan than the IFL regimen (weekly dose intensity).

Conclusion

Currently approved therapeutic options are reasonably well tolerated but provide limited efficacy (i.e., bevacizumab in the second-line setting used in combination with oxaliplatin median survival is 13 months compared to 10.8 months in the chemotherapy/placebo arm, HR 0.75 95% CI 0.63; 0.89). No monoclonal antibody targeting the VEGF pathway has been approved specifically in combination with FOLFIRI, a chemotherapy regimen commonly used in the U.S. after progression following an oxaliplatin-containing regimen.

Clinical benefit

Summary of evidence

The efficacy of aflibercept for the treatment of patients with metastatic colorectal carcinoma that has progressed after one line of treatment with an oxaliplatin-based therapy (for advanced/metastatic disease or in the adjuvant setting if progressed during treatment or within 6 months after treatment) was demonstrated in one Phase 3 study, EFC10262, “VELOUR.” VELOUR was a prospective, multicenter, multinational, randomized (1:1), double-blind, parallel-arm study of aflibercept versus placebo in patients with mCRC being treated with FOLFIRI. This type of trial design (“add on”) is common in the practice of oncology, where multiple drugs are used simultaneously in combination regimens, targeting different biological pathways and/or cellular phases. Additionally, monoclonal antibodies targeting the VEGF pathway have not demonstrated efficacy when used alone [with the exception of bevacizumab in glioblastoma (accelerated approval)], but increased the efficacy of the backbone chemotherapy regimen in different settings, including colorectal cancer.

This type of design isolates the effect of the investigational drug and allows for a direct comparison of the efficacy and toxicity between the active control and the investigational arm. The blinded nature of this study also reduced the chances of bias in the conduct and analysis of the trial. The IRC assessment of the images for the secondary endpoints of PFS and response rate were supportive of the primary findings on OS.

In the VELOUR study, treatment consisted of either aflibercept or placebo at 4 mg/kg on Day 1 every 2 weeks in combination FOLFIRI. Patients received treatment until disease progression,

unacceptable toxicity, or patient refusal. Patients were stratified at randomization according to prior therapy with bevacizumab (yes versus no), and ECOG PS (0 versus 1 versus 2).

Between November 19, 2007 and March 16, 2010, 1,226 patients were randomized (614 patients randomized to the placebo arm and 612 patients to the aflibercept arm). Patient demographics were balanced between the two treatment arms. Median age at randomization was 61 years, and 39% and 33% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively were 65 years of age or older. The majority of patients were men (58% and 60% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively). Disease characteristics were similar and well balanced between treatment arms. All patients had a diagnosis of adenocarcinoma. The most frequent primary site was colon (49% in the placebo/FOLFIRI arm and 47% in the aflibercept/FOLFIRI arm). All patients received prior oxaliplatin treatment. Regarding bevacizumab prior treatment, 29% and 28% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively received bevacizumab.

At the time of the data cutoff (February 7, 2011) for the final analysis, the median follow-up time was 22.28 months. The primary analysis was based on a total of 863 deaths: 460 events (75%) reported in the placebo arm and 403 events (66%) reported in the aflibercept arm. One hundred forty nine patients (24%) in the placebo arm and 201 patients (33%) in the aflibercept arm were alive at the cutoff date. Five hundred ninety eight patients (97%) in the placebo arm and 593 patients (97%) in the aflibercept arm had discontinued study treatment. The main reason for treatment discontinuation was disease progression [437 patients (71%) in the placebo arm and 305 patients (50%) in the aflibercept arm]. The analysis of the physician-provided reason for treatment discontinuation showed that 12% of patients in the placebo arm and 27% of patients in the aflibercept arm discontinued treatment because of an adverse event. However, the analysis of the safety database showed that AEs that led to treatment discontinuation (excluding fatal AEs) were more frequent in the aflibercept arm [80 patients (13%) in the placebo arm and 252 patients (41%) in the aflibercept arm]. This discrepancy in the results of the patients randomized to the aflibercept arm was a reflection of the difficulty of attribution in the context of a chemotherapy administered until disease progression. For example, while it was clear that sepsis was an adverse event, the majority of the gastrointestinal events (obstruction, ileus, etc) could not be easily classified as toxicity or as progression of disease.

The protocol was overall well conducted. Protocol violations were minimal and did not have an impact on the integrity of the data.

Survival estimates using the Kaplan Meier method were compared using a log-rank test stratified by factors specified at the time of randomization (ECOG PS, 0 vs. 1 vs. 2; prior bevacizumab, yes vs. no). The addition of aflibercept to the FOLFIRI regimen resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0032 (which met the pre specified efficacy boundary of 0.0466) and an estimated hazard ratio of 0.817 (95.34% CI: 0.713 to 0.937). The use of aflibercept resulted in a reduction in the risk of death of 18.3% when compared to placebo/FOLFIRI. Median overall survival (95.34% CI) in the placebo arm was 12.06 months (11.072 to 13.109), compared to 13.50 months (12.517 to 14.949) in the

aflibercept arm.

To test the interaction of the treatment with the stratification factors, pre-specified subgroup analyses using a Cox proportional hazard model were conducted. There were no significant interactions between treatment arms and stratification factors at a 2-sided 10% level, and a difference in overall survival in favor of aflibercept over placebo was observed in each stratification subgroup, with the exception of the subgroup of patients with ECOG PS of 2 at baseline (12 patients in the placebo arm and 13 patients in the aflibercept arm according to the IVRS form). Because of the small sample size of this stratum, no conclusions can be made. Also, although not statistically significant, patients previously exposed to bevacizumab appeared to benefit less from aflibercept treatment (median OS in the placebo arm 11.7 months vs. 12.5 months in the aflibercept arm; HR 0.86 95% CI 0.67; 1.1).

The final analysis of PFS was performed at the time of the second interim analysis of OS (cut off date 6 May 2010), and was conducted in the ITT population. The analysis was based on a total of 847 events, with 454 events in the placebo arm and 393 events in the aflibercept arm. There was a high rate of discrepancy between the investigator assessments and the IRC assessments (46% on the placebo arm and 39% on the aflibercept arm). Median PFS (IRC assessment, FDA analysis) in the placebo arm was 4.7 months (95% CI 4.074; 5.552), and 6.9 months (95% CI 5.881; 7.852) in the aflibercept arm, with an estimated stratified hazard ratio of 0.756 (95% CI 0.660; 0.876), and a stratified log-rank test p-value $p=0.00007$. PFS analyses of pre-specified subgroups (stratification factors, demographic, and baseline characteristics), and sensitivity analyses did not show evidence of significant interactions between treatment and any of these subgroups (with the exception of liver metastases only, a better prognosis group of patients), supporting a consistent effect of treatment across subgroups.

Response rate (assessed in 530 patients in the placebo arm and 531 patients in the aflibercept arm) was higher in the aflibercept arm: 59 (11%) patients in the placebo arm and 105 patients (20%) in the aflibercept arm were assessed as responders (complete or partial response).

Conclusion

There are no drugs approved for the treatment of mCRC specifically in combination with FOLFIRI and no drugs have been approved for patients with prior bevacizumab treatment in the first-line setting. VELOUR was a well conducted study that showed that the addition of aflibercept to the FOLFIRI regimen resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0032 (which met the pre specified efficacy boundary of 0.0466) and an estimated hazard ratio of 0.817 (95.34% CI: 0.713 to 0.937). The use of aflibercept resulted in a risk of death reduction of 18.3% when compared to placebo/FOLFIRI. Median overall survival (95.34% CI) in the placebo arm was 12.06 months (11.072 to 13.109), compared to 13.50 months (12.517 to 14.949) in the aflibercept arm. This benefit was supported by subgroup and sensitivity analyses, as well as the increased median PFS and response rates observed in the aflibercept arm. Furthermore, patients with prior exposure to bevacizumab appeared to benefit from treatment with aflibercept, although this benefit was of a smaller magnitude than in patients who have not been exposed bevacizumab (median OS for patients

with prior exposure to bevacizumab in the placebo arm 11.7 months vs. 12.5 months in the aflibercept arm; HR 0.86 95% CI 0.67; 1.1).

Risk

Summary of evidence

The main safety analyses were performed on data from VELOUR, the pivotal study for the proposed indication (611 patients exposed to aflibercept). Additionally, datasets from two other Phase 3, double-blind, placebo-controlled trials (VITAL and VANILLA, with 452 and 270 patients exposed to aflibercept respectively), as well as integrated data from 404 patients treated in Phase 1-2 studies were analyzed to evaluate the toxicity profile of aflibercept, both as monotherapy and in combination therapies. Additional data from other Phase 1-2 studies (total of 2,073 patients exposed to aflibercept) as well as data from NCI trials were available for the safety assessment.

Almost all patients in both arms of the VELOUR study experienced adverse events. Grade 3-4 AEs were more frequently observed in the aflibercept arm (84%) than in the placebo arm (63%). This imbalance was also observed in the incidence of SAEs: in the placebo arm, the incidence of SAEs was 33%, and in the aflibercept arm the incidence was 49%. Six patients in the placebo arm and 13 patients in the aflibercept arm had adverse events with a fatal outcome.

At the SOC level, the most frequently affected systems ($\geq 50\%$ incidence) were gastrointestinal (placebo arm 87%, aflibercept arm 94%), general disorders and administration sites (placebo arm 67%, aflibercept arm 76%), vascular disorders (placebo arm 44%, aflibercept arm 72%), respiratory, thoracic, and mediastinal SOC (placebo arm 45%, aflibercept arm 65%), nervous system (placebo arm 47%, aflibercept arm 61%), and skin and subcutaneous tissue disorders (placebo arm 47%, aflibercept arm 51%).

At the preferred term level, the most frequently reported events (incidence $\geq 20\%$) were diarrhea (placebo arm 57%, aflibercept arm 69%), nausea (placebo arm 54%, aflibercept arm 53%), stomatitis (placebo arm 33%, aflibercept arm 50%), fatigue (placebo arm 39%, aflibercept arm 48%), hypertension (placebo arm 11%, aflibercept arm 41%), neutropenia (placebo arm 34%, aflibercept arm 39%), vomiting (placebo and aflibercept arms 33%), decreased appetite (placebo arm 24%, aflibercept arm 32%), decreased weight (placebo arm 14%, aflibercept arm 32%), epistaxis (placebo arm 7%, aflibercept arm 28%), abdominal pain (placebo arm 24%, aflibercept arm 27%), dysphonia (placebo arm 3%, aflibercept arm 25%), constipation (placebo arm 25%, aflibercept arm 22%), and headache (placebo arm 9%, aflibercept arm 22%). With the exception of nausea, vomiting, and constipation, in all these events the incidence in the aflibercept arm was at least 3% higher. A similar pattern of toxicity was also observed in the analyses of Grade 3-4 events.

Regarding adverse events of special interest (VEGF/R inhibition related), these events were observed, as expected, more frequently in patients receiving aflibercept. The incidence of hypertension was 11% in the placebo arm and 41% in the aflibercept arm (Grades 3-4 incidences were 1.5% and 19.3% in the placebo and aflibercept arms, respectively). There was only one

case of Grade 4 hypertension (hypertensive encephalopathy) in the aflibercept arm. Although the incidence of hypertension was the same regardless of a prior history of hypertension, patients with prior hypertension had an increased incidence of Grade 3 hypertension. This can partly be explained by the use of the toxicity grading system (NCI CTCAE v3.0), whereas the addition of one more antihypertensive drug for blood pressure management qualified an increased blood pressure as Grade 3. More than half of patients with hypertension were diagnosed within the first 2 cycles.

Proteinuria was observed in 41% of patients in the placebo arm and 62% of patients in the aflibercept arm. However, more than a third of these patients had concomitant hematuria and in most cases, these Grade 1-2 events were diagnosed by urine dipstick. A more reliable assessment of clinically significant nephropathy was derived from the assessment of Grade 3-4 proteinuria, observed in 1% of patients in the placebo arm and 8% of patients in the aflibercept arm. There were two events of nephrotic syndrome in the aflibercept arm. Microangiopathic anemia was observed in one patient (two additional patients reported in the NCI trials).

Arterial thrombotic events were observed in 1.65% and 2.6% of patients in the placebo and aflibercept arms, respectively. Most of these events were of cardiac origin (myocardial ischemia/infarct, unstable angina, etc). Two patients in the aflibercept arm experienced cardiac dysfunction. Venous thromboembolic events were also observed more frequently in the aflibercept arm: 7% patients in the placebo arm and 9% patients in the aflibercept arm experienced a VTE, mostly pulmonary embolism (3% vs. 5% in the placebo and aflibercept arms, respectively).

Hemorrhage was increased in the aflibercept arm; 38% of patients experienced a Grade 1-4 hemorrhage, compared to 19% of patients in the placebo arm. Most events were Grades 1-2, and epistaxis was the most common site of bleeding (7% vs. 28% in the placebo and aflibercept arms, respectively). There were instances of fatal hemorrhages in the aflibercept arm.

In the placebo arm, fistula was reported in 3 patients (0.5%); in the aflibercept arm, fistula was reported in 9 patients. Five patients in the placebo arm and three patients in the aflibercept arm experienced wound healing issues. Although more frequent, events in the placebo arm appeared to be mild (all were Grade 1), while the severity of the events in the aflibercept arm was more pronounced (Grades 2-3) and led to cycle delay or discontinuation of study treatment.

Three patients per arm experienced gastrointestinal perforation (one fatal event in the aflibercept arm).

The addition of aflibercept to FOLFIRI caused an increased incidence of leukopenia, neutropenia, and thrombocytopenia. The incidence of Grade 3-4 leukopenia was 12% in the placebo arm and 16% in the aflibercept arm. Grade 3-4 neutropenia was 30% in the placebo arm and 36% in the aflibercept arm. The incidence of Grade 3-4 thrombocytopenia was 2% in the placebo arm and 3% in the aflibercept arm. No other laboratory abnormalities were increased with the use of aflibercept.

Subgroup analyses (age, gender, prior exposure to bevacizumab, ECOG PS status, and BMI category) did not show any significant differences in toxicity in these groups.

In summary, the addition of aflibercept to the FOLFIRI regimen in the VELOUR study increased the FOLFIRI-related toxicity, with the addition of VEGF/R inhibition-related toxicity. Patients in the aflibercept arm received a median of one more cycle of therapy than patients in the placebo arm, although dose intensity of all drugs was slightly reduced. More patients in the aflibercept arm experienced adverse events, toxicity-related deaths, dose modifications, and treatment-related withdrawals. However, the safety profile of aflibercept was within the known safety profile of bevacizumab, with the possible exception of hypertension and proteinuria, which appeared to be more frequent with aflibercept. However, any differences may be explained by differences in monitoring across trials and no comparative safety claims can thus be made.

The integrated safety database contained data from 2,073 aflibercept-treated patients. In the Phase 1 and 2 studies investigating aflibercept 4 mg/kg every other week as single therapy (n=258 patients), the most frequently reported (HLT) AE was asthenic conditions (asthenia and fatigue) in 46% of patients (12% Grades 3-4), followed by hypertension in 32% of patients (15% Grades 3-4). Nausea and vomiting were also frequent (29% and 28% respectively). AEs related to class-effects such as dysphonia, epistaxis, and proteinuria were observed in 26%, 10%, and 12% of patients respectively.

EFC10547/VANILLA was a Phase 3 study in patients with metastatic or locally advanced, unresectable pancreatic cancer. Aflibercept was administered at the dose and schedule of 4 mg/kg IV every other week in combination with gemcitabine. The study was prematurely discontinued for futility at the time of the interim analysis. The incidence rate of Grade 3-4 AEs (79% in the aflibercept arm and 67% in the placebo arm), SAEs (55% vs. 45%), and discontinuation of therapy due to AEs (28% vs. 12%) was higher in the aflibercept arm. The AEs (PT/HLT/SOC) that occurred most frequently in the aflibercept arm were asthenic conditions, nausea, hypertension, gastrointestinal and abdominal pains, vomiting, weight decrease, decreased appetite, infection, constipation, pyrexia, and dysphonia. At the PT level, the most important differences ($\geq 10\%$ between arms, difference in parentheses), were in the incidence rates of hypertension (30%, Grades 3-4 12%), weight decrease (14%, Grades 3-4 1%), epistaxis (12%, Grades 3-4 1%), headache (12%, no differences in the incidence of Grades 3-4), stomatitis (10%, Grades 3-4 1%), and proteinuria (9%, Grades 3-4 3%). The AEs that occurred most frequently in the aflibercept arm were similar to those of the VELOUR study: asthenic conditions, nausea, hypertension, gastrointestinal and abdominal pains, vomiting, weight decrease, decreased appetite, infection, alopecia, constipation, pyrexia, and dysphonia.

EFC10261/VITAL was a Phase 3 study in NSCLC. Aflibercept was administered at the dose and schedule of 6 mg/kg IV every 3 weeks in combination with docetaxel. Upon final analysis, the study failed to show an improvement in overall survival in the aflibercept arm (HR=1.01, CI: 0.868 to 1.174). The incidence of Grade 3-4 AEs, SAEs, and discontinuations due to AEs was

higher in the aflibercept arm. At the PT level, the most important differences ($\geq 10\%$ between arms, differences in parentheses) were in the incidence rates of stomatitis (27%, Grades 3-4 8%), hypertension (16%, Grades 3-4 6%), weight decrease (14%, Grades 3-4 2%), epistaxis (14%, Grades 3-4 2%), and dysphonia (14%, no Grades 3-4 observed). The AEs that occurred most frequently in the aflibercept arm were hypertension, weight decrease, decreased appetite, dysphonia, and epistaxis. All VEGF/R inhibition-related AEs were increased in the aflibercept arm. The incidence and pattern of AEs observed in the aflibercept arm of the VITAL trial was consistent with the toxicity observed in the pivotal study, VELOUR.

Reversible posterior leukoencephalopathy (RPLS) is an identified risk for patients administered anti-cancer treatment including cytotoxic drugs and targeted VEGF/R inhibitors (small molecule TKIs and bevacizumab). No cases of RPLS were diagnosed in the VELOUR study. In monotherapy and combination studies (including NCI sponsored studies), seventeen patients exposed to aflibercept experienced RPLS (one fatal event). The overall incidence of RPLS in the aflibercept development is was 0.44% (17/3795), an incidence comparable to that of bevacizumab.

In summary, the supportive data from Phase 1-2 and randomized controlled Phase 3 studies is consistent with the safety data from the pivotal study, VELOUR.

The safety database was adequate and allowed for the characterization of the toxicity profile of aflibercept.

Considering the clinical experience gained in the oncology community with the use of bevacizumab, it does not appear that the use of aflibercept will differ markedly from the conditions of use and monitoring followed in the VELOUR clinical study. Aflibercept has been studied in lung, pancreas, and prostate cancers, and these studies failed to prove aflibercept efficacy in these diseases.

Conclusion

The analysis of the database shows that aflibercept toxicity is within the range (both in the type of events and the incidence rates) of bevacizumab, the only other VEGFR2 biologic inhibitor approved. Although the incidence rates of hypertension and proteinuria were higher than with bevacizumab, these differences may be a reflection of differences in monitoring as these toxicities are better understood. There were no new or unexpected safety signals when compared with bevacizumab.

Risk management

The risks of aflibercept use in the treatment of metastatic colorectal carcinoma whose disease had progressed after a first-line treatment with an oxaliplatin-containing regimen will be managed through product labeling. The risks are also managed in that this drug will be administered by oncologists who have specific training in the administration of anti-neoplastic drugs and in the management of toxicities related to these drugs.

Benefit-risk summary and assessment

Relapsed or refractory metastatic colorectal cancer is in most cases an incurable disease and the

standard of care is treatment with successive drugs until progression or death. Metastatic colorectal carcinoma is a progressive disease with a fatal outcome. Median survival after diagnosis of the disease is approximately 22 months. The standard of care is to administer chemotherapy until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to quality of life. In the U.S., treatment of metastatic disease is a continuum of care, and once the first line of chemotherapy is no longer useful in preventing the progression of the disease, treatment generally continues with a different chemotherapy regimen that has not been used before in that particular patient.

Currently approved therapeutic options are reasonably well tolerated but provide limited efficacy. No monoclonal antibody targeting the VEGF pathway has been approved specifically in combination with FOLFIRI, a chemotherapy regimen commonly used in clinical practice in the U.S. after progression following an oxaliplatin-containing regimen.

The efficacy and safety of aflibercept was studied in a Phase 3 trial, VELOUR. VELOUR was a prospective, multicenter, multinational, randomized (1:1), double-blind, parallel-arm study of aflibercept versus placebo in patients with mCRC being treated with FOLFIRI. VELOUR was a well conducted study that randomized 1,226 patients (30% of these patients had received prior bevacizumab therapy) that showed that the addition of aflibercept to the FOLFIRI regimen resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0032 (which met the pre specified efficacy boundary of 0.0466) and an estimated hazard ratio of 0.817 (95.34% CI: 0.713 to 0.937). The use of aflibercept resulted in a risk of death reduction of 18.3% when compared to placebo/FOLFIRI. Median overall survival (95.34% CI) in the placebo arm was 12.06 months (11.072 to 13.109), compared to 13.50 months (12.517 to 14.949) in the aflibercept arm. This benefit is supported by subgroup and sensitivity analyses, as well as the increased median PFS and response rates observed in the aflibercept arm. Furthermore, patients with prior exposure to bevacizumab appear to benefit from treatment with aflibercept, although this benefit is of smaller magnitude than in patients who have not been exposed to bevacizumab (median OS for patients with prior exposure to bevacizumab in the placebo arm 11.7 months vs. 12.5 months in the aflibercept arm; HR 0.86 95% CI 0.67; 1.1).

The analysis of the database (3795 patients from three Phase 3 studies, monotherapy, and Phase 2 studies) shows that aflibercept toxicity is within the range (both in the type of events and the incidence rates) of bevacizumab, the only other VEGFR2 biologic inhibitor approved. There were no new or unexpected safety signals when compared with bevacizumab.

In summary, the approval is recommended based on a prolongation of overall survival with an acceptable toxicity profile (toxicity in this setting refers to the additional toxicity of aflibercept when added to the FOLFIRI regimen), for which the oncology community has experience in its management. The study effects were supported by secondary endpoints including PFS and ORR.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Sanofi will be required to provide progress reports as described in 21 CFR 600.80.

1.4 Recommendations for Postmarket Requirements and Commitments

A post marketing commitment (PMC) is proposed to obtain the data of study NCT0062241, a Phase 1 study of aflibercept in children with refractory solid tumors. This study was conducted under the NCI aflibercept IND 100137 by the Children's Oncology Group (protocol COG-ADVL0714) and it is complete. The purpose of this PMC is to analyze this data to include it in the pediatric section of the Zaltrap label.

2 Introduction and Regulatory Background

The Applicant seeks approval for the following indication: "Aflibercept is indicated in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen".

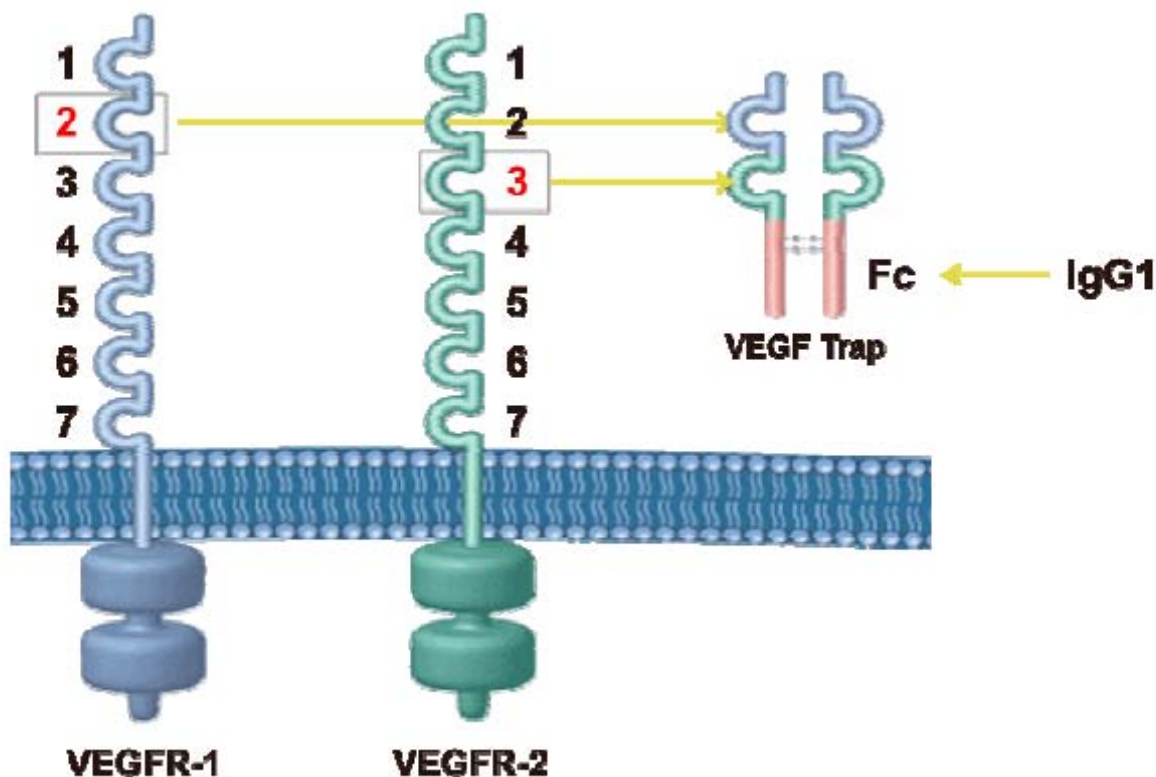
The application was submitted on February 2, 2012 and the PDUFA goal date is August 2, 2012. This review will describe the efficacy and safety data supporting approval and the recommendation of the clinical reviewer.

2.1 Product Information

Aflibercept (AVE0005), vascular endothelial growth factor (VEGF) trap, is a recombinant fusion protein, consisting of the extracellular domains of human VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2) fused to the Fc portion of a human IgG1.

Aflibercept is a dimeric glycoprotein with a molecular weight of 115 kDa. Aflibercept is manufactured recombinantly in Chinese hamster ovary cells. Figure 1 (copied from the application) shows the aflibercept structure.

Figure 1 - Aflibercept structure



The interaction of VEGF with receptors 1 and 2 can lead to endothelial cell proliferation and new blood vessel formation. VEGFR inhibition may prevent new tumor vessel growth, modulates regression of existing tumor vessels, and alters tumor cell function.

2.2 Tables of Currently Available Treatments for Proposed Indications

First-line therapy of advanced or metastatic colorectal carcinoma (CRC) usually consists of the administration of oxaliplatin or irinotecan in combination with leucovorin and fluorouracil. In the first or second-line settings, monoclonal antibodies can be added to chemotherapy. Bevacizumab (anti-VEGFR2 monoclonal antibody) is approved in combination with oxaliplatin and irinotecan containing regimens, and cetuximab is approved in combination with irinotecan in patients who are refractory to irinotecan-containing therapy (in patients who have KRAS wild-type tumors). Table 1 summarizes the most frequently used and recommended regimens for the treatment of metastatic colorectal carcinoma.

Table 1 - Chemotherapy for metastatic disease

	Dosing and schedule
Oxaliplatin-containing regimens	
FOLFOX ± bevacizumab	(mFOLFOX6) Each cycle is 2 weeks; repeat until progression: Oxaliplatin 85 mg/m ² IV over 2 hours, Day 1 Leucovorin 400 mg/m ² IV over 2 hours, Day 1 5-FU 400 mg/m ² bolus IV on Day 1, then 1200 mg/m ² day x 2 days (total 2400 mg/m ² IV over 46-48 hours) continuous infusion ± Bevacizumab 5 mg/kg
CapeOx ± bevacizumab	Each cycle is 3 weeks; repeat until progression: Oxaliplatin 130 mg/m ² IV Day 1 Capecitabine 850-1000 mg/m ² twice daily for 14 days ± Bevacizumab 7.5 mg/kg every three weeks
Irinotecan-containing regimens	
FOLFIRI ± bevacizumab	Each cycle is 2 weeks; repeat until progression: Irinotecan 180 mg/m ² IV over 30-90 minutes, Day 1 Leucovorin 400 mg/m ² IV over 2 hours, Day 1 5-FU 400 mg/m ² bolus IV on Day 1, then 1200 mg/m ² day x 2 days (total 2400 mg/m ² IV over 46-48 hours) continuous infusion ± Bevacizumab 5 mg/kg
Oxaliplatin and irinotecan-containing regimens	
IROX	Each cycle is 3 weeks; repeat until progression: Oxaliplatin 85 mg/m ² IV over 2 hours on Day 1 Irinotecan 200 mg/m ² IV over 30-90 minutes on Day 1
FOLFOXIRI	Each cycle is 2 weeks; repeat until progression: Irinotecan 165 mg/m ² IV over 30-90 minutes, Day 1 Oxaliplatin 85 mg/m ² IV over 2 hours, Day 1 Leucovorin 400 mg/m ² IV over 2 hours, Day 1 5-FU 3200 mg/m ² continuous infusion over 48 hours
Less-intensive regimens	
5-FU/leucovorin ± bevacizumab	Roswell-Park regimen (8 weeks cycle) Leucovorin 500 mg/m ² IV over 2 hours, Days 1, 8, 15, 22, 29, & 36 5-FU 500 mg/m ² bolus IV on Day 1, 8, 15, 22, 29, & 36. sLV5-FU2 (2 weeks cycle) Leucovorin 400 mg/m ² IV over 2 hours, Day 1 5-FU 400 mg/m ² bolus IV on Day 1, then 1200 mg/m ² day x 2 days (total 2400 mg/m ² IV over 46-48 hours) continuous infusion Weekly bolus 5FU/LV Leucovorin 20 mg/m ² IV over 2 hours, Day 1 5-FU 500 mg/m ² bolus IV on Day 1. Weekly infusional 5FU/LV Leucovorin 500 mg/m ² IV over 2 hours, Day 1 5-FU 400 mg/m ² bolus IV on Day 1, then 2600 mg/m ² day 24 hrs continuous infusion. ± Bevacizumab 5 mg/kg every 2 weeks
Capecitabine ± bevacizumab	Each cycle is 3 weeks, repeat until progression: Capecitabine 2000-2500 mg/m ² twice daily for 14 days, followed by 7 day rest.

	± Bevacizumab 7.5 mg/kg every 3 weeks
For patients with EGFR+ Kras WT only	
FOLFOX ± cetuximab or panitumumab	
FOLFIRI ± cetuximab or panitumumab	
Single-agent regimens	
	Irinotecan 125 mg/m ² IV over 30-90 minutes, Day 1, 8 (3-week cycles).
	Irinotecan 300-350 mg/m ² IV over 30-90 minutes, Day 1 (3-week cycles).
	Irinotecan 180 mg/m ² IV over 30-90 minutes, Day 1 (2-week cycles).
	Cetuximab (EGFR+ Kras WT only): 400 mg/m ² IV 1 st infusion, then 250 mg/m ² IV weekly.
	Cetuximab (EGFR+ Kras WT only): 500 mg/m ² IV every 2 weeks
	Panitumumab (EGFR+ Kras WT only): 6 mg/kg IV every 2 weeks

With the exception of metastatic disease confined to the liver and completely resected, metastatic colorectal carcinoma is generally considered incurable and the aim of therapy is to prolong survival and improve quality of life. The standard of care is to administer chemotherapy in first line until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to the patient's quality of life. As seen in Table 2 (modified from the 2011 NCCN guidelines), treatment of metastatic disease is a continuum of care, and once the first line of chemotherapy is not longer useful in preventing the progression of the disease, the treatment continues with a different chemotherapy regimen that has not been used before in that particular patient (i.e., if a patient received an oxaliplatin-based regimen for first line, an irinotecan-based regimen may be used for the second line treatment).

Table 2 - NCCN guidelines for the treatment of patients with metastatic colorectal carcinoma

Initial therapy	Therapy after progression	Therapy after 2 nd progression
Subjects who are able to tolerate intensive chemotherapy		
FOLFOX or CapeOX ± bevacizumab ± cetuximab or panitumumab (only if KRAS WT)	FOLFIRI or irinotecan ± cetuximab or panitumumab (only if KRAS WT)	- Single agent cetuximab or panitumumab (only if KRAS WT and was not given before) ± irinotecan. - Clinical trial - Best supportive care.
FOLFIRI ± bevacizumab ± cetuximab or panitumumab (only if KRAS WT)	FOLFOX or CapeOX	- Single agent cetuximab or panitumumab (only if KRAS WT) ± Irinotecan. - Clinical trial - Best supportive care.
	If not able to tolerate combination, irinotecan ± cetuximab or panitumumab (only if KRAS WT), or single agent cetuximab or panitumumab (only if KRAS WT).	FOLFOX or CapeOx
5FU/LA ± bevacizumab	FOLFOX or CapeOX	Irinotecan
	FOLFIRI	Single agent cetuximab or

Capecitabine ± bevacizumab	Irinotecan ± oxaliplatin	panitumumab (only if KRAS WT) ± Irinotecan.
FOLFOXIRI	Single agent cetuximab or panitumumab (only if KRAS WT) ± Irinotecan.	
Subjects who are NOT able to tolerate intensive chemotherapy		
5FU/LA ± bevacizumab	If improvement in functional status, consider any of the first-line regimens.	
cetuximab or panitumumab (only if KRAS WT)	If the functional status did not improve, best supportive care.	

*Inclusion of these Guidelines in this review does not necessarily equate to agreement by this reviewer or the Agency

2.3 Availability of Proposed Active Ingredient in the United States

Aflibercept is a new molecular entity (NME), available only for investigational use under INDs 9948 and 100137 (sponsored by the National Cancer Institute, NCI).

2.4 Important Safety Issues With Consideration to Related Drugs

Interference with the VEGF pathway induces a characteristic pattern of toxicity observed in all approved and experimental drugs targeting this pathway. Hypertension, gastrointestinal toxicity, proteinuria, thromboembolic events, hemorrhage, reversible posterior leukoencephalopathy (RPLS) and wound healing are consistently observed across clinical trials and in the postmarketing setting following the administration of both biologic and small molecules anti-VEGF and anti-VEGFR agents (approved and investigational). The spectrum of adverse events in individual patients and different disease settings is variable and may reflect several factors: dose of the VEGF inhibitor, specificity of the inhibition of the pathway, disease factors, co-morbidities, co-targeting of other pathways, and use of concomitant chemotherapy treatment.

This section of the review will focus on the safety issues observed primarily with bevacizumab, the biologic drug that directly targets VEGF, with no direct actions on tyrosine kinases involved in the VEGF pathway. The black box warning in the Avastin label describes gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. In addition to these adverse reactions, the Warnings and Precautions section describes non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and infusion reactions.

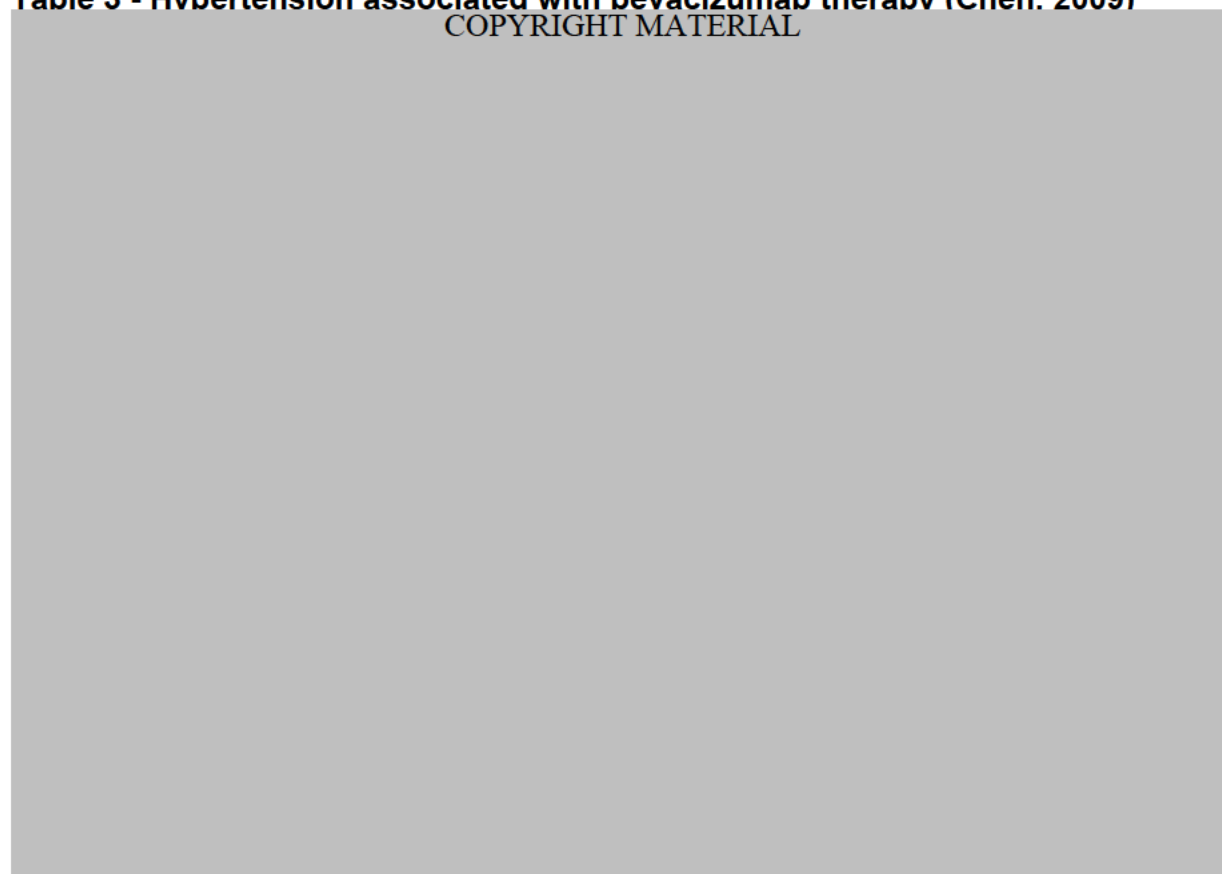
VEGFR-2 signaling generates nitric oxide and prostaglandin I₂, which induces vasodilatation in arterioles and venules, the component of vasculature that has the most impact on blood pressure. Blockage of VEGF leads to vasoconstriction. Vascular rarefaction, a phenomenon observed in patients with hypertension, has also been postulated as a mechanism for **hypertension** in patients receiving VEGF inhibitors.

As described in Dr. Chen's and Dr. Cleck's comprehensive review of adverse events related to inhibition of the VEGF pathway (Chen H., 2009), the effect of anti-VEGF agents on blood

pressure is dose-dependent. In a Phase 2 study in patients with renal-cell carcinoma (RCC) treated with placebo 3 mg/kg bevacizumab or 10 mg/kg bevacizumab, the rate of hypertension was significantly higher in the high-dose group (36%) compared with the low dose group (3%). This dose dependency has also been observed with small-molecule VEGF TKIs. Patients with pre-existing hypertension are generally more likely to develop further elevation in blood pressure when receiving anti-VEGF therapy.

The risk of hypertension may be also related to indication. As shown below (Table 3, copied from Dr. Chen's paper), the incidence of hypertension in patients with RCC is higher than in other indications.

Table 3 - Hypertension associated with bevacizumab therapy (Chen, 2009)
COPYRIGHT MATERIAL



In a recent meta-analysis (Rampura, 2010) of 20 randomized controlled trials that included 12,526 patients, bevacizumab was associated with a significantly increased risk of high-grade hypertension, with an incidence of 7.9% (95% CI: 6.1–10.2) and a RR of 5.28 (95% CI: 4.15–6.71). The risk of high-grade hypertension associated with bevacizumab significantly increased in patients with renal cell carcinoma (RR: 8.99, 95% CI: 2.72–29.72), non-small cell lung cancer (RR: 7.06; 95% CI: 3.66–13.62), pancreatic cancer (RR: 5.52; 95% CI: 2.12–14.35), and colorectal cancer (RR: 5.24, 95% CI: 3.89–7.05). Table 4 summarizes the results of this meta-analysis.

Table 4 - Incidence and RR of high grade hypertension with bevacizumab among patients with various tumor types (copied from Rampura, 2010)

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In most cases, hypertension can be controlled with oral hypertensive agents. However, a patient may develop uncontrolled hypertension, hypertensive crisis, or RPLS with life-threatening complications. Extensive guidelines for hypertension management were provided in the aflibercept clinical trials (Table 10) submitted in this application.

Reversible posterior leukoencephalopathy syndrome (RPLS) is severe condition that since the original description by Hinchey in 1996, has been associated with hypertensive encephalopathy, pre-eclampsia, eclampsia, LES, vasculitis, tumor lysis syndrome, infection, sepsis, shock, and exposure to cytotoxic agents (particularly platinum compounds), bevacizumab, other anti-VEGF/R inhibitory molecules, and biologic or immunosuppressive agents.

Clinically, RPLS causes a variety of acute to subacute neurologic symptoms that include headache, nausea, vomiting, altered mental status, seizures, stupor, and visual disturbances (from blurred vision to cortical blindness).

Radiological findings of RPLS include vasogenic edema that primarily affects the white matter and generally involves the bilateral parietal-occipital lobes and occasionally the basal ganglia, brainstem, or cerebellum; the edema may be asymmetrical. MRI with diffusion weighted imaging is the preferred diagnostic test. Vasogenic edema is best seen on T2 weighted images using fluid-attenuated inversion recovery (FLAIR) sequencing.

Any disorder that causes hypertension can lead to RPLS. Prior history of hypertension may provide a degree of protection. At any given increased blood pressure, preexisting chronic

hypertension may lower the probability of RPLS because of adaptive vascular changes as opposed to patients who develop new onset acute hypertension (Mukherjee P., 2001). Controversy exists over the RPLS mechanism. The initial Hinchey hypothesis of hypertension leading to failed auto regulation followed by capillary permeability damage cannot explain the approximately 20%-40% of RPLS cases with no documented hypertension. A more complex mechanism may exist involving direct endothelial damage/dysfunction; for some drugs associated with RPLS, like cyclosporine and tacrolimus, there is some evidence that they can cause perturbation the blood-brain barrier. Cyclosporin also has been reported to have direct toxic effects on vascular endothelial cells.

Empirica was searched to evaluate the EB05 scores for drugs used for the treatment of cancer and cases of RPLS in the AERS database (search from 4/17/2012). Table 5 summarizes this search.

Table 5 - RPLS and anticancer drugs: Empirica search

Drug	N	EBGM	EB05	EB95	PRR	RR	E
Gemcitabine	58	20.1	16.1	24.8	16	20.5	2.83
Bevacizumab	114	17.1	14.6	19.9	29.6	17.2	6.62
Asparaginase	75	16.8	13.8	20.2	118.5	17	4.41
Oxaliplatin	44	15.8	12.1	20.2	19.9	16.3	2.71
Vincristine	136	13	11.2	15	44.7	13.2	10.3
Folinic Acid	26	15.6	10.5	21.7	14	16.5	1.57
Cisplatin	67	11.9	9.44	14.8	15.1	12.4	5.4
Fluorouracil	36	10.4	7.23	14.5	8.42	11.8	3.06
Doxorubicin	83	8.81	7.22	10.7	18.8	9.52	8.72
Daunorubicin	32	10.1	6.85	14.5	43.7	11.8	2.72
Methotrexate	112	7.26	6.19	8.49	22.4	7.73	14.5
Cytarabine	58	7.65	6.07	9.63	24.1	8.64	6.72
Prednisolone	60	7.2	5.76	8.97	21.2	8.1	7.41
Rituximab	55	7.1	5.62	8.93	14.6	8.06	6.82
Cyclophosphamide	88	6.36	5.32	7.57	16.1	6.85	12.8
Bortezomib	21	5.27	3.63	7.49	10.4	7	3
Etoposide	38	4.56	3.47	5.91	13.7	5.18	7.33
Carboplatin	28	4.71	3.42	6.36	7.35	5.66	4.95
Basiliximab	9	6.76	3.28	17.2	40.3	14.2	0.632
Sunitinib	19	4.33	2.94	6.21	8.05	5.59	3.4
Pazopanib	8	6.13	2.93	16.6	21.8	14.4	0.557
Bleomycin	10	4.57	2.65	7.61	15	8.2	1.22
Busulfan	16	3.86	2.53	5.69	24.6	5.05	3.17
Fludarabine	16	3.75	2.46	5.53	10.2	4.86	3.29
Irinotecan	12	3.95	2.42	6.17	6.26	5.82	2.06
Idarubicin	7	4.38	2.26	8.36	19.8	10.5	0.664
Vinblastine	7	4.28	2.21	8.01	14.4	10.1	0.694
Paclitaxel	17	3.16	2.1	4.61	3.08	3.85	4.42

RPLS is described in the adverse reactions sections of the VEGF/R inhibitor drugs bevacizumab, axitinib, and sunitinib labels. In all drugs, the observed incidence was less than 1%. Note that Empirica is a data-mining tool and that scores alone should not be used to imply causality between a drug and an adverse event. For example, the scores do not necessarily account for concomitant use of other drugs [for example, a higher score for oxaliplatin may occur because it is administered with bevacizumab (a drug known to cause RPLS)].

Scappaticci et al. (Scappaticci, 2007) performed a meta-analysis the increased risk for thromboembolic events in patients receiving bevacizumab in clinical trials. Data were pooled from five randomized controlled trials that included a total of 1745 patients with metastatic colorectal, breast, or non-small-cell lung carcinoma. Combined treatment with bevacizumab and chemotherapy, compared with chemotherapy alone, was associated with an increased risk of arterial thromboembolic events (HR = 2.0, 95% confidence interval [CI] = 1.05 to 3.75; p = .031) but not for a venous thromboembolic event (HR = 0.89, 95% CI = 0.66 to 1.20; p = .44). The absolute rate of developing an arterial thromboembolism was 5.5 events per 100 person-years for those receiving combination therapy and 3.1 events per 100 person-years for those receiving chemotherapy alone (ratio = 1.8, 95% CI = 0.94 to 3.33; p = .076). Development of an arterial thromboembolic event was associated with a prior arterial thromboembolic event (p<0.001) or age of 65 years or older (p = 0.01).

Considering the inherent rate of venous thromboembolism related to cancer and chemotherapy, the fact that in most clinical trials for VEGF inhibitors exclude subjects who have been diagnosed with a thromboembolism in the 6 months prior to study enrollment or are receiving therapeutic doses of anticoagulants, the incidence of venous thromboembolism may be under evaluated.

Proteinuria has occurred in all bevacizumab clinical trials. Bevacizumab therapy has been associated with the development of proteinuria in up to 36% of patients with colorectal cancer (Avastin PI), where Grade 3–4 proteinuria (>3.5 g protein per 24 h urine or nephrotic syndrome) was observed in 6.5% of patients. A meta-analysis of randomized controlled trials with patients receiving bevacizumab indicated a relative risk of 1.4 for proteinuria with bevacizumab at a low dose (2.5 to 7.5 g/kg) and 1.6 for a high dose (10 to 15 mg/kg) suggesting a dose-dependency to bevacizumab-associated proteinuria (Izzedine H., 2010).

Table 6 (adapted from Izzedine, 2010) summarizes the incidence of proteinuria in several randomized Phase 2-3 trials.

Table 6 - Incidence of proteinuria in bevacizumab Phase 2-3 controlled randomized trials

Disease	Author	Treatment	n	Proteinuria (%)	
				Grades 1-4	Grades 3-4
Metastatic CRC	Hurwitz, 2004	IFL	397	21.7	0.8
		IFL + bevacizumab 5 mg/kg	393	26.5	0.8
	Hurwitz, 2005	5-FU/LV + placebo	98	25.1	0
		5-FU/LV + bevacizumab 5 mg/kg	109	34.9	1.8

	Giantonio, 2007	FOLFOX4	285	NA	0
		FOLFOX4 + bevacizumab 10 mg/kg	287	NA	0.7
Metastatic RCC	Yang, 2003	Placebo	40	15	0
		Placebo + bevacizumab 3 mg/kg	37	15	2
		Placebo + bevacizumab 10 mg/kg	39	25	3
	Rini, 2008	IFN- α	349	NA	0
		IFN- α + bevacizumab 10 mg/kg	366	NA	15
NSCLC	Sandler, 2006	Carboplatin/Paclitaxel	444	NA	0
		Carboplatin/Paclitaxel + bevacizumab 15 mg/kg	434	NA	3.1

The treatment of bevacizumab-induced proteinuria is not well established. Many patients receive angiotensin-convertase enzyme (ACE) inhibitors, commonly used for the treatment of hypertension and for renoprotective effects.

The risk of bleeding and hemorrhage is increased in patients treated with VEGF and VEGFR targeting agents. The most common types of bleeding described are mild spontaneous mucocutaneous bleeding and serious tumor-related bleeding. In all trials of bevacizumab, mucocutaneous hemorrhage has been observed in 20–40% of patients, with mild epistaxis being the most common presentation.

Lung carcinomas and gastrointestinal tract tumors are associated with the highest risk and greatest severity of bleeding following VEGF inhibition. Severe or fatal hemorrhage events described in the Avastin PI include hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding. Across indications, the incidence of \geq Grade 3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2% to 4.6%. In a Phase 2 randomized study comparing carboplatin/paclitaxel vs. bevacizumab and carboplatin/paclitaxel in previously untreated NSCLC (Johnson D., 2004), six out of 13 patients with squamous cell histology (31%) experienced a major life-threatening bleeding event described as hemoptysis or hematemesis, and four of these events were fatal. All six patients had centrally-located tumors close to major blood vessels. Five patients had cavitation or necrosis of tumors, either at baseline or developing during bevacizumab therapy. Because squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, it is not clear whether histology alone is the central risk factor for bleeding, or simply a surrogate for other risk factors.

E4599 was the trial leading to the approval of bevacizumab in NSCLC. E4599 (Sandler, 2006) was a randomized controlled trial that excluded patients with squamous histology. Grade 3–5 pulmonary hemorrhage events observed were 2.3% (10 of 427 patients) in the bevacizumab and chemotherapy arm compared with 0.5% (2 of 441) of those treated with chemotherapy only. Five of the hemoptysis events in the bevacizumab-containing arm were fatal.

The incidence of gastrointestinal perforation in the setting of CRC is 1.96 per 1000 procedures for colonoscopy and 0.88 for sigmoidoscopy. Perforation from either procedure occurs more frequently in older patients and in patients with co-morbidities (Wasif Said, 2007). Hypoxia,

inflammation, impaired wound healing, diarrhea, and other effects that result from VEGF blockage increase the risk of bowel perforation and fistula. Aside from ovarian carcinoma, these complications are not as commonly observed in other tumor types.

In patients with metastatic colorectal cancer treated with bevacizumab, the rate of bowel perforation or gastro intestinal fistula was around 2.4% across clinical studies, compared with <1% in the comparator arms. In a recent meta-analysis (Hapani, 2009) of the risk of gastrointestinal perforation in patients treated with bevacizumab that included 12,294 patients with a variety of solid tumors from 17 randomized controlled trials, the incidence was 0.9% (95% CI 0.7–1.2) among patients receiving bevacizumab, with a mortality of 21.7% (11.5–37.0). Patients treated with bevacizumab had a significantly increased risk of gastrointestinal perforation compared with patients treated with control medication, with a relative risk of 2.14 (95% CI 1.19–3.85; $p=0.011$). Risk varied with bevacizumab dose and tumor type. Relative risks for patients receiving bevacizumab at 5 and 2.5 mg/kg per week were 2.67 (95% CI 1.14–6.26) and 1.61 (0.76–3.38), respectively. Higher risks were observed in patients with colorectal carcinoma (relative risk 3.10, 95% CI 1.26–7.63).

Wound healing is a complex process involving angiogenesis and closely regulated interactions between endothelial cells, platelets, and the coagulation cascade. VEGF inhibition can impair wound healing at a surgical site through the dehiscence of a previously healed wound, or delay or cause failure of wound healing in patients who underwent surgery following treatment with an anti-VEGF agent. Although most clinical trials with antiangiogenesis therapies required at least 28 days from any major surgery before starting treatment, the incidence of wound healing complications in the bevacizumab trials described in the Avastin label in subjects with colorectal cancer during the course of treatment was 15%, compared to 4% in patients who did not receive bevacizumab.

In a retrospective analysis of randomized trials in patients with metastatic CRC, for a subset of patients who had surgeries 28–60 days before initiating bevacizumab, Scappaticci et al. (Scappaticci, 2005) described a lower incidence of wound complications (1.3%). A Phase 3 adjuvant trial (NSABP-C08) in patients with CRC who received bevacizumab and chemotherapy at least 28 days after colectomy confirmed that although the rate of serious wound complications was low (1.7%), the rate was significantly higher than that in the chemotherapy-alone control arm (0.3%) (Chen H, 2009). Current guidelines are largely empiric and recommend that bevacizumab be withheld for 4 weeks before elective surgery.

Cardiomyopathy and congestive heart failure have been reported following the administration of bevacizumab, mainly in the metastatic breast cancer setting and associated with anthracycline and taxane exposure. However, few trials have included prospective cardiac monitoring, and therefore, the extent of asymptomatic ventricular dysfunction cannot be fully assessed (Chen H, 2009).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On July 16, 2007, a meeting between Regeneron Pharmaceuticals, Inc. and FDA was scheduled to discuss the proposed trial EFC10262: a multinational, randomized, placebo controlled study investigating the effects of FOLFIRI (plus placebo) versus FOLFIRI in combination with aflibercept on overall survival (OS) in patients with metastatic colorectal cancer after failure of an oxaliplatin-containing regimen. After receiving FDA's draft responses to Regeneron's questions on July 13, 2007, Regeneron elected to cancel the meeting. FDA agreed with the study design, patient population, background chemotherapy, and the choice of OS as the primary endpoint, with PFS and ORR as secondary endpoints. Regeneron proposed the use of a composite radiologic and/or symptomatic deterioration assessment for the determination of PFS, to which FDA responded that the use of investigator-assessed symptomatic deterioration in a composite endpoint for determination of clinical progression would be acceptable only if such data were collected and analyzed in accordance with a pre-specified instrument that has been validated to correlate with objective disease progression in this specific disease and treatment setting. Regeneron anticipated that investigator assessment of progression will be adequately robust for the final analysis of PFS and therefore independent review of progression was not planned. FDA advised that assuming the blinded nature of the study is strictly maintained, a third party review of radiological source data would not be required.

On October 11, 2007, a Type C-CMC meeting was held to discuss Regeneron's 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 and validation, and immunogenicity sampling plans.

A statistical analysis plan (SAP) was submitted for the VELOUR study on January 13 2010. FDA issued a letter dated July 30, 2010 with comments related to the SAP (b) (4)

(b) (4) FDA re-stated comments previously conveyed on July 13 2007 communication, advising Regeneron that two Phase 3 studies are generally required for licensure and FDA would accept a single pivotal study to support licensure if results show a highly statistically significant effect on a major clinical benefit endpoint. The proposed pre-specified statistical significance boundary for PFS in protocol EFC10262 was a hazard ratio of (b) (4) that translated into a (b) (4) median PFS prolongation. FDA stated that it was unlikely that such a finding alone would predict a statistically significant result in overall survival (OS) for the final analysis.

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. FDA requested further clarifications regarding the SA (b) (4), which corresponds to a (b) (4) improvement in median PFS of aflibercept over placebo; this calculation did not coincide with Regeneron statement (b) (4)

(b) (4)
[REDACTED] FDA also reminded Regeneron that the magnitude of effect on PFS should be overwhelming and supported by a strong trend in improved overall survival (b) (4)

[REDACTED] FDA also requested Regeneron to describe the plans with summary of results for pharmacology related studies (QTc assessments, PK, and immunogenicity).

On May 12, 2011, a meeting between Regeneron Pharmaceuticals, Inc. and FDA was held to summarize product development since the type C pre-Phase 2 meeting held on October 11, 2007; inform FDA regarding how outstanding CMC issues discussed during 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, a pre-BLA meeting between Regeneron, sanofi aventis, and FDA was held to discuss the format of the proposed BLA application and review the results of the pivotal VELOUR study in patients with second-line metastatic colorectal cancer. FDA recognized that Regeneron submitted a biologics license application for aflibercept under STN 125387 and hence, the present submission should be filed as a supplement to the original BLA. Sanofi and Regeneron clarified that the oncology aflibercept application will be filed by sanofi, who will hold the license. Aflibercept will have a different trade name for the drug product intended to be used in the oncology setting under the original BLA and sanofi agreed to submit a proposal and rationale regarding why the product should be considered as a stand-alone BLA. Based on sanofi's response and because there will be different license holders for the two products, on September 7, 2011, FDA replied that "The sanofi-aventis U.S. LLC Zaltrap (aflibercept) BLA submission will be considered a stand-alone BLA requiring a complete data package as described in 21 CFR 601.2. Please also note that any CMC deficiencies identified for Eylea, which are relevant or applicable to the CMC section of the sanofi aflibercept submission, must be adequately addressed in the initial sanofi BLA".

On November 7, 2011, sanofi submitted amendment 6 to the protocol, with revisions that will allow patients who are on the aflibercept arm of the VELOUR trial to continue treatment once the unblinding occurs after the 120-safety update is completed and the database locked.

Sanofi filed the BLA on October 28, 2011 (b) (4) On September 13, 2011, in a teleconference with sanofi, FDA communicated CMC deficiencies found during the initial review that rose to the level of a refuse to file action. The following summarizes the main CMC issues:

[REDACTED] (b) (4)

(b) (4)



On December 16, 2011, sanofi withdrew BLA (b) (4) for aflibercept.

On February 2, 2012, sanofi submitted the revised dossier (with changes only to the CMC module), filed under BLA 125418.

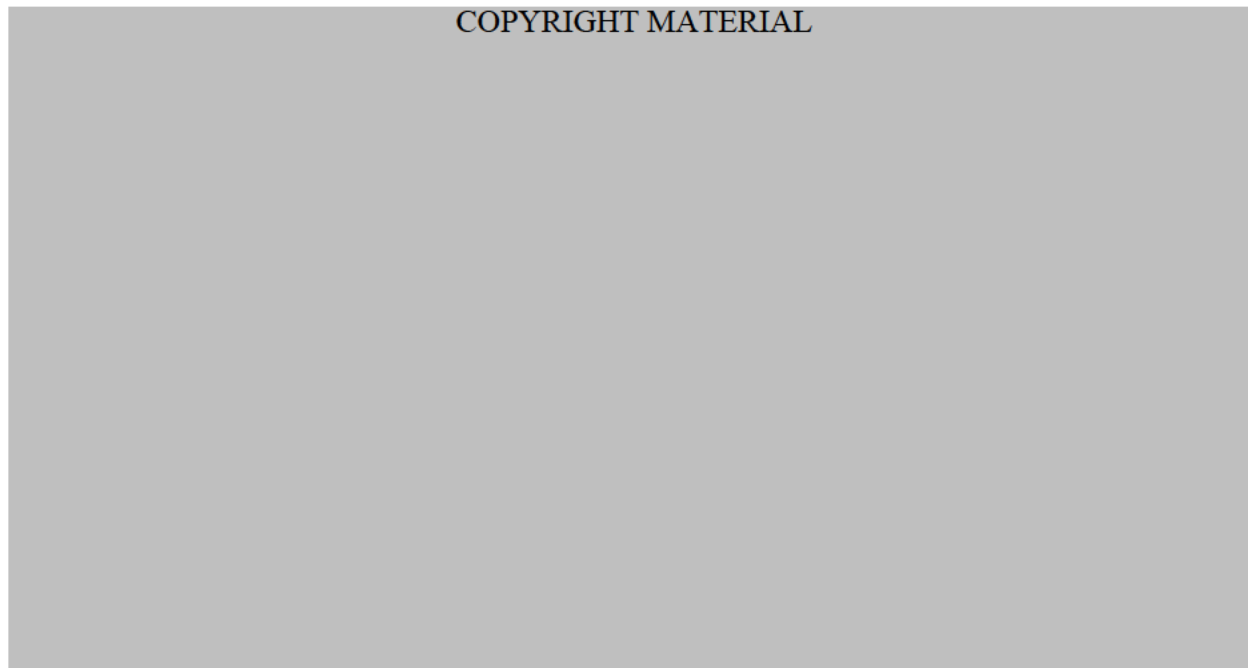
2.6 Other Relevant Background Information

2.6.1 VEGF Pathway

Angiogenesis is a multistep process, regulated by a complex balance of positive and negative regulatory factors. The two most potent regulatory molecules stimulating the formation of new blood vessels are VEGF and bFGF (beta fibroblast growth factor). The mammalian VEGF family consists of five glycoproteins: VEGFA, VEGFB, VEGFC, VEGFD (or FIGF) and placental growth factor (PlGF). The VEGF ligands bind to and activate three receptor tyrosine kinases: VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4). In response to ligand binding, the VEGFR tyrosine kinase activates a network of downstream signaling pathways, including phospholipase C, PI3K, GAP, the Ras GRPase-activating protein and MAPK (Rodhart

J., 2008). The activation of the VEGF pathway results in numerous changes within the tumor vasculature, including endothelial cell proliferation, migration, invasion, survival, vascular permeability, and vasodilation. Figure 2 (copied from Ellis L. and Hicklin D, 2008) displays the VEGF-VEGFR ligands and receptors.

Figure 2 - VEGF Pathway



The proliferative and mitogenic activities of VEGF, as well as vascular permeability, are primarily mediated by VEGFR-2. VEGFR-1 is expressed on endothelial cells and monocytes and mediates cell motility (Giles F. 2001). Transcription of the VEGF gene is regulated by hypoxia. Cellular and circulating levels of VEGF are increased in many malignancies, hematologic and non-hematologic, and are adversely associated with prognosis (Ellis L., 2008).

2.6.2 Metastatic colorectal cancer

Epidemiology

In the U.S., colorectal cancer is the third most common cancer in men and women. The updated Surveillance Epidemiology and End Results (SEER, <http://seer.cancer.gov/statfacts/html/colorect.html#incidence-mortality>, data from 10/13/2011) show that from 2004-2008, the median age at diagnosis for cancer of the colon and rectum (all stages) was 70 years of age. Less than 5% of patients were younger than 44 years (0.1% younger than 20 years old) at diagnosis. As population ages, the colorectal cancer incidence increases: 12.8% of patients are being diagnosed between 45 and 54 years old; 19.6% between 55 and 64; 24.1% between 65 and 74; 26.2% between 75 and 84; and 12.2% \geq 85 years of age. The age-

adjusted incidence rate was 47.2 per 100,000 men and women per year. These rates are based on cases diagnosed in 2004-2008 from 17 SEER geographic areas.

Men are more frequently diagnosed with colorectal cancer than women (55 per 100,000 males vs. 41 per 100,000 women). Distribution varies among ethnicities: the lowest incidence rates are found in Hispanic populations (39.9 and 28.4 per 100,000 males and females respectively). The incidence rates are higher in Whites (54.4 and 40.2 per 100,000 males and females respectively) and even higher in Black populations (67.7 and 51.2 per 100,000 males and females respectively).

Approximately 20% of patients are diagnosed in the metastatic stage. From 2003-2007, the median age at death for cancer of the colon and rectum was 75 years of age. The age-adjusted death rate was 17.6 per 100,000 men and women per year. These rates are based on patients who died in 2003-2007 in the US.

Table 7 summarizes the American Cancer Society (Cancer Facts and Figures 2011, reviewed 10/13/2011 <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-029771.pdf>) estimations of colon, rectal and the most common cancers incidence rates in the adult population for the year 2011. These estimates are based on incidence rates from 46 states and the District of Columbia from 1995-2007 as reported by the North American Association of Central cancer registries, representing about 95% of the US population.

Table 7 - Estimated new cancer cases and deaths by sex, US 2011

	Estimated new cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
All sites	1,596,670	822,300	774,370	571,950	300,430	271,520
Colon	101,340	48,940	52,400	49,380	25,250	24,130
Rectum	39,870	22,910	16,960	No data	No data	No data
Lung	221,130	115,060	106,070	156,940	85,600	71,340
Breast	232,620	2,140	230,480	39,970	450	39,520
Prostate	240,890	240,890	-	33,720	33,720	-

An estimated 101,340 cases of colon and 39,870 cases of rectal cancer are expected to occur in 2011. Colorectal cancer incidence rates have been decreasing for most of the past two decades. The decline accelerated from 1998 to 2007 and has largely been attributed to increases in the use of colorectal cancer screening tests that allow for the detection and removal of colorectal polyps before they progress to cancer. An estimated 49,380 deaths from colorectal cancer are expected to occur in 2011, accounting for about 9% of all cancer deaths. Mortality rates for colorectal cancer have declined in both men and women over the past two decades; since 1998, the rate has declined by 2.8% per year in men and by 2.7% per year in women.

Treatment

The first-line treatment of metastatic colorectal cancer, depending on the patient's clinical condition, can be palliative or in select cases curative. Palliative therapy aims to prolong survival while preserving or improving the quality of life, whereas select isolated organ metastases (typically limited hepatic metastases) can be resected with curative intent. The reported 5-year survival rate after the complete resection of hepatic metastases is 20% to 30% (Schmiegel, 2009). Thus, treatment is chosen depending on the clinical subgroup to which the patient belongs.

After decades of treating metastatic colorectal cancer with 5-fluorouracil (5-FU) alone or in combination with leucovorin, newer agents introduced in research in the 90s have resulted in significant improvements in disease-free and overall survival rates. These improvements stem from combinations of cytotoxic agents (irinotecan and oxaliplatin) and therapies targeting the VEGFR pathway, like bevacizumab, and the EGFR pathway (cetuximab and panitumumab). Current available therapy and guidelines for metastatic treatment are summarized in Table 1 and Table 2.

The FDA approved irinotecan in 1996 as first-line therapy for the treatment of patients with metastatic colorectal cancer in combination with 5-FU/LV based on data from 2 prospective Phase 3 studies that demonstrated a significantly prolonged OS when used in combination with 5-FU/LV as a first-line treatment for metastatic colorectal cancer compared with 5-FU/LV alone. Irinotecan is also approved for the second line treatment of patients with metastatic colorectal cancer after progression on 5-FU/LV therapy.

Oxaliplatin was granted accelerated approval in 2002, and regular approval in 2004 for use in combination therapy with 5-FU/LV for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within six months of completion of first line therapy with the combination of bolus 5-FU/LV/irinotecan, based on a NCI-NCCTG trial with multiple arms. The control arm was irinotecan plus bolus 5-FU/LV. The oxaliplatin plus infusional FU/LV regimen was compared to an approved control regimen of irinotecan plus bolus 5-FU/LV in 531 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer. The oxaliplatin plus infusional FU/LV regimen showed superior survival to the irinotecan plus bolus FU/LV regimen with median survivals of 19.4 and 14.6 months ($p=0.0001$), respectively. Time to tumor progression and tumor response rate were also superior on the oxaliplatin plus infusional FU/LV regimen.

Bevacizumab was approved first by the FDA for the first line treatment of metastatic colorectal cancer in 2004 based on the results of multinational, double-blind, randomized active-controlled study where patients were randomized (1:1:1) to IV bolus irinotecan/5-FU/LV (IFL regimen) plus placebo (Arm 1), IFL plus bevacizumab (Arm 2), or 5-FU/LV plus bevacizumab (Arm 3). IFL regimen consisted of irinotecan 125 mg/m², leucovorin 20 mg/m², and 5-FU 500 mg/m² administered once weekly for 4 weeks every 6 weeks. Bevacizumab or placebo dose was 5 mg/kg every 2 weeks. If the data monitoring committee found the safety of the addition of bevacizumab to IFL, the enrollment of patients in Arm 3 was to be discontinued. After the first

interim analysis, enrollment in Arm 3, as pre-specified, was discontinued. Median age for the 813 patients randomized to Arms 1 and 2 was 60 years old, 40% were women, 79% were White, 57% had an ECOG performance status of 0; 21% had a rectal primary tumor; and in 56% of patients the dominant site of disease was extra-abdominal. The addition of bevacizumab to IFL resulted in a significant improvement in overall survival (15.6 vs. 20.3 months in the IFL/placebo arm vs. IFL/bevacizumab, HR 0.66), PFS (6.2 vs. 10.6 months in the IFL/placebo arm vs. IFL/bevacizumab, HR 0.54), and response rate (35% vs. 45% in the IFL/placebo arm vs. IFL/bevacizumab respectively). The median duration of response was prolonged by 3 months in the bevacizumab arm. These results were observed across subgroups defined by age and gender.

Bevacizumab was approved for the second line treatment of metastatic colorectal cancer based on the results of the E3200 trial. E3200 was a cooperative group randomized, open-label, active controlled trial in patients who previously received treatment with irinotecan ± 5-FU for metastatic disease or adjuvant therapy. Patients were randomized 1:1:1 to FOLFOX4 with bevacizumab, FOLFOX4, or bevacizumab alone. The FOLFOX4 regimen consisted of oxaliplatin 85 mg/m² administered with LV 200 mg/m², and 5-FU 400 mg/m² IV bolus followed by 600 mg/m² continuously on Day 1. On Day 2, patients received LV 200 mg/m² with 5-FU 400 mg/m² IV bolus followed by 600 mg/m² continuously. This combination was repeated every 2 weeks. The bevacizumab dose was 10 mg/kg administered every 2 weeks.

Median age of the 829 patients randomized to the 3 arms was 61 years old, 40% were women, 87% were White; 49% had an ECOG performance status of 0; and 99% received prior irinotecan. After a planned interim analysis, the bevacizumab monotherapy arm was closed based on evidence of decreased survival compared to FOLFOX4 alone. The addition of bevacizumab to FOLFOX4 resulted in significant longer survival as compared to FOLFOX4 alone (median OS 13 vs. 10.8 months, HR 0.75 95%CI 0.63;0.89, p=0.001).

Wagner A. et al (Wagner A., 2009), through the Cochrane library, published a meta-analysis assessing the efficacy and toxicity of bevacizumab in addition to chemotherapy in patients with metastatic CRC. Primary endpoints of these randomized trials were PFS and OS. Response rates, toxicity and secondary resectability were secondary endpoints. Comparisons were first-line and second-line chemotherapy with or without bevacizumab. At the time of the analysis, there were 5 first-line trials including 3,101 patients eligible for the meta-analysis. The overall HRs for PFS (0.61, 95% CI 0.45 - 0.83) and OS (0.81, 95% 0.73 - 0.90) for the comparison of first-line chemotherapy with or without bevacizumab confirmed benefit favoring treatment with bevacizumab. However, the effect on PFS showed significant heterogeneity. For second-line chemotherapy, with or without bevacizumab, a benefit in both PFS (HR 0.61, 95% CI 0.51 - 0.73) and OS (HR 0.75, 95% CI 0.63-0.89) was demonstrated in a single, randomized trial. While differences in treatment-related deaths and 60-day mortality were not significant, higher incidence rates of Grade III/IV hypertension, arterial thromboembolic events, and gastrointestinal perforations were observed in the patients treated with bevacizumab. This meta-analysis included the trials described above. An extensive review of the toxicity of bevacizumab can be found in Section 2.4 of this review.

In 2004, cetuximab was granted accelerated approval (later converted to regular approval) based on the results of a multicenter clinical trial (Cunningham D., 2004) conducted in 329 patients with EGFR-expressing recurrent metastatic CRC. Patients were randomized (2:1) to receive either cetuximab plus irinotecan (218 patients) or cetuximab monotherapy (111 patients). Of the 329 patients, the median age was 59 years; 63% were men, 98% were White, and 88% had baseline Karnofsky Performance Status ≥ 80 . Approximately two-thirds had previously failed oxaliplatin treatment. The efficacy of the intervention was assessed based on durable objective responses in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and in patients whose disease progressed on or following irinotecan and oxaliplatin. In patients receiving cetuximab plus irinotecan, the objective response rate was 23% (95% CI 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving cetuximab monotherapy, the objective response rate was 11% (95% CI 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

The second study described in the cetuximab label was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent, metastatic CRC. Patients were randomized (1:1) to receive either cetuximab plus best supportive care (BSC) or BSC alone. Median age of patients was 63 years; 64% were men, 89% were White; and 77% had baseline ECOG Performance Status of 0–1. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen. The main outcome measure of the study was overall survival. Patients on the cetuximab arm had a median OS of 6.14 months (95% CI 5.36;6.7 months), compared with a median OS of 4.57 months (95% CI 4.21;4.86 months) in the BSC arm (HR 0.77, 95% CI 0.64;0.92). However, retrospective analyses across seven randomized clinical trials suggested that anti-EGFR monoclonal antibodies are not effective for the treatment of patients with metastatic CRC whose tumors contain *KRAS* mutations. In these trials, patients received standard of care (ie, BSC or chemotherapy) and were randomized to receive either an anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies, investigational tests were used to detect *KRAS* mutations in codons 12 or 13. The percentage of study populations for which *KRAS* status was assessed ranged from 23% to 92%. (Erbix label). Current guidelines recommend limiting the use of anti-EGFR agents only in subjects with EGFR positive/*KRAS* WT tumors (Table 2).

On 2006, FDA granted accelerated approval to panitumumab for the treatment of patients with EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Panitumumab approval was based on the results of a single, open-label, randomized, multinational study that enrolled 463 patients. Patients were randomized to either BSC alone or BSC plus panitumumab. The primary study endpoint was progression-free survival (PFS), determined by an independent review committee that was blinded as to treatment assignment. Median age was 62 years, with 40% aged 65 or older; 63% were men; 99% were White; 86% had a baseline ECOG performance status score of 0 or 1; and 67% had colon cancer. The PFS duration was longer among patients

randomized to receive panitumumab in addition to BSC (n = 231) compared with BSC alone (n = 232). The median and mean PFS times were 56 and 96.4 days, respectively, for patients receiving panitumumab and 51 and 59.7 days, respectively, for patients receiving BSC alone. Nineteen partial responses (8%, 95% CI 5.3%;12.5%) were observed in panitumumab-treated patients. The median duration of response was 17 weeks (95% CI, 16;25 weeks). There was no difference in overall survival between the two study arms.

Up to the date of this review, no randomized controlled study has shown significant survival advantage with the use of panitumumab.

2.6.3 Aflibercept development

Aflibercept was initially evaluated using subcutaneous administration in a phase 1, single-agent, dose-finding trial in patients with advanced cancer (TED6113/ TED6114). However, the biologically active dose required too large a volume to be administered via the subcutaneous route. The clinical development was then re-centered on IV administration, and a single-agent Phase 1 (TED6115/TED6116) study explored the every other week IV regimen. This study identified the recommended phase 2 dose of 4 mg/kg.

A series of dose finding Phase 1 studies of aflibercept combined with various standard chemotherapy regimens was conducted. Study TCD6118 evaluated aflibercept every other week combined with irinotecan and the LV/5FU2 regimen in patients with advanced solid tumors. Other phase 1 combination studies evaluated aflibercept every other week combined with FOLFOX4 (TCD6117), gemcitabine, and gemcitabine and erlotinib (TCD6121) or every three weeks combined with docetaxel, cisplatin, and 5-fluorouracil (TCD6119), or docetaxel, docetaxel and cisplatin, or pemetrexed (TCD6120).

Phase 2 studies explored single-agent activity in patients with advanced ovarian cancer and symptomatic malignant ascites (EFC6125, ARD6122, ARD6772) and non-small cell lung cancer (ARD6123).

Three phase 1 pharmacodynamic studies were conducted: 2 to evaluate blood pressure variation in healthy subjects (PDY6655, PDY6656) and 1 to evaluate potential for Q-T interval prolongation in patients with cancer in combination with docetaxel (TES10897).

Under IND 100137, the NCI also sponsored a program of single-agent and combination therapy phase 2 trials in a wide variety of malignancies, including pediatric cancers.

Rather than evaluating combination therapy in randomized phase 2 trials, the applicant launched a phase 3 program. The following Phase 3 studies have been completed:

- EFC10262/VELOUR (the pivotal trial for this submission): A multinational, randomized, double-blind study, comparing the efficacy of aflibercept every other week versus placebo in combination with FOLFIRI in previously treated mCRC patients;

- EFC10547/VANILLA: A multinational, randomized, double-blind study, comparing the efficacy of aflibercept every other week versus placebo combined with gemcitabine in patients with metastatic pancreatic cancer. On September 11, 2009, the Applicant informed the Agency that the planned interim analysis for Study EFC10547 (performed by an independent statistician after the 205th death event) by the IDMC resulted in a recommendation to stop the study for futility based on the pre-specified stopping rules.
- EFC10261/VITAL: A multinational, randomized, double-blind study comparing aflibercept every three weeks versus placebo combined with docetaxel after failure of one platinum based therapy in patients with locally advanced or metastatic NSCLC. On March 10, 2011, the Applicant communicated through a press release the results from EFC10261 (VITAL), and later submitted the information to the IND. The data showed that adding aflibercept to docetaxel did not meet the pre-specified criteria for the primary endpoint of an improvement in overall survival compared with a regimen of docetaxel plus placebo (HR=1.01, CI: 0.868 to 1.174). PFS HR was 0.82 (CI: 0.716 to 0.937) and the ORR was 23.3% in the aflibercept/docetaxel arm compared to 8.9% in the placebo arm.
- EFC6546 (VENICE): A multicenter, randomized, double-blind study comparing efficacy and safety of aflibercept versus placebo every 3 weeks in patients treated with docetaxel/prednisone for metastatic androgen-independent prostate cancer, was undergoing at the time of this BLA submission. On April 5, 2012, Sanofi communicated through a press release that the study failed to meet the pre-specified criterion of improvement in overall survival.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality for the clinical review. However, as described above CMC deficiencies were identified at the time that the BLA was initially submitted.

The applicant did a thorough job requesting information from investigators, and the CRFs and narratives are complete and provide the information needed to supplement the databases. The organization of the data was efficient.

This reviewer could not identify any issue that questions the integrity of the submission.

3.2 Compliance with Good Clinical Practices

All studies reports contained in the BLA included a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

On the basis of financial conflicts of interest, number of patients treated at the site, protocol violations, and efficacy results, FDA selected three clinical sites [#203001 (Dr. Radek) and #203004 (Dr Prausova) in the Czech Republic and # 6430003 (Dr. Moisevenko) in Russia] for inspection, with no non-compliance findings.

As a result of Sanofi's site inspection (dated April 24, 2012), a Form 483 was issued on 17 May to Sanofi during the closeout meeting for the Sponsor-monitor pre-approval inspection. FDA found that although Sanofi identified Site 036007 (Dr. Van Hazel, Australia) to be non-compliant, and Sanofi repeatedly attempted to secure compliance, the site's enrollment was increased as approved by the Sponsor despite the increase in non-compliance. By the data cut off date in February 2011, (23) subjects were randomized and received treatment and 20 out of the 23 subjects completed their treatments.

In correspondence to IND 9948 dated March 15, 2011, Sanofi had previously notified the Agency of ongoing GCP compliance concerns at site #36007 (Dr. Van Hazel, Australia), but assessed these issues as being of a nature that would not impact the integrity of the scientific conclusions of the study and/or patients safety. Among the issues/deviations occurring at the site included but not limited to the following: instances of failure to perform protocol required tests/procedures; including subjects into the trial despite meeting the exclusion criteria; inconsistencies in calculating the dosages of chemotherapy drugs; allowing sub-investigators to perform protocol related procedures even though they were not listed on the form "Delegation of Duties" and the 1572s prior to trial participation; and failure to maintain adequate training records.

In response to FDA form 483, on June 1, 2012, Sanofi submitted an amendment to the BLA acknowledging this issue, and reiterating the March 2011 statement that in their assessment, none of the protocol deviations at this site were of a nature that would impact the integrity of the scientific conclusions. Included in the June 1 2012 submission are the results of the analyses that Sanofi performed to evaluate whether exclusion of the 23 patients enrolled at this site changes the study efficacy conclusions. These sensitivity analyses for the primary endpoint of overall survival excluding the patients and the secondary endpoint PFS with exclusion of these patients were consistent with the primary analysis of the pivotal study VELOUR (see Table 108 and Table 109 in Appendices section). Dr. J. Zhang's (FDA statistician) analysis of the VELOUR study excluding these patients is summarized in Table 8.

Table 8 - VELOUR: OS analysis excluding site 036007

	Placebo/FOLFIRI (n=614)	Aflibercept/FOLFIRI (n=612)
# patients after exclusion	606	597
HR (95% CI)	0.822 (0.717; 0.941)	
P value	0.0047	

In summary, in both the Applicant and FDA analyses, the results of VELOUR on the primary endpoint excluding patients from site 036007 were consistent with those of the primary analysis; thus, it is reasonable to conclude that inclusion of data from site 036007 would not significantly affect the overall results.

3.3 Financial Disclosures

Financial disclosures were provided for two studies:

(b) (6)	
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Sanofi submitted Forms 3454, 3455 and a list of the investigators who did not respond to their request regarding the submission of disclosable arrangements. Table 9 summarizes the investigators with disclosable interests. The number of patients enrolled at these sites was obtained from subject ID#s in the datasets, where the center is represented in the first 6 digits. However, these numbers were discordant when using the demographics database and the “site” column. This column referred to the principal investigator at the center. The major discordance was for (b) (6), who according to the “site” column treated (b) (6) patients (b) (6)

Table 9 - Financial disclosable interests

Country	Center ID	Investigator name	Patients enrolled	Payments/concept
(b) (6)			(b) (6)	
				\$65,087
				Consulting and cancer courses
				\$30,470
				Speaking events, advisory board and symposia participation.
				\$164,982
				Advisory fees
				\$33,358
				Lectures fees
				\$39,450
				Speaking events

	(b) (6)	\$136,649
		Speaking events
		\$175,046
		Advisory board
		\$98,659
		Training events, advisory board, and symposia participation.
		\$45,175
		Speaking events

Sanofi stated that it did not enter into any financial compensation with the investigators listed in Table 9 where the value of the compensation to the investigator could affect the outcome of these two studies.

Sanofi was unable to obtain financial disclosure information from 83 clinical investigators. The reason listed in all 83 cases was that the investigator left the clinical trial site prior to obtaining the required information and attempts to locate and contact them were unsuccessful.

Reviewer's comment: *Although there are a number of investigators with financial conflicts, the number of patients treated at each one of these individual centers was less than 2.5% of the total population of the trial. The sum of all patients treated by conflicted investigators in the VELOUR trial was 89 patients (7.25% of the total population). In order to further explore if these findings have significance, Dr. Zhang (FDA statistical reviewer) conducted exploratory statistical analyses excluding these patients from the database, confirming that the study results did not significantly change.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Reviewer's comment: *FDA CMC reviewers are, at this time of the final editing of the clinical review (July 3, 2012), still receiving amendments as responses to information requests. Deficiencies and PMCs listed below may be revised or resolved as part of the ongoing review. For an updated status, refer to Dr. Sarah Kenneth, Dr. Kalavarti Suvama and Dr. Michelle Clark-Stuart final CMC reviews.*

4.1 Chemistry Manufacturing and Controls

The data submitted in this Biologics License Application supports 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 in the application. The CMC review team concluded that it is

recommended that Zaltrap™ (aflibercept) be approved for human use (under conditions specified in the package insert)."

There are still some outstanding issues that will necessitate PMCs, including release and stability specification criteria issues related to a new drug substance manufacturing site, closure integrity testing, and drug product endotoxin acceptance criteria.

4.2 Clinical Microbiology

FDA microbiology review was conducted by Dr. Kalavati Suvama and Michelle Clark Stuart. The microbiology team concluded that, after several amendments as per FDA request, approval is recommended from a CMC microbiology product quality perspective pending proposed labeling changes and with the following post-marketing commitments.

- Post-marketing commitment 1: To conduct a study to validate the container closure integrity test (b) (4)
- Post-marketing commitment 2: To evaluate the interference of the red dye with product in the dye ingress test method used for the stability program.
- Post-marketing commitment 3: To determine the sources of bioburden (b) (4) and implement additional controls such that the (b) (4) bioburden is reduced to an acceptable level (b) (4)
- Post-marketing commitment 4: To conduct a shipping qualification study to assess ability of the commercial shipper to maintain temperature during shipment of minimum and maximum loads under worst case conditions [temperature (summer and winter profile), duration] for shipment.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology toxicology data submitted in this BLA is identical to the data submitted and reviewed for the aflibercept original BLA (125387), supporting the aflibercept approval for wet macular degeneration. For a complete review, please refer to Dr. A. Putman's review.

Aflibercept was classified during the review as pregnancy Category C. Aflibercept was embryotoxic and teratogenic in rabbits at exposure levels lower than human exposures at the recommended dose, with external, visceral, and skeletal fetal malformations. Adverse embryo-fetal effects included post-implantation losses and external (including anasarca, umbilical hernia, diaphragmatic hernia and gastroschisis, cleft palate, ectrodactyly, and atresia), visceral (in the

heart, great vessels, and arteries), and skeletal fetal malformations (including fused vertebrae, sternbrae, and ribs; supernumary arches and ribs, and incomplete ossification). Systemic exposure (AUC) with a 3 mg/kg dose in rabbits resulted in approximately 30% of the AUC in patients at the recommended dose.

Aflibercept impaired reproductive function and fertility in monkeys. In a 6-month repeat-dose toxicology study in sexually mature monkeys, aflibercept inhibited ovarian function and follicular development, as evidenced by the following: 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 observed in male monkeys. These effects were observed at the lowest dose tested, 3 mg/kg, and above. Reversibility was observed within 18 weeks after cessation of treatment. Systemic exposure (AUC) with a 3 mg/kg dose in monkeys resulted in approximately 60% of the AUC in patients at the recommended dose.

Weekly/every two weeks IV administration of aflibercept to growing young adult (sexually mature) cynomolgus monkeys for up to 6 months resulted in changes in the bone (effects on growth plate and the axial and appendicular skeleton), nasal cavity, kidney, ovary, and adrenal gland. Aflibercept-related findings were observed in the lowest dose (3 mg/kg, correlating to 60% of the AUC at the human recommended dose) tested. The skeletal and nasal cavity effects were not reversible after a post-dosing recovery period.

Aflibercept administration resulted in a delay in wound healing in rabbits. In full-thickness excisional and incisional skin wound models, aflibercept administration reduced fibrous response, neovascularization, epidermal hyperplasia/re-epithelialization, and tensile strength.

4.4 Clinical Pharmacology

This section is based on Dr. Ruby Leong's and Dr. Kevin Kudrys review (clinical pharmacology and biometrics). Sanofi submitted a total of 19 clinical studies to support the Clinical Pharmacology Section of the BLA.

In FDA analyses, age, race, and gender did not have a clinically meaningful effect on the exposure to aflibercept. Patients weighing ≥ 100 kg had a 29% increase in drug exposure compared to patients weighing < 100 kg. In exploratory analyses performed on data from the VELOUR trial, overall survival (OS) and progression-free survival (PFS) appeared related to free and bound aflibercept exposure. An increase of 1000 $\mu\text{g}\cdot\text{h/mL}$ free aflibercept AUC was associated with a 21% and 19% decrease in the hazard ratio for OS and PFS, respectively.

An analysis of the impact of BMI on toxicity (Table 103) showed that, with the exception of hypertension and pulmonary embolism (two conditions for which the incidence is increased in

the obese population), there was no increased toxicity in the population with BMI greater than 30. Incidence of hypertension and hemorrhage during the first two cycles was found to be significantly related to exposure of free aflibercept. The odds of experiencing hypertension increased by 27% for an increase in AUC 0-336 of 1000 µg·h/mL.

Population PK analyses (n=1507) showed similar exposure in patients with renal and hepatic impairment compared to patients with normal organ function.

The overall incidence of anti-product antibody (APA) development across fifteen clinical oncology studies was 4.8% in IV aflibercept-treated patients (82/1706) and 3.5% in placebo-treated patients (41/1156). Among patients who tested positive for APA and had sufficient samples for further testing, neutralizing anti-aflibercept antibodies were detected in 35.4% aflibercept-treated patients (17/48) and 5.0% placebo-treated patients (2/40). The presence of neutralizing antibodies appeared to affect pharmacokinetics of aflibercept. Free aflibercept trough concentrations were approximately 30-fold lower (at or near lower limit of quantitation) than those of the overall population. The impact of positive APA on efficacy and safety could not be assessed due to limited data.

No clinically meaningful drug interactions were observed between aflibercept and combination chemotherapies (irinotecan/SN-38, 5-FU, oxaliplatin, cisplatin, docetaxel, gemcitabine, erlotinib, pemetrexed).

Aflibercept does not appear to prolong the QTc interval at a dosing schedule of 6 mg/kg administered Q3W. No large changes in mean QTcF intervals > 20 ms were detected.

4.4.1 Mechanism of Action

Aflibercept is an antiangiogenic agent. It is a recombinant fusion protein consisting of human VEGF receptor extracellular domains fused to the F_c portion of human IgG₁. Aflibercept contains sequences encoding the Ig domain 2 from VEGFR1 fused to the Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG₁ F_c domain.

Aflibercept interferes with the biological actions of VEGF by “trapping” VEGF in the blood stream and extravascular space and preventing it from interacting with its receptors on endothelial cells. It is described as having a high binding affinity to VEGF and can bind other related pro-angiogenic VEGFR ligands such as VEGF-B and the placental growth factors, PlGF1 and PlGF2.

4.4.2 Pharmacodynamics

The pharmacodynamic activity of aflibercept has been evaluated by in vitro and in vivo

assays. In vitro studies demonstrated that aflibercept binds with picomolar affinity to mouse, rat, rabbit and human VEGF-A, and to the related angiogenic molecules, human VEGF-B, human placental growth factor-1 (PlGF-1) and mouse and human PlGF-2, but not to human VEGF-C and VEGF-D, which are primarily involved in lymphangiogenesis. In cell-based assays, aflibercept inhibited VEGF-dependent receptor phosphorylation and subsequent calcium mobilization, but was not able to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Thus, aflibercept appears to function solely through binding and sequestration of VEGF-A and potentially other VEGFR-1 ligands, such as VEGF-B and PlGF.

Following administration of aflibercept, two distinct circulating forms of the drug can be detected, which include the native, free aflibercept form as well as the VEGF:aflibercept complex (also known as the bound aflibercept form), which is generated when free aflibercept binds its target ligand, VEGF. Plasma concentrations of aflibercept complex increase with the aflibercept dose until most bioavailable VEGF is bound and a near maximum aflibercept complex concentration is achieved. Further increases in the aflibercept dose result in dose-related increases in free aflibercept concentrations in plasma but, only small further increases in the aflibercept complex concentration.

Endogenous free VEGF plasma levels were measured at baseline in patients from the Phase 3 studies. An exploratory analysis showed that endogenous VEGF could be a prognostic factor. However, further exploration of the relationship between tumor burden and VEGF plasma levels is needed to assess this hypothesis.

4.4.3 Pharmacokinetics

Free aflibercept exhibits linear pharmacokinetics in the dose range of 2 to 9 mg/kg. Following 4 mg/kg every two weeks administration, the mean elimination half-life of free aflibercept was approximately 6 days with steady state concentrations reached by the second dose. Drug accumulation was approximately 1.3-fold with 4 mg/kg every two week administration. Based on a population pharmacokinetic analysis with data from 1378 patients who received 2-9 mg/kg of aflibercept every two or three weeks as monotherapy or in combination with chemotherapy agents, the estimated elimination half-life of VEGF-bound aflibercept was approximately 15 days. Time to steady state of VEGF-bound aflibercept was estimated to be 70 days, corresponding to the sixth dose.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

One study was used to support efficacy (EFC10262 / VELOUR). Refer to Section 7 below regarding studies used to support safety.

5.2 Review Strategy

The efficacy analysis will be centered on the evaluation of one trial, EFC10262 or “VELOUR”, A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer (MCRC) Treated with Irinotecan / 5-FU Combination (FOLFIRI) after failure of an oxaliplatin based regimen.

The safety analysis will be based on data from VELOUR, and an integrated database with 2073 patients treated with aflibercept in several phase 1, 2, and 3 trials

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. EFC10262 / VELOUR: A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer (MCRC) Treated with Irinotecan / 5-FU Combination (FOLFIRI) after failure of an oxaliplatin based regimen.

The following protocol synopsis is based on the latest version of the protocol. Amendment #5 was received on May 6, 2011. Table 16, at the end of the protocol review, summarizes the major changes in the protocol since it was first submitted.

Study Design

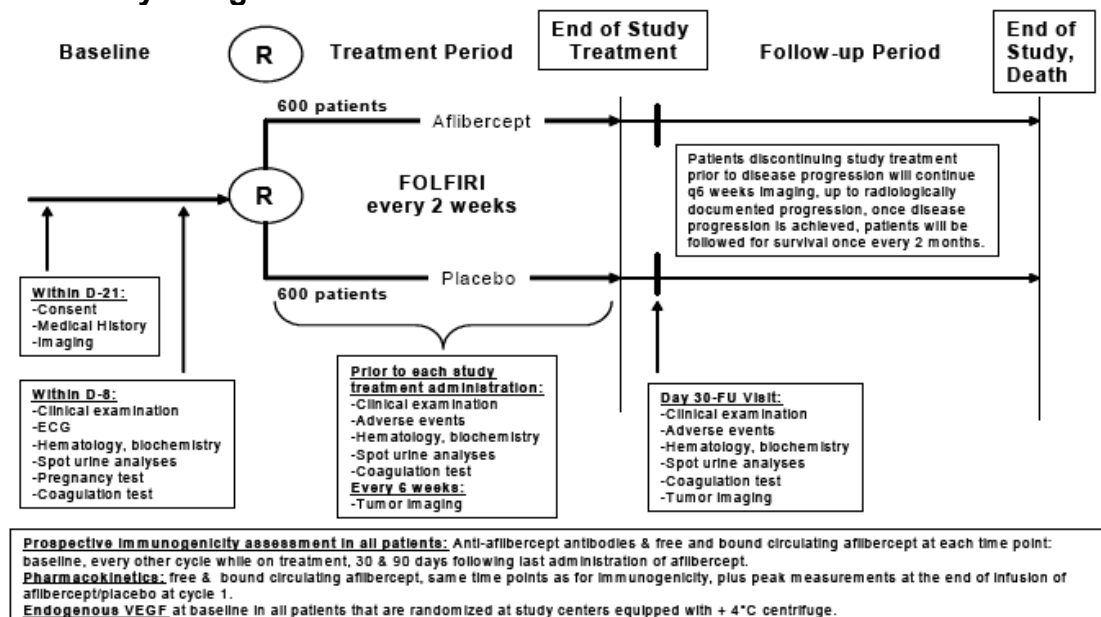
Velour was an industry-sponsored, prospective, multicenter, multinational, randomized (1:1), double-blind, controlled study of aflibercept versus placebo in patients with mCRC being treated with FOLFIRI after failure of an oxaliplatin based regimen.

Patients were treated until disease progression, unacceptable toxicity, or patient refusal. Following documentation of progressive disease, patients were followed for survival status. An independent Data Monitoring Committee (IDMC) periodically assessed the progress of the trial, the safety data, and the efficacy data from the interim analysis, and advised the Executive Steering Committee regarding the patients’ safety as well as on potential courses of action regarding the conduct of the trial.

Treatment assignment was done centrally via an IVRS using permuted-block randomization stratified by prior therapy with bevacizumab (yes vs. no) and ECOG performance status (0 vs. 1 vs. 2).

The following figure (copied from the submission) shows the study design.

Figure 3 - Study design



Objectives

The **primary objective** was to demonstrate improvement in overall survival (OS) with aflibercept by comparison to placebo in patients with colorectal cancer treated with FOLFIRI as second-line treatment for metastatic disease.

Secondary objectives were:

- To compare progression free survival (PFS) in the two treatment arms.
- To evaluate overall response rate (RR), as per RECIST criteria, in the two treatment arms.
- To evaluate the safety profile in the two treatment arms.
- To assess immunogenicity of IV aflibercept.
- To assess pharmacokinetics of IV aflibercept and perform population pharmacokinetic evaluation.

Inclusion and Exclusion Criteria (copied from the protocol with slight modifications for brevity)

Inclusion criteria

- Histologically or cytologically proven adenocarcinoma of the colon or rectum.
- Metastatic disease not amenable to potentially curative treatment.
- Measurable or non-measurable disease (as per RECIST criteria).
- One and only one prior chemotherapeutic regimen for metastatic disease. This prior chemotherapy should have been an oxaliplatin containing regimen. Patients must have progressed during or following the last administration of the oxaliplatin based chemotherapy.

Patient who relapsed within 6 month of completion of oxaliplatin based adjuvant chemotherapy were eligible.

Exclusion criteria

Exclusion criteria related to methodology:

- Prior therapy with irinotecan.
- Less than 28 days from prior (to the time of randomization) radiotherapy, surgery, and/or chemotherapy. Less than 42 days from prior major surgery.
- Adverse events (with exception of alopecia, peripheral sensory neuropathy and those listed in specific exclusion criteria) from any prior anti cancer therapy of Grade >1 (NCI CTCAE v.3.0) at the time of randomization.
- Adverse events (with exception of alopecia, peripheral sensory neuropathy and those listed in specific exclusion criteria) from any prior anti cancer therapy of grade >1 (NCI CTCAE v.3.0) at the time of randomization.
- Age < 18 years.
- ECOG PS > 2.
- History of brain metastases, uncontrolled spinal cord compression, carcinomatous meningitis, or new evidence of brain or leptomeningeal disease.
- Other prior malignancy. Adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or any other cancer from which the patient has been disease free for > 5 years were allowed.
- Participation in another clinical trial with an investigational drug and any concurrent treatment with any investigational drug within 30 days prior to randomization.
- Any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack.
- Any of the following within 3 months prior to randomization: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event.
- Occurrence of deep vein thrombosis within 4 weeks prior to randomization.
- Known AIDS-related illnesses or known HIV disease requiring antiretroviral treatment
- Any severe acute or chronic medical condition, which could impair the ability of the patient to participate in the study or to interfere with interpretation of study results.
- Pregnant or breast feeding women. Patients with reproductive potential (female and male) who do not agree to use an accepted effective method of contraception (hormonal or barrier methods,

abstinence) during the study treatment period and for at least 6 months following completion of study treatment.

- Absence of signed and dated IRB/Independent Ethical Committee (IEC)-approved patient informed consent form prior to enrolment in the study.

Exclusion criteria related to aflibercept:

- UPCR >1 on morning spot urinalysis or proteinuria > 500 mg/24-h.
- Serum creatinine > 1.5 x ULN. If creatinine 1.0-1.5 x ULN, a creatinine clearance < 60 ml/min will exclude the patient.
- History of uncontrolled hypertension, defined as blood pressure > 150/100 mmHg or systolic blood pressure >180 mmHg when diastolic blood pressure < 90 mmHg, on at least 2 repeated determinations on separate days within 3 months prior to study enrollment.
- Patients on anticoagulant therapy with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3) within the 4 weeks prior to study entry.
- Evidence of clinically significant bleeding diathesis or underlying coagulopathy or non-healing wound.

Exclusion criteria related to chemotherapy (FOLFIRI):

- Known dihydropyrimidine dehydrogenase deficiency.
- Inadequate bone marrow function: ANC < $1.5 \times 10^9/L$, platelet count < $100 \times 10^9/L$, hemoglobin < 9.0 g/dL. Inadequate liver function tests: total bilirubin >1.5 x ULN, transaminases >3 x ULN (unless liver metastasis are present, 5 x ULN in that case), alkaline phosphatase >3 x ULN (unless liver metastasis are present, 5 x ULN in that case).
- Predisposing colonic or small bowel disorders in which the symptoms were uncontrolled as indicated by baseline of > 3 loose stools daily.
- Prior history of chronic enteropathy, inflammatory enteropathy, chronic diarrhea, unresolved bowel obstruction/sub-obstruction, more than hemicolectomy, extensive small intestine resection with chronic diarrhea.
- History of anaphylaxis or known intolerance to atropine sulphate or loperamide or appropriate antiemetics to be administered in conjunction with FOLFIRI.
- Treatment with concomitant anticonvulsivant agents that are CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine), unless discontinued >7 days.
- Known Gilbert's syndrome.

Protocol Specified Study Discontinuation Criteria

All patients who discontinued study treatment under the following circumstances were continued to be assessed and followed in the study (unless the patient refused):

- Patients decision to withdraw.
- If, in the investigator's opinion, continuation of the study treatment would have been detrimental to the patient's well being, such as disease progression and unacceptable AE(s) not manageable by symptomatic therapy, dose delay or dose modification.
- Intercurrent illness that prevented further administration of study treatment
- Non compliance to the study protocol.
- Lost to follow-up.

Treatment Plan

* **Arm A, aflibercept** 4 mg/kg IV over 1 hour on Day 1, every 2 weeks.

* **Arm B, placebo** 4 mg/kg IV over 1 hour on Day 1, every 2 weeks.

Immediately after the aflibercept/placebo infusion, **all patients received the FOLFIRI** regimen:

- Irinotecan 180 mg/m² IV over 90 minutes and racemic leucovorin 400 mg/m² IV over 2 hours at the same time (if using l-isomer the dose was 200 mg/m²), followed by
- 5-FU 400 mg/m² IV bolus, followed by
- 5-FU 2400 mg/m² continuous IV infusion over 46 hours.

Patients received premedication with atropine and antiemetic agents according to institutional guidelines. G-CSF was recommended upon recurrence of a \geq Grade 3 neutropenia as treatment and prophylaxis for subsequent treatment cycles.

Premedication for aflibercept was not routinely recommended. If an infusion reaction occurred, management was instituted as per guidelines. In case of severe reactions (\geq Grade 3) aflibercept/placebo were discontinued.

Dose adjustments/modifications

In case of toxicity, treatment administration should have been delayed until ANC $\geq 1.5 \times 10^9/L$ and platelet count $\geq 75 \times 10^9/L$ and all other toxicities recovered to \leq Grade 1 or baseline. The maximum authorized delay was 2 weeks.

If FOLFIRI was permanently discontinued, then aflibercept/placebo could have been continued until disease progression or unacceptable toxicity. If aflibercept/placebo was permanently discontinued, then FOLFIRI could have been continued until disease progression or unacceptable toxicity.

Only one aflibercept dose reduction to 2 mg/kg was allowed. Once a dose was decreased, no re-escalation back to the previous level was allowed.

Table 10 summarizes the hypertension management (modified from the protocol for clarity and brevity) and Table 11 summarizes the aflibercept dose reductions for toxicities related to VEGFR inhibition.

Table 10 - Aflibercept dose modifications for hypertension

Action

Grade ≤ 2	Initiate antihypertensive therapy (calcium channel blockers preferred). No dose modification or delay.
Grade 3	<p>1- Modify antihypertensive drug therapy.</p> <p>2- Delay the administration of both FOLFIRI and aflibercept/placebo (for a max. of 2 weeks) until recovery to BP ≤ 150/100 or to systolic < 180 if diastolic < 90 for patients with known history of isolated systolic hypertension.</p> <p>If BP is controlled within 2 weeks:</p> <ul style="list-style-type: none"> - First episode: readminister FOLFIRI and aflibercept/placebo at the same dose - Second episode: readminister FOLFIRI and aflibercept placebo at 2 mg/kg. - Third episode: discontinue aflibercept/placebo. <p>If BP is uncontrolled despite appropriate antihypertensive treatment and after 2 week delay:</p> <ul style="list-style-type: none"> - Administer FOLFIRI and discontinue aflibercept/placebo for 1 cycle; if BP is controlled at the time of subsequent cycle, consider administering aflibercept/placebo at 2 mg/kg. - If re-occurrence of ≥ Grade 3 BP despite dose reduction or if BP is still uncontrolled despite omission of aflibercept/placebo in one cycle, permanently discontinue aflibercept/placebo.
Grade 4	Seek cardiologist opinion and permanently discontinue aflibercept/placebo.
When hypertension is accompanied by signs or symptoms of end organ damage such as hypertensive retinopathy, kidney function abnormalities (like progressive proteinuria), or any signs or symptoms of cardiovascular morbidity or central nervous system (CNS) morbidity, treatment with aflibercept/placebo should be interrupted.	

Table 11 - Aflibercept Dose Modifications for Anti-VEGFR Inhibition-Related AEs

Toxicity	Grade	Action
Arterial thromboembolic events	3-4	Permanently discontinue aflibercept/placebo
Hemorrhage	3-4	Permanently discontinue aflibercept/placebo
GI Perforation or fistula	Any	Permanently discontinue study treatment
RPLS	Any	Permanently discontinue study treatment
VTE (DVT)	3	Treat DVT and continue treatment (discontinue if an event occurs on anticoagulation)
VTE (PE)	4	Permanently discontinue aflibercept/placebo

Prior to each aflibercept/placebo administration, UPCR and dipstick urinalyses were scheduled in order to monitor for proteinuria. If UPCR >1, 24-hour urine collection to assess the severity of proteinuria was scheduled. If UPCR was greater than 2 or in case of proteinuria of renal origin (according to urinary protein electrophoresis) associated with hematuria (microscopic or macroscopic), then a blood work-up in search for hemolytic anemia of microangiopathic origin was mandated. Table 12 (copied from the submission) summarizes the clinical management and aflibercept/placebo dose modifications for proteinuria.

Table 12 - Proteinuria management

Prior to cycle n afibercept/placebo administration	Afibercept/placebo dosing for cycle n	During cycle n Repeat 24-h proteinuria as necessary ^a	Afibercept/placebo dosing for cycle n+1	During cycle n+1 Repeat 24-h proteinuria as necessary ^a	Afibercept/placebo dosing for cycle n+2
UPCR [0-1]	Administer afibercept/placebo				
UPCR [1-2] Absence of hematuria	Administer afibercept/placebo, then perform 24-h proteinuria: - if ≤ 3.5 g/24-h - if > 3.5 g/24-h	≤ 2 g/24-h prior n+1 dosing : Administer afibercept/placebo > 2 g/24-h prior n+1 dosing : Omit dosing afibercept/placebo	≤ 2 g/24-h prior n+2 dosing : Administer afibercept/placebo > 2 g/24-h prior n+2 dosing : Omit dosing afibercept/placebo	≤ 2 g/24-h prior n+2 dosing : Resume afibercept/placebo level -1 ^d > 2 g/24-h prior n+2 dosing : Permanently discontinue afibercept/placebo	≤ 2 g/24-h prior n+2 dosing : Resume afibercept/placebo level -1 ^d > 2 g/24-h prior n+2 dosing : Permanently discontinue afibercept/placebo
		≤ 2 g/24-h prior n+1 dosing : Administer afibercept/placebo level -1 ^d $> 2 \leq 3.5$ g/24-h prior n+1 dosing : Omit dosing afibercept/placebo > 3.5 g/24-h prior n+1 dosing : Permanently discontinue afibercept/placebo			

Prior to cycle n afibercept/placebo administration	Afibercept/placebo dosing for cycle n	During cycle n Repeat 24-h proteinuria as necessary ^a	Afibercept/placebo dosing for cycle n+1	During cycle n+1 Repeat 24-h proteinuria as necessary ^a	Afibercept/placebo dosing for cycle n+2
UPCR [1-2] ^b Presence of hematuria Or UPCR > 2	Omit dosing afibercept/placebo	Perform nephrologic work-up ^c and seek nephrologist opinion : - TMA ruled out and ≤ 2 g/24-h prior n+1 dosing : Administer afibercept/placebo - TMA ruled out and $> 2 \leq 3.5$ g/24-h prior n+1 dosing : Omit dosing afibercept/placebo - TMA ruled out and > 3.5 g/24-h prior n+1 dosing : Permanently discontinue afibercept/placebo - TMA diagnosed ^b : Permanently discontinue afibercept/placebo, seek nephrologist opinion for continuation of chemotherapy	≤ 2 g/24-h prior n+2 dosing : Administer afibercept/placebo > 2 g/24-h prior n+2 dosing : Omit dosing afibercept/placebo	≤ 2 g/24-h prior n+2 dosing : Resume afibercept/placebo level -1 ^d > 2 g/24-h prior n+2 dosing : Permanently discontinue afibercept/placebo	≤ 2 g/24-h prior n+2 dosing : Resume afibercept/placebo level -1 ^d > 2 g/24-h prior n+2 dosing : Permanently discontinue afibercept/placebo
Nephrotic syndrome ^b	Permanently discontinue afibercept/placebo, perform nephrologic work-up ^c , seek nephrologist opinion for continuation of chemotherapy				

TMA: Thrombotic micro-angiopathy

a: Patients can be monitored with UPCR as necessary, however 24-hour proteinuria should be performed prior to make dosing decision.

b: Start detection of anti-afibercept antibodies and measurements of circulating free and bound afibercept (see Sections 9.3 and 12.1.6.1)

c: 24-hour proteinuria, urinary protein electrophoresis, haptoglobin, orosomucoid, schistocytes and LDH

d: When a patient is already treated at dose level -1, afibercept/placebo should be discontinued.

Table 13 summarizes the dose reduction levels for the FOLFIRI regimen. Table 14 and Table 15 summarize dose modifications to the FOLFIRI regimen for common toxicities.

Table 13 - FOLFIRI dose reduction levels

Drug	Initial dose mg/m ²	Dose reduction 1	Dose reduction 2
Irinotecan	180 mg/m ²	150 mg/m ²	120 mg/m ²
Bolus 5-FU	400 mg/m ²	320 mg/m ²	240 mg/m ²
Infusional 5-FU	2400 mg/m ²	2000 mg/m ²	1500 mg/m ²

Table 14 - FOLFIRI dose modifications for hematologic toxicity

Toxicity	Grade 2	Grade 3-4
Isolated neutropenia	NA	Dose reduction only if Grade 4 neutropenia > 7 days. Administer G-CSF upon first event of Grade 3-4 neutropenia. Administer prophylactic G-CSF in subsequent cycles.
Febrile neutropenia	Na	First episode: reduce irinotecan by one dose level.

Neutropenic sepsis		Second episode: reduce 5-FU bolus by one dose level. Third episode: discontinue chemotherapy.
Thrombocytopenia	Full dose	First episode: reduce 5-FU (bolus and infusion) by one dose level. Second episode: reduce irinotecan bolus by one dose level. Third episode: discontinue chemotherapy.

Table 15 - FOLFIRI dose modifications for non-hematologic toxicity

Toxicity	Grade 2	Grade 3	Grade 4
Diarrhea	Full dose	1 st episode: reduce irinotecan by one dose level 2 nd episode: reduce 5-FU (bolus and infusion) by one dose level 3 rd episode: discontinue chemotherapy	
Stomatitis	Full dose	Reduce 5-FU (bolus and infusion) by one dose level	Reduce 5-FU (bolus and infusion) by two dose levels
Palmar-plantar erythrodysesthesia	Full dose	Reduce 5-FU (bolus and infusion) by one dose level	NA
Bilirubin increase	Delay infusion until ≤ Grade 1: 1 st episode: no dose reduction 2 nd episode: reduce irinotecan by one dose level 3 rd episode: reduce irinotecan by a second dose level 4 th episode: permanently discontinue irinotecan. Persisting Grade 2 after 2 week delay: 1 st episode: reduce irinotecan by 2 dose levels 2 nd episode: permanently discontinue irinotecan	Delay infusion until ≤ Grade 2. Persisting Grade 3 after 2 week delay: permanently discontinue irinotecan.	Permanently discontinue FOLFIRI.
ALT/AST increase	Full dose	Delay infusion until ≤ Grade 2. Persisting Grade 3 after 2 week delay: permanently discontinue irinotecan.	Permanently discontinue FOLFIRI.
ALK increase	Full dose	Persisting Grade 3 after 2 week delay: permanently discontinue irinotecan.	Permanently discontinue FOLFIRI.
Hypersensitivity reaction	Discontinue irinotecan if related to irinotecan.		

Efficacy Assessments

At all time points, tumor evaluations must have consisted of a CT or MRI scan. At baseline, a CT or MRI scan of the abdomen and pelvis, or other relevant organ system with target lesion(s) was required. Chest X-ray was performed, and then chest CT was performed in case target lesions in the lungs were identified. Tumor assessments were performed every 6 weeks. The same imaging techniques were to be used from baseline to disease progression and

systematically collected for the purpose of an independent third party review, blinded to randomization. Imaging tests were repeated to confirm a partial or complete response (at least 4 weeks after initial documentation of response). Response was evaluated by the investigators according to the RECIST criteria.

Once progression was documented, patients should have been followed once every 2 months for survival until death.

Safety Monitoring

The NCICTCAE v 3.0 dictionary was used to grade clinical and laboratory AEs. Standard definitions of AEs and SAEs were used. A chart describing all monitoring procedures can be found in Table 107 of this review.

Immunogenicity and Pharmacokinetic Assessments

Immunogenicity assessments were to be performed prospectively in all randomized and treated patients, before the first administration of aflibercept/placebo, during the treatment period with aflibercept/placebo, and finally following the last administration of aflibercept/placebo. At each time point, the assessment should have included detection of anti-aflibercept antibodies and measurements of circulating free and bound aflibercept to indirectly assess the neutralizing capacity of anti-aflibercept antibodies, when present. Sampling was scheduled to occur during Cycles 1, 2, 3, 5, 7, 9, and every other cycle after that. Follow-up sampling was scheduled at the end of treatment, 30-days after the end of treatment, and 90 days after end of treatment.

Event driven assessments were to be performed in case of occurrence of:

- Grade ≥ 2 infusion related allergic or allergic type reaction
- Patients reporting proteinuria $>3.5\text{g}/24\text{-h}$ or proteinuria of renal origin associated with hematuria.

Statistical Considerations

Three populations were defined for the statistical analyses:

- The Intent-to-Treat (ITT) population included all patients who provided informed consent and for whom there was confirmation of successful allocation of a randomization number through the IVRS. This population was the primary population for efficacy analyses (with the exception of response rate). All analyses using this population were based on the treatment assigned by IVRS.
- The evaluable patient (EP) population for tumor response included all randomized patients with measurable disease at study entry, as per IRC evaluation, and with at least one valid post-baseline tumor evaluation. Patients who died due to progression disease (PD) or who had documented radiological PD before having first protocol scheduled post-baseline imaging evaluation were not excluded. All analyses using the EP population were based on the treatment assigned by IVRS. Only those patients who consented for third party review were part of the EP analysis.
- The safety population comprised the subset of the ITT population that received at least one dose of study treatment (aflibercept, placebo or FOLFIRI). Analyses using data from this population were based on the treatment actually received (any patient who received at least one

dose of aflibercept, even when receiving the rest of study treatment with placebo, was counted in the aflibercept treatment arm).

The primary endpoint was overall survival (OS) defined as the time interval from the date of randomization to the date of death, due to any cause. If death was not observed during the study, data on OS was to be censored at the earlier of the last date the patient was known to be alive and the cutoff date. Secondary efficacy endpoints included PFS (defined as the time interval from the date of randomization to the date of first observation of disease progression or the date of death) and tumor response. Tumor assessments followed RECIST criteria.

The expected median survival time in the control arm (FOLFIRI + placebo) was 11 months. Assuming that survival times were exponentially distributed in both treatment arms, with an expected 20% risk reduction in the aflibercept plus FOLFIRI arm compared to the FOLFIRI plus placebo arm (hazard ratio of 0.80, corresponding to a median overall survival improvement from 11 months in the control arm to 13.75 months in the test arm), a total of 863 deaths were required to detect this magnitude of effect with 90% power using a two sided log-rank test at a significance level of 0.05. This calculation took into account the stopping boundaries for overwhelming efficacy at two interim analyses of OS (36.5% and 65% information times) using the group sequential approach based on the O'Brien-Fleming alpha spending function and a stopping boundary for futility based on the Gamma (-5) β -spending function at the first interim analysis.

To achieve the targeted number of events, and based on an anticipated accrual period of 30 months followed by 9 months of follow-up after the randomization of the last patient, a total of 1,200 patients (600 in each arm) were required.

The cut-off date for the OS analysis was calculated at the time where 863 deaths were observed. The final PFS was planned to occur at the time of the formal interim analysis of OS (second interim analysis, at 65% of information). Assuming a median PFS of 4 months for the control arm, it was expected that approximately 845 PFS events were to occur, allowing the detection of a 20% risk reduction in PFS with 90% power (corresponding to an increase in median PFS from 4 to 5 months).

Table 16 - VELOUR Amendments

Amendment	Date	Major changes
Amendment 1	August 3, 2007	<ul style="list-style-type: none">- Change in stratification factor performance status from PS 0-1 vs. 2 to 0 vs. 1 vs. 2.- Deletion of the biased coin dynamic allocation method.- Addition of response rate as a secondary endpoint, with only descriptive statistics to be used for this analysis.
Amendment 2	April 23, 2008	<ul style="list-style-type: none">- Addition of prior bevacizumab as a stratification factor.- Changes in the immunogenicity evaluation.- Addition of a third party review of radiographs.
Amendment 3	November 16, 2009	<ul style="list-style-type: none">- Addition of an early efficacy analysis (OS and PFS as per investigator)

		<p>when 36.5% of the planned OS have occurred, following the DMC request.</p> <ul style="list-style-type: none"> - Specification that the final PFS analysis will be based on the IRC assessment. - Specification that the evaluable patient population is based on randomization and not treatment actually received. - Prolongation of anticonception requirement to 6 months after the last dose of study treatment.
Amendment 4	February 11, 2010	Following the DMC meeting after 880 patients completed at least 1 cycle, addition of recommendation to administer G-CSF upon occurrence of \geq Grade 3 neutropenia and prophylactic administration of GCF for subsequent cycles.
Amendment 5	April 27, 2011	Extension of study participation beyond the cut-off date for the primary analysis of overall survival.

6 Review of Efficacy

Efficacy Summary

The efficacy of aflibercept in the treatment of metastatic colorectal carcinoma (mCRC) that has progressed after one line of treatment with an oxaliplatin-based therapy (for advanced/metastatic disease or in the adjuvant setting if progressed during treatment or within 6 months after treatment) was demonstrated in one well conducted clinical trial, EFC10262, “VELOUR.” VELOUR was a prospective, multicenter, multinational, randomized (1:1), double-blind, parallel-arm study of aflibercept versus placebo in patients with mCRC being treated with FOLFIRI. A total of 1,200 patients were planned for inclusion in order to reach the pre-determined number of deaths.

The primary objective of the study was to demonstrate improvement in overall survival (OS). The secondary objectives were to compare PFS, response rate (both as per RECIST 1.1 criteria as assessed by an IRC) between the two treatment arms, to evaluate the safety profile in the two treatment arms, to assess immunogenicity of IV aflibercept, and to assess pharmacokinetics of IV aflibercept and perform population PK evaluation.

Treatment consisted of either aflibercept or placebo at 4 mg/kg on Day 1 every 2 weeks in combination with FOLFIRI (irinotecan 180 mg/m² IV over 90 minutes and dl leucovorin 400 mg/ m² IV infusion over 2 hours, at the same time, in bags using a Y-line, followed by 5-FU 400 mg/ m² IV bolus given over 2-4 minutes, followed by 5-FU 2400 mg/ m² continuous IV infusion over 46 hours).

Patients were stratified at randomization according to prior therapy with bevacizumab (yes versus no), and ECOG PS (0 versus 1 versus 2).

Patients received treatment until disease progression, unacceptable toxicity, or patient's refusal. Following documentation of progressive disease, patients were followed for survival status every 2 months until death or withdrawal of patient consent or until cutoff date for final analysis.

CT scans or MRI and chest X-ray (or chest CT or MRI scan in case of thoracic target lesions) and other exams, as clinically indicated, were performed to assess disease status at baseline, every 6 weeks during study treatment, and at the end of study treatment. If patients discontinued study treatment without documented disease progression, then tumor assessments were performed every 6 weeks until disease progression was documented. The same imaging method was to be used at each assessment.

For the primary endpoint of OS, the expected median survival time in the placebo/FOLFIRI arm was 11 months. The study aimed for a 20% risk reduction in aflibercept/FOLFIRI arm compared to placebo/FOLFIRI (hazard ratio of 0.80, corresponding to a median overall survival improvement from 11 months in the control arm to 13.75 months in the test arm). Assuming that survival times would be exponentially distributed in both treatment arms, a total of 863 deaths were required to detect with 90% power a 20% risk reduction in the aflibercept arm relative to the placebo arm, using a two sided log-rank test at a significance level of 0.0499. This calculation took into account the stopping boundaries for overwhelming efficacy at two interim analyses of OS (36.5% and 65% information times) using the O'Brien-Fleming alpha spending function and a stopping boundary for futility based on the gamma (-5) β -spending function at the first interim analysis. The cutoff date for OS was the date when the required 863 deaths had been observed (February 7, 2011). For the primary analysis of OS, the two treatments were compared using the log-rank test procedure stratified by stratification factors.

The first patient was enrolled on November 19, 2007 and the last patient was enrolled on March 16, 2010. A total of 1,226 patients were randomized, 614 patients randomized to the placebo arm and 612 patients to the aflibercept arm. Five patients in each treatment arm were not treated. At the time of data cut-off, 598 patients (97%) in the placebo arm and 593 patients (97%) in the aflibercept arm had discontinued study treatment.

Patients' demographics were balanced between the two treatment arms. Median age at randomization was 61 years old, and 39% and 33% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively were 65 years of age or older. The majority of patients were men (58% and 60% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively). The vast majority of patients were White (85% and 90% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively). Initial disease characteristics were similar and balanced between treatment arms. All patients had a diagnosis of adenocarcinoma. The most frequent primary site was colon (49% in the placebo/FOLFIRI arm and 47% in the aflibercept/FOLFIRI arm). All patients received prior oxaliplatin treatment. Regarding prior bevacizumab treatment, according to the CRFs, 29% and 28% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively received bevacizumab. As per IRVS, 30% of patients in each arm were randomized in the prior bevacizumab stratum.

At the time of the data cut-off, 97% of patients in each arm had discontinued treatment. The main reason for treatment discontinuation was disease progression [437 patients (71%) in the placebo arm and 305 patients (50%) in the aflibercept arm]. The analysis of the physician stated reason for treatment discontinuation showed that 12% patients in the placebo arm and 27% of patients in the aflibercept arm discontinued treatment because of an adverse event. However, the analysis of the safety database showed that AEs that lead to treatment discontinuation (excluding fatal AEs) were more frequent in the aflibercept arm [80 patients (13%) in the placebo arm and 252 patients (41%) in the aflibercept arm]. This discrepancy in the results of the patients randomized to the aflibercept arm was a reflection of the difficulty of attribution in the context of a chemotherapy administered until disease progression. For example, while it was clear that sepsis was an adverse event, the majority of the gastrointestinal events (obstruction, ileus, etc) could not be easily classified as toxicity or as progression of disease.

The protocol was overall well conducted, and protocol violations were minimal and did not impact the integrity of the data.

The analysis of OS was performed on the ITT population, 614 patients in the placebo/FOLFIRI arm and 612 patients in the aflibercept/FOLFIRI arm. FDA statistical review (see Dr. Zhang statistical review) agrees with most of the results as presented by Sanofi, and there were no statistical significant differences between Sanofi's and FDA review.

At the time of the data cutoff for the final analysis, the median follow-up time was 22.28 months. The analysis was based on a total of 863 deaths: 460 events (75%) reported in the placebo arm and 403 events (66%) reported in the aflibercept arm. One hundred forty nine patients (24%) in the placebo arm and 201 patients (33%) in the aflibercept arm were alive at the cutoff date. Information on survival was available for all but 13 patients: 5 patients in the placebo arm and 8 patients in the aflibercept arm were censored >2 months before the cutoff date; all 5 patients in the placebo arm were lost to follow up, while in the aflibercept arm, there were 2 patients lost to follow up and 6 patients who withdrew consent.

Survival estimates using the Kaplan Meier method were compared using a log-rank test stratified by factors specified at the time of randomization (ECOG PS, 1 vs. 0 and 2 vs. 0; prior bevacizumab, yes vs. no). The addition of aflibercept to the FOLFIRI regimen resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0032 (which met the pre specified efficacy boundary of 0.0466) and an estimated hazard ratio of 0.817 (95.34% CI: 0.713 to 0.937). The use of aflibercept resulted in a risk of death reduction of 18.3% when compared to placebo/FOLFIRI. Median overall survival (95.34% CI) in the placebo arm was 12.06 months (11.072 to 13.109), compared to 13.50 months (12.517 to 14.949) in the aflibercept arm.

To test the interaction of the treatment with the stratification factors, pre-specified subgroup analyses using a Cox proportional hazard model were conducted. There were no significant

interactions between treatment arms and stratification factors at the 2-sided 10% level, and a difference in overall survival in favor of aflibercept over placebo was observed in each stratification subgroup, with the exception of the subgroup of patients with ECOG PS of 2 at baseline (12 patients in the placebo arm and 13 patients in the aflibercept arm according to the IVRS form). Because of the small sample size of this stratum, no conclusions can be made. Also, although not statistically significant, an exploratory analysis showed that patients previously exposed to bevacizumab appeared to benefit less from aflibercept treatment: the HR for patients who were previously exposed to bevacizumab (n=253) was 0.86 (95% CI 0.67; 1.1) versus 0.78 (95% CI 0.67; 0.92) in patients who did not receive prior bevacizumab (n= 853).

The final analysis of PFS was performed at the time of the second interim analysis of OS (cut off date 6 May 2010), and was conducted in the ITT population. The analysis was based on a total of 847 events, with 454 events in the placebo arm and 393 events in the aflibercept arm. There was a high rate of discrepancy between the investigator assessments and the IRC assessments (46% on the placebo arm and 39% on the aflibercept arm). Median PFS (IRC assessment, FDA analysis) in the placebo arm was 4.7 months (95% CI 4.074; 5.552) and 6.9 months (95% CI 5.881; 7.852) in the aflibercept arm, with an estimated stratified hazard ratio of 0.756 (95% CI 0.660; 0.876), and a stratified log-rank test p-value of 0.00007. PFS analyses by pre-specified subgroups (stratification factors, demographic, and baseline characteristics), and sensitivity analyses did not show evidence of significant interactions between treatment and any of these subgroups (with the exception of liver metastases only, a better prognosis group of patients), supporting a consistent effect of treatment across subgroups.

Response rate (assessed in 530 patients in the placebo arm and 531 patients in the aflibercept arm) was higher in the aflibercept arm: 59 (11%) patients in the placebo arm and 105 patients (20%) in the aflibercept arm were assessed as responders (complete or partial response).

In conclusion, the EFC10262/VELOUR study demonstrated a clinically and statistically significant improvement of OS in patients treated with aflibercept and FOLFIRI over patients treated with placebo and FOLFIRI (stratified hazard ratio: 0.817, 95.34% CI: 0.713 to 0.937; p = 0.0032, equivalent to an 18.3% reduction in the risk of death). These results are supported by both PFS and response rate improvements in patients treated with aflibercept/FOLFIRI, as well as subgroup and sensitivity analyses.

6.1 Indication

Sanofi Aventis proposed the following indication for this submission: Aflibercept is indicated in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

The recommended aflibercept dose is 4 mg/kg every two weeks.

6.1.1 Methods

The efficacy analysis was focused on the results of one trial, EFC10262 or “VELOUR”, A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer (MCRC) Treated with Irinotecan / 5-FU Combination (FOLFIRI) after failure of an oxaliplatin based regimen.

Additional trials evaluated for safety analyses were reviewed in the Safety Section.

6.1.2 Demographics

The first patient was enrolled on November 19, 2007 and the last patient was enrolled on March 16, 2010. The study data cut-off date was February 7, 2011, when the 863rd death occurred.

A total of 1,401 patients signed the informed consent form for the study, and 175 patients were considered screening failures and consequently were not randomized. The majority of screening failures (70%) were related to patients not being eligible for the trial for having one or more of the exclusion criteria.

The trial recruited patients from Argentina (6), Australia (96), Austria (7), Belgium (82), Brazil (48), Chile (64), Czechoslovakia (77), Germany (35), Denmark (15), Spain (55), Estonia (10), France (2), UK (99), Greece (19), Italy (49), Korea (65), Netherlands (34), Norway (33), New Zealand (20), Poland (56), Puerto Rico (6), Romania (32), Russia (75), Sweden (14), Turkey (6), Ukraine (22), US (132), and South Africa (67). Table 17 summarizes patient enrollment by region.

Table 17 - VELOUR: Geographic region of precedence.

Region	Placebo/FOLFIRI; n (%) N=614	Aflibercept/FOLFIRI; n (%) N=612
Western Europe	217 (35)	208 (34)
Eastern Europe	136 (22)	161 (26)
North America	75 (12)	63 (10)
South America	56 (9)	62 (10)
Other countries	130 (21)	118 (19)

Patient demographics were balanced between the two treatment arms (Table 18). Median age at randomization was 61 years, and 39% and 33% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively were 65 years of age or older. The majority of patients were men (58% and 60% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively). The majority of patients were White (85% and 90% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively).

Table 18 - VELOUR: Demographics (ITT population)

	Placebo/FOLFIRI; n (%) N=614	Aflibercept/FOLFIRI; n (%) N=612
Gender		
Male	353 (58)	365 (60)
Female	261 (42)	247 (40)
Race		
White	523 (85)	548 (90)
Asian	51 (8)	35 (6)
Black	27 (4)	16 (3)
Other	13 (2)	13 (2)
Age (years)		
Range	19-86	21-82
Mean (SD)	60.16 (10.8)	59.46 (10.5)
Median	61	61
65 years and older	238 (39)	205 (33)
75 years and older	39 (6)	33 (5)

Initial disease characteristics were similar and balanced between treatment arms (Table 19). All patients had a diagnosis of adenocarcinoma. The most frequent primary site was colon (49% in the placebo/FOLFIRI arm and 47% in the aflibercept/FOLFIRI arm).

Table 19 - VELOUR: Disease characteristics at baseline (ITT population)

	Placebo/FOLFIRI; n (%) N=614	Aflibercept/FOLFIRI; n (%) N=612
Tumor site		
Colon	302 (49)	289 (47)
Rectum	174 (28)	197 (32)
Recto-sigmoid	136 (22)	123 (20)
Other site	2 (<1)	3 (<1)
Time from initial diagnosis		
Median time [months; (range)]	13.6 (2.3-214)	14.6 (2-325)
Mean time [months; (SD)]	20.87 (21)	20.98 (24)
Metastatic organ involvement		
Liver	431 (70)	459 (75)
Lung	277 (45)	271 (44)
Lymph nodes	181 (30)	173 (28)
Peritoneum	88 (14)	68 (11)
Liver metastasis only	146 (24)	153 (25)

Patients enrolled with disease in “other site” (see table above) in the placebo/FOLFIRI arm included a patient with metastatic disease presumed to have a colorectal primary because of CEA and CK positivity, and another patient with synchronous cecal and rectal primary tumors. In the aflibercept/FOLFIRI arm, the primary sites for the “other sites” category were the appendix, colon plus appendix, and a patient with a history of colon cancer more than 20 years prior with a rising CEA antigen.

The median time from colon cancer diagnosis was 13.67 months in the placebo/FOLFIRI arm and 14.62 months in the aflibercept/FOLFIRI arm. The median time from end of advanced/metastatic disease treatment to randomization was 2.10 months (range 0.2-32 months) in the placebo/FOLFIRI arm and 2.26 months (0.4-57 months) in the aflibercept/FOLFIRI arm.

In most patients, determination of metastatic disease was assessed by the IRC (with the exception of 42 patients who either died before they could sign the IRC consent form or refuse to sign it). For the remaining 42 patients, investigators' assessments were used for the analyses presented in Table 19. Six patients in the placebo/FOLFIRI arm and 2 patients in the aflibercept/FOLFIRI arm were determined not to have metastatic disease at baseline. Fifty-five percent (337 patients) in the placebo/FOLFIRI arm and 58% (354 patients) in the aflibercept/FOLFIRI arm had two or more sites of metastatic disease. Twenty four percent and twenty five percent of patients in the placebo/FOLFIRI and aflibercept arms respectively had liver involvement as the only site of metastatic disease.

Prior to enrolling in VELOUR, all patients received oxaliplatin, and 97% received a combination oxaliplatin/fluoropyrimidine regimen. For patients in the advanced setting only, the median duration of oxaliplatin treatment was 5.12 and 5.19 months in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively. Seventy five percent of patients in each arm received oxaliplatin treatment for less than 6.7 months.

Table 20 - VELOUR: Prior treatments (ITT population)

	Placebo/FOLFIRI; n (%) N=614	Aflibercept/FOLFIRI; n (%) N=612
Prior surgery	510 (83)	513 (84)
Prior radiotherapy	137 (22)	125 (20)
Prior chemotherapy	614 (100)	612 (100)
Prior chemotherapy treatment		
Adjuvant only	64 (10)	60 (10)
Neoadjuvant/adjuvant AND advanced	108 (18)	102 (17)
Advanced therapy only	442 (72)	450 (73)
Oxaliplatin only*	20 (3)	17 (3)
Oxaliplatin/fluoropyrimidine*	409 (67)	422 (69)
Oxaliplatin/fluoropyrimidine/bevacizumab*	216 (35)	202 (33)
Prior surgical treatment**		
Colon primary resection	349 (57)	322 (53)
Rectal primary resection (including rectosigmoidectomy)	169 (28)	193 (32)
Metastasectomies	94 (15)	103 (17)
Palliative surgery only	52 (8)	42 (7)

* Because patients received oxaliplatin, fluoropyrimidines, and bevacizumab in one or more lines of treatment, the sum is larger than the number of patients enrolled in each arm.

** Because patients may have been treated with more than one surgery, the sum is larger than the number of patients enrolled in each arm.

Table 21 summarizes the responses to prior treatment in the subset of patients who received treatment for advanced/metastatic disease.

Table 21 - VELOUR: Prior response to advanced treatment (patients who received treatment only for metastatic/advanced disease)

	Placebo/FOLFIRI; n (%) N=442	Aflibercept/FOLFIRI; n (%) N=450
Complete response	25 (6)	17 (4)
Partial response	166 (38)	193 (43)
Stable disease	168 (38)	163 (36)
Progressive disease	62 (14)	63 (14)
Unknown/not assessed/not evaluable	21 (5)	13 (3)

Regarding prior bevacizumab treatment, according to the CRFs, 29% and 28% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively received bevacizumab. As per the IRVS, 30% of patients in each arm were randomized in the prior bevacizumab strata. Table 22 summarizes the ITT population by stratification factors as per the investigator filled IVRS forms.

Table 22 - VELOUR: ITT population by stratification factors (IVRS)

Stratification factors	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
ECOG PS		
0	350 (57)	349 (57)
1	250 (41)	250 (41)
2	14 (2)	13 (2)
Prior bevacizumab		
Yes	187 (30)	186 (30)
No	427 (70)	426 (70)

An analysis of the disposition database showed discordances between the IVRS forms and the CRFs regarding the ECOG performance status score and prior bevacizumab stratum. The listings of patients with discordant ECOG PS and/or bevacizumab prior administration can be found in Table 111, Table 112, and Table 113 in the appendices section (FDA analysis). Table 23 summarizes the discordances between the IVRS and CRF forms and the actual composition of the ITT population.

Table 23 - VELOUR: Stratification errors at randomization and actual composition of the ITT population (by CRF)

Stratification factors	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Patients with stratification error on ECOG PS score	13 (2)	17 (3)
Patients with stratification error on prior bevacizumab treatment strata	14 (2)	14 (2)
ITT actual composition (CRF)		
No prior bevacizumab	437 (71)	443 (72)
Prior bevacizumab	177 (29)	169 (28)
ECOG PS 0	354 (58)	350 (57)
ECOG PS 1	248 (40)	249 (41)
ECOG PS 2	12 (2)	13 (2)

Reviewer's comment: these stratification errors resulted in a similar composition of the ITT population and it is unlikely that these small differences impacted the analysis of the results. Please refer to Dr. Zhang's review for further analysis.

Before randomization, 137 (22%) and 125 (20%) patients in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively received radiotherapy. The majority of these patients received rectal/pelvis irradiation. A complete summary of radiotherapy treatments received prior to randomization can be found in the appendices section (Table 110).

The previous medical history of all patients was recorded. The sponsor further analyzed the previous medical history in two categories: medical/surgical history and prior thrombovascular events and/or the presence of cardiovascular risk factors.

Table 114 in the appendices section summarizes the incidence of medical/surgical co-morbidities by SOC. Co-morbidities observed in more than 10% of patients were gastrointestinal disorders (39% and 38% in the placebo and aflibercept arms respectively), general disorders and administration site conditions (16% and 14% in the placebo and aflibercept arms respectively), infections and infestations (13% and 12% in the placebo and aflibercept arms respectively), musculoskeletal and connective tissue disorders (20% and 21% in the placebo and aflibercept arms respectively), nervous system disorders (34% and 30% in the placebo and aflibercept arms respectively), psychiatric disorders (15% and 13% in the placebo and aflibercept arms respectively), respiratory, thoracic and mediastinal disorders (15% and 16% in the placebo and aflibercept arms respectively), and renal and urinary disorders (10% and 11% in the placebo and aflibercept arms respectively). Table 24 summarizes the PTs for those conditions observed in more than 5% of patients. Most of these co-morbidities are expected for patients with cancer or prior treatment with cancer (e.g., neurological toxicities in patients receiving oxaliplatin).

Table 24 - VELOUR: Baseline medical/surgical co-morbidities observed in > 5% of patients (by PT, ITT population)

SOC	PT	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Gastrointestinal disorders	Abdominal pain	55 (9)	39 (6)
	Constipation	47 (8)	25 (4)
General disorders and administration site conditions	Fatigue	53 (9)	47 (8)
Musculoskeletal and connective tissue disorders	Back pain	42 (7)	31 (5)
Nervous system disorders	Neuropathy peripheral	79 (13)	62 (10)
	Paraesthesia	35 (6)	34 (6)
	Peripheral sensory neuropathy	49 (8)	36 (6)
Psychiatric disorders	Depression	26 (4)	41 (7)
	Insomnia	42 (7)	32 (5)

Four hundred one (65%) patients in the placebo/FOLFIRI arm and 397 (65%) in the aflibercept arm had a history of cardiovascular risk factors or thrombovascular events. The most commonly reported factor was the presence of hypertension in 44% of patients in both arms. Table 25 summarizes the baseline incidence of cardiovascular risk factors/disease and thromboembolic events by group terms and PTs when relevant.

Table 25 - VELOUR: Baseline cardiovascular risk factors or thromboembolic events (ITT population)

HLGT PT	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Patients with cardiovascular risk factors and/or thrombovascular events	401 (65)	397 (65)
Cardiac dysfunction	12 (2)	5 (1)
Hypertension	268 (44)	266 (44)
Arterial thromboembolic event	55 (9)	59 (10)
- myocardial ischemia	14 (2)	18 (3)
- myocardial infarction	13 (2)	17 (3)
- angina pectoris	10 (2)	13 (2)
- cerebrovascular accident	10 (2)	10 (2)
- TIA	10 (2)	6 (1)
Venous thromboembolic event	41 (7)	54 (9)
- deep vein thrombosis	18 (3)	28 (5)
- pulmonary embolism	16 (3)	20 (3)
Aneurysm	3 (<1)	2 (<1)
Arteriosclerosis	18 (3)	20 (3)
Cardiac arrhythmia	30 (5)	29 (5)
Conduction defects	6 (1)	5 (1)
Dyslipidemia	87 (14)	105 (17)
- Hypercholesterolemia	85 (14)	95 (15)
Valvular disease	5 (1)	4 (1)
Tobacco use	126 (21)	137 (22)
Diabetes mellitus	74 (12)	69 (11)
Obesity	13 (2)	12 (2)

At the time of study entry, 509 (83%) and 510 (83%) patients in the placebo/FOLFIRI and aflibercept/ FOLFIRI arms, respectively were on treatment with drugs other than anti-cancer treatment drugs. Table 26 summarizes the therapeutic classes of drugs that patients were being treated with at the time of study entry (drugs used in more than 10% of patients; a complete summary can be found in Table 115 in the appendices section).

Table 26 - VELOUR: Baseline non-cancer concomitant medication (in ≥10% of the ITT population)

Therapeutic class	Placebo/FOLFIRI (n=614)		Aflibercept/FOLFIRI (n=612)	
	N	%	N	%
Analgesics	257	42	233	38
Agents acting on the rennin-angiotensin system	165	27	169	28
Drugs for acid-related issues	145	24	161	26
Ophthalmologicals	110	18	129	21

Therapeutic class	Placebo/FOLFIRI (n=614)		Aflibercept/FOLFIRI (n=612)	
	N	%	N	%
Psycholeptics	122	20	111	18
Stomatological preparations	114	19	110	18
Topical products for joint and muscular pain	114	19	110	18
Antithrombotic agents	96	16	108	18
Beta blocking agents	98	16	99	16
Calcium channel blockers	89	14	90	15
Anti-inflammatory and antirheumatic agents	76	12	85	14
Lipid modifying agents	75	12	75	12
Vitamins	69	11	71	12
Anti-acne preparations	60	10	59	10
Psychoanaleptics	59	10	64	10
Antidiarrheal agents	66	11	56	9
Drugs in diabetes treatment	68	11	57	9
Laxatives	88	14	52	8
Diuretics	65	11	48	8

Forty four percent and forty three percent of patients in the placebo and aflibercept arms, respectively were on treatment for hypertension before study enrollment. Table 27 summarizes the use of antihypertensive medications at baseline.

Table 27 - VELOUR: Antihypertensive treatment at baseline

Therapeutic class	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Agents acting on the renin-angiotensin system	188 (31)	182 (30)
Antihypertensives	15 (2)	11 (2)
Beta blocking agents	109 (18)	107 (17)
Calcium channel blockers	95 (15)	101 (17)
Cardiac therapy	5 (1)	6 (1)
Diuretics	75 (12)	53 (9)
Total number patients*	270 (44)	262 (43)

* Some patients received multidrug antihypertensive treatment

Sixteen percent and eighteen percent of patients in the placebo and aflibercept arms, respectively were on treatment or prophylactic treatment for thrombosis/embolism before study enrollment. Table 28 summarizes the use of anticoagulants, antiplatelet drugs, and heparins at baseline.

Table 28 - VELOUR: Anticoagulant treatment at baseline

Chemical class	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Enzymes (serrapeptase)	1	0
Heparin group	24 (4)	41 (7)
Platelet aggregation inhibitors (excluding heparin)	74 (12)	76 (12)
Vitamin K antagonists	10 (2)	21 (3)
Total number patients*	96 (16)	108 (18)

* Some patients received multidrug anticoagulant treatment.

6.1.3 Subject Disposition

A total of 1226 patients were randomized, 614 patients to the placebo/FOLFIRI arm and 612 patients to the aflibercept/FOLFIRI arm. Five patients in each arm were randomized but did not receive treatment. Table 29 summarizes the patient population in the VELOUR study.

Table 29 - VELOUR: Patient population

	Placebo/FOLFIRI (n, %)	Aflibercept/FOLFIRI (n, %)
Randomized population	614 (100)	612 (100)
ITT	614 (100)	612 (100)
Safety population	605 (99)	611 (100)
Tumor response evaluable population (EP)	530 (86)	531 (87)

In the response evaluable population, 84 (14%) patients in the placebo arm and 81 (13%) patients in the aflibercept arm were excluded from the IRC assessment of response because there were no target lesions at baseline [57 (9%) and 41 (7%) patients in the placebo and aflibercept arms respectively], no post-baseline images were available for assessment [9 (2%) and 16 (3%) patients in the placebo and aflibercept arms, respectively], and when no images were available for IRC reading [18 (3%) and 24 (4%) patients in the placebo and aflibercept arms, respectively].

At the time of the data cut-off 598 (97%) in the placebo arm and 593 (97%) patients in the aflibercept arm had discontinued treatment. Reasons for treatment discontinuation are summarized in Table 30 (data from the disposition dataset adds.xpt).

Table 30 - VELOUR: Patients disposition

	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Randomized and treated	609 (99)	607 (99)
Discontinued study treatment	598 (97)	593 (97)
Reasons for treatment discontinuation (including patients randomized but not treated)		
Adverse event	74 (12)	163 (27)
Disease progression	437 (71)	305 (50)
Lost to follow-up	2 (0.3)	0
Poor compliance	4 (0.6)	4 (0.6)
Other	86 (14)	126 (21)

Although in this analysis 12% and 27% of patients discontinued treatment because of an adverse event, the analysis of the safety database (adae.xpt) shows that AEs that lead to treatment discontinuation (excluding the fatal AEs, that were analyzed separately) were more frequent in the aflibercept arm. Eighty patients (13%) in the placebo arm and 252 patients (41%) in the aflibercept arm permanently discontinued treatment. Further analysis of these patients can be found in Section 7.3.3, Dropouts and Discontinuations.

The majority of reasons listed as “other” were withdrawal of consent, refusal of further treatment, or investigator’s decision. However, in the placebo/FOLFIRI arm, at least 11 (2%)

patients discontinued study drugs because they underwent surgery, two subjects because of administration of off-protocol radiotherapy, five subjects for progressive disease that did not qualify as such by RECIST criteria, one subject because of violation of inclusion criteria (patient on anticoagulation therapy with unstable dose of warfarin and/or INR > 3), and one subject because of hypertension exacerbation. In the aflibercept/FOLFIRI arm, 10 (2%) patients discontinued study drugs because they underwent surgery, one subject because of administration of off-protocol radiotherapy, one subject for progressive disease that did not qualify as such by RECIST criteria, two subjects because of delay in treatment of more than 28 days, and one subject because of violation of inclusion criteria (elevated alkaline phosphatase).

At the time of data cut-off, 149 (24%) patients in the placebo/FOLFIRI arm and 207 (34%) patients in the aflibercept/FOLFIRI arm were alive; 460 (75%) and 403 (66%) patients died in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively. Twenty five patients (11 and 14 in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively) remain on treatment and 7 patients were lost to follow-up (2 in the aflibercept/FOLFIRI arm).

6.1.3 Protocol Violations

Blind breaking

The applicant reported that the study blind was broken in three patients (#ID 380001005, 410004020, and 840026002) in the placebo/FOLFIRI arm; in all three cases, an adverse event precipitated the call to the IVRS center to determine if the patient had received aflibercept. All three patients discontinued treatment after the event.

In the aflibercept/FOLFIRI arm, the blind was broken because an adverse event in one patient (ID#410005010), and at the investigator's request after disease progression (cycle 14) in another patient (ID#056002004).

For the purpose of regulatory reporting, the applicant broke the blind in 19 patients (6 patients in the placebo/FOLFIRI arm and 13 patients in the aflibercept/FOLFIRI arm). The AEs in the aflibercept/FOLFIRI arm that triggered the breaking of the blind were ADRS, coagulopathy, hemorrhagic cystitis, death, diabetes mellitus, hepatic hemorrhage, intracardiac thrombus, migraine, peripheral sensory neuropathy, pneumonitis, pulmonary hypertension, and skin ulcer. In the placebo/FOLFIRI arm, the AEs that triggered breaking the blind were arterial thrombosis of the limb, ascites, lobar pneumonia, neutropenic infection, pericarditis, and small intestinal obstruction.

Randomization errors and deviations of eligibility criteria

Randomization errors regarding the stratification factors ECOG performance status and previous bevacizumab treatment were reviewed in Section 6.1.2 (Demographics, Table 22 and Table 23). Listings with the patient IDs can be found in Table 111, Table 112 & Table 113.

Table 31 summarizes the eligibility criteria violations from the protocol deviations dataset (ADDV.xpt).

Table 31 - VELOUR: Eligibility criteria violations

Eligibility criteria violation	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Non RECIST compliant	13 (2)	18 (3)
Chemotherapy, radiotherapy, biologic treatment, or investigational therapy \leq 28 days before randomization or chemotherapy \geq 6 months before enrollment	24 (4)	16 (3)
ALP criterion	5 (1)	7 (1)
Prior history of chronic enteropathy, chronic diarrhea, etc	5 (1)	7 (1)
Tumor assessment performed \geq 29 days before randomization	7 (1)	5 (1)
Hematology/coagulation criterion	5 (1)	4 (1)
Surgery within 28 days of randomization	5 (1)	3 (<1)
Patient with only adjuvant therapy and relapse > 7 months after the end of oxaliplatin.	5 (1)	2 (<1)
Uncontrolled hypertension	2 (<1)	2 (<1)
History of other cancer \leq 5 years	2 (<1)	2 (<1)
Angina pectoris \leq 6 months before enrollment	0	2 (<1)
Serum creatinine criterion	6 (1)	1 (<1)
Location is other than colorectal	2 (<1)	1 (<1)
Vein thrombosis \leq 4 weeks before enrollment	2 (<1)	1 (<1)
UPN criterion	2 (<1)	1 (<1)
AST criterion	1 (<1)	1 (<1)
Non-metastatic disease	1 (<1)	1 (<1)
No previous treatment with oxaliplatin	1 (<1)	1 (<1)
Bilirubin criterion	2 (<1)	0
Arterial thrombosis/embolism \leq 3 months before enrollment	1 (<1)	0
Patient with date of progression missing for oxaliplatin	1 (<1)	0
Informed consent signed after enrollment	1 (<1)	0

Five patients in the placebo/FOLFIRI arm (ID# 032006002, 056005007, 076001008, 826007002, and 840084002) and two patients in the aflibercept/FOLFIRI arm (ID# 032006003 and 643002009) were randomized having experienced a relapse more than 6 months after receiving an oxaliplatin-containing regimen.

Three patients (826009015 in the placebo arm, and 056003007 & 642004001 in the aflibercept arm) did not have confirmed colorectal adenocarcinoma: primary colorectal cancer was assumed based on positive CEA and CK20 in one patient, primary colorectal cancer was assumed based on a colon cancer diagnosed more than 20 years before enrollment and a positive CEA test in another patient, and a primary cecal cancer was diagnosed in the third patient.

Reviewer's comment: *due to the low number of major eligibility criteria violations, it is unlikely that these violations will have impact the final results of the trial. Also, the number and quality of these violations were generally balanced between arms.*

Placebo/aflibercept allocation and administration errors

Four patients (ID# 410002002, 528001003, 840001001, and 380002001) who were randomized to the placebo arm received at least one dose of aflibercept and were analyzed in the aflibercept arm for the purposes of *safety* analyses.

Three patients (ID#076002001, 208003001, and 710001002) who were randomized to the aflibercept arm received at least one dose of placebo (see Table 29).

In summary, of the 614 randomized to the placebo arm, 605 received the correct treatment, while 4 patients received at least one dose of aflibercept. The safety population of the placebo arm has 605 patients. In the aflibercept arm, 607 of the 612 randomized patients received at least one dose of aflibercept. The safety population of the aflibercept arm has these 611 patients (the 607 patients described above plus the 4 patients from the placebo arm that received aflibercept in at least one occasion).

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of the VELOUR study was overall survival, measured as the time from study enrollment to the date of death. The analysis of OS was performed on the ITT population, 614 patients in the placebo/FOLFIRI arm and 612 patients in the aflibercept/FOLFIRI arm. Cutoff date was February 7, 2011. FDA review (see Dr. Zhang's statistical review) confirmed most of the results presented by Sanofi, and there were no significant differences between Sanofi's and FDA review.

At the time of the data cutoff for the final analysis, the median follow-up time was 22.28 months. The analysis was based on a total of 863 deaths: 460 events (75%) reported in the placebo arm and 403 events (66%) reported in the aflibercept arm. One hundred forty nine patients (24%) in the placebo arm and 201 patients (33%) in the aflibercept arm were alive at the cutoff date. Information on survival was available for all but 13 patients: 5 patients in the placebo arm and 8 patients in the aflibercept arm were censored >2 months before the cutoff date; all 5 patients in the placebo arm were lost to follow up, while in the aflibercept arm there were 2 patients lost to follow up and 6 patients who withdrew consent.

Survival estimates using the Kaplan Meier method were compared using a log-rank test stratified by factors specified at the time of randomization (ECOG PS, 1 vs. 0 and 2 vs. 0; prior bevacizumab, yes vs. no). The addition of aflibercept to the FOLFIRI regimen resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0032 (which met the pre specified efficacy boundary of 0.0466) and an estimated hazard ratio of 0.817 (95.34% CI: 0.713 to 0.937). The use of aflibercept resulted in a risk of death reduction of 18.3% when

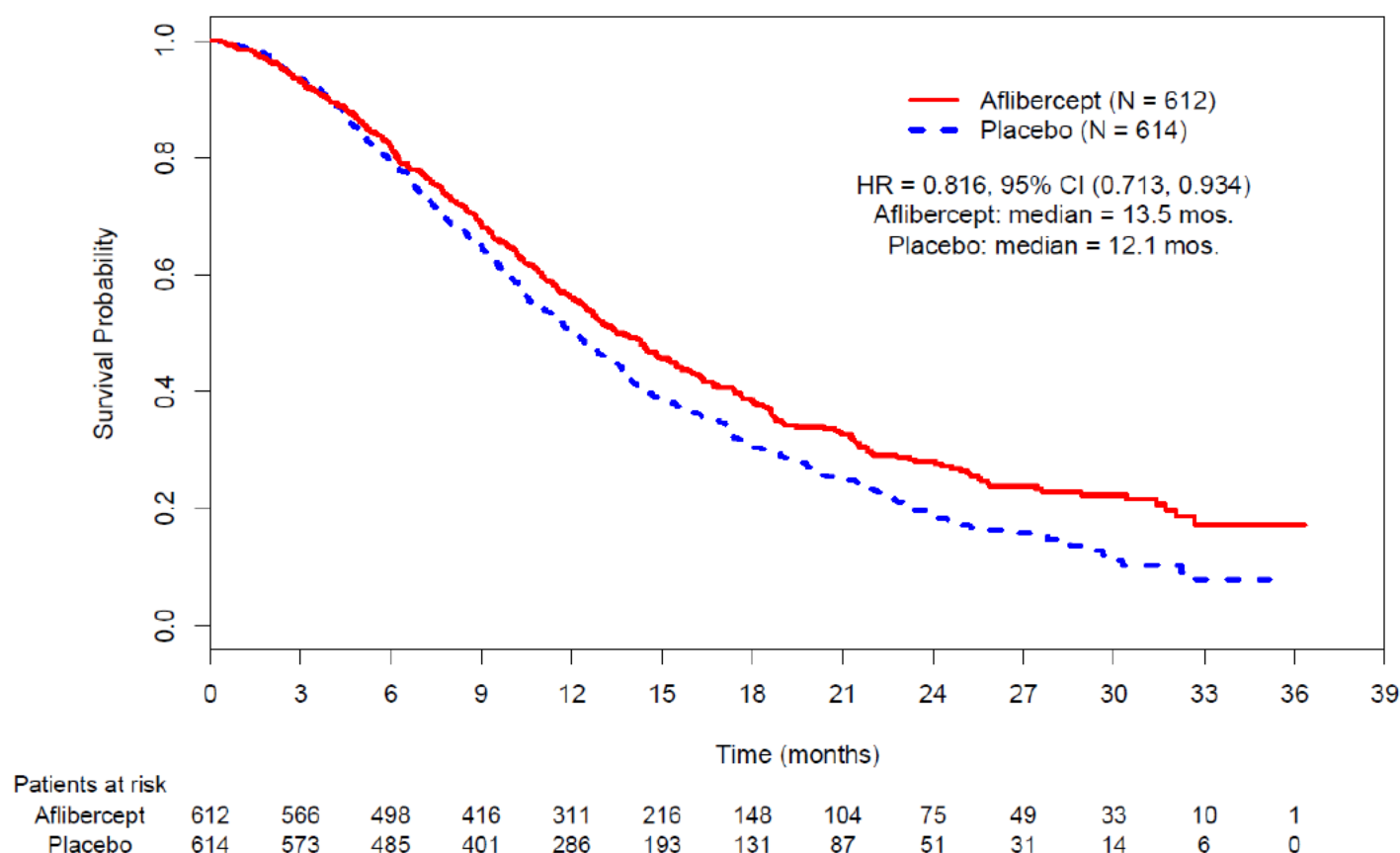
compared to placebo/FOLFIRI. Median overall survival (95.34% CI) in the placebo arm was 12.06 months (11.072 to 13.109), compared to 13.50 months (12.517 to 14.949) in the aflibercept arm. These results are summarized in Table 32.

Table 32 - VELOUR: Overall survival analysis

	Placebo/FOLFIRI (n=614)	Aflibercept/FOLFIRI (n=612)
Deaths	460 (75%)	403 (66%)
Median OS (95% CI), months	12.06 (11.07;13.10)	13.50 (12.51;14.94)
Stratified log rank test p value	0.0032	
Stratified HR (95%CI)	0.81 (0.71;0.93)	
Unstratified log rank test p value	0.0019	
Unstratified HR (95%CI)	0.80 (0.70;0.92)	

The Kaplan-Meier curve is shown in Figure 4 (copied from Dr. J. Zhang review).

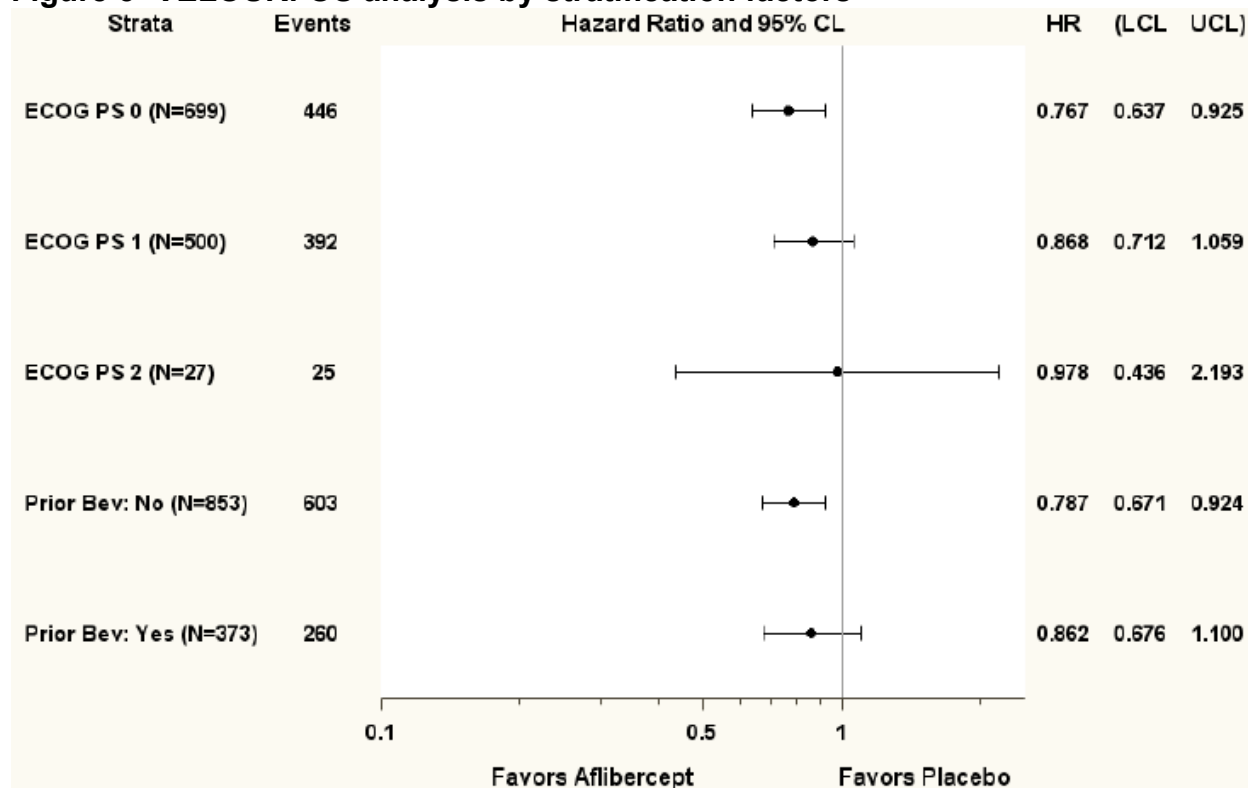
Figure 4 - VELOUR: OS Kaplan Meier curves



To test the interaction of the treatment with the stratification factors, pre-specified subgroup analyses using a Cox proportional hazard model were conducted. There were no significant interactions between treatment arms and stratification factors at the 2-sided 10% level, and a

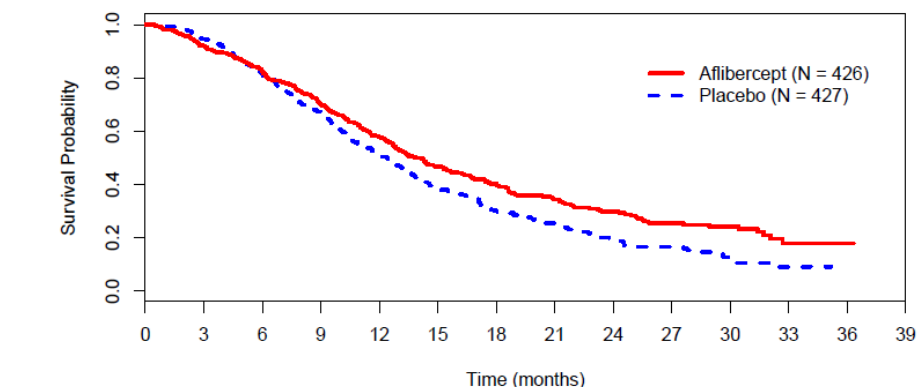
difference in overall survival in favor of aflibercept over placebo was observed in each stratification subgroup, with the exception of the subgroup of patients with ECOG PS of 2 at baseline (12 patients in the placebo arm and 13 patients in the aflibercept arm according to the IVRS form). Because of the small sample size of this stratum, no conclusions can be drawn. Figure 5 (copied from Dr. Zhang's review) shows the hazard ratios for the OS analysis (by IVRS stratification).

Figure 5- VELOUR: OS analysis by stratification factors



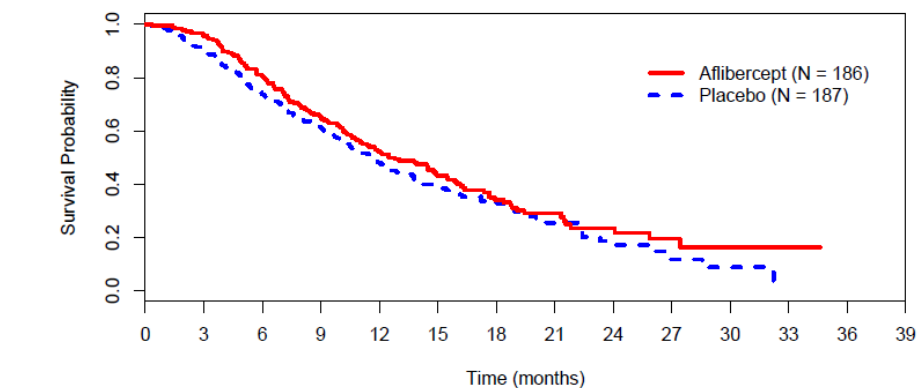
Also, although not statistically significant (and there were fewer patients in the bevacizumab group), patients previously exposed to bevacizumab appeared to benefit less from aflibercept treatment (Figure 6, copied from Dr. J. Zhang review).

Figure 6 - VELOUR: OS Kaplan Meier plot by prior bevacizumab use
No Prior Bevacizumab



Patients at risk													
Aflibercept	426	388	348	295	222	157	112	82	62	43	29	8	1
Placebo	427	403	347	286	205	139	94	65	38	27	12	6	0

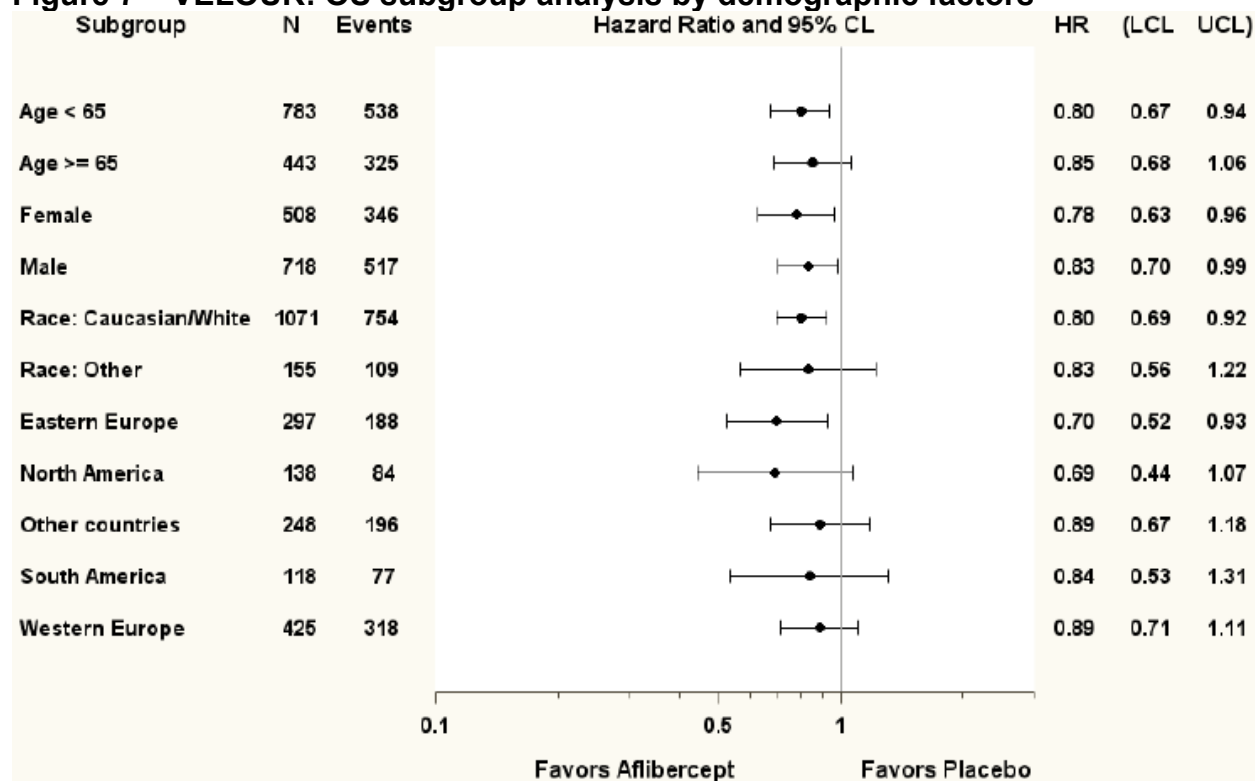
Prior Bevacizumab



Patients at risk													
Aflibercept	186	178	150	121	89	59	36	22	13	6	4	2	0
Placebo	187	170	138	115	81	54	37	22	13	4	2	0	0

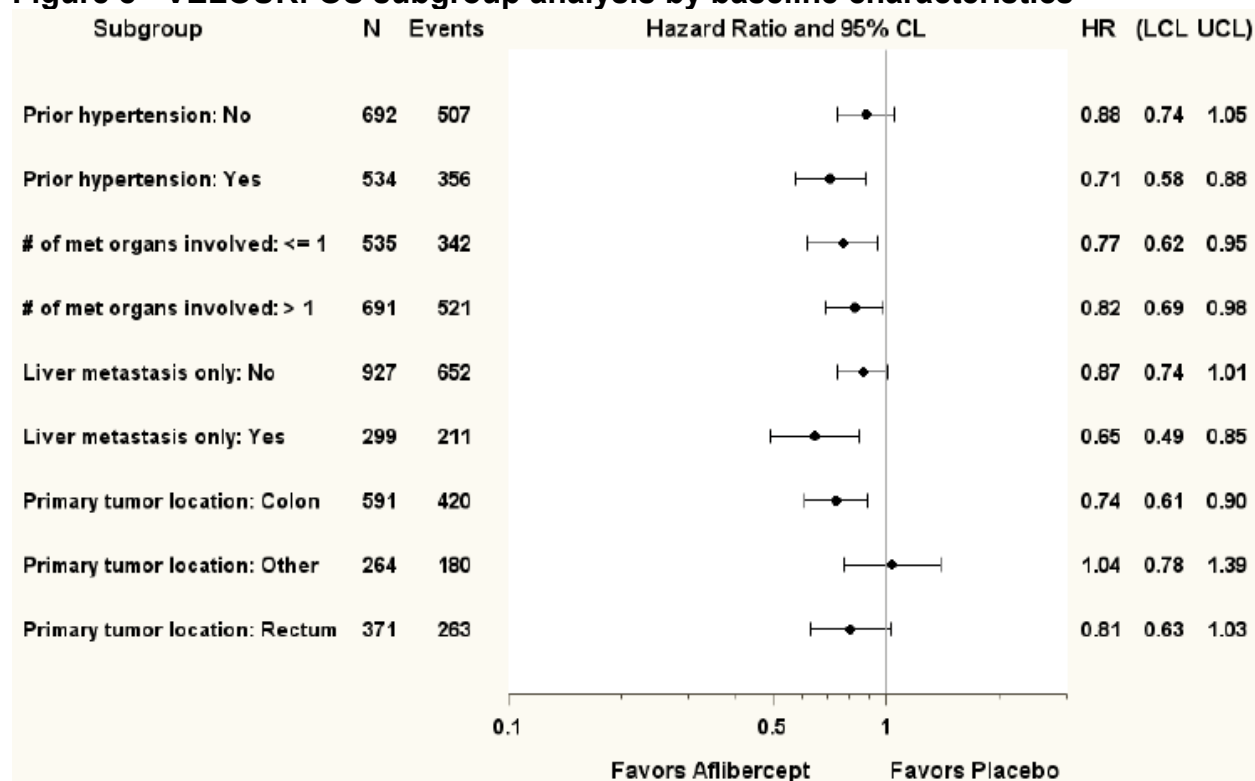
No evidence of treatment interaction was shown between treatment groups and demographic subgroups (age, gender, race, geographical location), as shown in Figure 7 (copied from Dr. Zhang's review).

Figure 7 – VELOUR: OS subgroup analysis by demographic factors



Sanofi conducted additional subgroup analyses to look for interactions with other baseline characteristics such as prior hypertension, number of metastatic organs involved as per IRC, liver metastasis only, and location of primary tumor. No significant interaction was observed at the 10% level except for patients with liver metastases as the only site of metastatic disease: a greater effect of treatment was observed in patients with liver metastases only (HR: 0.649, 95.34% CI: 0.492 to 0.855) compared to those with no liver metastasis or liver metastasis with other organs involved (HR: 0.868, 95.34% CI 0.742 to 1.015) (quantitative interaction, $p=0.0899$). Isolated liver disease is considered a group of better prognosis regardless of the systemic therapy treatment, and this effect is consistently observed in most clinical trials. A treatment effect in favor of aflibercept over placebo ($HR < 1$) was observed for all subgroups except the rectosigmoid primary tumor subgroup. FDA analysis reached the same results, and the HR forest plot is shown in Figure 8 (copied from Dr. Zhang's review).

Figure 8 - VELOUR: OS subgroup analysis by baseline characteristics



In conclusion, the addition of aflibercept to the FOLFIRI regimen resulted in an improvement in overall survival. Pre-specified and exploratory subgroup analyses suggest consistent effects across most demographic subgroups. FDA analysis supports the Applicant's conclusions.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary objectives in the VELOUR trial were

- To compare progression free survival (PFS) in the two treatment arms.
- To evaluate overall response rate (RR), as per RECIST criteria, in the two treatment arms.
- To evaluate the safety profile in the two treatment arms.
- To assess immunogenicity of IV aflibercept.
- To assess pharmacokinetics of IV aflibercept and perform population PK evaluation.

This subsection will focus on PFS and RR. Safety, PK and immunogenicity are extensively reviewed in the Safety section of this review.

Progression Free Survival (PFS)

PFS was defined as the time interval from the date of randomization to the date of first observation of disease progression or the date of death. After amendment 3 (see Table 16), the

disease progression event in the analysis of PFS was based on assessment of radiological tumor progression by the IRC. For 16 patients in the placebo arm and 26 patients in the aflibercept arm (42 patients total, 3.5% of the ITT population) who died prior to the implementation of IRC review or who refused consent for the IRC review, the investigator's tumor assessment was used.

The final analysis of PFS was performed at the time of the second interim analysis of OS (cut off date 6 May 2010), and was conducted in the ITT population. The analysis was based on a total of 847 events, with 454 events in the placebo arm and 393 events in the aflibercept arm. Table 33 summarizes the timing for censoring patients.

Table 33 - VELOUR: Censored patients for IRC PFS assessment

	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
# patients with no event	160 (26)	219 (36)
# patients with PFS events	454 (74)	393 (612)
Time of censoring		
Censored at randomization*	2 (1)	5 (2)
Censored at tumor assessment**	130 (81)	181 (83)
Censored at the cut-off date	28 (18)	33 (15)
Time from last tumor assessment* to cut-off date		
# patients	132	186
≤ 2 weeks	28 (21)	39 (21)
> 2 weeks ≤ 1 month	40 (30)	48 (26)
> 1 month ≤ 2 months	12 (9)	26 (14)
> 2 months	52 (39)	73 (39)

* No post baseline tumor assessment and alive at the time of data cut-off

** Tumor assessment with response different than PD or not evaluable

Forty one patients in the placebo arm and 48 patients in the aflibercept arm who were censored at the last tumor assessment had documented disease progression as per imaging according to investigator, and 5 patients had clinical disease progression (symptomatic deterioration).

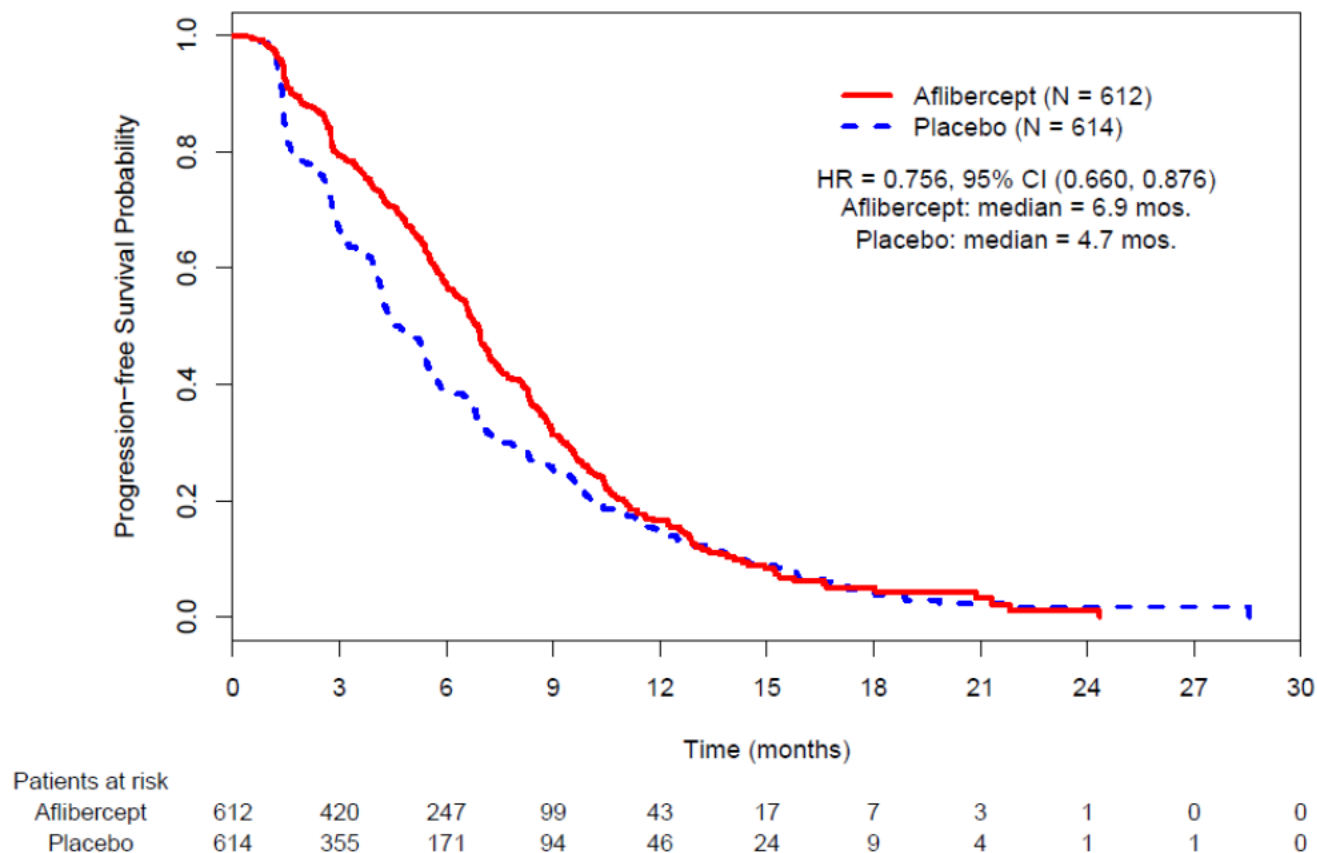
Median PFS in the placebo arm was 4.7 months (95% CI 4.074; 5.552), and 6.9 months (95% CI 5.881; 7.852) in the aflibercept arm, with an estimated stratified hazard ratio of 0.756 (95% CI 0.660; 0.876), and a stratified log-rank test p-value p=0.00007. Table 34 summarizes the PFS analysis (copied from Dr. Zhang statistical review) and Figure 9 shows the Kaplan Meier curves.

Table 34 - VELOUR: FDA PFS analysis

	Placebo/FOLFIRI N=614	Aflibercept/FOLFIRI N=612
Primary analysis		
# events	454	393
Median PFS (months)	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	
Stratified HR (95% CI)	0.756 (0.660; 0.866)
p- value	0.00005

Figure 9 - VELOUR: PFS Kaplan Meier analysis



There was a high rate of discrepancy between the investigator assessments and the IRC assessments (46% on the placebo arm and 39% on the aflibercept arm). Table 35 summarizes these disagreements between assessments.

Table 35 - VELOUR: PFS discrepancies between IRC and investigator assessments.

	Placebo/FOLFIRI (n, %) N=592	Aflibercept/FOLFIRI (n, %) N=588
Disagreement on PD status or date	273 (46)	231 (39)
Disagreement on PD status	142 (24)	138 (23)
Disagreement on PD date	131 (22)	93 (16)

To assess the robustness of the data, Dr. Zhang conducted several sensitivity analyses. Table 36 summarizes the results of two of these analyses. In both cases (worst and best case scenarios), patients in the aflibercept arm had an increased PFS when compared to patients treated in the placebo arm, supporting the results of the primary PFS analysis.

Table 36 – VELOUR: PFS sensitivity analyses

	Placebo/FOLFIRI N=614	Aflibercept/FOLFIRI N=612
Sensitivity analysis (IRC assessment) censoring late progressions, deaths, and new anti-cancer therapy		
# events	353	281
Median PFS (months)	4.5	7
Stratified HR (95% CI)	0.652 (0.556; 0.764)	
p- value	< 0.00001	
Sensitivity analysis (investigator's assessment) including clinical progression (symptomatic deterioration)		
# events	485	452
Median PFS (months)	4.5	6.2
Stratified HR (95% CI)	0.813 (0.714; 0.925)	
p- value	0.0017	

Sanofi conducted PFS analyses by pre-specified subgroups (stratification factors, demographic, and baseline characteristics). There was no evidence of significant interaction between treatment and any of these subgroups (with the exception of liver metastases only, a better prognosis group of patients), supporting a consistent effect of treatment across subgroups.

In conclusion, the addition of aflibercept to the FOLFIRI regimen resulted in an improvement in PFS. Pre-specified and exploratory subgroup analyses suggest consistent effects across most demographic subgroups.

Response rate (ORR)

Evaluation of response rate was based on assessment by the IRC. Patients presenting with only non-target lesions were eligible for randomization; the absence of target lesions was the most common reason for exclusion from ORR analysis (57 patients in the placebo arm, 41 patients in the aflibercept arm). Table 37 summarizes the reason for exclusion from the evaluable population for the ORR analysis. Overall, 530 patients (86%) in the placebo arm and 531 (87%) pts in the aflibercept arm were evaluable for ORR.

Table 37 - VELOUR: Evaluable population for IRC ORR analysis

	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Any reason	84 (14)	81 (13)
Reason for exclusion		
No IRC reading	18 (3)	24 (4)

	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Non-target lesions at baseline	57 (9)	41 (7)
No post-baseline tumor assessment*	9 (1)	16 (3)

* Except for early death or progressive disease

Response rate was higher in the aflibercept arm: 59 (11%) patients in the placebo arm and 105 patients (20%) in the aflibercept arm were assessed as responders (complete or partial response). More patients in the placebo arm experienced progressive disease (114 patients in the placebo arm and 55 patients in the aflibercept arm). Table 38 summarizes the IRC response rates assessment.

Table 38 - VELOUR: Response rates (IRC assessment)

Response	Placebo/FOLFIRI (n, %) N=530	Aflibercept/FOLFIRI (n, %) N=531
Complete response	2 (0.4)	0
Partial response	57 (11)	105 (20)
Stable disease	344 (65)	350 (66)
Progressive disease	114 (22)	55 (10)
Not evaluable	13 (2)	21 (4)
Responders (CR+PR)	59 (11)	105 (20)
95%CI	8.5% - 13.8%	16.4% - 23.2%
Stratified Cochran-Mantel p value	0.0001	

Although response rate was higher in the aflibercept arm, in the context of metastatic colorectal carcinoma, where just a few patients with localized isolated liver or lung disease may benefit from metastasis resection, these results should be interpreted as a measure of activity and it is unclear if any benefit can be derived from the increase in response rates of this magnitude. In the U.S., metastatic colorectal cancer is treated as a continuum of care, and once the disease progresses, patients are switched to another regimen. After receiving treatment in the VELOUR study, 60% of patients in the placebo arm and 59% of patients in the aflibercept arm went on to receive further anti-cancer therapy. The number of patients receiving further therapy, and the types of therapy received, were comparable between the two treatment arms (Table 39).

Table 39 - VELOUR: Post-study treatments

Post-study treatment	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
Any	366 (60)	364 (59)
Surgery	31 (5)	47 (8)
Radiotherapy	81 (13)	79 (13)
Systemic anti-cancer treatment	329 (54)	329 (54)
Cetuximab/panitumumab	143 (23)	160 (26)
Bevacizumab	75 (12)	55 (9)
Chemotherapy	297 (48)	287 (47)

Of interest, 26% of patients in the placebo arm and 28% of patients in the aflibercept arm received further therapy with irinotecan, and 11% of patients in the placebo arm and 9% of

patients in the aflibercept arm received further oxaliplatin treatment, despite having received both oxaliplatin- and irinotecan-based regimens in first and second line and having progressive disease after each treatment line. This reflects the lack of effective choices for third line therapy in mCRC.

6.1.6 Other Endpoints

Additional analyses based on exposure can be found in the OCP review. Primary and secondary endpoints have been analyzed in Sections 6.1.4, 6.1.5, and Safety.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

The main safety analyses were performed on EFC10262/VELOUR, the pivotal study for the proposed indication (611 patients exposed to aflibercept). Additionally, datasets from two other Phase 3, double-blind, placebo-controlled trials (VITAL and VANILLA, with 452 and 270 patients exposed to aflibercept respectively), as well as integrated data from 404 patients treated in Phase 1-2 studies were analyzed to evaluate the toxicity profile of aflibercept, both as monotherapy and in combination therapies. Additional data from other Phase 1-2 studies (total of 2073 patients exposed to aflibercept) as well as data from NCI trials were available for the safety assessment.

Pivotal trial: VELOUR

VELOUR was a multinational double-blind, placebo controlled study of IV aflibercept or placebo 4 mg/kg administered in combination with the FOLFIRI regimen. Eligible patients with mCRC should have progressed during or after discontinuation of a prior oxaliplatin-based chemotherapy regimen for metastatic disease or progressed within 6 months following adjuvant therapy with an oxaliplatin containing regimen. Prior treatment with bevacizumab was allowed. Patients received treatment until documentation of disease progression, intolerable toxicity, or death.

Among the 1,216 patients who received study treatment, at the time of data cut-off, 97% of patients discontinued study treatment. In the analysis of disposition using the disposition dataset (reasons stated by the attending physician for treatment withdrawal) the main reason for treatment discontinuation was disease progression, which occurred with greater frequency in the placebo arm (71%) than in the aflibercept arm (50%). Adverse events leading to treatment discontinuation occurred with higher frequency in the aflibercept arm (27%) than in the placebo arm (12%). However, the analysis of disposition using the adverse events dataset showed that adverse events caused treatment discontinuation at a higher rate in the aflibercept arm: 41% of patients experienced an adverse event that led to discontinuation. Some of these events may be attributed to disease progression, and the review of the narratives and CRFs did not always allow for a clear distinction of the causes of withdrawal. Toxicities leading to discontinuation included hypertension, diarrhea, fatigue/asthenia, pulmonary embolism, and proteinuria.

Patients treated in the placebo arm received a median of 8 infusions. Patients treated in the aflibercept arm received a median of 9 infusions. Median relative dose intensity for placebo was 0.91 in the placebo group and 0.82 in the aflibercept group. Aflibercept/placebo dose modifications (dose delays and dose modifications) were more frequent in the aflibercept arm (78% and 17%, respectively) than in the placebo arm (60% and 5%, respectively). The relative dose intensity of both irinotecan and 5-FU were higher in the placebo arm compared to the aflibercept arm: irinotecan relative dose intensity was 0.91 and 0.84 in the placebo and aflibercept arms, respectively; 5-FU relative dose intensity was 0.91 and 0.83 in the placebo and aflibercept arms, respectively. Subjects 65 years or older treated with aflibercept had slightly less exposure to aflibercept than younger subjects (relative dose intensity 0.84 vs. 0.80 in subjects younger than 65 and older than 65, respectively). The same pattern of exposure (slightly more infusions/patient with decreased relative dose intensity of aflibercept and individual components of backbone therapy) was observed in the VITAL and VANILLA studies.

Almost all patients in both arms of the VELOUR study experienced adverse events. Grade 3-4 AEs were more frequently observed in the aflibercept arm (84%) than in the placebo arm (63%). This imbalance was also observed in the incidence of SAEs: in the placebo arm, the incidence of SAEs was 33%, and in the aflibercept arm the incidence was 49%. Six patients in the placebo arm and 13 patients in the aflibercept arm had adverse events with a fatal outcome.

At the SOC level, the most frequently affected systems ($\geq 50\%$ incidence) were gastrointestinal (placebo arm 87%, aflibercept arm 94%), general disorders and administration sites (placebo arm

67%, aflibercept arm 76%), vascular disorders (placebo arm 44%, aflibercept arm 72%), respiratory, thoracic, and mediastinal SOC (placebo arm 45%, aflibercept arm 65%), nervous system (placebo arm 47%, aflibercept arm 61%), and skin and subcutaneous tissue disorders (placebo arm 47%, aflibercept arm 51%).

At the preferred term level, the most frequently reported events (incidence $\geq 20\%$) were diarrhea (placebo arm 57%, aflibercept arm 69%), nausea (placebo arm 54%, aflibercept arm 53%), stomatitis (placebo arm 33%, aflibercept arm 50%), fatigue (placebo arm 39%, aflibercept arm 48%), hypertension (placebo arm 11%, aflibercept arm 41%), neutropenia (placebo arm 34%, aflibercept arm 39%), vomiting (placebo and aflibercept arm 33%), decreased appetite (placebo arm 24%, aflibercept arm 32%), decreased weight (placebo arm 14%, aflibercept arm 32%), epistaxis (placebo arm 7%, aflibercept arm 28%), abdominal pain (placebo arm 24%, aflibercept arm 27%), dysphonia (placebo arm 3%, aflibercept arm 25%), constipation (placebo arm 25%, aflibercept arm 22%), and headache (placebo arm 9%, aflibercept arm 22%). With the exception of nausea, vomiting, and constipation, the incidence of the events in this list in the aflibercept arm was at least 3% higher. This pattern of toxicity was also observed for Grade 3-4 events.

Regarding adverse events of special interest (VEGF/R inhibition related), these events were observed, as expected, more frequently in patients in the aflibercept arm. The incidence of hypertension was 11% in the placebo arm and 41% in the aflibercept arm (Grades 3-4 incidence rates were 1.5% and 19.3% in the placebo and aflibercept arms, respectively). There was one case of Grade 4 (hypertensive encephalopathy) hypertension in the aflibercept arm, and although the incidence of hypertension was the same regardless of prior history of hypertension, patients with prior hypertension had an increased incidence of Grade 3 hypertension. This can partially be explained by the use of the specific toxicity grading system (i.e., NCI CTCAE v3.0), where the addition of one additional antihypertensive drug for blood pressure management qualified increased blood pressure as Grade 3 in severity. More than half of patients with hypertension were diagnosed within the first 2 cycles.

Proteinuria was observed in 41% of patients in the placebo arm and 62% of patients in the aflibercept arm. However, more than a third of these patients had concomitant hematuria and in most cases, these Grade 1-2 events were diagnosed by urine dipstick. A more reliable assessment of clinically significant nephropathy was derived from the assessment of Grade 3-4 proteinuria, observed in 1% of patients in the placebo arm and 8% of patients in the aflibercept arm. There were two events of nephrotic syndrome in the aflibercept arm. Microangiopathic anemia was observed in one patient (two additional patients reported in the NCI trials).

Arterial thrombotic events were observed in 1.65% and 2.6% patients in the placebo and aflibercept arms, respectively. Most of these events were of cardiac origin (myocardial ischemia/infarct, unstable angina, etc). Two patients in the aflibercept arm experienced cardiac dysfunction. Venous thromboembolic events were observed more frequently in the aflibercept arm: 7% of patients in the placebo arm and 9% of patients in the aflibercept arm experienced a VTE [mostly pulmonary embolism (3% vs. 5% in the placebo and aflibercept arms respectively)].

Hemorrhage was increased in the aflibercept arm: 38% patients experienced a Grade 1-4 hemorrhage, compared with 19% patients in the placebo arm. Most events were Grades 1-2, and epistaxis was the most frequently reported site of bleeding (7% vs. 28% in the placebo and aflibercept arms, respectively). Fatal hemorrhage was reported in the aflibercept arm.

In the placebo arm, fistula was reported in 3 patients (0.5%), and in the aflibercept arm, fistula was reported in 9 patients. Five patients in the placebo arm and three patients in the aflibercept arm experienced wound healing issues. Although more frequent, events in the placebo arm appeared to be mild (all were Grade 1), while the severity of the events in the aflibercept arm was more pronounced (Grades 2-3) and led to cycle delay or discontinuation of study treatment.

Three patients per arm experienced gastrointestinal perforations (one fatal event in the aflibercept arm).

The addition of aflibercept to FOLFIRI caused an increased incidence of leukopenia, neutropenia, and thrombocytopenia. The incidence of Grade 3-4 leukopenia was 12% in the placebo arm and 16% in the aflibercept arm. The incidence of Grade 3-4 neutropenia was 30% in the placebo arm and 36% in the aflibercept arm. The incidence of Grade 3-4 thrombocytopenia was 2% in the placebo arm and 3% in the aflibercept arm. No other laboratory abnormalities were increased with the use of aflibercept.

Subgroup analyses (age, gender, prior exposure to bevacizumab, ECOG PS status, and BMI category) did not show any significant differences in toxicity in these groups.

In summary, the addition of aflibercept to the FOLFIRI regimen in the VELOUR study increased FOLFIRI-related toxicity, and subjected patients to VEGF/R inhibition-related toxicities. Patients in the aflibercept arm received a median of one more cycle than patients in the placebo arm, although dose intensity of all drugs was slightly reduced. More patients in the aflibercept arm experienced adverse events, toxicity-related deaths, dose modifications, and treatment-related withdrawals. However, the safety profile of aflibercept was generally consistent with the known safety profile of bevacizumab, with the possible exception of hypertension and proteinuria, which appear to be more frequent with aflibercept. However, these differences may have been explained by differences in monitoring among aflibercept and bevacizumab trials.

Supportive data:

The integrated safety database contained data from 2,073 aflibercept-treated patients. In the Phase 1 and 2 studies investigating aflibercept 4 mg/kg every other week as single therapy (n=258 patients), the most frequently reported (HLT) AE was asthenic conditions (asthenia and fatigue) in 46% of patients (12% Grades 3-4), followed by hypertension in 32% of patients (15% Grades 3-4). Nausea and vomiting were also frequent (29% and 28% respectively). AEs related to class-effects such as dysphonia, epistaxis, and proteinuria were observed in 26%, 10%, and 12% of patients respectively.

EFC10547/VANILLA was a Phase 3 study in patients with metastatic or locally advanced, unresectable pancreatic cancer. Aflibercept was administered at the dose and schedule of 4 mg/kg IV every other week in combination with gemcitabine. The study was prematurely discontinued for futility at the time of the interim analysis. The incidence rate of Grade 3-4 AEs (79% in the aflibercept arm and 67% in the placebo arm), SAEs (55% vs. 45%), and discontinuation of therapy due to AEs (28% vs. 12%) was higher in the aflibercept arm. The AEs (PT/HLT/SOC) that occurred most frequently in the aflibercept arm were asthenic conditions, nausea, hypertension, gastrointestinal and abdominal pains, vomiting, weight decrease, decreased appetite, infection, constipation, pyrexia, and dysphonia. At the PT level, the most important differences ($\geq 10\%$ between arms, difference in parentheses), were in the incidence rates of hypertension (30%, Grades 3-4 12%), weight decrease (14%, Grades 3-4 1%), epistaxis (12%, Grades 3-4 1%), headache (12%, no differences in the incidence of Grades 3-4), stomatitis (10%, Grades 3-4 1%), and proteinuria (9%, Grades 3-4 3%). The AEs that occurred most frequently in the aflibercept arm were similar to those of the VELOUR study: asthenic conditions, nausea, hypertension, gastrointestinal and abdominal pains, vomiting, weight decrease, decreased appetite, infection, alopecia, constipation, pyrexia, and dysphonia.

EFC10261/VITAL was a Phase 3 study in NSCLC. Aflibercept was administered at the dose and schedule of 6 mg/kg IV every 3 weeks in combination with docetaxel. Upon final analysis, the study failed to show an improvement in overall survival in the aflibercept arm (HR=1.01, CI: 0.868 to 1.174). The incidence of Grade 3-4 AEs, SAEs, and discontinuations due to AEs was higher in the aflibercept arm. At the PT level, the most important differences ($\geq 10\%$ between arms, differences in parentheses) were in the incidence rates of stomatitis (27%, Grades 3-4 8%), hypertension (16%, Grades 3-4 6%), weight decrease (14%, Grades 3-4 2%), epistaxis (14%, Grades 3-4 2%), and dysphonia (14%, no Grades 3-4 observed). The AEs that occurred most frequently in the aflibercept arm were hypertension, weight decrease, decreased appetite, dysphonia, and epistaxis. All VEGF/R inhibition-related AEs were increased in the aflibercept arm. The incidence and pattern of AEs observed in the aflibercept arm of the VITAL trial was consistent with the toxicity observed in the pivotal study, VELOUR.

No cases of RPLS were diagnosed in the VELOUR study. A total of 17 patients were diagnosed with RPLS during the aflibercept development. Three of these patients were enrolled in a Phase 1/2 study of aflibercept in combination with cisplatin and pemetrexed in patients with advanced carcinomas. Eight patients experienced RPLS in different studies of aflibercept as single-agent treatment. The dosing regimen of 4 mg/kg aflibercept administered every 2 weeks was the background treatment in 11 of the 17 patients. RPLS was diagnosed more frequently in female patients (13 females and 4 males), median age was 59 years (range 34 to 76 years), and the mean cycle at diagnosis was 4.8 (SD 5.3). There was one fatal outcome. Twelve patients were reported as having recovered. RPLS is an identified risk for patients receiving anti-cancer treatment including cytotoxic drugs and targeted VEGF/R inhibitors (small molecule TKIs and bevacizumab). The overall incidence in of RPLS in the aflibercept development was 0.44% (17/3795).

In summary, the supportive data from Phase 1-2 and randomized controlled Phase 3 studies is consistent with the safety data from the pivotal study, VELOUR. The safety database was adequate and allowed for the characterization of the toxicity profile of aflibercept.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary study used to evaluate safety was Study EFC10262, VELOUR. All the safety review is based on the VELOUR study, unless specified. The protocol was designed to record all adverse events regardless of severity. The safety database from VELOUR included data from 1216 patients. Aflibercept was administered to 611 of these patients.

Table 40 summarizes the studies used to evaluate the safety of aflibercept (copied from the submission).

Table 40- Summary of studies used to evaluate safety

Integrated safety database	Completed studies not included in the integrated database (summaries)	Ongoing studies (summary of SAEs)	NCI studies (summary of SAEs)
Pivotal study - EFC10262/VELOUR Supportive studies - Pool single agents Phase 1 & 2 studies TED6115/6, ARD6122/3, ARD6772, EFC6125. - Combination Phase 1 studies TCD 6117/21 - Phase 3 studies EFC10547/VANILLA & EFC10261/VITAL. - Meta analysis of completed Phase 3 studies	- SC administration (TED6113/4) - Healthy subjects (PDY6655/6) - NHL Phase 1 combination study (TCD10173) - QTc study (TES10897)	- EFC6546/VENICE - EFC10668/AFFIRM - Japanese studies TED10069, TCD10091, TCD10794 - Chinese study TCD11382	- ARD5537/8 - ARD6836 - ARD6839 - ARD6842/4 - ARD10576 - ARD6124 - LOI5-0802 - NABTC07-01 - TED5540/2

7.1.2 Categorization of Adverse Events

The severity of the events was documented using NCI-CTCAE version 3.0. The MedDRA 13.1 dictionary was used to code adverse event data. The dataset (ADAE.xpt) contained 64,914 individual adverse event listings (safety population) in 594 patients in the placebo arm and 606 patients in the aflibercept arm. A total of 919 preferred terms (PT) described all adverse events.

Verbatim terms in the adverse event dataset were reviewed to determine whether MedDRA preferred terms were appropriately coded. Coding was adequate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The integrated safety database contained data from 2073 aflibercept-treated patients who were enrolled into one of the following studies (Table 40):

- One single-agent Phase 1 study (TED6115/6116) and 4 Phase 2 single-agent trials (ARD6772, ARD6122, EFC6125, ARD6123), comprised a total of 404 aflibercept-treated patients every other week, of whom 258 received 4 mg/kg. For these studies, a pooled analysis by dose was submitted.
- Five combination therapy Phase 1 studies (TCD6118, TCD6117, TCD6121, TCD6119, TCD6120), comprising 336 patients. The data from combination studies were not pooled due to the different chemotherapy regimens (the applicant presented the data side-by-side).
- Two other completed placebo-controlled phase 3 studies (EFC10547/VANILLA, 270 aflibercept-treated patients and 271 patients in the placebo arm; EFC10261/VITAL, 452 aflibercept-treated patients treated and 453 patients in the placebo arm). Separate presentations for each of the 2 supportive Phase 3 studies was included, as well as a meta analysis of the 3 phase 3 studies, intended to determine the odds-ratio of aflibercept versus placebo of specific adverse events.

Safety data from several studies, not included in the integrated safety database, were included in the Clinical Safety Summary:

- A clinical Q-T interval prolongation study in solid tumor patients (TES10897);
- Aflibercept single IV/SC administration studies in healthy male subjects PDY6655 and PDY6656;
- Single-agent aflibercept SC Phase 1 dose escalation studies in cancer patients TED6113/6114;
- Dose escalation phase 1 study of IV aflibercept in combination with RCHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone) in patients with non-Hodgkin lymphoma (TCD10173).

Additionally, information on SAEs from NCI sponsored studies was included in the application.

7.1.3.1 Safety data from EFC10261/VITAL

VITAL was a multinational, randomized, double-blind study comparing aflibercept when administered every 3 weeks versus placebo combined with docetaxel after failure of one platinum based therapy for locally advanced or metastatic NSCLC.

The primary objective of the study was to demonstrate overall survival improvement for the aflibercept plus docetaxel arm. Aflibercept or placebo 6 mg/kg was administered every 3 weeks, along with docetaxel 75 mg/m² every 3 weeks until patients experienced progressive disease, unacceptable toxicity, or refused further therapy.

The severity of the events was determined using the NCI-CTCAE version 3.0, and the MedDRA 13.1 coding dictionary was used to code adverse event data. The study collected safety data in the same manner as in the VELOUR study (Grades 1-4).

On March 10, 2011, the applicant communicated the results from EFC10261 (VITAL), through a press release and later submitted the information to the IND. The data on 913 patients showed that adding aflibercept to docetaxel did not result in an improvement in overall survival compared with a regimen of docetaxel plus placebo (HR=1.01, CI: 0.868 to 1.174). PFS HR was 0.82 (CI: 0.716 to 0.937) and ORR of 23.3% in the aflibercept/docetaxel arm compared to 8.9% in the placebo arm.

Sanofi stated in the CSR that patients in the aflibercept group received slightly more infusions of both treatment components compared to patients in the placebo group; with a longer duration of study treatment on average and a higher median cumulative dose. The median number of placebo/aflibercept infusions was 4 in the placebo/docetaxel group and 5 in the aflibercept/docetaxel group. The median relative dose intensity was higher for exposure to placebo/aflibercept (1.00 and 0.97 [range 0.1 to 1.1]) than that of placebo/docetaxel (0.97 and 0.92 [range 0.1 to 1.3]).

In VITAL, the incidence of Grade 3-4 AEs, SAEs, and discontinuations due to AEs was higher in the aflibercept arm. Table 41 summarizes the AEs (FDA analysis) by SOC in the safety population. The most important differences in incidence rates ($\geq 10\%$ between arms, difference in parentheses) occurred in the general disorders SOC (6%, however the difference in Grade 3-4 events was 14%), gastrointestinal disorders SOC (19%, Grades 3-4 11%), vascular disorders SOC (20%, Grades 3-4 8%), and psychiatric disorders SOC (16%, Grades 3-4 1%).

Table 41 - VITAL: AEs by SOC (safety population)

SOC	Placebo/docetaxel (n, %) N=453		Aflibercept/docetaxel (n, %) N=452	
	All	Grades 3-4	All	Grades 3-4
General disorders and administration site conditions	284 (63)	85 (19)	313 (69)	149 (33)
Respiratory, thoracic and mediastinal disorders	279 (62)	90 (20)	317 (70)	90 (20)
Gastrointestinal disorders	240 (53)	34 (8)	326 (72)	84 (19)
Blood and lymphatic system disorders	61 (13)	51 (11)	93 (21)	78 (17)
Vascular disorders	137 (30)	39 (9)	228 (50)	67 (15)
Infections and infestations	154 (34)	57 (13)	175 (39)	67 (15)
Nervous system disorders	202 (45)	31 (7)	239 (53)	44 (10)
Cardiac disorders	182 (40)	38 (8)	168 (37)	43 (10)
Musculoskeletal and connective tissue disorders	167 (37)	13 (3)	166 (37)	27 (6)
Metabolism and nutrition disorders	157 (35)	20 (4)	164 (36)	27 (6)

Skin and subcutaneous tissue disorders	211 (47)	9 (2)	220 (49)	23 (5)
Renal and urinary disorders	43 (9)	5 (1)	76 (17)	19 (4)
Psychiatric disorders	63 (14)	7 (2)	137 (30)	13 (3)
Investigations	55 (12)	6 (1)	123 (27)	12 (3)
Immune system disorders	23 (5)	4 (1)	36 (8)	8 (2)
Neoplasms benign, malignant and unspecified	22 (5)	12 (3)	23 (5)	10 (2)
Injury, poisoning and procedural complications	37 (8)	5 (1)	45 (10)	5 (1)
Eye disorders	41 (9)	0	67 (15)	2 (<1)
Reproductive system and breast disorders	15 (3)	1 (<1)	21 (5)	1 (<1)
Ear and labyrinth disorders	20 (4)	2 (<1)	18 (4)	1 (<1)
Endocrine disorders	6 (1)	3 (1)	7 (2)	1 (<1)
Hepatobiliary disorders	6 (1)	2 (<1)	5 (1)	2 (<1)
Pregnancy, puerperium and perinatal conditions	0	0	1 (<1)	1 (<1)

Table 42 summarizes the most frequently observed AEs by preferred term that occurred in the VITAL study. The most important differences in incidence rates ($\geq 10\%$ between arms, difference in parentheses), in all cases more frequent in the aflibercept arm, were in the incidence rates of stomatitis (27%, Grades 3-4 8%), hypertension (16%, Grades 3-4 6%), weight decrease (14%, Grades 3-4 2%), epistaxis (14%, Grades 3-4 2%), and dysphonia (14%, no Grades 3-4 observed).

Table 42 - VITAL: AEs with $\geq 10\%$ incidence by PT (safety population)

PT	Placebo/docetaxel (n, %) N=453		Aflibercept/docetaxel (n, %) N=452	
	All	Grades 3-4	All	Grades 3-4
Fatigue	130 (29)	22 (5)	143 (32)	52 (12)
Stomatitis	69 (15)	3 (1)	188 (42)	40 (9)
Hypertension	23 (5)	4 (1)	96 (21)	33 (7)
Dyspnea	100 (22)	25 (6)	96 (21)	28 (6)
Asthenia	85 (19)	14 (3)	85 (19)	23 (5)
Diarrhea	108 (24)	11 (2)	127 (28)	19 (4)
Decreased appetite	95 (21)	6 (1)	125 (28)	12 (3)
Weight decreased	42 (9)	2 (<1)	113 (25)	10 (2)
Epistaxis	29 (6)	0	92 (20)	7 (2)
Cough	94 (21)	4 (1)	111 (25)	3 (1)
Vomiting	57 (13)	3 (1)	57 (13)	3 (1)
Peripheral sensory neuropathy	67 (15)	6 (1)	54 (12)	5 (1)
Back pain	29 (6)	2 (<1)	43 (10)	3 (1)
Nausea	93 (21)	6 (1)	81 (18)	1 (<1)
Constipation	57 (13)	4 (1)	66 (15)	0
Edema peripheral	56 (12)	5 (1)	30 (7)	1 (<1)
Alopecia	148 (33)	0	134 (30)	0
Dysphonia	17 (4)	2 (<1)	83 (18)	1 (<1)
Headache	25 (6)	2 (<1)	59 (13)	1 (<1)
Pyrexia	43 (9)	0	56 (12)	2 (<1)

The AEs that occurred most frequently in the aflibercept arm were similar to AEs in study EFC10262/VELOUR: hypertension, weight decrease, decreased appetite, dysphonia, and epistaxis. As summarized, all “typical” VEGF/R inhibition-related AEs were increased in the

aflibercept arm. The incidence and pattern of AEs observed in the aflibercept arm of the VITAL trial was consistent with the toxicity observed in the pivotal study, VELOUR. As in VELOUR, the backbone therapy-related toxicity was increased.

7.1.3.2 Safety data from EFC10547/VANILLA

VANILLA was a multinational, randomized, double-blind study, comparing the efficacy of aflibercept administered every other week versus placebo combined with gemcitabine in patients with metastatic pancreatic cancer. The primary objective of the study was to demonstrate overall survival improvement for the aflibercept plus gemcitabine arm. Aflibercept or placebo 4 mg/kg was administered every 2 weeks, along with gemcitabine every 2 weeks until patients experienced progressive disease, unacceptable toxicity, or refused further therapy.

The severity of adverse events was determined using NCI-CTCAE version 3.0, and the MedDRA 13.1 dictionary was used to code adverse event data. The study collected safety data in the same manner as in the VELOUR study (Grades 1-4).

On September 11, 2009, the applicant informed the Agency that the IDMC planned interim analysis for Study EFC10547 after 546 patients enrolled (performed by an independent statistician after the 205th death event, or 40% of the planned events) resulted in a recommendation to stop the study for futility based on the pre-specified boundary rules.

In this Phase 3 study, the incidence of Grade 3-4 AEs (79% in the aflibercept arm and 67% in the placebo arm), SAEs (55% vs. 45%), and discontinuation of therapy due to AEs (28% vs. 12%) was higher in the aflibercept arm. The AEs (PT/HLT/SOC) that occurred most frequently in the aflibercept arm were asthenic conditions, nausea, hypertension, gastrointestinal and abdominal pains, vomiting, weight decrease, decreased appetite, infection, constipation, pyrexia, and dysphonia.

Table 43 summarizes the AEs by SOC that occurred in the VANILLA study. The most important differences in incidence rates ($\geq 10\%$ between arms, difference in parentheses), in all cases more frequent in the aflibercept arm, occurred in the vascular disorders SOC (30%, Grades 3-4 12%), central nervous system SOC (21%, Grades 3-4 2%), psychiatric disorders SOC (18%, Grades 3-4 1%), respiratory, thoracic and mediastinal disorders SOC (13%, Grades 3-4 1%), renal disorders SOC (11%, Grades 3-4 2%), general disorders SOC (11%, Grades 3-4 8%), and blood disorders (10%, Grades 3-4 10%).

Table 43 - VANILLA: AEs by SOC (safety population)

SOC	Placebo/gemcitabine (n, %) N=271		Aflibercept/gemcitabine (n, %) N=270	
	All	Grades 3-4	All	Grades 3-4
Blood and lymphatic system disorders	109 (40)	74 (27)	134 (50)	101 (37)
General disorders and administration site conditions	176 (65)	59 (22)	204 (76)	80 (30)

Vascular disorders	77 (28)	44 (16)	156 (58)	76 (28)
Gastrointestinal disorders	209 (77)	58 (21)	219 (81)	75 (28)
Hepatobiliary disorders	42 (15)	27 (10)	42 (16)	26 (10)
Cardiac disorders	78 (29)	15 (6)	83 (31)	23 (9)
Investigations	73 (27)	27 (10)	106 (39)	24 (9)
Respiratory, thoracic and mediastinal disorders	84 (31)	28 (10)	120 (44)	23 (9)
Metabolism and nutrition disorders	116 (43)	26 (10)	128 (47)	23 (9)
Renal and urinary disorders	41 (15)	10 (4)	69 (26)	15 (6)
Infections and infestations	71 (26)	21 (8)	77 (29)	17 (6)
Musculoskeletal and connective tissue disorders	75 (28)	8 (3)	82 (30)	10 (4)
Skin and subcutaneous tissue disorders	65 (24)	6 (2)	83 (31)	10 (4)
Nervous system disorders	73 (27)	16 (6)	130 (48)	12 (4)
Injury, poisoning and procedural complications	13 (5)	1	23 (9)	7 (3)
Psychiatric disorders	47 (17)	8 (3)	94 (35)	5 (2)
Endocrine disorders	6 (2)	2 (1)	6 (2)	4 (1)
Neoplasms benign, malignant and unspecified	22 (8)	9 (3)	16 (6)	4 (1)
Pregnancy, puerperium and perinatal conditions	0	0	1 (<1)	1 (<1)
Immune system disorders	11 (4)	1 (<1)	7 (3)	0
Ear and labyrinth disorders	8 (3)	0	11 (4)	0
Eye disorders	7 (3)	1 (<1)	11 (4)	0
Reproductive system and breast disorders	6 (2)	0	13 (5)	0

Table 44 summarizes the most frequently observed AEs by PT that occurred in the VANILLA study. The most important differences in incidence rates ($\geq 10\%$ between arms, difference in parentheses) were in the incidence of hypertension (30%, Grades 3-4 12%), weight decrease (14%, Grades 3-4 1%), epistaxis (12%, Grades 3-4 1%), headache (12%, no differences in the incidence of Grades 3-4), stomatitis (10%, Grades 3-4 1%), and proteinuria (9%, Grades 3-4 3%).

Table 44 - VANILLA: AEs (PT) with an incidence of $\geq 10\%$ (safety population)

PT	Placebo/gemcitabine (n, %) N=271		Aflibercept/gemcitabine (n, %) N=270	
	All	Grades 3-4	All	Grades 3-4
Nausea	125 (46)	6 (2)	103 (38)	10 (4)
Hypertension	17 (6)	8 (3)	97 (36)	41 (15)
Fatigue	106 (39)	18 (7)	97 (36)	27 (10)
Neutropenia	71 (26)	54 (20)	87 (32)	69 (26)
Vomiting	78 (29)	4 (1)	86 (32)	12 (4)
Weight decreased	43 (16)	3 (1)	81 (30)	6 (2)
Decreased appetite	74 (27)	9 (3)	79 (29)	5 (2)
Diarrhea	59 (22)	3 (1)	65 (24)	3 (1)
Constipation	74 (27)	3 (1)	64 (24)	2 (1)
Abdominal pain	69 (25)	15 (6)	59 (22)	16 (6)
Asthenia	43 (16)	10 (4)	54 (20)	13 (5)
Pyrexia	48 (18)	1 (<1)	53 (20)	1 (<1)
Headache	19 (7)	1 (<1)	51 (19)	1 (<1)
Thrombocytopenia	18 (7)	9 (3)	47 (17)	22 (8)
Stomatitis	16 (6)	3 (1)	43 (16)	3 (1)

Disease progression	28 (10)	25 (9)	42 (16)	41 (15)
Dysphonia	6 (2)	0	40 (15)	0
Epistaxis	5 (2)	0	39 (14)	2 (1)
Abdominal pain upper	28 (10)	3 (1)	34 (13)	5 (2)
Edema peripheral	44 (16)	4 (1)	33 (12)	0
Proteinuria	6 (2)	1 (<1)	31 (11)	8 (3)
Dyspnea	19 (7)	4 (1)	26 (10)	3 (1)
Insomnia	18 (7)	2 (1)	28 (10)	0
Back pain	23 (8)	0	27 (10)	4 (1)

The AEs that occurred most frequently in the aflibercept arm were similar to those that occurred in study EFC10262/VELOUR: asthenic conditions, nausea, hypertension, gastrointestinal and abdominal pains, vomiting, weight decrease, decreased appetite, infection, alopecia, constipation, pyrexia, and dysphonia. The incidence and pattern of AEs observed in the aflibercept arm of the VANILLA study was consistent with the toxicity observed in the pivotal study, VELOUR.

7.1.3.3 Safety data from Phase 1-2 aflibercept single-agent studies

This section of the review includes those patients (n=258) who received aflibercept at 4 mg/kg every other week in studies TED6115/6, ARD6122/3, ARD6772, EFC6125. Table 45 summarizes the AEs by SOC observed in the single-agent aflibercept studies. The gastrointestinal and general disorders were the most frequently reported, and the SOC's were more AEs Grades 3-4 were reported.

Table 45 - Single-agent aflibercept Phase 1-2 studies: AEs by SOC (safety population, 4 mg/kg every 2 weeks cohorts)

SOC	All Grades (n, %) N=258	Grades 3-4 (n, %) N=258
Blood and lymphatic system disorders	32 (12)	10 (4)
Cardiac disorders	94 (36)	32 (12)
Ear and labyrinth disorders	9 (3)	1 (<1)
Endocrine disorders	4 (2)	2 (1)
Eye disorders	15 (6)	1 (<1)
Gastrointestinal disorders	151 (59)	66 (26)
General disorders and administration site conditions	144 (56)	67 (26)
Hepatobiliary disorders	15 (6)	8 (3)
Immune system disorders	10 (4)	0
Infections and infestations	58 (22)	14 (5)
Injury, poisoning and procedural complications	19 (7)	3 (1)
Investigations	46 (18)	12 (5)
Metabolism and nutrition disorders	89 (34)	28 (11)
Musculoskeletal and connective tissue disorders	107 (41)	13 (5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (5)	5 (2)
Nervous system disorders	127 (49)	26 (10)
Pregnancy, puerperium and perinatal conditions	1 (<1)	1

Psychiatric disorders	88 (34)	12 (5)
Renal and urinary disorders	61 (24)	23 (9)
Reproductive system and breast disorders	20 (8)	0
Respiratory, thoracic and mediastinal disorders	124 (48)	35 (14)
Skin and subcutaneous tissue disorders	78 (30)	4 (2)
Vascular disorders	122 (47)	51 (20)

Table 46 summarizes the AEs by PT. The most frequently reported (HLT) AE was asthenic conditions (asthenia and fatigue) in 46% of patients (12% Grades 3-4), followed by hypertension in 32% of patients (15% Grades 3-4). Nausea and vomiting were also frequent (29% and 28% respectively). AEs related to class-effect such as dysphonia, epistaxis, and proteinuria were observed in 26%, 10%, and 12% of patients, respectively.

Table 46 - Single agent aflibercept Phase 1 and 2 studies: AEs (PT) with an incidence of ≥ 5% (safety population)

PT	All Grades (n, %) N=258	Grades 3-4 (n, %) N=258
Hypertension	82 (32)	38 (15)
Fatigue	75 (29)	13 (5)
Nausea	74 (29)	6 (2)
Vomiting	71 (28)	16 (6)
Headache	73 (28)	7 (3)
Abdominal pain	70 (27)	21 (8)
Dysphonia	66 (26)	3 (1)
Diarrhoea	63 (24)	11 (4)
Decreased appetite	56 (22)	10 (4)
Asthenia	44 (17)	18 (7)
Constipation	43 (17)	4 (2)
Dyspnoea	41 (16)	16 (6)
Cough	40 (16)	1 (<1)
Arthralgia	36 (14)	6 (2)
Proteinuria	31 (12)	13 (5)
Oedema peripheral	31 (12)	4 (2)
Pyrexia	30 (12)	3 (1)
Abdominal pain upper	30 (12)	2 (1)
Back pain	31 (12)	2 (1)
Myalgia	27 (10)	2 (1)
Epistaxis	26 (10)	0
Disease progression	22 (9)	22 (9)
Weight decreased	22 (9)	4 (2)
Mucosal inflammation	24 (9)	3 (1)
Rash	22 (9)	0
Dehydration	20 (8)	12 (5)
Dizziness	20 (8)	3 (1)
Musculoskeletal pain	20 (8)	0
Dyspepsia	17 (7)	0
Insomnia	18 (7)	0
Anemia	15 (6)	7 (3)
Abdominal distension	16 (6)	6 (2)

Oropharyngeal pain	16 (6)	1 (<1)
Intestinal obstruction	14 (5)	12 (5)
Pollakiuria	12 (5)	2 (1)
Anxiety	14 (5)	1 (<1)
Depression	13 (5)	1 (1)
Pain in extremity	13 (5)	1 (1)
Muscle spasms	12 (5)	0
Nasopharyngitis	13 (5)	0

The incidence and pattern of AEs observed in the single-arm studies for those patients who received aflibercept at 4 mg/kg/dose was consistent with the toxicity observed in the aflibercept arm of the pivotal study, VELOUR. Some toxicities, particularly myelotoxicity, that were most likely related to the concomitant use of chemotherapy in the randomized trials, were not frequently reported in the single-agent studies.

7.1.3.4 Sanofi's meta-analysis of the placebo-controlled Phase 3 studies (VELOUR/VITAL/VANILLA)

To assess the relative risk of adverse events associated with aflibercept versus placebo, Sanofi conducted a meta-analysis of the following toxicities of interest: hypertension, hemorrhage, cardiac dysfunction, arterial and venous thromboembolic events, fistula, gastrointestinal perforation, compromised wound healing, osteonecrosis, reversible posterior leukoencephalopathy syndrome (RPLS), thrombotic microangiopathy (TMA), hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The meta-analysis was conducted using data from the 2,662 patients (1,329 placebo treated patients and 1,333 aflibercept treated patients). Since conditions and background chemotherapies differed across studies, the consistency of treatment effects for each of these events was verified before conducting the analyses.

Table 47 summarizes (FDA analysis) the incidence of the most frequent AEs (PT) in the aflibercept arms of the randomized Phase 3 trials.

Table 47 - Phase 3 trials: Most frequent AEs in the aflibercept arms (by PT)

PT	VITAL (%) N= 452		VANILLA (%) N= 270		VELOUR (%) N= 611	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Hypertension	21	7	36	15	41	19
Diarrhea	28	4	24	1	69	19
Fatigue/asthenia	41	12	56	15	66	18
Stomatitis	42	9	16	1	50	13
PE	2	2	9	9	5	5
Decreased appetite	28	3	29	2	32	3
Weight decreased	25	2	30	2	32	3
Vomiting	13	1	32	4	33	3

Proteinuria			11	3	10	3
Nausea	18	<1	38	4	53	2
Headache	13	<1	19	<1	22	2
Dyspnea	21	6	10	1	12	1
Epistaxis	20	2	14	1	28	<1
Constipation	15	0	24	1	22	<1
Edema peripheral	7	<1	12	0	9	<1
Dysphonia	18	<1	15	0	25	<1
Pyrexia	12	<1	20	<1	13	<1

The incidence of hypertension, asthenic conditions, stomatitis, decreased appetite, decreased weight, nausea, headache, epistaxis, and dysphonia was increased in the aflibercept-treated patients in the VELOUR trial when compared to the patients in the VITAL and VANILLA trials.

Because the disease settings and backbone therapy were different, an analysis of AEs of special interest (VEGF/R inhibition related) are summarized in Table 48. The data in this table is from the applicant's analysis; the FDA analyses for each event can be found in the following paragraphs.

Table 48 - Phase 3 trials: AEs of special interest

	VITAL (n=452) %	VANILLA (n=270) %	VELOUR (n=611) %
Acute drug reaction	6	3	4
ATE	1	3	3
Cardiac dysfunction	<1	2	<1
GI Fistula	1	<1	1
GI perforation	1	<1	1
Hemorrhage	28	24	38
Hypertension	21	37	41
Osteonecrosis	<1	<1	<1
VTE	3	9	9
Wound healing	1	1	1
RPLS	0	0	0

Hypertension

All three Phase 3 studies used NCICTCAE v3.0, where the severity of hypertension is defined as follows:

- Grade 1: Asymptomatic, transient (< 24hrs) increase by > 20 mmHg (diastolic) or to >150/100 mm Hg if previously within normal limit; intervention not indicated.
- Grade 2: Recurrent or persistent (> 24hrs) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mm Hg if previously within normal limits; monotherapy may be indicated.
- Grade 3: Requiring more than one drug or more intensive therapy than previously.
- Grade 4: Life-threatening consequences (i.e., hypertensive crisis, etc).

In the clinical overview summary that accompanies the above table, Sanofi stated that in the meta-analysis, the summary incidence of all Grade hypertension in patients treated with aflibercept was 33.5% versus 7.9% in placebo-treated patients. The risk of occurrence of hypertension was consistently higher in the aflibercept arms compared to placebo, whatever the background chemotherapy (p-value for interaction: 0.32). The risk of developing hypertension was multiplied by 4.24-fold in aflibercept as compared to placebo (RR = 4.24, 95% CI: 3.48 to 5.18). The incidence of hypertension in the placebo arms was 10.7% and 41.4% in the aflibercept arms, with a risk-ratio of 3.85 (3.01-4.94).

As shown in Table 42, Table 44, Table 59, and Table 60, in FDA analyses, the incidence of hypertension was consistently higher in the aflibercept arms. Table 49 summarizes the incidences of hypertension (all grades) in the Phase 3 trials.

Table 49 - Hypertension in Phase 3 placebo-controlled studies, FDA analysis.

Study	Placebo/Chemotherapy N=1329		Aflibercept/Chemotherapy N= 1333	
	All Grades	Grade 3-4	All Grades	Grade 3-4
VANILLA	6%	3%	36%	15%
VITAL	5%	1%	21%	7%
VELOUR	11%	1%	41%	19%

In the VELOUR study, more than half of the patients who experienced hypertension had the first occurrence during the first two cycles of treatment with a median time to onset similar between both groups. Most patients responded to standard anti hypertensive therapy and could continue on study treatment, although 11.5% of the aflibercept-treated patients who experienced hypertension discontinued aflibercept or all the study therapy (4.7% of the overall population).

Hemorrhage

In the clinical overview summary in the submission, Sanofi stated that in the meta-analysis, the summary incidence of all Grade hemorrhagic events in patients treated with aflibercept was 31.6% versus 14.6% in placebo-treated patients. The risk of occurrence of hemorrhage was consistently higher in the aflibercept arms compared to placebo, whatever the background chemotherapy (p-value for interaction: 0.32). The risk of developing hemorrhage was multiplied by 2.16-fold in aflibercept as compared to placebo (RR = 2.16, 95% CI: 1.86 to 2.52). The incidence of Grade 3-4 hemorrhage was also increased following the use of aflibercept (3.1% vs. 1.5% in the placebo arms). However, the results summarized in Table 47 differ from the ones in the summary: the incidence of hypertension in the placebo arms was 19% and 37.8% in the placebo and aflibercept arms, with a risk-ratio of 1.99 (1.64-2.41).

In the meta-analysis, the most frequently reported hemorrhage was epistaxis, in both the placebo and aflibercept arms, reported in 7.4% and 27.7% of patients, respectively. The timing of the first occurrence of hemorrhage was comparable between arms, with more than half of the patients in each treatment arm experiencing such events during the first 3 treatment cycles.

As shown in Table 50 (FDA analysis), hemorrhagic events were consistently increased in all studies in the aflibercept arms, and epistaxis constituted the most frequent manifestation. In all studies, the incidence of Grades 3-4 hemorrhagic events was 2% or less; however, there were fatalities in all three studies attributed to hemorrhage. In the VELOUR trial, one patient (826011003) in the aflibercept arm died due to a duodenal ulcer hemorrhage. In the VITAL trial, 2 patients in the placebo arm (100003012, 38004007) died due to a gastrointestinal hemorrhage and hemoptysis respectively; in the aflibercept arm, 3 patients (203005006, 616003002 & 724008007) died secondary to hemoptysis and bronchopulmonary hemorrhage. In the VANILLA trial, 5 patients in the aflibercept arm (124003, 250002005, 380005004, 616005007 & 840017001) died because of upper gastrointestinal bleeding, and at least in some patients, there was evidence of progressive disease.

Table 50 – Hemorrhagic events in Phase 3 placebo-controlled studies, FDA analysis

Study	Placebo/Chemotherapy N=1329		Aflibercept/Chemotherapy N= 1333	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Hemorrhage				
VANILLA	2%	<1%	16%	1%
VITAL	11%	1%	26%	2%
VELOUR	9%	<1%	30%	1%
Epistaxis				
VANILLA	5%	0	14%	1%
VITAL	6%	0	20%	2%
VELOUR	7%	0	28%	<1%

Amongst patients who developed hemorrhage, 86.1% of placebo treated patients had one single episode whereas 55% of aflibercept treated patients had one episode, 22.9% had 2 and 8.2% had 3. Grade 3 or 4 hemorrhagic events observed in other studies also included intracranial and pulmonary hemorrhage (total of 43/1462 including 15 fatal events).

Arterial thromboembolic events (ATE)

In the clinical overview summary included in the submission, Sanofi stated that in the meta-analysis, the summary incidence of all grade arterial thrombotic events in patients treated with aflibercept was slightly more frequent following aflibercept treatment, occurring in 1.7% of placebo-treated patients in the 3 Phase 3 studies and 2.3% in aflibercept-treated patients. The risk ratio of aflibercept versus placebo for all Grades ATE was 1.36 (95% CI: 0.79 to 2.34).

However, the results summarized in Table 47 differed from the ones in the summary: the incidence of ATE in the placebo arms was 1.5% and 2.6% in the placebo and aflibercept arms, with a risk-ratio of 1.76 (0.78-3.95).

In the VELOUR study (Table 76), ATEs of all grades were infrequent and reported in 9 patients (1.5%) in the placebo arm and 16 patients (2.6%) in the aflibercept arm. These arterial events were primarily of from cardiac ischemic origin (placebo: 7 patients, aflibercept, 10 patients),

including angina pectoris, myocardial infarction, and intracardial thrombus. Other ATEs included transient ischemic attack, cerebrovascular accident, arterial embolism, splenic infarction, and ischemic colitis. No specific pattern of occurrence could be identified in the aflibercept treatment arms. The incidences of ATEs were similar in single-agent (2.7%) and combination (1.8%) Phase 1 and Phase 2 studies.

Venous thromboembolic events (VTE)

VTEs included deep venous thrombotic events and pulmonary embolism. In aflibercept-treated patients in the 3 Phase 3 studies, VTEs of all Grades were reported at incidence rates varying from 6% in patients with non-small cell lung cancer to 13% in patients with pancreatic cancer. However, VELOUR was the only Phase 3 study where the incidence of VTE in the aflibercept arm was higher (2%) than in the placebo arm (Table 51).

Table 51 - Venous thromboembolic events in Phase 3 placebo-controlled trials, FDA analysis

Study	Placebo/Chemotherapy N=1329		Aflibercept/Chemotherapy N= 1333	
	All Grades	Grade 3-4	All Grades	Grade 3-4
All VTE				
VANILLA	21%	17%	15%	13%
VITAL	8%	7%	6%	6%
VELOUR	7%	7%	9%	9%
Pulmonary embolism*				
VANILLA		11%		9%
VITAL		2%		2%
VELOUR		3%		5%

* All pulmonary embolisms are Grade 4 by NCICTCAE dictionary definition

The results of the FDA analysis of the VANILLA and VITAL studies differed from the applicant's analysis, where the incidences of VTE were lower in both studies (in the applicant's analysis of VANILLA, VTE occurred in 11.1% of patients receiving placebo versus 8.9% of patients receiving aflibercept, and in VITAL, VTE occurred in 4.6% of patients in the placebo arm versus 3.1% of patients receiving aflibercept). Despite of the differences in results, this reviewer shares the conclusion that aflibercept did not significantly increase the risk of VTE compared to placebo (RR = 1.28 [95% CI: 0.88 to 1.87] in the applicant's meta analysis).

The risk of pulmonary embolism was higher in the pancreatic cancer setting (a cancer with a high background incidence rate of VTE). However, the risk of pulmonary embolism associated with aflibercept appeared to be slightly increased only in the metastatic colorectal study VELOUR.

Fistula

In the applicant's meta-analysis, amongst patients treated with aflibercept, the summary incidence of all grade fistulae was 1.1% versus 0.2% in the placebo arm. The overall risk of

fistula was significantly increased with aflibercept, with respect to placebo (OR = 4.57, 95% CI: 1.42 to 20.01).

Gastrointestinal perforation

In the 3 Phase 3 studies, gastrointestinal perforation was uncommon and occurred at rates of 0.3% and 0.8% for placebo and aflibercept patients, respectively. In the applicant's analysis, the risk ratio of aflibercept over placebo for GI perforation of all grades was 2.49 (95% CI: 0.78 to 7.93).

In the integrated safety database, 23 patients experienced GI perforation, 19 of them were treated with aflibercept (1%); 9 cases occurred in women with ovarian or cervical cancer, 6 occurred in patients with non-small cell lung cancer, 3 occurred in patients with rectum/rectosigmoid cancer, and 1 occurred in a patient with pancreatic cancer (all but one were Grade 3 or 4). Overall, gastrointestinal perforation events were fatal in 7 patients (3 with ovarian cancer, 3 with non-small cell lung cancer and 1 rectosigmoid) and 6 of these patients were diagnosed during Cycle 1 or 2.

Compromised wound healing

In the integrated safety database (applicant's analysis), amongst the 2,073 patients exposed to aflibercept, 9 patients (0.4%) experienced compromised wound healing. All occurred following a minor surgical procedure (e.g., tooth extraction, abscess drainage), a local minor injury (skin abrasion), or catheter site inflammation or infection. Compromised wound healing led to aflibercept treatment discontinuation or cycle delay in 7 patients. The events resolved in 7 patients and were still present at the time of death for the other 2 patients. None of these events was fatal.

In VELOUR, compromised wound healing was reported in 3 patients (0.5%) in the aflibercept arm and 5 patients (0.8%) in the placebo arm. Grade 3 compromised wound healing was reported in 2 patients treated with aflibercept (0.3%) and in none of the placebo-treated patients.

Osteonecrosis

In the integrated safety database (applicant's analysis), a total of 7 cases of osteonecrosis have been reported, 6 of them in aflibercept treated patients (0.3%). No specific pattern was observed in the timing of the occurrences. In 3 cases, there was a history of jaw inflammation and in 3 other cases, there was a history of biphosphonate use. Treatment was continued for 4 out of 6 patients.

Two cases of osteonecrosis were reported in patients receiving aflibercept in VELOUR (patients 203001 & 203004012).

Reversible posterior leukoencephalopathy syndrome

Identified risk factors for RPLS include hypertensive disorders, renal disease, and immunosuppressive therapies. In one of the first papers describing the syndrome, (Hinchey, 1996) in 15 patients diagnosed with RPLS, immunosuppressant drugs were described as a risk factor; however, the immunosuppressant drugs identified were cyclosporine and tacrolimus, both

with renal toxic effects. SLE, eclampsia, and hypertensive encephalopathy were also identified as risk factors for RPLS. The authors identified common precipitating factors including increased blood pressure, renal decompensation, fluid retention, and treatment with immunosuppressive drugs (i.e., cyclosporine and tacrolimus). The authors considered RPLS to be related to impairment of the auto-regulatory capacity of the brain vasculature.

Despite the initial Hinchey hypothesis of hypertension leading to failed auto-regulation followed by capillary permeability damage, in approximately 20% of RPLS cases, no documented hypertension has been described. Since the description by Hinchey in 1996, RPLS has been associated with LES, vasculitis, tumor lysis syndrome, infection, sepsis, and shock.

No cases of RPLS were diagnosed in the VELOUR study. This section will review all cases of RPLS in the aflibercept development, including RPLS cases reported in the NCI-sponsored trials.

A total of 17 cases of RPLS have been diagnosed during aflibercept development (data cut-off July 28, 2011): 3 in study VGFT-0708, 8 in other studies under Regeneron-Sanofi IND 9948, and 6 in NCI sponsored studies under IND 100137.

Study VGFT-ST-0708 was a Phase 1/2 study of aflibercept administered in combination with pemetrexed and cisplatin in patients with advanced carcinoma. Aflibercept dose was 6 mg/kg every 3 weeks. The event of RPLS occurred in three female patients, ages 38, 51, and 72 in Cycles 2, 1, and 5, respectively. All were MRI confirmed, and the younger patients were graded as CTCAE Grade 4; both recovered. The oldest patient had Grade 2 RPLS but did not recover from the event; several areas of acute ischemic changes were also described in her MRI. RPLS is a known adverse reaction associated with cisplatin, first published by Ito et al in 1996, and RPLS is described in the cisplatin label. On February 15, 2011, study 0708 was permanently closed to patient accrual due to the higher than anticipated rate of RPLS.

Study EFC6546/VENICE was a Phase 3 trial of the combination of docetaxel and prednisone plus placebo or aflibercept at 6 mg/kg every 3 weeks for the first line treatment of patients with metastatic prostate cancer. The event of RPLS occurred in two patients, ages 59 (Cycle 6) and 71 (Cycle 10) and were MRI confirmed. The younger patient's toxicity was assessed as Grade 1, although the patient experienced seizures. He did not recover, and the MRI is informed as showing microangiopathy. The oldest patient, with Grade 2 RPLS, had an MRI informed as having concomitant multiple hyper-intense ischemic lesions. He did not recover from the event.

In Study TCD6121 (a Phase 1 study exploring the combination with aflibercept 4 mg/kg every 2 weeks in combination with gemcitabine), there was one event of Grade 3 RPLS in a 52 year old woman that occurred in Cycle 6, MRI confirmed. The patient recovered from the event.

There was one event of Grade 2 RPLS in a 72 year old woman (MRI confirmed) in Study EFC10668 (a Phase 2 study exploring aflibercept 4 mg/kg every 2 weeks in combination with FOLFOX6). The patient recovered from the event. Another Grade 3 RPLS event occurred when

aflibercept 4 mg/kg every two weeks was administered in combination with a fluoropyrimidine (S1, an oral investigational agent) in Study TED10089. A 34 year old woman was diagnosed after Cycle 2 (MRI confirmed) and recovered after 24 hours. The only RPLS case with a fatal outcome occurred in Study TCD6117 (Phase 1 dose-escalation trial of aflibercept in combination with FOLFOX4), where a 69 year old man with metastatic pancreatic carcinoma experienced RPLS after receiving aflibercept 5 mg/kg in Cycle 2, and died 13 days after. His death was attributed to progressive disease with RPLS as a contributing factor.

In the company-sponsored single agent studies ARD6122 and ARD6123 (aflibercept 4 mg/kg every 2 weeks), two female patients (75 and 76 years of age) experienced Grade 3 and 4 RPLS (MRI confirmed), and recovered after 14 days.

All 6 RPLS cases reported in the NCI-sponsored trials occurred in aflibercept single-agent studies administered at 4 mg/kg every 2 weeks. Five patients were females. Ages were 52, 54, 58, 59, and 66 years old. The only male patient was 71 years old at the time of the event. All events were Grades 3-4, in 4 patients the diagnosis was supported by MRI, in one case the MRI was “suggestive” of RPLS, and there is no information regarding imaging in the remaining patients (this patient experienced a hypertensive encephalopathy with seizures). All patients recovered from the event.

All 6 RPLS cases reported in the NCI-sponsored trials occurred in aflibercept single-agent studies administered at 4 mg/kg every 2 weeks. Five of the six patients were women and ages of the patients were 52, 54, 58, 59, and 66 years. The only male patient was 71 years old at the time of the event. All events were Grades 3-4; in 4 patients the diagnosis was supported by MRI, in one case the MRI was “suggestive” of RPLS, and there was no information regarding imaging in the remaining patients (this patient experienced a hypertensive encephalopathy with seizures). All patients recovered from the events.

In summary, RPLS was diagnosed more frequently in female patients (13 females and 4 males), median age was 59 years (range 34 to 76 years), and the mean cycle at diagnosis was 4.8 (SD 5.3). There was one fatal case. Twelve cases were reported as having recovered, and the mean duration for these 12 events was 13.5 days (SD 11.2). Twelve of the 17 cases were reported in patients treated in the United States; other countries included Argentina, Australia (2 patients), Brazil, and Japan. There was no single center/investigator with more than one case.

The dosing regimen of 4mg/kg aflibercept administered every 2 weeks was given in 11 of the 17 cases. Of these 11 cases, 8 were with single-agent aflibercept and 3 were with aflibercept administered in combination with cytotoxic chemotherapy.

The most common presenting symptoms included altered mental status in 10 patients, seizure in 9 patients, and headache in 6 patients. Additional symptoms and signs included visual hallucinations, blurred vision, falls, amnesia, nausea, vomiting, and dysarthria.

Prior history of hypertension was present in 8 patients. Of the 9 patients with no past medical history of hypertension, 5 developed increased blood pressure on treatment prior to the event. Blood pressure was documented in 10 patients at the time of RPLS diagnosis: for these patients, median blood pressure was 173/92 mmHg, systolic blood pressure ranged from 143-219 mmHg and diastolic blood pressure ranged from 68 mmHg to 130 mmHg. The average mean arterial pressure (MAP) was approximately 123 mmHg.

With the exception of Study 0708, where 3 cases occurred in 62 patients (4.8%), the incidence of RPLS in all other Phase 1-2 single-agent company-sponsored studies was 0.5% (2/404), 0.7% (4/577) in Phase 1-2 studies in combination with other cytotoxic agents, and 0.09% (2/2069) in Phase 3 trials, similar to the incidence of RPLS observed with bevacizumab, axitinib, and sunitinib. The incidence of RPLS in NCI-sponsored trials (all single-agent studies) was 0.9% (6/683). The triple combination of pemetrexed cisplatin and aflibercept may increase the risk of RPLS, although the mechanism is not clear. In other Phase 1 studies where aflibercept has been combined with either cisplatin or pemetrexed alone, there were no reported cases of RPLS. The applicant hypothesizes that decreased creatinine clearance may be a risk factor, as it was observed in 2 of the 3 patients in Study 0708 (but not confirmed in the other cases reported).

In conclusion, RPLS is an identified adverse event in patients administered anti-cancer treatments including cytotoxic drugs and targeted VEGF/R inhibitors (small molecule TKIs and bevacizumab). As in other agents with the same class effect, aflibercept treatment also increases the risk for developing of RPLS. Hypertension, a known class effect of anti-VEGF agents was observed in the majority of patients who developed RPLS. It is unknown why the RPLS incidence markedly increased in study VGFT-ST-0708, and based on the data, Sanofi decided not to further investigate this combination in clinical studies. The overall incidence in of RPLS in the aflibercept development was 0.44% (17/3795).

Thrombotic microangiopathy (TMA), hemolytic uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP)

In the applicant's analysis of the integrated safety database, 9 patients (0.4%) were reported as having TMA including one patient in VELOUR. Most of the cases appeared as mild or moderate in severity (associated with proteinuria Grade 1 or 2, hypertension grade 0 to 2). Of these 9 patients, three were biopsy-confirmed; all of these events led to treatment discontinuation, needed corrective treatment (requiring plasmapheresis of 2 patients), and resolved.

Two patients were diagnosed as having TTP and 1 patient as HUS. The HUS and TTP events appeared moderate in severity and were associated with proteinuria (\leq grade 2), hypertension (grade 2 or 3), and mild thrombocytopenia. Two events led to treatment discontinuation and all resolved.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1226 patients were randomized in the VELOUR study, and 1216 patients received at least one dose of study treatment (605 patients in the placebo arm, 611 patients in the aflibercept arm). Five patients who were randomized to the placebo arm and 5 patients who were randomized to the aflibercept arm did not receive study treatment. Four patients who were randomized to the placebo arm received at least one dose of aflibercept and were included in the aflibercept arm for safety and exposure analyses.

Patients in the aflibercept arm remained on treatment for a median of 3.3 weeks longer than patients on the placebo arm, and received a median of 1 more cycle (8 cycles median in the placebo arm and 9 cycles median in the aflibercept arm). Table 52 summarizes the overall exposure (placebo/aflibercept and FOLFIRI) in the safety population.

Table 52 - VELOUR: Overall exposure (safety population)

	Placebo/FOLFIRI (n=605)	Aflibercept/FOLFIRI (n=611)
# cycles/patient		
- median	8	9
- mean (SD)	10.2 (8.09)	10.4 (7.6)
- range	1-67	1-50
Duration of exposure (weeks)		
- median	18.1	21.4
- mean	22.5 (17.8)	24.2 (17.3)
- range	2-135	2-105.4
Max. number of cycles received by patient (n, %)		
- 1	23 (4)	34 (6)
- 2	29 (5)	38 (6)
- 3	86 (14)	62 (10)
- 4	32 (5)	36 (6)
- 5	28 (5)	33 (5)
- 6	49 (8)	32 (5)
- 7	27 (4)	26 (4)
- 8	33 (5)	30 (5)
- 9	45 (7)	32 (5)
- 10	21 (3)	33 (5)
- 11-15	116 (19)	111 (18)
- 16-20	56 (9)	80 (13)
- 21-25	28 (5)	37 (6)
- ≥ 26	32 (5)	27 (4)

Median duration of exposure to aflibercept/placebo was comparable between patients in the placebo arm (18 weeks) and the aflibercept arm (17.8 weeks). The planned aflibercept dose was

4 mg/kg every 2 weeks (dose intensity of 2 mg/kg/week). Median relative dose intensity for aflibercept/placebo was higher in the placebo arm (91%) than in the aflibercept arm (82%). As summarized in Table 53, more patients in the aflibercept arm required dose delays, dose modifications, or discontinuation of aflibercept than in the placebo arm.

Table 53 - VELOUR: Aflibercept/placebo exposure

	Placebo/FOLFIRI (n=605)	Aflibercept/FOLFIRI (n=611)
# cycles/patient		
- median	8	7
- mean (SD)	9.9 (7.9)	9.2 (7.1)
- range	1-67	1-35
Duration of exposure (weeks)		
- median	18	17.8
- mean	22.2 (17.5)	21.6 (16.7)
- range	2-135	2-85.1
Max. number of cycles received by patient (n, %)		
- 1	24 (4)	43 (7)
- 2	32 (5)	52 (9)
- 3	85 (14)	70 (11)
- 4	31 (5)	45 (7)
- 5	32 (5)	43 (7)
- 6	45 (7)	29 (5)
- 7	29 (5)	28 (5)
- 8	34 (6)	29 (5)
- 9	45 (7)	29 (5)
- 10	21 (3)	28 (5)
- 11-15	112 (19)	94 (15)
- 16-20	57 (9)	68 (11)
- 21-25	28 (5)	34 (6)
- ≥ 26	30 (5)	19 (3)
Median dose intensity (mg/kg/week)	1.83	1.65
Relative dose intensity	0.91	0.82
# patients with at least 1 cycle delayed (n, %)	420 (60)	475 (78)
# patients with at least 1 dose modification (n, %)	29 (5)	102 (17)
# patients whose dose was stopped (n, %)	14 (2)	95 (16)

Two subjects (one per arm) did not receive irinotecan: subject 578002005 experienced a hypersensitivity reaction during the first infusion of placebo and withdrew from treatment, and subject 724001018 experienced Grade 2 hypertension during 5-FU administration and withdrew from treatment before receiving irinotecan or aflibercept.

Median duration of exposure to irinotecan was higher in patients in the aflibercept arm (18 weeks vs. 21 weeks in the placebo and aflibercept arms respectively). The planned irinotecan dose was 180 mg/m² every 2 weeks (dose intensity of 90 mg/m²/week). Median relative dose intensity for irinotecan was higher in the placebo arm (91%) than in the aflibercept arm (84%).

As summarized in Table 54, more patients in the aflibercept arm required irinotecan dose delays, dose modifications, or discontinuation than in the placebo arm.

Table 54 - VELOUR: Irinotecan exposure

	Placebo/FOLFIRI (n=605)	Aflibercept/FOLFIRI (n=611)
# cycles/patient		
- median	8	9
- mean (SD)	9.9 (7.7)	10 (7.4)
- range	1-67	1-50
Duration of exposure (weeks)		
- median	18	21
- mean	22.2 (17.2)	23.5 (16.9)
- range	2-135	2-105
Max. number of cycles received by patient (n, %)		
- 1	23 (4)	34 (6)
- 2	29 (5)	39 (6)
- 3	87 (14)	64 (10)
- 4	33 (5)	36 (6)
- 5	29 (5)	37 (6)
- 6	48 (8)	31 (5)
- 7	27 (4)	27 (4)
- 8	32 (5)	29 (4)
- 9	47 (8)	29 (4)
- 10	21 (3)	38 (6)
- 11-15	114 (19)	111 (18)
- 16-20	58 (10)	78 (13)
- 21-25	31 (5)	35 (6)
- ≥ 26	25 (4)	22 (4)
Median dose intensity (mg/kg/week)	82	75.6
Relative dose intensity	0.91	0.84
# patients with at least 1 cycle delayed (n, %)	420 (69)	475 (78)
# patients with at least 1 dose modification (n, %)	137 (23)	227 (37)
# patients whose dose was stopped (n, %)	21 (3)	44 (7)

Median duration of exposure to 5-FU was higher in patients in the aflibercept arm (18 weeks vs. 21 weeks in the placebo and aflibercept arms, respectively). The planned fluorouracil dose was 2800 mg/m² (400 mg/m² Iv bolus followed by 2400 mg/m² continuous infusion over 46 hours) every 2 weeks (dose intensity of 1900 mg/m²/week). Median relative dose intensity for 5-FU was higher in the placebo arm (91%) than in the aflibercept arm (83%). As summarized in Table 55, more patients in the aflibercept arm required 5-FU dose delays, dose modifications, or discontinuation than in the placebo arm.

Table 55 - VELOUR: 5-FU exposure

	Placebo/FOLFIRI (n=605)	Aflibercept/FOLFIRI (n=611)
# cycles/patient		

- median	8	9
- mean (SD)	10 (7.8)	10 (7.4)
- range	1-67	1-50
Duration of exposure (weeks)		
- median	18.1	21
- mean	22.3 (17.4)	23.4 (16.9)
- range	2-135	2-105.4
Max. number of cycles received by patient (n, %)		
- 1	22 (4)	35 (6)
- 2	28 (5)	39 (6)
- 3	88 (15)	63 (10)
- 4	33 (5)	35 (6)
- 5	28 (5)	37 (6)
- 6	48 (8)	32 (5)
- 7	27 (5)	28 (5)
- 8	33 (5)	28 (5)
- 9	47 (8)	29 (5)
- 10	20 (3)	39 (6)
- 11-15	114 (19)	113 (18)
- 16-20	29 (5)	77 (13)
- 21-25	28 (5)	35 (6)
- ≥ 26	28 (5)	21 (3)
Median dose intensity (mg/kg/week)	1276.3	1165.5
Relative dose intensity	0.91	0.83
# patients with at least 1 cycle delayed (n, %)	420 (69)	475 (78)
# patients with at least 1 dose modification (n, %)	131 (22)	239 (39)
# patients whose dose was stopped (n, %)	16 (3)	42 (7)

Exposure to aflibercept was higher in patients younger than 65 years of age (9.5 cycles vs. 8 cycles in patients ≥ 65 years old). As summarized in Table 56, there were no meaningful differences in median dose intensity and relative dose intensity between age groups, but, as shown above, patients in all age groups had greater exposure to all drugs in the placebo arm.

Table 56 - VELOUR: Exposure by age groups

	Placebo/FOLFIRI (n=605)		Aflibercept/FOLFIRI (n=611)	
	≤64 y.o. (n=372)	≥ 65 y.o. (n=233)	≤64 y.o. (n=406)	≥ 65 y.o. (n=205)
# cycles/patient				
- median	8	8	9.5	8
- mean (SD)	10 (7.7)	10.2 (8.5)	11 (7.8)	9.2 (7.1)
- range	1-48	1-67	1-50	1-37
Duration of exposure (weeks)				
- median	18.3	18	22.8	18.14
- mean	22.3 (17.3)	22.9 (18.7)	25.4 (17.6)	21.8 (16.5)
- range	2-109	2-135	2-105	2-74
Median dose intensity (mg/kg/week)				
- aflibercept	1.8	1.8	1.6	1.6

- irinotecan	83.2	80.9	76	74.4
- 5-FU	1288.7	1258.7	1166.88	1149.4
Relative dose intensity				
- aflibercept	0.92	0.91	0.84	0.80
- irinotecan	0.92	0.89	0.84	0.82
- 5-FU	0.92	0.89	0.83	0.82

7.2.2 Explorations for Dose Response

The selection of aflibercept dose in the VELOUR study was based on findings of study TCD6118, which explored a range of doses of aflibercept (2, 4, 5 and 6 mg/kg) in combination with standard doses of the irinotecan/5-FU/LV regimen in patients with solid tumors. The 4 mg/kg dose was selected because the PK/PD analyses showed that this dose provided an adequate aflibercept free/bound ratio (> 1) at the end of a 2-week cycle in most patients.

The VELOUR study administered only one dose of aflibercept (4 m/kg every 2 weeks) and therefore, no dose-response assessments were conducted.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring were analyzed, and the results of these analyses are described in the Laboratory and Safety Sections of this review (Sections 7.3 and 7.4).

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal drug-drug interaction studies were conducted to evaluate the use of aflibercept in combination with irinotecan, 5-FU, and leucovorin. Although interactions between a fusion protein targeting VEGFR and small molecules that act on cell proliferation are not expected, as analyzed in Section 7.4, patients who received aflibercept experienced more chemotherapy-related adverse events than patients who received chemotherapy alone, such as diarrhea, stomatitis, palmar-plantar erythrodysesthesia, hematologic toxicity (with the exception of anemia), and neutropenia-associated infection.

The incidence rates of neutropenia and febrile neutropenia were increased in patients receiving bevacizumab plus chemotherapy compared to chemotherapy alone in different chemotherapy and disease settings, and febrile neutropenia was observed in patients treated with bevacizumab monotherapy (Avastin label). Other chemotherapy-related toxicities such as asthenic conditions, diarrhea, vomiting, stomatitis, etc, were also observed more frequently in the bevacizumab arms of the studies described in the label.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

A complete review of the toxicity of other VEGFR inhibitors can be found in Section 2.4. The safety profile of anti-VEGF agents is characterized by the occurrence of hypertension, proteinuria, arterial and venous thromboembolic events, hemorrhagic events (e.g., epistaxis, gastrointestinal bleeding, and hemoptysis), compromised wound healing, and less frequently, events such as reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation and fistula, and cardiac dysfunction.

A review of the VEGF/R inhibition-dependent toxicities found with the use of aflibercept is described in Section 7.3.5, Submission specific safety concerns.

7.3 Major Safety Results

The safety population of the placebo arm included 605 patients. In the aflibercept arm, 607 of the 612 randomized patients received at least one dose of aflibercept. The safety population of the aflibercept arm was composed of 611 patients: the 607 patients randomized to the arm plus 4 patients (ID# 410002002, 528001003, 840001001, and 380002001) from the placebo arm that received aflibercept at least once.

Almost all patients in both arms experienced adverse events. Grade 3-4 AEs occurred more frequently in the aflibercept arm (84%) than in the placebo arm (63%). This imbalance was also observed in the incidence of SAEs: in the placebo arm, the incidence of SAEs was 33%, and in the aflibercept arm, the incidence was 49%. Table 57 summarizes the major safety results in the VELOUR trial, including all outcomes and for the duration of the study since patient enrollment.

Table 57 - VELOUR: Major safety results summary

	Placebo/FOLFIRI (n, %) N= 605	Aflibercept/FOLFIRI (n, %) N=611
Subjects who experienced an AE	594 (98)	606 (99)
Subjects who experienced an AE Grade 1-2	588 (97)	605 (99)
Subjects who experienced an AE Grade 3-4	382 (63)	514 (84)
Subjects who experienced a SAE	201 (33)	299 (49)
Deaths related to an AE	21 (4)	29 (5)

All following analyses in the safety section of this review were based on adverse events that occurred between the first administration of study drugs and the follow-up visit that occurred 30 days after the last study drug administration.

At the SOC level, the most frequently affected systems ($\geq 50\%$ incidence) were gastrointestinal (placebo arm 87%, aflibercept arm 94%), general disorders and administration sites (placebo arm 67%, aflibercept arm 76%), vascular disorders (placebo arm 44%, aflibercept arm 72%), respiratory, thoracic, and mediastinal SOC (placebo arm 45%, aflibercept arm 65%), nervous system (placebo arm 47%, aflibercept arm 61%), and skin and subcutaneous tissue disorders

(placebo arm 47%, aflibercept arm 51%). Table 58 summarizes all the adverse events (regardless of the outcomes) by SOC.

Table 58 - VELOUR: AEs by SOC

SOC	Placebo/FOLFIRI (n, %) N=605		Aflibercept/FOLFIRI (n, %) N=611	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Gastrointestinal disorders	526 (87)	143 (24)	575 (94)	246 (40)
General disorders and administration site conditions	405 (67)	110 (18)	464 (76)	164 (27)
Vascular disorders	267 (44)	67 (11)	439 (72)	201 (33)
Respiratory, thoracic, and mediastinal disorders	272 (45)	44 (7)	395 (65)	61 (10)
Nervous system disorders	282 (47)	37 (6)	375 (61)	72 (12)
Skin and subcutaneous tissue disorders	285 (47)	10 (2)	311 (51)	25 (4)
Infections and infestations	199 (33)	42 (7)	282 (46)	75 (12)
Blood and lymphatic system disorders	241 (40)	153 (25)	275 (45)	182 (30)
Metabolism and nutrition disorders	191 (32)	28 (5)	273 (45)	60 (10)
Psychiatric disorders	136 (22)	10 (2)	243 (40)	19 (3)
Investigations*	117 (19)	21 (3)	236 (39)	38 (6)
Musculoskeletal and connective tissue disorders	206 (34)	25 (4)	227 (37)	16 (3)
Cardiac disorders	162 (27)	26 (4)	185 (30)	31 (5)
Renal and urinary disorders	102 (17)	17 (3)	171 (28)	41 (7)
Injury, poisoning, and procedural complications	73 (12)	11 (2)	103 (17)	11 (2)
Eye disorders	68 (11)	1 (<1)	69 (11)	0
Immune system disorders	33 (5)	6 (1)	42 (7)	2 (<1)
Hepatobiliary disorders	44 (7)	16 (3)	38 (6)	16 (3)
Reproductive system and breast disorders	43 (7)	2 (<1)	39 (6)	5 (1)
Neoplasm benign, malignant and unspecified	22 (4)	7 (1)	23 (4)	9 (1)
Ear and labyrinth disorders	18 (3)	1 (<1)	24 (4)	0
Endocrine disorders	6 (1)	1 (<1)	10 (2)	5 (1)
Pregnancy, puerperium, and perinatal conditions	1 (<1)	1 (<1)	1 (<1)	0
Surgical and medical procedures	1 (<1)	0 (<1)	3 (<1)	0

* Laboratory abnormalities reported as AEs if they led to study treatment discontinuation, dose modification, or fulfilled seriousness criteria.

At the preferred term level, the most frequently reported events (incidence $\geq 20\%$) were diarrhea (placebo arm 57%, aflibercept arm 69%), nausea (placebo arm 54%, aflibercept arm 53%), stomatitis (placebo arm 33%, aflibercept arm 50%), fatigue (placebo arm 39%, aflibercept arm 48%), hypertension (placebo arm 11%, aflibercept arm 41%), neutropenia (placebo arm 34%, aflibercept arm 39%), vomiting (placebo and aflibercept arm 33%), decreased appetite (placebo arm 24%, aflibercept arm 32%), decreased weight (placebo arm 14%, aflibercept arm 32%), epistaxis (placebo arm 7%, aflibercept arm 28%), abdominal pain (placebo arm 24%, aflibercept arm 27%), dysphonia (placebo arm 3%, aflibercept arm 25%), constipation (placebo arm 25%, aflibercept arm 22%), and headache (placebo arm 9%, aflibercept arm 22%). With the exception of nausea, vomiting (similar incidences), and constipation (where the placebo arm had a 3%

higher incidence), in all these events the incidence in the aflibercept arm was at least 3% higher. This pattern of toxicity was also observed in the incidences of Grade 3-4 events (Table 60).

Table 59 summarizes the adverse events (regardless of the outcome) by preferred term, Grades 1-4 that occurred with an incidence of 5% or more. Table 116, in the appendices section, summarizes the adverse events by PT, Grades 1-4 that occurred with an incidence of 2-4%.

Table 59 - VELOUR: AEs by PTs that occurred in ≥5% of patients (all Grades)

PT	Placebo/FOLFIRI N= 605		Aflibercept/FOLFIRI N=611	
	N	%	N	%
Diarrhea	342	57	423	69
Proteinuria	246	41	380	62
Nausea	327	54	326	53
Stomatitis	199	33	306	50
Fatigue	236	39	292	48
Hypertension	65	11	252	41
Neutropenia	205	34	238	39
Vomiting	202	33	201	33
Decreased appetite	144	24	195	32
Weight decreased	87	14	195	32
Epistaxis	45	7	169	28
Alopecia	182	30	164	27
Abdominal pain	143	24	164	27
Dysphonia	20	3	155	25
Constipation	149	25	137	22
Headache	53	9	136	22
Asthenia	80	13	112	18
Pyrexia	84	14	82	13
Back pain	72	12	75	12
Dyspnea	52	9	72	12
Cough	58	10	68	11
Upper abdominal pain	48	8	66	11
Palmar-plantar erythrodysesthesia syndrome	26	4	67	11
Edema peripheral	44	7	52	9
Urinary tract infection	37	6	56	9
Dehydration	18	3	55	9
Dyspepsia	56	9	50	8
Insomnia	45	7	47	8
Oropharyngeal pain	19	3	46	8
Skin hyperpigmentation	17	3	50	8
Rash	35	6	41	7
Dysgeusia	32	5	42	7
Dizziness	53	9	36	6
Pain in extremity	33	5	34	6
Peripheral neuropathy	30	5	34	6
Hemorrhoids	13	2	35	6
Rhinorrhea	11	2	38	6
Arthralgia	40	7	31	5
Lethargy	28	5	33	5
Hiccups	22	4	28	5

	Placebo/FOLFIRI N= 605		Aflibercept/FOLFIRI N=611	
Pulmonary embolism	21	3	28	5
Aphthous stomatitis	14	2	30	5
Proctalgia	11	2	32	5
Rectal hemorrhage	15	2	32	5
Nasopharyngitis	15	2	28	5
Hyperhidrosis	33	5	17	3

Table 60 summarizes the AEs Grades 3-4 by PTs, regardless of the outcome that occurred with an incidence of 2% or more.

Table 60 - VELOUR: AEs by PTs, Grades 3-4 (incidence ≥2%)

PT	Placebo/FOLFIRI N=605		Aflibercept/FOLFIRI N=601	
	N	%	N	%
Neutropenia	133	22	153	25
Diarrhea	47	8	118	19
Hypertension	9	1	117	19
Fatigue	47	8	77	13
Stomatitis	28	5	78	13
Asthenia	18	3	31	5
Pulmonary embolism	21	3	28	5
Abdominal pain	14	2	27	4
Febrile neutropenia	10	2	26	4
Dehydration	8	1	26	4
Vomiting	21	3	17	3
Disease progression	16	3	19	3
Decreased appetite	11	2	21	3
Weight decreased	5	1	16	3
Palmar-plantar erythrodysesthesia syndrome	3	0	17	3
Proteinuria	0	0	18	3
Nausea	18	3	11	2
Deep vein thrombosis	11	2	13	2
Pneumonia	4	1	11	2
Syncope	9	1	10	2
Headache	2	0	10	2
Back pain	11	2	7	1
Intestinal obstruction	12	2	8	1

When grouped by high level term, the most frequent AEs were non-infectious diarrhea (placebo arm 57%, aflibercept arm 69%), asthenic conditions (placebo arm 54%, aflibercept arm 65%), nausea and vomiting (placebo and aflibercept arm 59%), and stomatitis and ulceration (placebo arm 35%, aflibercept arm 55%). As observed before, with the exception of nausea and vomiting (same incidence in both arms), diarrhea, asthenic conditions, stomatitis and ulcerations were observed more often in the aflibercept arm.

The most frequently observed Grade 3-4 HLTs were neutropenias (placebo arm 24%, aflibercept arm 28%), diarrhea (placebo arm 8%, aflibercept arm 19%), asthenic conditions (placebo arm 11%, aflibercept arm 18%), stomatitis and ulceration (placebo arm 5%, aflibercept arm 14%),

and hypertension (placebo arm 1%, aflibercept arm 19%). All these Grade 3-4 AEs were observed at a higher frequency in the aflibercept arm. Table 61 summarizes the HLTs observed with an incidence of $\geq 10\%$.

Table 61 - VELOUR: AEs by HLT with an incidence $\geq 10\%$

HLT	Placebo/FOLFIRI (n, %) N=605		Aflibercept/FOLFIRI (n, %) N=611	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Diarrhea (excl. infectious)	342 (57)	47 (8)	423 (69)	118 (19)
Asthenic conditions	325 (54)	69 (11)	395 (65)	111 (18)
Nausea and vomiting	359 (59)	30 (5)	363 (59)	24 (4)
Stomatitis and ulceration	211 (35)	30 (5)	335 (55)	84 (14)
Neutropenias	217 (36)	144 (24)	251 (41)	174 (28)
Vascular hypertensive disorders	65 (11)	9 (1)	253 (41)	118 (19)
GI and abdominal pains (excl oral and throat)	176 (29)	20 (3)	208 (34)	33 (5)
Physical examination procedures	92 (15)	5 (1)	199 (33)	16 (3)
Appetite disorders	144 (24)	11 (2)	195 (32)	22 (4)
Upper respiratory tract symptoms	51 (8)	0	197 (32)	4 (1)
Hemorrhages NEC	54 (9)	1 (<1)	183 (30)	5 (1)
Nasal disorders NEC	49 (8)	0	172 (28)	1 (<1)
Alopecias	182 (30)	0	164 (27)	0 (<1)
Speech and language abnormalities	24 (4)	0	161 (26)	3 (<1)
Speech articulation and rhythm disturbances	22 (4)	0	156 (26)	3 (<1)
GI atonic and hypomotility disorders	156 (26)	7 (1)	145 (24)	6 (1)
Musculoskeletal connective tissue pain and discomfort	128 (21)	14 (2)	141 (23)	8 (1)
Headaches	53 (9)	2 (<1)	136 (22)	10 (2)
Sensory abnormalities	62 (10)	5 (1)	115 (19)	17 (3)
Febrile disorders	92 (15)	13 (2)	102 (17)	29 (5)
Coughing and associated symptoms	66 (11)	0	78 (13)	1 (<1)
Breathing abnormalities	62 (10)	5 (1)	77 (13)	6 (1)
Upper respiratory tract infections	55 (9)	0	81 (13)	2 (<1)
Dyspneas	61 (10)	5 (1)	76 (12)	6 (1)
Urinary abnormalities	28 (5)	2 (<1)	71 (12)	19 (3)
General signs and symptoms	85 (14)	20 (3)	65 (11)	25 (4)
Urinary tract infection	44 (7)	6 (1)	68 (11)	6 (1)
Skin and subcutaneous conditions	26 (4)	3 (<1)	68 (11)	17 (3)
Cardiac signs and symptoms	63 (10)	12 (2)	62 (10)	10 (2)
Heart failure signs and symptoms	55 (9)	5 (1)	59 (10)	5 (1)
GI signs and symptoms	42 (7)	3 (<1)	61 (10)	4 (1)
Total fluid volume increase	45 (7)	1 (<1)	59 (10)	0
Circulatory collapse and shock	64 (11)	12 (2)	53 (9)	14 (2)
Dyspeptic signs and symptoms	58 (10)	1 (<1)	51 (8)	1 (<1)

7.3.1 Deaths

For the purpose of this review, deaths analyzed in this section are those that occurred from the start of treatment up to 30 days after the last dose. As summarized in Table 62, the leading cause of death was disease progression: 2% of patients died during this evaluation period due to

disease progression in both the placebo and aflibercept arms. However, treatment related deaths were more frequent in the aflibercept arm (18 patients, 3%) compared to the placebo arm (8 patients, 1.8%). In the applicant's analysis, only 16 patients in the aflibercept arm and 6 patients in the placebo arm experienced fatal events not associated with progressive disease, and only 6 events in the aflibercept arm were considered to be related to aflibercept by the investigator.

Table 62 - VELOUR: Deaths during treatment and up to 30-days after last study treatment drugs.

PT	Placebo/FOLFIRI N=605	Aflibercept/FOLFIRI N=611
Disease progression	13	11
Death	1	2
Dehydration	0	2
Intestinal obstruction	1	1
Sepsis	1	1
Acute respiratory failure	0	1
Duodenal ulcer hemorrhage	0	1
Gastrointestinal inflammation	0	1
Hypovolemic shock	0	1
Ileal perforation	0	1
Large intestinal obstruction	0	1
Metabolic encephalopathy	0	1
Neutropenic sepsis	0	1
Pneumonia aspiration	0	1
Pulmonary embolism	0	1
Rectal abscess	0	1
Septic shock	0	1
Ileus	1	0
Interstitial lung disease	1	0
Lobar pneumonia	1	0
Neutropenic infection	1	0
Sudden death	1	0
Total	21	29

It is difficult, in some cases, to establish if disease progression was the sole underlying cause of death. With certain toxicities, such as neutropenic sepsis, it was clear that the patient's death was associated with chemotherapy. However, some events, such as intestinal obstruction, can be both related to either disease or therapy. As stated above, this reviewer found more cases of deaths related to study drugs (analysis of adverse events database, narratives and CRFs) compared to the Applicant's analysis. Table 62 summarized the results of the analysis of the adverse events database, and each AE was confirmed by the review of the narrative and/or CRF.

The second most common group of adverse events associated with death were gastrointestinal disorders (2 patients in the placebo arm and 6 patients in the aflibercept arm), followed by infections (3 patients in the placebo arm and 5 patients in the aflibercept arm).

When analyzing the disposition dataset, for those patients who died within the treatment period, the cause of death was classified as death due to adverse event, disease progression, or “other reason”. In the aflibercept/FOLFIRI arm, the verbatim terms for reason “other” were adverse events in 8 patients (digestive hemorrhage, fecal peritonitis, heart failure, pneumonia [2], and pulmonary thromboembolism [3]), unknown cause of death in 6 patients and euthanasia (patient 056001001, treated in Belgium) in one patient.

In the placebo/FOLFIRI arm, the verbatim terms for reason “other” are adverse events in 7 patients (pneumonia, hematemesis, hepatic toxic syndrome, infection, leukopenic sepsis, sepsis and intestinal subocclusion, and small bowel obstruction), cardiac arrest (2), euthanasia (patient #528001010, treated in The Netherlands’), and unknown (3).

Reviewer’s comment: In summary, the leading cause of death for in both arms was disease progression. Treatment related deaths were more frequent in the aflibercept arm (35 patients, 6%) than in the placebo arm (24 patients, 4%).

7.3.2 Nonfatal Serious Adverse Events (SAEs)

This section focused on non-fatal SAEs and analyses by SOC. Serious adverse events that are known to be related to VEGF inhibition will be further reviewed in Section 7.3.5, Submission Specific Safety Concerns.

The protocol definition for a Serious Adverse Event (SAE) was any untoward medical occurrence that, at any dose resulted in death or, was life-threatening (an event in which the patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe); or required inpatient hospitalization or prolongation of existing hospitalization or; resulted in persistent or significant disability/incapacity or; caused a congenital anomaly/birth defect, or; was a medically important event. For the purposes of the analysis of this section, fatal SAEs were excluded and analyzed in Section 7.3.1. The results differed slightly from the applicant’s results due to the exclusion of the events with fatal outcomes.

A total of 470 patients experienced a non-fatal SAE, 185 patients (31%) in the placebo arm and 285 patients in the aflibercept arm (47%). Of the 454 SAEs in the placebo arm, 16 (4%) were Grade 1, 76 (17%) were Grade 2, 294 (65%) were Grade 3, and 68 (15%) were Grade 4. Of the 766 SAEs in the aflibercept arm, 28 (4%) were Grade 1, 177 (23%) were Grade 2, 439 (57%) were Grade 3, and 122 (16%) were Grade 4.

More events in the aflibercept arm resulted in hospitalization or prolongation of hospitalization (421 vs. 659 in the placebo and aflibercept arms respectively). More events in the aflibercept arm were medically important (45 vs. 73 in the placebo and aflibercept arms respectively) or life threatening (13 vs. 42 in the placebo and aflibercept arms respectively). More patients in the placebo arm experienced disabilities as a result of the SAE (11 vs. 3 in the placebo and aflibercept arms respectively).

Table 63 summarizes all non-fatal SAEs by SOC.

Table 63 - VELOUR: Non-fatal SAEs (by SOC)

SOC	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Gastrointestinal disorders	71 (12)	133 (22)
Vascular disorders	41 (7)	78 (13)
Infections	35 (6)	67 (11)
General disorders and administration sites conditions	41 (7)	60 (10)
Respiratory, thoracic and mediastinal conditions	34 (6)	52 (9)
Blood and lymphatic system disorders	23 (4)	48 (8)
Metabolism and nutrition disorders	18 (3)	31 (5)
Renal and urinary disorders	14 (2)	27 (4)
Cardiac disorders	17 (3)	19 (3)
Hepatobiliary disorders	16 (3)	11 (2)
Injury and procedural complications	10 (2)	11 (2)
Nervous system disorders	12 (2)	14 (2)
Musculoskeletal and connective tissue disorders	11 (2)	8 (1)
Investigations	4 (1)	6 (1)
Neoplasms	8 (1)	9 (1)
Psychiatric disorders	5 (1)	6 (1)
Skin and subcutaneous tissue disorders	1 (<1)	4 (1)
Endocrine disorders	1 (<1)	3 (<1)
Eye disorders	0	1 (<1)
Immune system disorders	2 (<1)	1 (<1)
Pregnancy, puerperium, and perinatal conditions	1 (<1)	0
Reproductive system	1 (<1)	3 (<1)

A greater incidence of SAEs was observed in the aflibercept/FOLFIRI arm (differences in parentheses) in the gastrointestinal SOC (10%), vascular SOC (6%), infections (5%), general disorders and administration site conditions SOC (3%), respiratory SOC (3%), blood SOC (4%), metabolism and nutrition SOC (2%), and renal SOC (2%).

As summarized in Table 64, the most frequently reported PTs (SAEs analysis) were diarrhea and dehydration. The incidence of diarrhea, dehydration, and febrile neutropenia was 5%, 3%, and 2% higher respectively than patients in the placebo arm.

Table 64 - VELOUR: Non-fatal SAEs with incidences \geq 2% (by PT)

PT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Diarrhea	14 (2)	44 (7)
Dehydration	7 (1)	23 (4)
Pulmonary embolism	12 (2)	18 (3)
Febrile neutropenia	6 (1)	19 (3)
Pyrexia	15 (2)	10 (2)
Abdominal pain	7 (1)	12 (2)

Neutropenia	4 (1)	11 (2)
Pneumonia	5 (1)	11 (2)
Vomiting	7 (1)	10 (2)
Hypertension	0	10 (2)
Intestinal obstruction	10 (2)	9 (1)

When analyzing the data by HLT (Table 65), the differences between arms for diarrhea were the same, but patients in the aflibercept arm experienced more neutropenias (4% difference), febrile disorders (2% difference), and decreased total fluid volume (3%).

Table 65 - VELOUR: Non-fatal SAEs with incidences \geq 3% (by HLT)

HLT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Diarrhea	14 (2)	44 (7)
Neutropenias	14 (2)	37 (6)
Febrile disorders	19 (3)	29 (5)
Total fluid volume decreased	7 (1)	23 (4)
Gastrointestinal obstruction and stenosis	18 (3)	17 (3)
Gastrointestinal and abdominal pains	11 (2)	17 (3)
Pulmonary embolism and thrombosis	12 (2)	19 (3)

The most frequently reported Grades 1-2 SAEs were diarrhea (2 patients and 13 patients in the placebo and aflibercept arms respectively) and febrile disorders (13 patients and 8 patients in the placebo and aflibercept arms respectively).

7.3.3 Dropouts and/or Discontinuations

This analysis differed from the applicant's analysis, which used the disposition dataset to determine the patients who discontinued treatment because of an adverse event, as stated in the CSR and summarized in Table 30. This reviewer's analysis focused on the outcome of the adverse event in the adverse event dataset.

In the applicant's analysis, a total of 237 patients (placebo arm: 74; aflibercept arm: 163) permanently discontinued from study treatment due to an AE. The events most frequently leading to permanent discontinuation were fatigue/asthenia, (31 patients overall), infections (31 patients), diarrhea (18 patients), myelosuppression, (18 patients), hypertension (14 patients), pulmonary embolism (14 patients), proteinuria (including nephrotic syndrome, 10 patients) and deep vein thrombosis (10 patients). In the aflibercept arm, the most frequent reasons were in relation to asthenia/fatigue, infections, diarrhea, hypertension, venous thromboembolic events (collectively DVT and pulmonary embolism), myelosuppression and proteinuria. There was no leading cause for study treatment discontinuation due to AE. The biggest differences between treatment arms were seen for hypertension (2.3% in the aflibercept arm versus 0.0% in the placebo arm), infections and infestations (3.4% versus 1.7%), proteinuria or nephritic syndrome (1.7% versus 0.0%), diarrhea (2.3% versus 0.7%), and fatigue/asthenia (3.8% versus 1.3%).

The analysis of the safety database showed that AEs leading to treatment discontinuation (excluding the fatal AEs, which are analyzed separately) were more frequent in the aflibercept arm. Eighty patients (13%) in the placebo arm and 252 patients (41%) in the aflibercept arm permanently discontinued treatment. Additionally, 6 patients in the placebo arm and 13 patients in the aflibercept arm died because of treatment-related toxicities.

As summarized in Table 66, the majority of patients in the aflibercept arm who experienced an AE that lead to withdrawal had vascular disorders, gastrointestinal disorders, and renal disorders. Differences in incidences between arms (in all SOC, the incidence was higher in the aflibercept arm) were more marked in the (differences in parentheses) vascular disorders SOC (10%), gastrointestinal disorders SOC (7%), renal disorders SOC (7%), and general disorders SOC (5%).

Table 66 - VELOUR: AEs (by SOC) leading to treatment withdrawals

SOC	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Vascular disorders	19 (3)	82 (13)
Gastrointestinal disorders	20 (3)	66 (11)
Renal and urinary disorders	5 (1)	46 (8)
General disorders and administration site conditions	11 (2)	43 (7)
Respiratory, thoracic and mediastinal disorders	18 (3)	33 (5)
Blood and lymphatic disorders	9 (1)	18 (3)
Infection	7 (1)	21 (3)
Nervous system disorders	5 (1)	17 (3)
Investigations	2 (<1)	20 (3)
Metabolism and nutrition disorders	1 (<1)	12 (2)
Injuries and procedural complications	5 (1)	5 (1)
Cardiac disorders	3 (<1)	8 (1)
Neoplasms	0	5 (1)
Psychiatric disorders	2 (<1)	7 (1)
Reproductive system disorders	1 (<1)	4 (1)
Skin and subcutaneous tissue disorders	3 (<1)	6 (1)
Hepatobiliary disorders	4 (<1)	3 (<1)
Musculoskeletal and connective tissue disorders	4 (<1)	2 (<1)
Eye disorders	0	1 (<1)
Immune system disorders	3 (<1)	2 (<1)

The events leading to treatment discontinuations are summarized in Table 67.

Table 67 - VELOUR: Most frequent AEs (PT) leading to treatment discontinuation

PT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Hypertension	1 (<1)	29 (5)
Proteinuria	0	33 (5)
Pulmonary embolism	13 (2)	18 (3)
Diarrhea	7 (1)	21 (3)
Fatigue	6 (1)	18 (3)
Asthenia	2 (<1)	10 (2)

Stomatitis	1 (<1)	11 (2)
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7.3.4 Significant Adverse Events (Non-Fatal Grade 3-4 Adverse Events)

This section focused on non-fatal Grade 3-4 AEs and analysis by SOC. Adverse events that are known to be related to VEGF inhibition will be further reviewed in section 7.3.5, Submission Specific Safety Concerns. Table 68 summarizes the incidence of non-fatal Grade 3-4 AEs analyzed by SOC.

Table 68 - VELOUR: Grade 3-4 non-fatal AEs by SOC

SOC	Placebo/FOLFIRI N=605		Aflibercept/FOLFIRI N=611	
	N	%	N	%
Gastrointestinal	141	23	244	40
Vascular	67	11	197	32
Blood and lymphatic	152	25	182	30
General disorders and administration site conditions	99	16	154	25
Infections	39	6	72	12
Nervous system	37	6	71	12
Respiratory, thoracic and mediastinal disorders	43	7	60	10
Metabolism and nutrition	28	5	59	10
Renal and urinary	17	3	41	7
Investigations	21	3	38	6
Cardiac	25	4	31	5
Skin and subcutaneous tissue	10	2	25	4
Musculoskeletal and connective tissue	25	4	16	3
Hepatobiliary	16	3	16	3
Psychiatric	10	2	19	3
Injury, poisoning, and procedural complications	11	2	11	2
Neoplasms	7	1	9	1
Endocrine	1	0	5	1
Reproductive system and breast disorders	2	0	5	1
Immune system	6	1	2	0
Ear and labyrinth	1	0	0	0
Eye	1	0	0	0
Pregnancy, puerperium, and perinatal	1	0	0	0

As summarized in Table 69, patients in the aflibercept/FOLFIRI arm experienced more frequently (differences in parentheses) non-fatal Grade 3-4 hypertension (18%), diarrhea (11%), stomatitis (8%), fatigue (5%), neutropenia (3%), dehydration (3%), palmo-plantar erythrodysesthesia (3%), proteinuria (3%), asthenia (2%), abdominal pain (2%), weight decrease (2%), and febrile neutropenia (2%).

Table 69 - VELOUR: Non-fatal Grade 3-4 AEs by PT (incidence ≥ 2%)

PT	Placebo/FOLFIRI N=605		Aflibercept/FOLFIRI N=611	
	N	%	N	%
Neutropenia	133	22	153	25
Diarrhea	47	8	118	19
Hypertension	9	1	117	19
Fatigue	47	8	77	13
Stomatitis	28	5	78	13
Asthenia	18	3	31	5
Pulmonary embolism	21	3	27	4
Abdominal pain	14	2	27	4
Febrile neutropenia	10	2	26	4
Dehydration	8	1	25	4
Vomiting	21	3	17	3
Decreased appetite	11	2	21	3
Weight decreased	5	1	16	3
Palmar-plantar erythrodysesthesia syndrome	3	0	17	3
Proteinuria	0	0	18	3
Nausea	18	3	11	2
Deep vein thrombosis	11	2	13	2
Pneumonia	4	1	11	2
Syncope	9	1	10	2
Headache	2	0	10	2
Back pain	11	2	7	1
Intestinal obstruction	11	2	7	1

Gastrointestinal disorders

Grade 3-4 non-fatal AEs in this SOC were reported in 141 patients (23%) in the placebo arm and 244 patients (40%) in the aflibercept arm. The main difference between arms in severe AEs was the higher incidence of diarrhea (8% and 19% in the placebo and aflibercept arms, respectively), stomatitis (5% and 13% in the placebo and aflibercept arms respectively), and abdominal pain (2% and 4% in the placebo and aflibercept arms, respectively) in the aflibercept/FOLFIRI arm. For all other PTs, the incidence was similar between arms. When analyzing severe AEs by HLTs, diarrhea (8% and 19% in the placebo and aflibercept arms respectively), stomatitis and ulceration (5% and 14% in the placebo and aflibercept arms, respectively), and gastrointestinal pain (3% and 5% in the placebo and aflibercept arms respectively) were the categories where there was at least a 2% difference in incidence between arms.

Severe nausea, vomiting, intestinal hemorrhages, and intestinal obstruction occurred infrequently in both arms.

It appeared that the use of aflibercept intensified some of the toxicities associated with the administration of FOLFIRI such as diarrhea and stomatitis. This interaction was also observed with regards to the FOLFIRI associated myelotoxicity.

Vascular disorders

Grade 3-4 non-fatal AEs were reported in 67 patients (11%) in the placebo arm and 197 patients (32%) in the aflibercept arm. Hypertension was the most frequently reported severe AE in this SOC (1% and 19% in the placebo and aflibercept arms respectively) and is presented separately in Section 7.3.5.

The most frequently observed (severe) vascular disorders other than hypertension were deep vein thrombosis (2% in each arm), syncope (1% and 2% in the placebo and aflibercept arms respectively), hypotension, post-procedural hemorrhage, and rectal hemorrhage (1% in the aflibercept arm, lower than 1% in the placebo arm).

Blood and lymphatic disorders

For this section of the review, only the severe lab abnormalities reported as adverse events were analyzed. Further effects of therapy on bone marrow function are presented in Section 7.4.2, Laboratory Findings. The addition of aflibercept to the FOLFIRI backbone regimen caused an increased incidence of leucopenia, neutropenia, and thrombocytopenia.

The most common severe event observed in the study was anemia. Patients in the placebo arm experienced anemia more frequently than patients in the aflibercept arm [544 patients (89%) in the placebo arm and 502 patients (82%) in the aflibercept arm]. Grade 3 or 4 hemoglobin values were infrequent in this study.

Grade 3-4 non-fatal neutrophil-related AEs were reported in 152 patients (25%) in the placebo arm and 182 patients (30%) in the aflibercept arm. Neutropenia was observed in 22% of patients in the placebo arm and 25% of patients in the aflibercept arm, and febrile neutropenia occurred in 2% and 4% of patients in the placebo and aflibercept arms, respectively. However, when grouping all neutropenic complications (PTs “febrile neutropenia”, “neutropenic infections”, “neutropenic colitis”, and “neutropenic sepsis”), the incidence was 3% and 6% in the placebo and aflibercept arms, respectively. Table 70 summarizes the neutropenia and neutropenic complications in the VELOUR trial regardless of the outcome.

Table 70 - VELOUR: Neutropenia and neutropenic complications (regardless of outcome)

PT	Placebo/FOLFIRI (N, %) N=605		Aflibercept/FOLFIRI (n, %) N=611	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Neutropenia*	205 (34)	133 (22)	238 (39)	51 (8)
ANC decreased*	10 (2)	5 (1)	13 (2)	2 (<1)
Neutropenia by lab dataset	342 (57)	179 (30)	411 (67)	223 (36)
Febrile neutropenia	10 (2)	10 (2)	26 (4)	26 (1)
Neutropenic infection	8 (1)	7 (1)	11 (2)	6 (1)
Neutropenic colitis	0	0	1 (<1)	1 (<1)
Neutropenic sepsis	0	0	3 (<1)	3 (<1)

* neutropenia and ANC decreased as per AE dataset

General disorders and administration conditions

Grade 3-4 non-fatal AEs were reported in 99 patients (16%) in the placebo arm and 154 patients (25%) in the aflibercept arm. The most common adverse event in this SOC was fatigue (8% of patients in the placebo arm and 13% of patients in the aflibercept arm), followed by asthenia (3% and 5% in the placebo and aflibercept arms respectively). When grouped by HLT, the “asthenic conditions” occurred in 11% and 18% of patients in the placebo and aflibercept arms, respectively.

All other AEs reported (i.e. device-related infection, general physical deterioration, catheter-site infection, erythema, etc) occurred at an incidence rate of 1% or less.

Nervous system disorders

Grade 3-4 non-fatal AEs were reported in 37 patients (6%) in the placebo arm and 71 patients (12%) in the aflibercept arm. The most frequent AE observed in this SOC was palmar-plantar erythrodysesthesia, reported in 3 patients in the placebo arm (0.5%) and 17 patients in the aflibercept arm (3%). Palmar-plantar erythrodysesthesia is described as an adverse reaction in the 5FU labeling. Syncope was reported in 1-2% of patients, and all other PTs were reported with incidences less than 1%.

When grouped by HLTs, disturbances in consciousness was observed in 3% of patients in both arms; sensory abnormalities in 1% and 3% of patients in the placebo and aflibercept arms, respectively; peripheral neuropathies in 1% and 3% of patients in the placebo and aflibercept arms, respectively; and headaches in 0.3% and 2% of patients in the placebo and aflibercept arms, respectively.

Respiratory, thoracic and mediastinal disorders

Grade 3-4 non-fatal AEs were reported in 43 patients (7%) in the placebo arm and 60 patients (10%) in the aflibercept arm. Pulmonary embolism was the most frequently reported PT (3% and 4% in the placebo and aflibercept arms, respectively), followed by pneumonia (1% and 2% in the placebo and aflibercept arms, respectively), and dyspnea (1% in each arm). When grouped by HLT, pulmonary thrombotic and embolic conditions incidence were 3% and 5% in the placebo and aflibercept arms, respectively, and lower respiratory tract infections incidences occurred in 2% of patients per arm.

Metabolism and nutritional disorders

Grade 3-4 non-fatal AEs were reported in 28 patients (5%) in the placebo arm and 59 patients (10%) in the aflibercept arm. Severe dehydration was more frequently observed in the aflibercept arm (1% in the placebo arm and 4% in the aflibercept arm). Severe decreased appetite was also more frequent in the aflibercept arm (2% and 3% in the placebo and aflibercept arms, respectively for the PT decreased appetite, and 2% and 4% in the placebo and aflibercept arms, respectively for the HLT appetite disorders).

Infections

Grade 3-4 non-fatal AEs were reported in 39 patients (6%) in the placebo arm and 72 patients (12%) in the aflibercept arm. Because of the granularity of the reported events, HLTs were more representative of the infections observed in the study. Table 71 summarizes the Grade 3-4 non-fatal infections that occurred in at least 1% of patients

Table 71 – VELOUR: Grade 3-4 non-fatal infections by HLT

HLT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Infections NEC	14 (2)	18 (3)
Lower respiratory tract and lung infections	13 (2)	14 (2)
Sepsis, bacteriemia, viremia, and fungemia NEC	4 (1)	13 (1)
Abdominal and gastrointestinal infections	2 (<1)	11 (2)
Urinary tract infections	6 (1)	6 (1)

PTs included in the “Infections NEC” HLT in the placebo arm were device related infections (7 patients), neutropenic infections (6 patients), and infection (1 patient). PTs included in the “Infections NEC” HLT in the aflibercept arm are device related infections (6 patients), neutropenic infections (6 patients), catheter site infection (2 patients), pelvic abscess (1 patient), respiratory tract infection (1 patient), and infection (2 patients).

In most cases (for Grades 3-4 events) a specific pathogen was not identified (6% and 11% incidence in the placebo and aflibercept arms, respectively). The occurrence of bacterial infections was low (1 and 5 patients in the placebo and aflibercept arm, respectively).

Renal and urinary disorders

Grade 3-4 non-fatal AEs were reported in 17 patients (3%) in the placebo arm and 41 patients (7%) in the aflibercept arm. The most frequently observed (severe) AE was proteinuria. No patients experienced proteinuria in the placebo/FOLFIRI arm, while 18 patients (7%) in the aflibercept/FOLFIRI arm experienced Grade 3-4 proteinuria. Additionally there were 2 cases of nephrotic syndrome in the aflibercept arm. These are well described class effects of VEGF/VEGFR inhibitors and will be further presented in section 7.3.5.

With the exception of urinary tract infections (5 patients in each arm), and 5 patients (4 patients in the aflibercept arm and the remaining one in the placebo arm) who experienced acute renal failure or renal failure, all other severe AEs in the SOC were observed in 1-2 patients.

In three patients in the aflibercept arm (ID# 152004016, 203004005, and 203001008), the diagnosis of severe renal failure was preceded by diarrhea, dehydration, fever, nausea, and vomiting. In the fourth patient (#840012002) in the aflibercept arm who experienced severe renal failure, this diagnosis was a laboratory finding (pre-cycle 5), and the patient recovered, although treatment was discontinued.

Severe renal failure was diagnosed in only one patient in the placebo arm (#056003017); this patient was found to have an elevated creatinine in pre-treatment labs for Cycle 39, and the patient was withdrawn from treatment.

Musculoskeletal and connective tissue disorders

Grade 3-4 non-fatal AEs were reported in 25 patients (4%) in the placebo arm and 16 patients (3%) in the aflibercept arm. The most frequently reported PT was back pain in 11 patients (2%) and 7 patients in the aflibercept arm (1%).

Other SOC's

As summarized in Table 68, severe AEs were reported with incidences of $\leq 3\%$. Table 72 summarizes the incidences of severe AEs by PT that were reported in at least 3 patients. The most frequently reported event was palmar-plantar erythrodysesthesia, reported in 3 patients in the placebo arm (0.5%) and 17 patients in the aflibercept arm (3%). Palmar-plantar erythrodysesthesia is described as an adverse reaction in the 5FU labeling.

Table 72 - VELOUR: Non-fatal Grade 3-4 AEs (by PTs) in other SOC's

PT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Palmar-plantar erythrodysesthesia	3 (<1)	17 (3)
Syncope	9 (1)	10 (2)
Ascites	8 (1)	10 (2)
Lethargy	5 (1)	8 (1)
Dyspnea	5 (1)	5 (1)
Post-procedural hemorrhage	1 (<1)	4 (1)
Hyperbilirubinemia	6 (1)	3 (<1)
Confusional state	2 (<1)	3 (<1)
Atrial fibrillation	1 (<1)	3 (<1)
Cholecystitis	1 (<1)	3 (<1)
Dysphonia	0	3 (<1)
Gastrointestinal stoma complication	0	3 (<1)
Angioedema	4 (1)	2 (<1)

All other severe AEs occurred at low incidence rates, with no significant differences between arms. There was one report of non-fatal Grade 3 liver failure in a 54 year old male patient (ID#643002010) in the placebo arm, experienced after Cycle 16. However, the lab dataset shows Grade 2 AST/ALT and an elevated total bilirubin. There was no CRF provided for this patient.

7.3.5 Submission Specific Primary Safety Concerns

This section will review class-related adverse events. In Section 2.4 described the effects of anti-VEGF and VEGFR targeted therapies and the experience with other drugs and other disease settings. This section will focus on the findings in the VELOUR trial, with the exception of the

review of reversible posterior leukoencephalopathy (RPLS) which will be inclusive of the whole aflibercept experience.

The applicant grouped in the safety database events of interest and the grouping terms (PTs or HLTs) may differ from the PTs used to define standard MedDRA SMQs. For the purposes of this review, for each group, a comparison between the applicant's terms and the SMQ PTs was performed (see below Table 73 as an example) and the database was queried for missing terms when relevant. Most investigations were reported as adverse events only when they had clinical repercussion, and analyzed separately in Section 7.4.2. Specific investigations such as results from cardiac catheterization were not included in the analysis because in most cases, these were associated with clinical events.

FDA SMQ analysis (using the MAED application) using standard MedDRA SMQs is presented in Table 118 in the appendices section. Result for each group of events will be summarized in the following sections.

7.3.5.1 Cardiac Dysfunction

Cardiomyopathy and congestive heart failure (CHF) have been reported with the use of VEGF and VEGFR targeting therapy, including bevacizumab and sunitinib. Table 73 summarizes the terms searched by the applicant and the SMQ PTs.

Table 73 - VELOUR: Cardiac dysfunction list of terms.

Sanofi's grouping	SMQ
Acute left ventricular failure	Acute left ventricular failure
Acute pulmonary oedema	
Acute right ventricular failure	Acute right ventricular failure
	Cardiac asthma
Cardiac cirrhosis	Cardiac cirrhosis
Cardiac failure	Cardiac failure
Cardiac failure acute	Cardiac failure acute
Cardiac failure chronic	Cardiac failure chronic
Cardiac failure congestive	Cardiac failure congestive
	Cardiac failure high output
Cardiac index decreased	Cardiac index decreased
Cardiac output decreased	Cardiac output decreased
	Cardiac re-synchronization therapy
Cardiogenic shock	Cardiogenic shock
	Cardiomegaly
Cardiomyopathy	
Cardiopulmonary failure	Cardiopulmonary failure
	Cardiorenal syndrome
Cardio-respiratory distress	Cardio-respiratory distress
Cardiovascular insufficiency	
Chronic left ventricular failure	Chronic left ventricular failure
Chronic right ventricular failure	Chronic right ventricular failure

Cor pulmonale	Cor pulmonale
Cor pulmonale acute	Cor pulmonale acute
Cor pulmonale chronic	Cor pulmonale chronic
Dilatation ventricular	Dilatation ventricular
Dyspnoea paroxysmal nocturnal	Dyspnoea paroxysmal nocturnal
	Edema
Ejection fraction decreased	Ejection fraction decreased
	Hepatic congestion
	Hepatojugular reflex
Hepatic vein dilatation	Hepatic vein dilatation
Jugular vein distension	Jugular vein distension
Left ventricular dysfunction	Left ventricular dysfunction
Left ventricular failure	Left ventricular failure
Low cardiac output syndrome	Low cardiac output syndrome
Myocardial depression	Myocardial depression
Nocturnal dyspnoea	Nocturnal dyspnoea
Oedema due to cardiac disease	Oedema due to cardiac disease
	Oedema peripheral
Orthopnoea	Orthopnoea
Pulmonary oedema	Pulmonary oedema
	Pulmonary congestion
Right ventricular dysfunction	Right ventricular dysfunction
Right ventricular failure	Right ventricular failure
	Systolic dysfunction
Ventricular dysfunction	Ventricular dysfunction
	Ventricular dysynchrony
Ventricular failure	Ventricular failure

*Neonatal cardiac failure, pulmonary neonatal edema, heart transplant, etc, were not included in the list of SMQs because they were not relevant to the population in this study.

Investigations not included in the list of terms in the SMQ column: atrial natriuretic brain peptide abnormal/increased, brain natriuretic brain peptide abnormal/increased, cardiac ventriculogram abnormal, cardiac right ventriculogram abnormal, cardiac left ventriculogram abnormal, cardiothoracic ration increased, central venous pressure increased, diastolic dysfunction, dilatation ventricular, N-preterminal pro hormone brain natriuretic peptide abnormal/increased, scan myocardial perfusion abnormal, venous pressure increased, venous jugular pressure abnormal/increased.

According to the applicant's grouping, only two subjects experienced a cardiac dysfunction event (subject 056003021, a 71 year old man who experienced acute pulmonary edema after the first drug infusion, and subject 152004004, a 41 year old woman who experienced acute congestive heart failure after cycle 6 and was permanently discontinued from study drugs). When adding the "missing" terms from the standard SMQ, there was one subject (aflibercept arm) who experienced "pulmonary congestion" (#036006001, CRF not informative), 6 subjects with "edema" (5 in the aflibercept arm) and 96 subjects who experienced "peripheral edema" (44 in the placebo arm and 52 in the aflibercept arm). From the review of the available narratives and CRFs, these events were more likely related to drug reactions and confounded by multiple

factors (i.e., proteinuria, hypoalbuminemia, sepsis, etc.) and cannot be definitively attributed to cardiac dysfunction.

The cardiac events by PT that occurred with an incidence $\geq 2\%$ were as follows: dyspnea (9% vs. 12% placebo and aflibercept arms, respectively), edema peripheral (7% vs. 9% placebo and aflibercept arms, respectively), dizziness (9% vs. 6% placebo and aflibercept arms, respectively), ascites (2% in each arm), syncope (1% vs. 2% placebo and aflibercept arms, respectively), and hemoptysis (0% vs. 2% placebo and aflibercept arms, respectively). When analyzed by HLT, the incidence of heart failures (sign and symptoms) was similar between arms, 9% and 10% in the placebo and aflibercept arms, respectively.

FDA SMQ analysis of cardiac failure showed 2 subjects in the aflibercept arm and none in the placebo arm (RR 0.25, 95% CI 0.028-2.25, p value 0.24).

Reviewer's conclusion: this reviewer agrees with the applicant's conclusion that aflibercept did not increase the risk of cardiac dysfunction in the VELOUR trial. However, this conclusion cannot be extrapolated if aflibercept is used in other settings (for example, with different background chemotherapy regimes or in earlier stage cancer settings).

7.3.5.2 Acute Drug Reactions

Patients in the VELOUR study did not receive prophylaxis prior to the administration of aflibercept/placebo. The protocol established that the diluted volume of aflibercept/placebo (in 0.9% NaCl or 5% dextrose) should be infused not exceeding 2 hours at ambient temperature (approximately 25°C). Following the administration of aflibercept/placebo, premedication was provided prior to the administration of the FOLFIRI regimen (atropine and antiemetics were administered according to institutional guidelines).

In the Sanofi analysis, acute drug reactions occurred in 4% of patients in both arms, and 0.5% of these events were Grade 3 (hypersensitivity and circulatory collapse). No Grade 4 acute drug reactions were reported. Hypersensitivity/drug hypersensitivity were observed in 18 (3%) and 15 (2%) of patients in the placebo and aflibercept arms, respectively. Flushing was observed in 9 (2.5%) patients in the placebo arm and 2 patients in the aflibercept arm; urticaria was observed in one patient in the placebo arm and 7 patients in the aflibercept arm (1%).

In both arms, 69% of acute drug reactions were reported within the first three treatment cycles. Two patients in each treatment arm discontinued study treatment due to acute drug reactions.

The Grade 3 events in the placebo arm were hypersensitivity to an anesthetic for bronchoscopy, hypersensitivity to irinotecan (with a history of cholinergic syndrome in previous cycles), and hypersensitivity to placebo (dyspnea, bronchospasm, and hypotension).

Grade 3 events in the aflibercept arm were late hypersensitivity (8 days after infusion treatment in cycle 3), angioedema, and circulatory collapse (patient #276006006 experienced bradycardia, dyspraxia and aphasia; brain MRI was normal and assumed as transient cerebral ischemia due to changes in blood pressure). All patients recovered and had negatives tests for ADA.

Table 74 and Table 75 summarize the PTs and HLTs in the FDA analyses. These terms were grouped by the applicant as “acute drug reaction” (column AEGRP2 in the adverse event database).

Table 74 - VELOUR: Acute drug reactions by PT, incidence ≥ 1%

PT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Edema peripheral	44 (7)	52 (9)
Rash	35 (6)	41 (7)
Conjunctivitis	10 (2)	13 (2)
Hypersensitivity	15 (2)	11 (2)
Pruritus	12 (2)	11 (2)
Drug hypersensitivity	3 (<1)	4 (1)
Erythema	3 (<1)	7 (1)
Edema	1 (<1)	5 (1)
Urticaria	1 (<1)	7 (1)
Flushing	9 (1)	2 (<1)

Table 75 - VELOUR: Acute drug reactions by HLT, incidence ≥ 1%

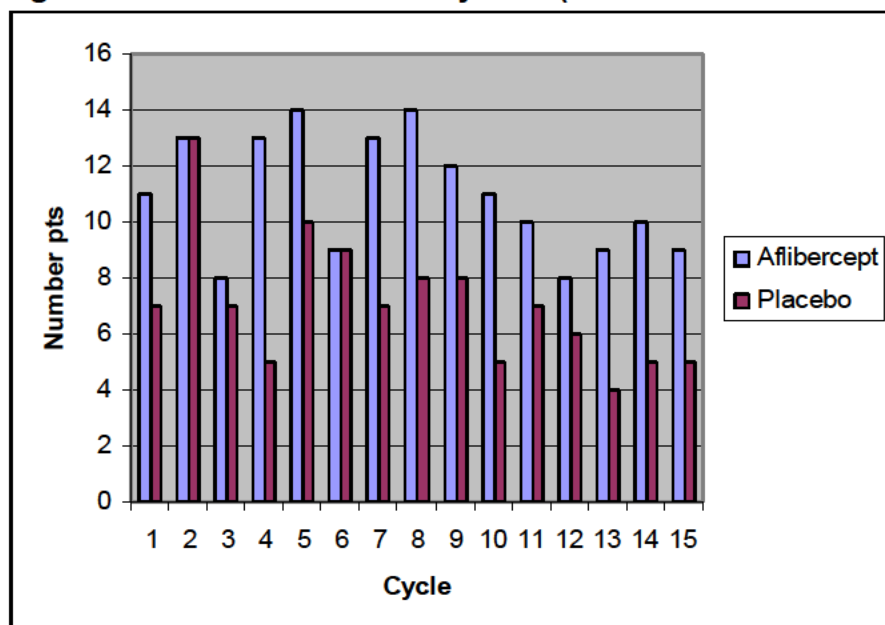
HLT	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Total fluid volume increased	45 (7)	59 (10)
Edema NEC	46 (8)	57 (9)
Heart failure signs and symptoms	45 (7)	52 (9)
Rashes, eruptions, and exanthemas	36 (6)	44 (7)
Allergic conditions	15 (2)	14 (2)
Conjunctival infections, irritations, and inflammations,	10 (2)	13 (2)
Pruritus	14 (2)	14 (2)
General signs and symptoms	10 (2)	5 (1)
Angioedemas	4 (1)	7 (1)
Allergies to foods, additives, drugs, and other chemicals	3 (<1)	5 (1)
Bronchospasms and obstructions	1 (<1)	4 (1)
Bullous conditions	0	4 (1)
Erythemas	3 (<1)	8 (1)
Urticarias	1 (<1)	7 (1)
Peripheral vascular disorders	9 (1)	2 (<1)
Skin vasomotor conditions	9 (1)	2 (<1)

An possible explanation for differences in the applicant’s analysis compared to the FDA analysis may be related to criteria used for grouping events. As an example, when searching the PTs that contain “edema” (allergic edema, angioedema, eye edema, eyelid edema, face edema, generalized edema, gingival edema, lip edema, localized edema, edema, edema peripheral, and periorbital edema), 50 unique events were observed among patients enrolled in the placebo arm

(8%) and 70 unique events were observed in patients enrolled in the aflibercept arm (11%). Most events were Grades 1-2, with the exceptions of two subjects in the placebo arm (#80400402 & 276006008) and one patient in the aflibercept arm (#840201002) who experienced Grade 3 angioedema, and one patient with Grade 3 peripheral edema in the placebo arm (#724007003).

Although there was a slight increase in the incidence of edema in the aflibercept arm, as shown in Figure 10, the incidence of reported edema remained relatively constant throughout visits. Allergic reactions were described in the labels of all administered drugs, and the etiology of edema was multifactorial. Thus, the applicant's analyses as described in the complete study report appeared to be more comprehensive than the analysis of the database.

Figure 10 - VELOUR: Edema by visit (in absolute number of patients/visit)



7.3.5.3 Arterial Thrombotic Events (ATE) and Venous Thromboembolic Events (VTE)

Twenty five patients (10 patients [1.65%] in the placebo arm and 16 patients [2.6%] in the aflibercept arm) experienced ATE. As summarized in Table 76, most events were from cardiac in origin [7 (1%) events in the placebo arm and 12 (2%) events in the aflibercept arm]. Grade 3 events were reported in 3 patients in the placebo arm and 11 patients in the aflibercept arm; none of these events were fatal, however, the ATE lead to treatment discontinuation in 1 patient in the placebo arm and 9 patients in the aflibercept arm.

Table 76 - VELOUR: Arterial thromboembolic events (ATE)

PT	Placebo/FOLFIRI N=605		Aflibercept/FOLFIRI N=611	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Angina pectoris	6	1	4	1
Transient ischemic attack	0	0	3	3
Acute myocardial infarction	0	0	2	2
Colitis ischemic	1	0	1	1
Myocardial ischemia	1	1	1	0
Cerebrovascular accident	0	0	1	1
Arterial embolism	0	0	1	1
Intermittent claudication	0	0	1	0
Intracardiac thrombus	0	0	1	1
Myocardial infarction	0	0	1	1
Arterial thrombosis limb	1	1	0	0
Splenic infarction	1	1	0	0

Table 77 summarizes the VTE. Fifty-four events in 44 patients (7%) in the placebo arm and 66 events in 57 patients (9%) in the aflibercept arm experienced VTE. The majority of these events were pulmonary embolism.

Table 77 - VELOUR: Venous thromboembolic events (VTE)

PT	Placebo/FOLFIRI (n, %) N=605		Aflibercept/FOLFIRI (n, %) N=611	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Pulmonary embolism	21 (3)	21 (3)	28 (5)	28 (5)
Deep vein thrombosis	13 (2)	11 (2)	18 (3)	13 (2)
Vena Cava thrombosis	2 (<1)	2 (<1)	4 (1)	3 (<1)
Jugular vein thrombosis	3 (<1)	2 (<1)	3 (<1)	2 (<1)
Pelvis venous thrombosis	3 (<1)	3 (<1)	2 (<1)	2 (<1)
Subclavian vein thrombosis	2 (<1)	2 (<1)	2 (<1)	1 (<1)
Renal vein thrombosis	1 (<1)	0	2 (<1)	2 (<1)
Thrombophlebitis	1 (<1)	1 (<1)	1 (<1)	0
Infusion site thrombosis	0	0	1 (<1)	0
Mesenteric vein thrombosis	0	0	1 (<1)	1 (<1)
Portal vein thrombosis	2 (<1)	0	1 (<1)	0
Pulmonary artery thrombosis	0	0	1 (<1)	1 (<1)
Superior vena Cava thrombosis	0	0	1 (<1)	0
Venous thrombosis	0	0	1 (<1)	0
Venous thrombosis limb	1 (<1)	0	0	0

More patients in the aflibercept arm (26 patients, 45.6% of patients with VTE) discontinued study treatment (premature discontinuation or permanent discontinuation) due to VTE than in the placebo arm (16 patients, 36.4%). One patient (#840004002) with a history of a prior pulmonary embolism treated in the aflibercept arm experienced a fatal VTE.

Figure 11 shows the relationship between the occurrence of VTE and cycle. Patients who received aflibercept were at higher risk of having a VTE.

Figure 11 - VELOUR: VTE by Cycle

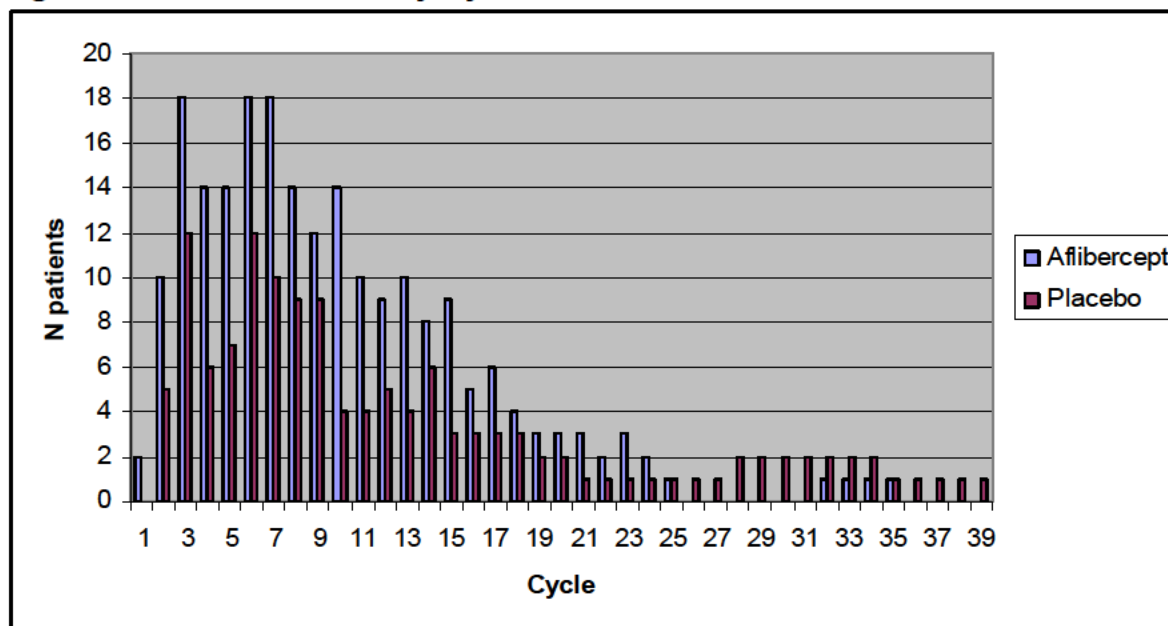


Table 78 summarizes FDA's SMQs for ATE and VTE, consistent with the analyses of the database and the applicant's interpretation.

Table 78 - VELOUR: SMQs for ATEs and VTEs

SMQ	Placebo/FOLFIRI		Aflibercept/FOLFIRI		RR (95% CI)	P value
	Events	N (%)	Events	N (%)		
Arterial embolic and thrombotic events	3	2 (0.33)	22	8 (1.31)	0.25 (0.05;1.18)	0.108
Myocardial infarction	0	0	6	3 (0.49)	0.25 (0.02;2.25)	0.249
Ischemic colitis	2	1 (0.17)	4	2 (0.33)	0.50 (0.04;5.5)	1
Venous embolic and thrombotic events	201	44 (7.2)	305	55 (9)	0.80 (0.55;1.18)	0.295
Embolic and thrombotic events	204	45 (7.4)	327	62 (10.15)	0.73 (0.50;1.05)	0.105
Ischemic heart disease	34	8 (1.32)	26	8 (1.31)	1.01 (0.38;2.67)	1
Other ischemic heart disease	34	8 (1.32)	20	5 (0.82)	1.61 (0.53;4.9)	0.41
Thromboflebitis	4	4 (0.66)	11	3 (0.49)	1.34 (0.30;5.99)	0.72

7.3.5.4 Hypertension

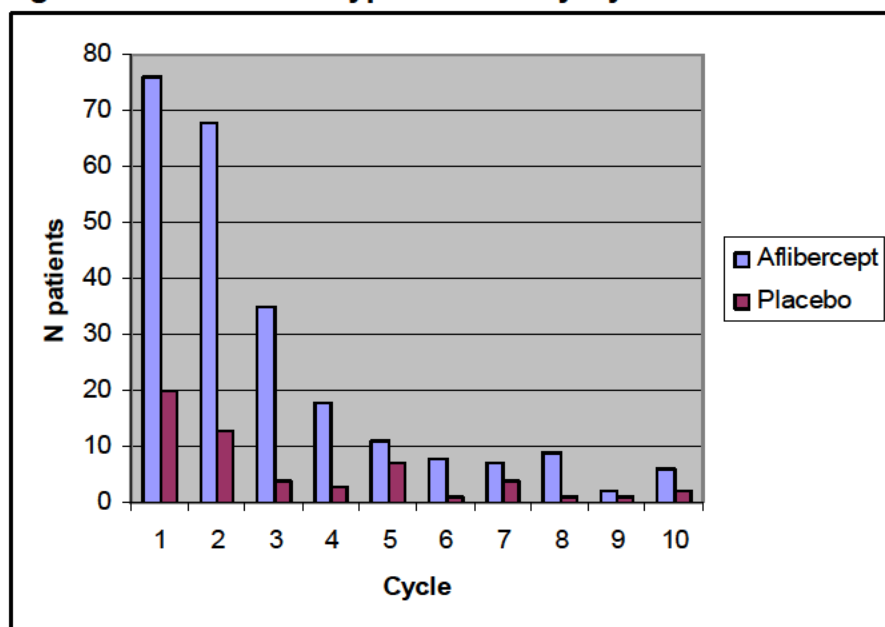
There were 132 events of hypertension in 65 patients (11%) in the placebo arm and 1035 events in 253 patients (41%) in the aflibercept arm (FDA SMQ analysis matched the applicant's

analysis, see Table 118). Grades 3-4 events were reported in 1.5% patients in the placebo arm and 19.3% patients in the aflibercept arm.

There was one reported event of Grade 4 hypertension in patient 152001006, a 52 year-old man treated in the aflibercept arm (normal blood pressure at baseline) who experienced Grade 3 hypertension during the administration of aflibercept in Cycle 2 (during infusion of aflibercept; the event resolved with captopril treatment), followed by Grade 4 hypertension, with blood pressure of 200/110 mmHg 2 days later. He was treated with nifedipine and recovered the following day (blood pressure 110/65 mmHg). Treatment with aflibercept was permanently discontinued due to this event.

In both treatment arms, more than half the patients who experienced hypertension did so for the first time during the first two treatment cycles (Figure 12).

Figure 12 - VELOUR: Hypertension by Cycle



The majority of patients in the placebo arm who experienced hypertension did not undergo any study treatment modifications due to these events. In the aflibercept arm, 29 patients (5%) discontinued study treatment due to hypertension events.

The following table summarizes the different incidence of hypertension according to blood pressure status at baseline (i.e., history of hypertension at baseline).

Table 79 - VELOUR: Hypertension by baseline BP status

	Placebo/FOLFIRI (N=605)		Aflibercept/FOLFIRI (N=611)	
	HTN at baseline (n=265)	No HTN at baseline (n=340)	HTN at baseline (N=262)	No HTN at baseline (N=349)
Worsened/new HTN	40 (15)	25 (10)	122 (47)	131 (38)
Cycle of first occurrence				
Cycle 1	15 (38)	5 (20)	46 (38)	30 (23)
Cycle 2	5 (13)	8 (32)	34 (28)	34 (26)
Cycle 3	2 (5)	2 (8)	15 (12)	20 (15)
Cycle 4	2 (5)	1 (4)	6 (5)	12 (9)
Cycle 5	4 (10)	3 (12)	4 (3)	7 (5)
Cycle 6	0	1 (4)	3 (2)	5 (4)
Cycle 7	3 (8)	1 (4)	3 (2)	4 (3)
Cycle 8	0	1 (4)	5 (4)	4 (3)
Cycle 9	1 (3)	1 (4)	2 (2)	2 (2)
Cycle 10	1 (3)	1 (4)	0	4 (3)

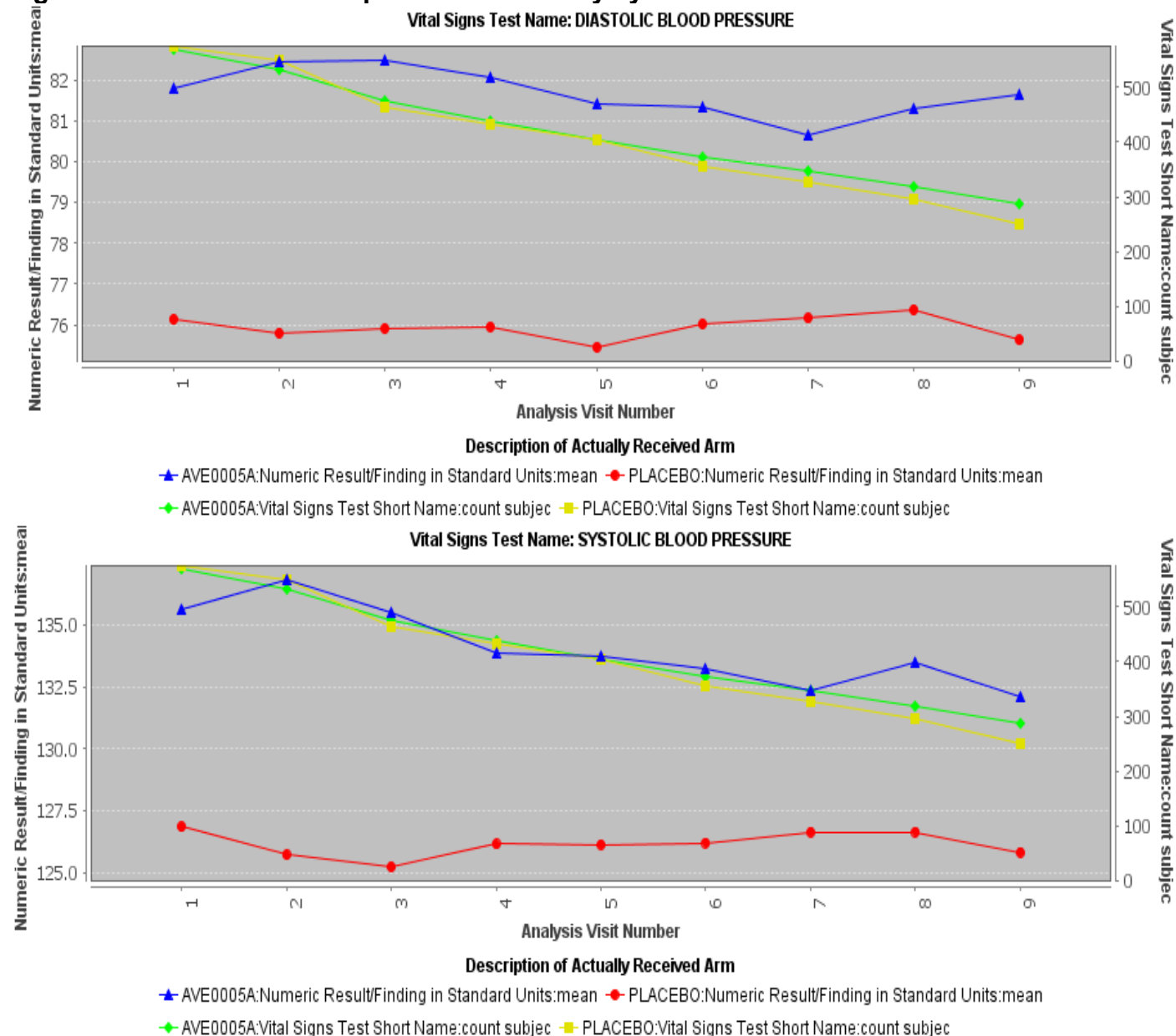
The incidence of worsening hypertension was 30% higher in the aflibercept arm. A similar imbalance was also observed for the incidence of new events of hypertension in patients who did not have hypertension at baseline; the difference in the incidence of hypertension between the two treatment arms remained about 30% regardless of the pre-existing hypertension status.

The incidence of Grade 3-4 events was greater in patients with preexisting hypertension (3% in and 28% in the placebo and aflibercept arms respectively) than in patients who developed hypertension (<1% and 13% in the placebo and aflibercept arms, respectively).

Analysis of the vital signs database (ADVS) supported the clinical data. As shown in Figure 13, an increase in mean systolic blood pressure of approximately 5 mmHg in the aflibercept arm was observed at the first cycle (regardless of the prior hypertension status). The increased blood pressures were sustained for the first 3 cycles, and then trended towards the baseline values (it is unclear if this was related to management of hypertension, etc). In patients treated in the placebo arm, a slight decrease of systolic blood pressure was initially observed.

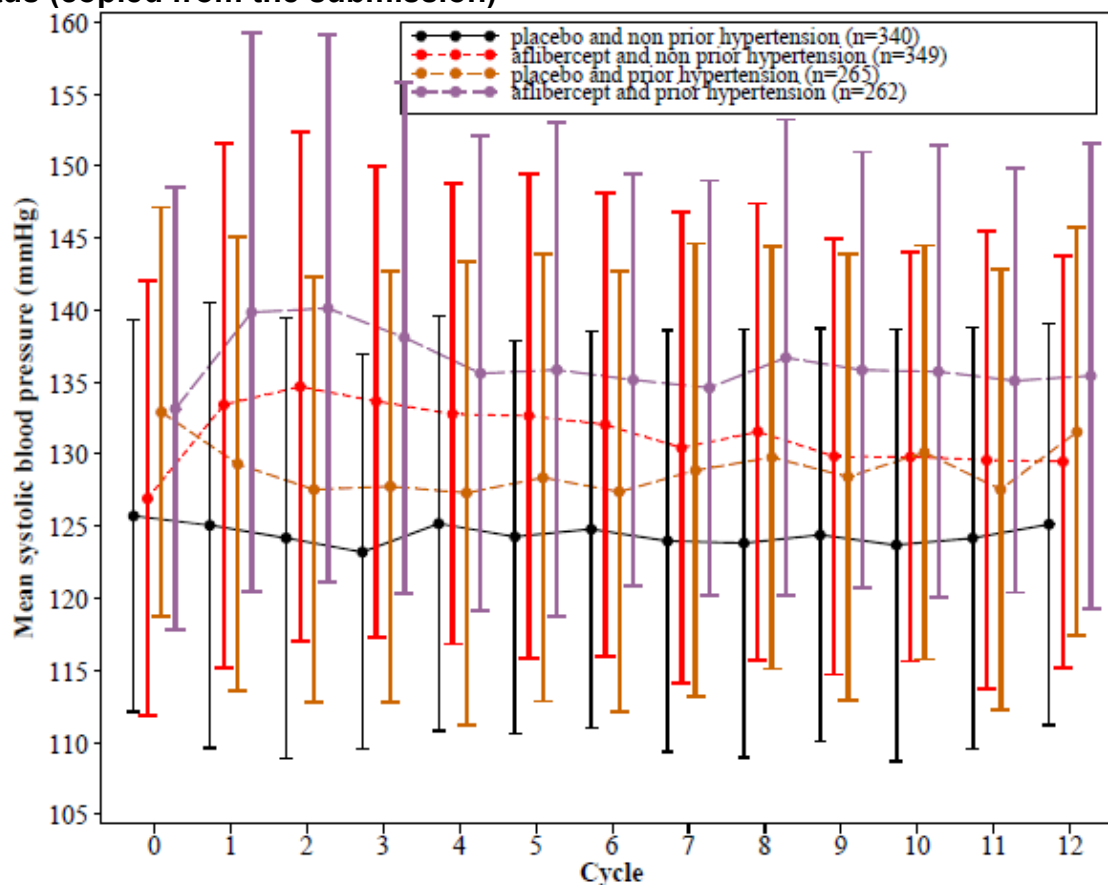
Similar changes were observed for diastolic blood pressure measurements. Patients with no history of hypertension experienced a slightly higher mean increase of the diastolic BP (5 mm Hg vs. 3 mmHg) than patients with a history of hypertension. Diastolic blood pressure was unchanged in patients treated in the placebo arm.

Figure 13 - VELOUR: Blood pressure means by cycle



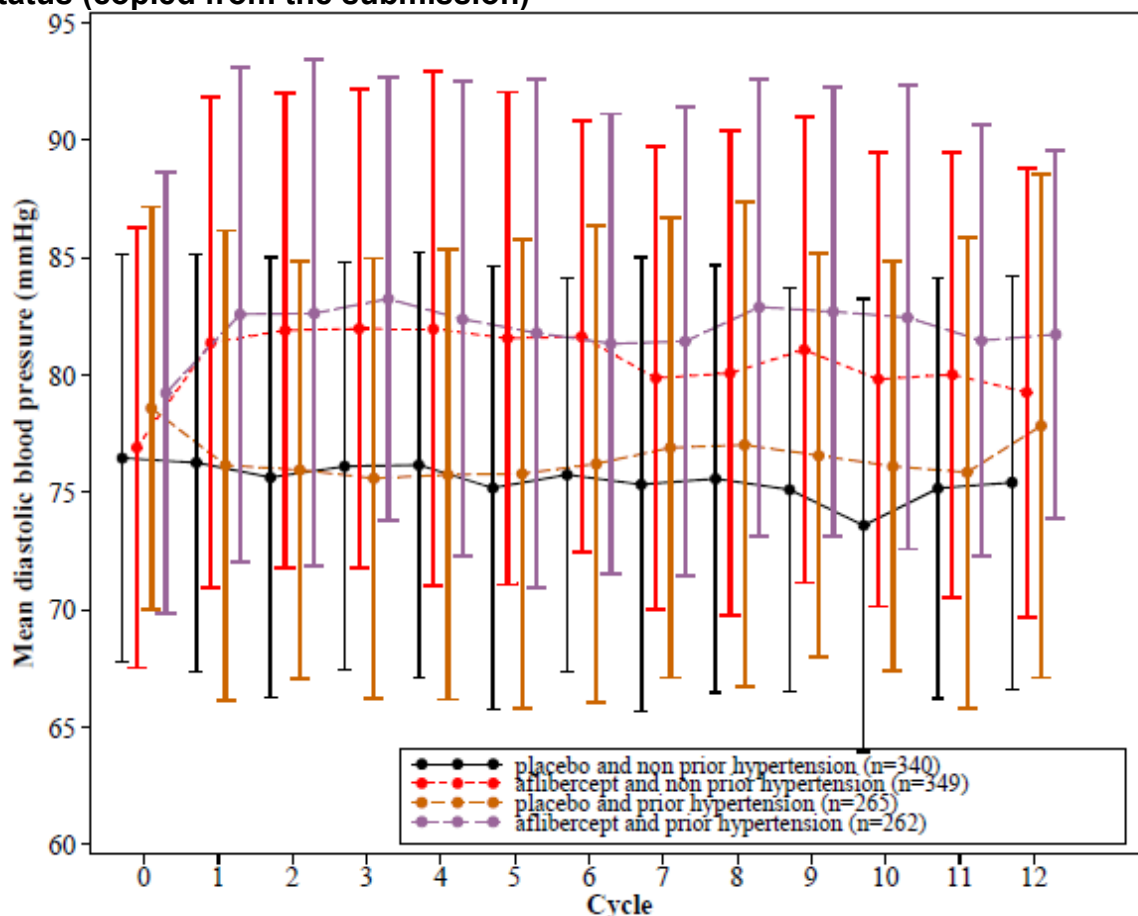
The following two figures (copied from the submission) show the mean BP by cycle according to prior hypertension status.

Figure 14 - VELOUR: Systolic blood pressure by cycle by prior hypertensive status (copied from the submission)*



* Blood pressure was assessed prior to each cycle, thus number 0 is immediately prior to Cycle 1, drug administration, number 1 is immediately prior to Cycle 2 drug administration and so on.

Figure 15 - VELOUR: Diastolic blood pressure by cycle by prior hypertensive status (copied from the submission)*



* Blood pressure was assessed prior to each cycle, thus number 0 is immediately prior to Cycle 1, drug administration, number 1 is immediately prior to Cycle 2 drug administration and so on.

In summary, patients treated with aflibercept experienced more hypertension. Hypertension is a class-effect of VEGF/R inhibition. Although for some adverse events, such as febrile neutropenia, different backbone chemotherapy regimens would prevent direct comparisons, one study [Study 1 (Hurwitz, 2004)] in the Avastin label used, in different doses and frequencies, the same drugs as in the VELOUR study (for the treatment of metastatic colorectal cancer in the first line setting): irinotecan, 5-FU, and leucovorin. None of the chemotherapy drugs produce hypertension, and the increased incidence of hypertension found in Study 1 was directly attributable to the use of bevacizumab. As summarized in Table 80, hypertension was more frequently observed with bevacizumab and aflibercept when compared to chemotherapy and placebo; however, it appears that the incidence of hypertension with the use of aflibercept is higher than the hypertension observed with bevacizumab (*note to reader, caution should be used in interpreting this analysis because there may have been inter-study differences preventing a valid direct comparison*).

Table 80 - Hypertension in VELOUR and Bevacizumab-IFL

Hypertension	Bevacizumab Study 1		VELOUR	
	Placebo/IFL (n=411)	Bevacizumab/IFL (n=402)	Placebo/FOLFIRI (n=605)	Aflibercept/FOLFIRI (n=611)
All Grades	23%	34%	11%	41%
Grades 3-4	2%	12%	2%	19%

7.3.5.5 Hemorrhage

One hundred fifteen patients (19%) in the placebo arm and 231 patients (38%) in the aflibercept arm experienced hemorrhage. Table 81 summarizes the hemorrhagic events that occurred with an incidence of $\geq 1\%$.

Table 81 - VELOUR: Hemorrhages with incidence $\geq 1\%$ (by PT)

PT	Placebo/FOLFIRI (n, %) N=605		Aflibercept/FOLFIRI (n, %) N=611	
	All Grades	Grade 3*	All Grades	Grades 3-4
Epistaxis	45 (7)	0	169 (28)	1 (<1)
Rectal hemorrhage	15 (2)	3 (<1)	32 (5)	4 (1)
Hematuria	18 (3)	2 (<1)	12 (2)	1 (<1)
Hemoptysis	1 (<1)	0	10 (2)	0
Post-procedural hemorrhage	2 (<1)	1 (<1)	10 (2)	4 (<1)
Contusion	7 (1)	0	8 (1)	0
Hematochezia	6 (1)	0	8 (1)	0
Gastrointestinal hemorrhage	0	0	5 (1)	3 (<1)
Gingival bleeding	1 (<1)	0	6 (1)	0
Hematoma	3 (<1)	0	4 (1)	0
Hemorrhoidal hemorrhage	2 (<1)	0	7 (1)	1 (<1)
Vaginal hemorrhage	2 (<1)	0	6 (1)	0
Anal hemorrhage	3 (<1)	1	3	0

* There were no Grade 4 hemorrhage events in the placebo arm.

The most frequently reported hemorrhage event was epistaxis (7% in the placebo arm and 28% in the aflibercept arm). More hemorrhage events (all grades) from gastrointestinal origin were reported in patients receiving aflibercept (5% vs. 10% in the placebo and aflibercept arms, respectively). Hematuria was reported in more patients receiving placebo (3% vs. 1.6% in the placebo and aflibercept arms, respectively).

When grouped by HLT (terms containing “hemorrhage” or “bleeding”), 7 patients in the placebo arm (1%) and 17 patients in the aflibercept arm (3%) experienced Grade 3-4 hemorrhage.

The timing of the first incidence of hemorrhagic events was comparable between arms, with more than half of the patients with hemorrhagic events in each treatment arm first experiencing such events during the first three treatment cycles. However, the incidence of thrombocytopenia did not vary between cycles (Figure 19).

One patient treated in the afibercept arm experienced a fatal hemorrhagic event. Patient 826011003 was a 76-year-old woman who died secondary to complications derived from a Grade 4 bleeding duodenal ulcer (Cycle 6).

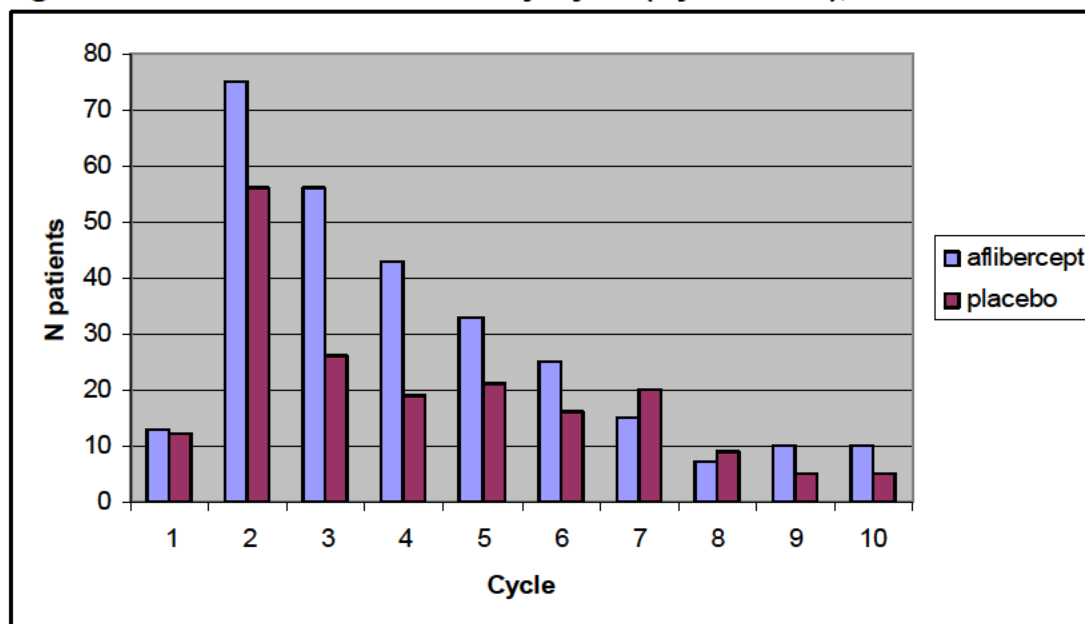
FDA SMQ analysis (Table 118) was similar to the results of the applicant's analysis.

7.3.5.6 Proteinuria, Nephrotic Syndrome, and Renal Impairment

Proteinuria, mostly Grades 1-2, was reported in 246 patients (41%) in the placebo arm and 380 patients (62%) in the afibercept arm. Grade 3-4 events were reported in 7 patients (1%) in the placebo arm and 47 patients (8%) in the afibercept arm, including 2 patients with nephrotic syndrome.

In the majority of patients (55% and 63% patients in the placebo and afibercept arms respectively), proteinuria was diagnosed during the course of the first three cycles (Figure 16). In the placebo arm, 96% of patients with proteinuria did not require treatment modification. In the afibercept arm, 62 patients (16% of patients with proteinuria) underwent treatment modification and 10% of patients with proteinuria discontinued treatment as a result.

Figure 16 - VELOUR: Proteinuria by Cycle (Cycles 1-10), worst Grade.



In the afibercept arm, among the 162 patients with Grade ≥ 2 proteinuria, 59 patients (36%) had concomitant hematuria, 17 patients (11%) had concomitant hypertension, and 7 patients (4%) had both concomitant hematuria and hypertension. Table 117 (copied from the application) in the appendices summarizes the urinalysis abnormalities.

Nephrotic syndrome was diagnosed in patient 380001013, a 66 year old female with no relevant medical history who on Day 15 Cycle 2, having being diagnosed with hypertension on Cycle 1, presented with urine protein (0.188 g/dL). Laboratory analysis one week later showed urine protein was 0.29 g/dL, UPCR was 4.296, serum creatinine was 44.2 µmol/L, and platelet count was 391 x 10⁹/L. No edema or hypo-albuminemia (albumin 39g/L) were reported. The patient was treated with lercanidipine and olmesartan, and recovered 1 month after the diagnosis (urine protein 0.027 g/dL, UPCR 0.027, serum albumin 41g/L). Treatment with aflibercept was discontinued.

Patient 724006003, a 73-year-old woman, with pre-existing hypertension at baseline, was diagnosed with nephrotic syndrome on Day 1 of Cycle 3. Three weeks later she was hospitalized with Grade 1 peripheral edema, urine protein 6g/24hr, hypoalbuminemia (23g/L), serum creatinine 80 µmol/L, platelet count 194 x 10⁹/L, LDH 479 IU/L, and schistocytes in peripheral blood smears. She was treated and showed progressive resolution of edema and proteinuria, recovering from nephrotic syndrome approximately 10 weeks after diagnosis. Treatment with aflibercept was permanently discontinued.

In the adverse events dataset, 6 patients (5 patients in the aflibercept arm and the remaining patient in the placebo arm) experienced acute renal failure or renal failure. In four of the patients in the aflibercept arm (ID# 152004016, 203004005, 152004011, and 203001008), the diagnosis of renal failure was preceded by diarrhea, dehydration, fever, nausea, and/or vomiting. Acute renal failure with fatal outcome was reported in one of these patients (#152004011), who after receiving Cycle 2, experienced diarrhea, dehydration and acute renal failure, followed by sepsis and bilateral pneumonia (listed as the cause of death).

In the fifth patient (#840012002) in the aflibercept arm who experienced a renal failure, this diagnosis was a laboratory finding (pre-cycle 5), and the patient recovered, although treatment was discontinued.

In the only patient with renal failure in the placebo arm (#056003017), on pre-treatment labs for Cycle 39, elevated creatinine was discovered and the patient was withdrawn from treatment.

Results from the serum creatinine analyses and calculated creatinine clearance (lab dataset ADLB) are summarized in Table 82. Although there was a slight increase in the incidence of Grade 2 toxicities, renal impairment was similar between arms.

Table 82 - VELOUR: Renal function laboratory analysis

	Placebo/FOLFIRI (n %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Serum creatinine		
Grade 1	97 (16)	116 (19)
Grade 2	13 (2)	22 (4)
Grade 3	2 (<1)	0
Grade 4	1 (<1)	0

Calculated creatinine clearance		
N pts tested	596	602
< 30 ml/min	13 (2)	15 (2)
≥ 30-60 ml/min	135 (23)	162 (27)
≥ 60 ≤ 80 ml/min	196 (33)	197 (33)

When considering both the renal failure events reported as an adverse event in addition to patients with creatinine clearance < 30 ml/min, there were 13 and 18 patients with renal failure in the placebo and aflibercept arms, respectively. In the placebo arm, all but four patients had simultaneously diarrhea, vomiting, dehydration, infection, and/or obstructive uropathy/nephropathy as contributing factors. In the aflibercept arm, all but one patient had simultaneously diarrhea, vomiting, dehydration, and/or infection/sepsis as contributing factors. One patient in the aflibercept arm (patient #152004011, narrative described above) did not recovered from renal failure, and at least 4 patients in the placebo arm did not recovered before death of progressive disease or other event (follow-up creatinine clearance values are not available for 5 patients).

Thrombotic microangiopathy (Grade 1) was reported in one patient in the aflibercept arm [patient 076006001, a 51 year old man with no relevant medical history with hypertension, proteinuria (0.086 g/dL), and thrombocytopenia ($107 \times 10^9/L$) on Cycle 12. He was treated with enalapril. Two weeks later, platelet counts dropped to $70 \times 10^9/L$]. No renal biopsy was performed, no neurological symptoms were reported, and renal function remained within normal range.

Reviewer's comment: two additional cases of thrombotic microangiopathy were observed in patients exposed to aflibercept in two NCI-sponsored studies. A 40-year old woman diagnosed with metastatic thyroid carcinoma was diagnosed with thrombotic microangiopathy three days after receiving a second dose of aflibercept (monotherapy), with Grade 3 proteinuria and Grade 2 ALT/AST increases. The second patient was a 33 year old man diagnosed with anaplastic oligodendroglioma who was diagnosed with renal failure and thrombotic microangiopathy (biopsy confirmed) while receiving treatment with aflibercept and temozolomide.

Thrombotic microangiopathy is described in the bevacizumab label, and there are also reported cases in the literature with the use of sunitinib (Izzidine H., 2010).

7.3.5.7 Other VEGF/R Inhibition Related Toxicities

Other VEGF/VEFR inhibition-related toxicities were uncommon in the VELOUR trial, with incidences less than 2%.

Fistula

In the placebo arm, fistula was reported in 3 patients (0.5%); one of these patients had a rectosigmoid carcinoma (present at baseline, prior radiotherapy). In the aflibercept arm, fistula was reported in 9 patients (1.5%, 5 female patients and 4 male patients); 8 of these patients had

rectal or rectosigmoid carcinomas, 4 patients received prior radiotherapy and in 3 of them the tumor was still present at baseline.

Most of the events occurred early in therapy: all 3 events in the placebo arm and 5 of 9 events in the aflibercept arm occurred during cycles 1 and 2. In the aflibercept arm, 6 of 9 patients recovered from the fistula, compared to 1 of 3 patients in the placebo arm. In the placebo arm, fistulas were Grade 2 (2 patients) or Grade 3 (1 patient). In the aflibercept arm, events were Grade 1 (2 patients), Grade 2 (5 patients) or Grade 3 (2 patients).

Wound healing

Five patients in the placebo arm and three patients in the aflibercept arm experienced wound healing issues. Although more frequent, events in the placebo arm appeared to be mild (all were Grade 1), while the severity of the events in the aflibercept arm was more pronounced (Grades 2-3) and led to cycle delay or discontinuation of study treatment. All cases of wound healing in the aflibercept arm were observed as a complication of events occurring during study treatment: tooth extraction, wound dehiscence of central catheter, and extravasation followed by catheter site infection.

Gastrointestinal perforation

Three patients per arm experienced gastrointestinal perforations. Primary tumor location in the placebo arm was colon (2) or rectum (1), and all patients in the placebo arm had rectosigmoid tumors. Perforations in the placebo arm occurred in the gastrojejunum in 2 patients and small bowel in one patient; perforations in the aflibercept arm occurred in the small intestine in 2 patients and the duodenum in one patient. Events in the aflibercept arm occurred later (Cycles 9 to 12) than events in the placebo arm (Cycles 1, 3, and 5).

There was one event in the aflibercept arm that resulted in death. Patient #380001006 was a 73-year-old man who experienced Grade 1-2 abdominal pain starting in Cycle 3 and was treated with ranitidine. On Day 16 of Cycle 10, while hospitalized with serious Grade 3 stomatitis, the patient developed significant abdominal pain, and following CT-scan and X-ray he was diagnosed with Grade 4 ileal perforation, with surgery not indicated. He received morphine as required, and died the following day.

Osteonecrosis

Two cases of osteonecrosis were reported in patients treated in the aflibercept arm. Osteonecrosis of the jaw was reported in patient #203001013, 5 weeks after a tooth extraction with impaired healing, and resolved 3 weeks later. Patient #203004012 received biphosphonates for 10 months at the time of diagnosis. Osteonecrosis of the jaw was not associated with dental surgery, and although biphosphonate treatment was stopped, the event did not resolve and was ongoing at the time of the patient's death, 6 months later (progressive disease).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Almost all patients in both arms experienced adverse events. Table 83 summarizes the most frequent Grade 1-2 adverse events (incidence $\geq 5\%$). Some of the characteristic less serious toxicities of VEGF/R inhibition, such as dysphonia and epistaxis, were frequently observed in the aflibercept arm.

As discussed above in the analyses of Grade 3-4 and SAEs, administration of aflibercept increased the common toxicities related to FOLFIRI.

Table 83 - VELOUR: Grade 1-2 AEs by PT (incidence $\geq 5\%$)

PT	Placebo/FOLFIRI (n=605)		Aflibercept/FOLFIRI (n=611)	
	N	%	N	%
Diarrhea	329	54	397	65
Nausea	325	54	324	53
Stomatitis	193	32	290	47
Fatigue	222	37	277	45
Hypertension	60	10	207	34
Weight decrease	87	14	194	32
Decreased appetite	139	23	189	31
Vomiting	198	33	191	31
Epistaxis	45	7	168	27
Alopecia	182	30	164	27
Dysphonia	20	3	155	25
Neutropenia	135	22	151	25
Abdominal pain	138	23	149	24
Headache	53	9	133	22
Constipation	147	24	135	22
Asthenia	70	12	102	17
Pyrexia	82	14	81	13
Palmar-plantar erythrodysesthesia	25	4	66	11
Dyspnea	50	8	67	11
Cough	58	10	68	11
Back pain	66	11	70	11
Proteinuria	9	1	61	10
Abdominal upper pain	45	7	62	10
Urinary tract infection	33	5	54	9
Edema peripheral	43	7	52	9
Skin hyperpigmentation	17	3	50	8
Insomnia	45	7	47	8
Dyspepsia	56	9	49	8
Oropharyngeal pain	19	3	45	7
Dysgeusia	32	5	42	7
Rash	35	6	40	7
Hemorrhoids	13	2	35	6
Rhinorrhea	11	2	38	6

Pain in extremity	31	5	34	6
Dizziness	52	9	35	6
Aphthous stomatitis	14	2	30	5
Dehydration	11	2	33	5
Nasopharyngitis	15	2	28	5
Proctalgia	10	2	32	5
Rectal hemorrhage	12	2	29	5
Lethargy	26	4	32	5
Neuropathy peripheral	30	5	33	5
Arthralgia	39	6	30	5

Events observed with a difference of more than 5% between arms were (differences in parenthesis, all more frequent in the aflibercept arm) hypertension (24%), dysphonia (22%), epistaxis (20%), weight decrease (18%), stomatitis (15%), headache (13%), diarrhea (11%), proteinuria (9%), fatigue (8%), palmar-plantar erythrodysesthesia (7%), and asthenia (5%).

Some of these differences were more evident when grouping terms by HLTs (Table 84), such as asthenic conditions (difference 11%), stomatitis and ulcerations (difference 18%), upper respiratory tract signs and symptoms (difference 24%), hemorrhages NEC (difference 20%), nasal disorders (difference 20%), and speech abnormalities (difference 22%).

Table 84 - VELOUR: Grade 1-2 AEs by HLT (incidence \geq 10%)

HLT	Placebo/FOLFIRI (n=605)		Aflibercept/FOLFIRI (n=611)	
	N	%	N	%
Diarrhea	329	54	397	65
Asthenic conditions	301	50	375	61
Nausea and vomiting	357	59	356	58
Stomatitis and ulcerations	204	34	319	52
Vascular hypertensive disorders	60	10	207	34
Upper respiratory tract signs and symptoms	51	8	196	32
Gastrointestinal and abdominal pain	169	28	193	32
Appetite disorders	139	23	189	31
Hemorrhages NEC	53	9	179	29
Nasal disorders	49	8	171	28
Speech and language abnormalities	24	4	161	26
Speech articulation and rhythm disturbances	22	4	156	26
Gastrointestinal atonic and hypomotility disorders	154	25	142	23
Headaches	53	9	133	22
Musculoskeletal and connective tissue pain	122	20	136	22
Sensory abnormalities	61	10	114	19
Upper respiratory tract infections	55	9	79	13
Coughing and associated symptoms	66	11	78	13
Febrile disorders	82	14	81	13
Breathing abnormalities	60	10	71	12
Skin and subcutaneous conditions	25	4	67	11
Urinary abnormalities	26	4	68	11

Urinary tract infections	40	7	66	11
Dyspneas	59	10	70	11
Total fluid volume increased	44	7	59	10

Table 85 summarizes the Grade 1-2 AEs by SOC. As described above, adverse events were at least 5% more frequent (difference in parentheses) in the aflibercept arm in the gastrointestinal SOC (8%), general disorders SOC (9%), vascular disorders SOC (23%), respiratory SOC (20%), nervous system SOC (15%), skin SOC (13%), metabolism and nutrition SOC (11%), infections (10%), psychiatric SOC (17%), renal and urinary SOC (10%), and injury, poisoning, and procedural complications SOC.

Table 85 - VELOUR: Grade 1-2 AEs by SOC

SOC	Placebo/FOLFIRI (n=605)		Aflibercept/FOLFIRI (n=611)	
	N	%	N	%
Gastrointestinal	513	85	566	93
General disorders and administration sites conditions	376	62	433	71
Vascular disorders	235	39	377	62
Respiratory, thoracic and mediastinal disorders	255	42	377	62
Nervous system	273	45	366	60
Skin and subcutaneous tissue	283	47	306	50
Metabolism and nutrition	180	30	252	41
Infections	181	30	242	40
Psychiatric	131	22	239	39
Musculoskeletal and connective tissue	197	33	220	36
Blood and lymphatic system	167	28	188	31
Cardiac disorders	145	24	165	27
Renal and urinary disorders	94	16	156	26
Injury, poisoning, and procedural complications	64	11	99	16
Eye disorders	67	11	69	11
Immune system disorders	30	5	40	7
Reproductive system	42	7	36	6
Ear and labyrinth disorders	17	3	24	4
Hepatobiliary disorders	31	5	25	4
Neoplasms	15	2	14	2
Endocrine	5	1	5	1
Pregnancy, puerperium, and perinatal conditions	0	0	1	0
Surgical and medical complications	1	0	3	0

7.4.2 Laboratory Findings

Hematologic parameters

Table 86 summarizes the hematologic effects of aflibercept as ascertained using laboratory datasets. The addition of aflibercept to the FOLFIRI backbone regimen caused an increased incidence of leucopenia, neutropenia, and thrombocytopenia.

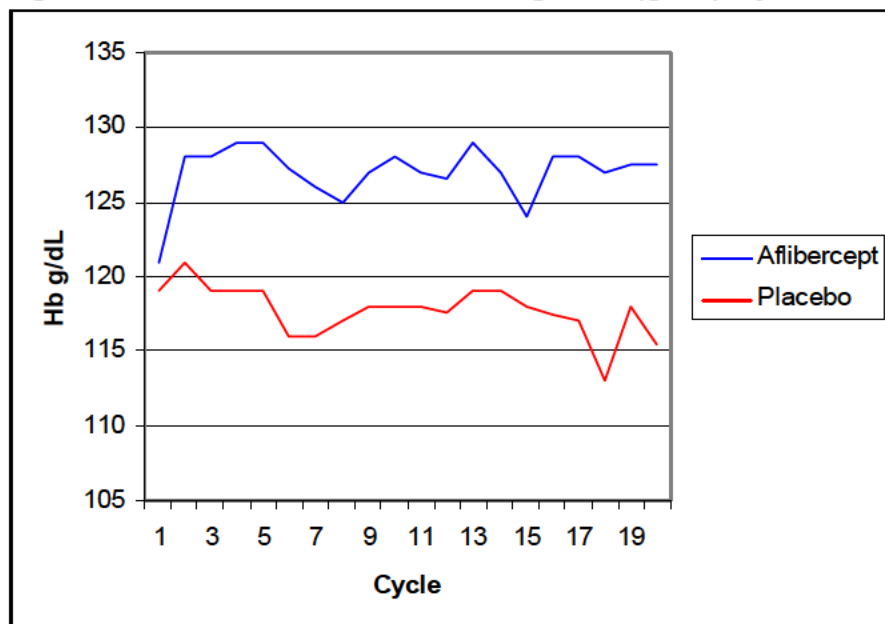
The most common event observed was anemia. Patients in the placebo arm experienced anemia more frequently than patients in the aflibercept arm [544 patients (89%) in the placebo arm and 502 patients (82%) in the aflibercept arm]. Grades 3-4 hemoglobin values were infrequent in this study.

Table 86 - VELOUR: Hematologic toxicity (lab dataset)

	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Hemoglobin		
Grade 1	369 (61)	369 (60)
Grade 2	159 (26)	128 (21)
Grade 3	26 (4)	21 (3)
Grade 4	5 (1)	4 (1)
Leukocytes		
Grade 1	211 (35)	222 (37)
Grade 2	151 (25)	160 (26)
Grade 3	57 (9)	74 (12)
Grade 4	17 (3)	22 (4)
Neutrophils		
Grade 1	65 (11)	70 (11)
Grade 2	98 (16)	118 (19)
Grade 3	115 (19)	141 (23)
Grade 4	64 (11)	82 (13)
Platelets		
Grade 1	178 (29)	240 (39)
Grade 2	22 (4)	35 (6)
Grade 3	6 (1)	10 (2)
Grade 4	7 (1)	11 (2)

Figure 17 shows median hemoglobin values per arm in Cycles 1-20. Median hemoglobin was higher throughout treatment in the aflibercept arm.

Figure 17 - VELOUR: Median hemoglobin (g/dL) Cycles 1-20



Leukopenia was slightly more frequent in the aflibercept arm: the incidence of Grades 1-2 was 60% in the placebo arm and 63% in the aflibercept arm, and the incidence of Grades 3-4 was 12% in the placebo arm and 16% in the aflibercept arm. Table 87 displays the shift from the initial baseline value through treatment period.

Table 87 - VELOUR: WBC shift table

Baseline grade	Placebo/FOLFIRI (n=591)*					Aflibercept/FOLFIRI (n=598)*				
	Max toxicity					Max toxicity				
	Normal	Grade 1	Grade 2	Grade 3	Grade 4	Normal	Grade 1	Grade 2	Grade 3	Grade 4
0	163	196	117	46	11	129	203	141	60	17
1	0	11	29	8	5	1	13	18	9	5
2	0	0	2	2	1	0	0	0	2	0

* N based on the number of patients with available baseline and at least one post-treatment WBC counts in the database.

Neutropenia was observed more frequently in the aflibercept arm: the incidence of Grades 1-2 was 27% in the placebo arm and 30% in the aflibercept arm, and the incidence of Grades 3-4 was 30% in the placebo arm and 36% in the aflibercept arm. Table 88 displays the shift from the initial baseline value through treatment period.

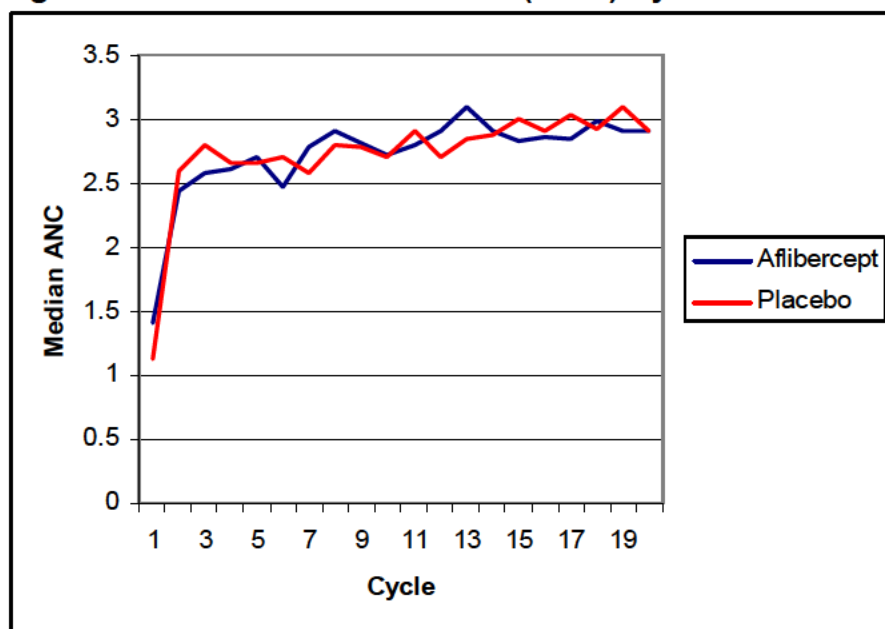
Table 88 - VELOUR: ANC shift table

Baseline grade	Placebo/FOLFIRI (n=586)*					Aflibercept/FOLFIRI (n=592)*				
	Max toxicity					Max toxicity				
	Normal	Grade 1	Grade 2	Grade 3	Grade 4	Normal	Grade 1	Grade 2	Grade 3	Grade 4
0	252	61	95	107	60	190	67	119	132	79
1	0	2	1	5	1	0	0	0	4	1
2	0	0	0	0	1	0	0	0	0	0
3	0	0	0	1	0	0	0	0	0	0

* N based on the number of patients with available baseline and at least one post-treatment WBC counts in the database.

As shown in Figure 18, granulocyte-related toxicity did not increase over time.

Figure 18 - VELOUR: Median ANC ($10^9/L$) Cycles 1-20



Thrombocytopenia was observed more frequently in the aflibercept arm: 35% vs. 49% in the placebo and aflibercept arms respectively. However, this difference was observed mainly in the incidence of Grades 1-2 thrombocytopenia: 33% in the placebo arm and 45% in the aflibercept arm. The incidence of Grades 3-4 thrombocytopenia was 2% in the placebo arm and 3% in the aflibercept arm. Table 89 summarizes the shift in platelet toxicity through treatment.

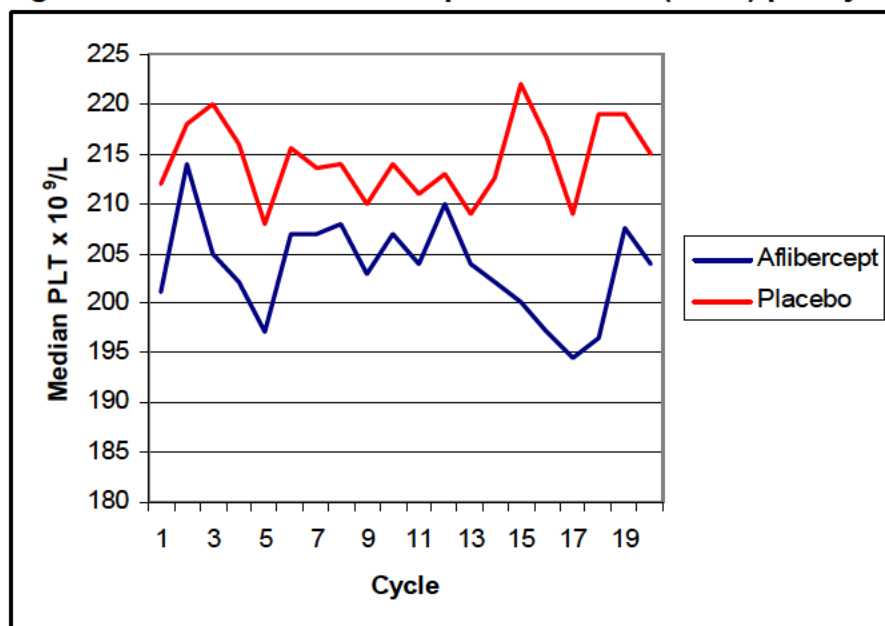
Table 89 - VELOUR: Platelets shift table

Baseline grade	Placebo/FOLFIRI (n=586)*					Aflibercept/FOLFIRI (n=592)*				
	Max toxicity					Max toxicity				
	Normal	Grade 1	Grade 2	Grade 3	Grade 4	Normal	Grade 1	Grade 2	Grade 3	Grade 4
0	348	118	8	4	3	309	185	13	8	9
1	6	53	11	1	2	5	44	21	2	1

* N based on the number of patients with available baseline and at least one post-treatment WBC counts in the database.

Median platelet counts through time are displayed in Figure 19.

Figure 19 - VELOUR: Median platelet count (10⁹/L) per cycle (Cycles 1-20)



Hepatic function

Table 90 summarizes the hepatic function laboratory analyses. Grade 1 alkaline phosphatase was the most frequently reported hepatic lab abnormality with similar incidences in both arms. There was a 10% difference in the reported Grade 1-2 ALT events and 6% difference in Grade 1-2 AST events in the aflibercept arm. However, there were no differences in severe toxicity.

Table 90 - VELOUR: Hepatic function laboratory analysis

	Placebo/FOLFIRI (n, %)	Aflibercept/FOLFIRI (n, %)
	N=605	N=611
ALT	N=605	N=611
Grade 1	191 (32)	222 (36)
Grade 2	33 (5)	66 (11)
Grade 3	14 (2)	15 (2)
Grade 4	0	1 (<1)

AST	N=602	N=602
Grade 1	256 (43)	285 (47)
Grade 2	57 (9)	68 (11)
Grade 3	10 (2)	17 (3)
Grade 4	1 (<1)	2 (<1)
BIT	N=605	N=611
Grade 1	100 (17)	99 (16)
Grade 2	36 (6)	41 (7)
Grade 3	13 (2)	8 (1)
Grade 4	3 (<1)	2 (<1)
ALT >3 xULN AND BIT >2 xULN	7 (1)	7 (1)
ALP	N=605	N=611
Grade 1	282 (47)	300 (49)
Grade 2	102 (17)	109 (18)
Grade 3	40 (7)	31 (5)

A review of the CRFs of the patients that met the laboratory criteria of Hy's law (7 per arm, 5 CRFs available in each arm) is summarized in Table 91.

Table 91 - VELOUR: Summary of Hy's law cases

Placebo/FOLFIRI	Aflibercept/FOLFIRI
Pt 36005011: 34 yo man who experienced drug induced hepatitis (biopsy confirmed) after receiving Cycle 8. Therapy was discontinued.	Pt 152001016: 60 year old man, event occurred concomitantly with fever after Cycle 4. Recovered and re-challenged with no further toxicity.
Pt 643003002: 66 yo man. Liver dysfunction attributed to liver progressive disease (CT confirmed).	Pt 152004004: 41 yo woman, event occurred after Cycle 1 concomitantly with fever and diarrhea. Re-challenged with no further hepatic toxicity, but treatment discontinued after Cycle 6 because congestive heart failure.
Pt 554009004: 48 yo woman with progressive ALT/AST increase in Cycles 1-3. Therapy discontinued because of acute renal failure secondary to obstructive nephropathy.	Pt 56003023: 68 yo man, event occurred after Cycle 8. Diagnosed with cholangitis, discontinued treatment.
Pt 56003029: 58 yo man, event occurred after Cycle 1. Resolved after ERCP.	Pt 56003028: 67 yo man, event occurred after Cycle 4, concomitantly with diagnosis of disease progression.
Pt 710003001: 58 yo man, event occurred after Cycle 5. Diagnosed with obstructive jaundice.	Pt 616007007: 61 yo man, event occurred after Cycle 26. Diagnosis of disease progression.

As summarized, the diagnosis of drug-induced liver toxicity was attributed by the treating physician to irinotecan in only one case in the placebo arm (patient 36005011).

Renal function

A complete review and analysis of renal function and proteinuria can be found in Section 7.3.5.6 and Table 82.

Other laboratory parameters

Table 92 summarizes the toxicity in both arms related to other lab parameters such as albumin, electrolytes, and glucose. Although in most cases patients on the aflibercept arm experienced more frequently Grades 1-2 toxicity, there were no noteworthy differences in the incidence of

Grade 3-4 toxicity. Grade 1-2 hyperglycemia was experienced at a higher incidence in both arms. The incidence of all other lab abnormalities was within the expected range in the context of patients with advanced disease exposed to intensive chemotherapy, and experiencing nausea, vomiting, dehydration, anorexia, etc.

Table 92 - VELOUR: Other lab parameters

	Placebo/FOLFIRI (n, %) N=605	Aflibercept/FOLFIRI (n, %) N=611
Albumin		
Grades 1-2	252 (42)	309 (51)
Grade 3	16 (3)	11 (2)
Calcium		
Grades 1-2	248 (41)	309 (51)
Grade 3-4	22 (4)	27 (4)
Phosphorus		
Grades 1-2	145 (24)	153 (25)
Grade 3-4	36 (6)	37 (6)
Sodium		
Grades 1-2	256 (42)	271 (44)
Grade 3-4	39 (6)	47 (8)
Potassium		
Grades 1-2	201 (33)	231 (38)
Grade 3-4	39 (6)	45 (7)
Glucose		
Grades 1-2	420 (70)	445 (73)
Grade 3-4	40 (7)	41 (7)
Magnesium		
Grades 1-2	208 (35)	248 (41)
Grade 3-4	14 (2)	18 (3)

7.4.3 Vital Signs

Blood pressure was analyzed in Section 7.3.5.4. The incidence of hypertension was 30% higher in the aflibercept arm, regardless of the pre-existing hypertension status. There were 132 events of hypertension in 65 patients (11%) in the placebo arm and 1035 events in 253 patients (41%) in the aflibercept arm. Grades 3-4 events were reported in 1.5% patients in the placebo arm and 19% patients in the aflibercept arm. Table 79, Figure 12, and Figure 13 summarize FDA analyses of blood pressure assessments.

7.4.4 Electrocardiograms (ECGs)

No analysis of this parameter across clinical studies was performed (ECG was systematically performed at baseline and during study treatment only when clinically indicated).

The applicant conducted and submitted the results of Study TES10897, QUTIE, a randomized, double-blind, placebo-controlled study comparing aflibercept versus placebo (6 mg/kg) on the QTc interval in cancer patients treated with docetaxel 75 mg/m² every 3 weeks. The primary objective of this study was to assess the effect on QTcF interval of aflibercept vs. placebo. Secondary objectives included assessments of heart rate, QT, QTcB, QTcN, and PKs at Cycles 1 and 3.

A total of 88 patients with solid tumors were enrolled and randomized and 87 patients received treatment (one patient with an inclusion criteria violation -more than 2 prior lines of cytotoxic treatment- did not receive treatment). A plane crash with the data of three patients prevented the applicant from being able to analyze the data from three patients; thus, there were 84 patients available for ECG parameters assessment.

Using data prior to the cut-off date for the primary analysis (February 5, 2010), a total of 73 (83.9%) patients had discontinued study treatment while 14 (16.1%) were still receiving treatment. Primarily, treatment was stopped for disease progression (41 patients), adverse events (16 patients), or other reasons (16 patients) including patient decision (6 patients), Investigator's decision (5 patients), withdrawal of consent (3 patients) and "other" reason that was unspecified (2 patients).

All patients except one were Caucasian/White, 49 (56.3%) were men, 38 (43.7%) were women; median age was 61 years (range: 31 to 81 years) with 63 (72.4%) patients in the category <65 years, 17 (19.5%) in the category 65 - 75 years, and 7 (8.0%) in the category ≥75 years. Blood pressure, ECOG performance status, and ECG values showed similar distributions between the aflibercept and placebo arms at baseline. In the majority of patients, ECG results were considered normal or abnormal but not clinically significant. No patient received radiotherapy and 25 patients (29%) received prior therapy with anthracyclines.

The applicant concluded that in clinical study TES10897, after infusion of 6 mg/kg of aflibercept, the upper bound of the two sided 90% CI for the baseline-adjusted QTcF change was below 20 msec at both cycle 1 and cycle 3 (below the largest estimated level of acceptable QTc liability for an oncology agent). Exposure-QT relationship was consistent with both preclinical and clinical findings, every increase in 100 µg/mL of free aflibercept being associated with null or small (5 msec) increase in QTcF. From the data presented in the report, Sanofi concluded that aflibercept does not affect the ventricular repolarization to an extent that would require additional risk-benefit considerations.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted or reported.

7.4.6 Immunogenicity

Serum samples were evaluated for binding anti-aflibercept antibodies using a sandwich or a bridging immunoassay (ADA assay). Serum samples that were positive in this bridging ADA assay were further evaluated for neutralizing activity in the neutralizing antibody (NAb) assay.

In the placebo arm, a low percentage of the patients tested positive in the ADA assay (3.2% overall), usually demonstrated very low titers (<250), and in most cases the assay responses fluctuated above and below the assay cut point, resulting in both positive and negative responses at different time points. This pattern of response observed in the ADA assay suggested the presence of pre-existing immunoreactivity and not a drug induced antibody response. The sponsor stated that the presence of elevated serum levels of rheumatoid factor may have explained the immunoreactivity in patients receiving placebo, although other matrix components may be involved.

Overall, of the patients evaluable for immunogenicity in clinical studies with aflibercept, 35/1105 (3.2%) placebo-treated patients and 63/1671 (3.8%) aflibercept-treated patients exhibited a positive low titer assay response at any time during treatment; with positive response for neutralizing anti-aflibercept antibodies in 2 (0.2%) placebo-treated patients and 17 (1.3%) aflibercept-treated patients, respectively. In the VELOUR study, 18/526 (3.4%) placebo-treated evaluable patients and 8/521 (1.5%) aflibercept-treated evaluable patients exhibited a positive assay response including one positive for neutralizing antibody in the aflibercept arm. The majority of the samples positive in the ADA assay exhibited only the minimum assay titer (30), and none of the patients with a positive assay response exhibited a high titer result (>500) or a greater than 4-fold increase in the titer in subsequent samples. The applicant concluded that since the level of low titer ADA assay responses in the aflibercept-treated patients was similar to that observed in the placebo-treated patients, it is likely that most if not all the positive assay responses observed in the aflibercept-treated patients were due to high assay background levels and not due to treatment-emergent immune response to aflibercept.

Given the low incidence of positive assay responses, the low titer, and the absence of any trend for an increase in titer over time, Sanofi concluded that it is highly unlikely that any positive responses observed in the ADA assay were clinically meaningful. No specific safety conclusion or correlation could be drawn from these patients with positive ADA. There was no evidence of any impact of positive anti aflibercept antibodies on the aflibercept PK.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This study administered a single aflibercept dose for all patients, 4 mg/kg. Cumulative dose was explored as time dependency for AEs and presented in the following section.

7.5.2 Time Dependency for Adverse Events

As summarized in Table 93, there were no significant differences in the incidence of AEs per cycle. The incidence of AEs events in both arms was similar when evaluated by cycle throughout the first 10 cycles, with the exception of AEs after Cycle 5 in the placebo arm (which appears to be an outlier result).

Table 93 - VELOUR: Patients with AEs per cycle

Visit	Placebo/FOLFIRI		Aflibercept/FOLFIRI	
	N	N (%)	N	N (%)
1	605	487 (80)	611	534 (87)
2	582	487 (84)	577	537 (93)
3	553	470 (85)	539	492 (91)
4	467	390 (84)	477	437 (92)
5	435	372 (96)	441	408 (93)
6	407	350 (86)	408	379 (93)
7	358	302 (84)	376	344 (91)
8	331	280 (85)	350	317 (91)
9	298	253 (85)	320	291 (91)
10	253	221 (87)	288	267 (93)

Figure 20 displays the same data in a graphic.

Figure 20 - VELOUR: Incidence of subjects (%) with AEs per cycle

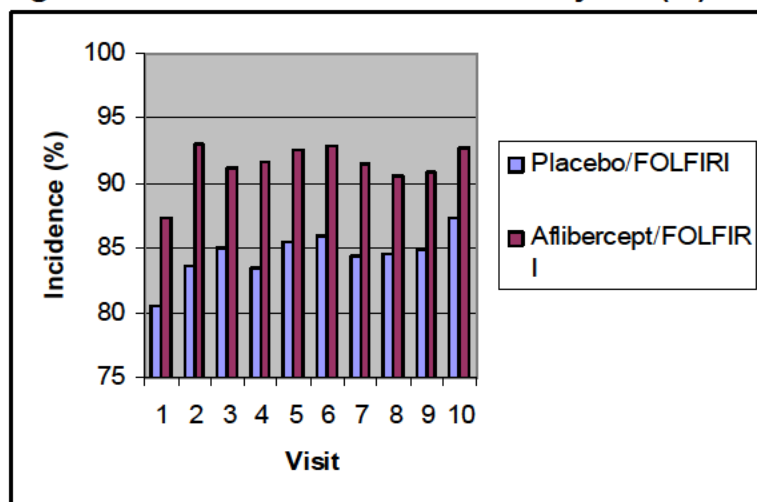


Table 94 and Table 95 summarize the percentages of AEs observed in $\geq 5\%$ of patients in the first 10 cycles of treatment (median number of cycles in the placebo arm was 8, and 9 cycles in the aflibercept arm).

Table 94 - VELOUR: Most frequent AEs ($\geq 5\%$) per cycle, Placebo/FOLFIRI arm

PT	Visit 1 N=605	Visit 2 N=582	Visit 3 N=553	Visit 4 N=467	Visit 5 N=435	Visit 6 N=407	Visit 7 N=358	Visit 8 N=331	Visit 9 N=298	Visit 10 N=253
Diarrhea	27	24	26	22	22	25	22	20	19	20
Nausea	33	29	31	29	28	29	24	25	20	19
Fatigue	17	20	24	23	25	29	25	28	27	26
Stomatitis	11	12	12	13	12	14	12	12	10	10
Vomiting	14	13	11	8	7	9	11	7	7	9
Dysphonia	1	1		1	1	1	2	2		
HTN	3	4	2	1	2	1	2	1		
Appetite	9	9	10	10	9	11	8	8	8	8
Abd.pain	7	7	7	8	8	12	10	8	8	
Constipation	12	10	8	7	10	10	9	5	6	
Headache	3	2		4	2	4	3	2		
Asthenia	2		3	4	4	6	4	5		
Epistaxis	2	2			3	4	3	3		
Weight		4	6	3	6	8	6	7	8	8
PPES				1	1	1	2	2		
Deaths	5	2	4	2	0	2	1	1	1	0

Table 95 - VELOUR: Most frequent AEs ($\geq 5\%$) per cycle, Aflibercept/FOLFIRI

PT	Visit 1 N=611	Visit 2 N=577	Visit 3 N=539	Visit 4 N=477	Visit 5 N=441	Visit 6 N=408	Visit 7 N=376	Visit 8 N=350	Visit 9 N=320	Visit 10 N=288
Diarrhea	39	33	30	31	30	28	28	26	25	25
Nausea	30	28	25	21	20	21	18	18	18	18
Fatigue	22	24	26	29	31	34	30	31	31	29
Stomatitis	18	22	23	24	24	28	24	25	24	24
Vomiting	14	10	8	8	9	7	6	7	10	6
Dysphonia	13	20	19	20	20	22	20	21		
HTN	12	18	15	18	15	14	14	15		
Appetite	9	11	13	11	12	15	14	12	11	11
Abd.pain	9	8	6	6	7	8	5	8	6	
Constipation	8	8	10	9	8	8	6	5	6	
Headache	8	8	7	9	7	8	8	6		
Asthenia	6		6	7	8	7	7	7		
Epistaxis	6	10	11	13	15	18	16	17		
Weight		5	12	14	16	20	18	19	19	23
PPES			4	5	7	10	10	10		
Deaths	7	3	2	4	3	3	0	1	1	1

In both arms, the incidence of diarrhea was increased in the first 4-5 cycles, and then stabilized (but it was always more frequent in the aflibercept arm). Fatigue increased through time in both arms, as did weight loss; however, the increase of weight loss through time (and overall incidence) was marked. The incidence of stomatitis increased in the aflibercept arm, while it remained relatively stable in the placebo arm. Palmar-plantar erythrodysesthesia, as expected, started after drug accumulation (Cycle 3 in the aflibercept arm and Cycle 4 in the placebo arm). Some characteristic effects of VEGF/R inhibition, like dysphonia and hypertension, started in Cycle 2-3 and then remained stable through treatment in the aflibercept arm. The incidence of nausea and vomiting decreases over time.

7.5.3 Drug-Demographic Interactions

Eighty seven percent of patients were White, precluding comparisons between patients with regards to the incidence of adverse events in different ethnic groups.

Gender

The applicant concluded that overall, there was no unexpected difference between genders that would result in differential monitoring or particular dosing adjustment. Table 96 and Table 98 summarize the AEs by SOC and the non-fatal Grade 3-4 AEs by gender.

Table 96 - VELOUR: AEs by SOC by gender (all Grades)

SOC	Females (n,%)		Males (n,%)	
	Placebo/FOLFIRI N= 259	Aflibercept/FOLFIRI N= 245	Placebo/FOLFIRI N= 346	Aflibercept/FOLFIRI N= 366
Gastrointestinal disorders	230 (89)	235 (96)	296 (86)	340 (93)
General disorders	172 (66)	181 (74)	233 (67)	283 (77)
Vascular disorders	111 (43)	189 (77)	156 (45)	250 (68)
Respiratory disorders	109 (42)	158 (64)	163 (47)	237 (65)
Nervous system disorders	122 (47)	151 (62)	160 (46)	224 (61)
Metabolism disorders	82 (32)	101 (41)	109 (32)	172 (47)
Skin and subcutaneous tissue disorders	124 (48)	144 (59)	161 (47)	167 (46)
Infections	90 (35)	125 (51)	109 (32)	157 (43)
Psychiatric disorders	59 (23)	93 (38)	77 (22)	150 (41)
Investigations	50 (19)	85 (35)	67 (19)	151 (41)
Blood disorders	121 (47)	130 (53)	120 (35)	145 (40)
Musculoskeletal disorders	92 (36)	94 (38)	114 (33)	133 (36)
Cardiac disorders	62 (24)	72 (29)	100 (29)	113 (31)
Renal and urinary disorders	51 (20)	82 (33)	51 (15)	89 (24)
Injury and procedural complications	37 (14)	39 (16)	36 (10)	64 (17)
Eye disorders	27 (10)	33 (13)	41 (12)	36 (10)
Hepatobiliary disorders	20 (8)	17 (7)	24 (7)	21 (6)
Immune system disorders	18 (7)	24 (10)	15 (4)	18 (5)
Reproductive system disorders	25 (10)	23 (9)	18 (5)	16 (4)

Neoplasms	11 (4)	9 (4)	11 (3)	14 (4)
Ear and labyrinth disorders	8 (3)	12 (5)	10 (3)	12 (3)
Endocrine disorders	1 (<1)	5	5 (1)	5 (1)
Surgical and medical procedures	0	1 (<1)	1 (<1)	2 (<1)
Pregnancy	1 (<1)	1 (<1)	0	0

Infections were more frequent in female patients (51%) receiving aflibercept than in male patients (43%). This difference was not observed in the placebo arm. The disparity in the aflibercept arm was mainly due to a higher incidence of urinary tract infections in women than in men (17% versus 4%).

The incidence of metabolism and nutrition disorders in the aflibercept arm was higher in male patients (47%) than in female patients (41%). The most frequently reported AE in this SOC was decreased appetite, which occurred more frequently in men patients than in women (36% versus 26%). The incidence in the placebo arm was the same for both genders (32%). Similarly, weight loss (in the investigations SOC) was more frequent in men exposed to aflibercept than in women (35% vs. 27% respectively), but the difference was not observed in the placebo arm.

The incidence of gastrointestinal disorders was similar between genders, but nausea and vomiting were more frequent in women than in men in both arms (Table 97).

Table 97 - VELOUR: GI SOC most common AEs by gender

PT	Females (n, %)		Males (n, %)	
	Placebo/FOLFIRI N= 259	Aflibercept/FOLFIRI N= 245	Placebo/FOLFIRI N= 346	Aflibercept/FOLFIRI N= 366
Constipation	68 (26)	50 (20)	81 (23)	87 (24)
Diarrhea	150 (58)	166 (68)	192 (55)	257 (70)
Nausea	162 (63)	149 (61)	165 (48)	177 (48)
Vomiting	98 (38)	98 (40)	104 (30)	103 (28)

In the aflibercept arm, there was a slightly higher incidence of ATE and fistula from gastrointestinal or non- gastrointestinal origin in men compared to women (3% vs. 2% and 2% vs. 1%). The same disparity was observed in the placebo arm. No cases of GI perforation were observed in women.

Vascular disorders were more frequent in the aflibercept arm in women (77%) than in men (68%). This difference was not observed in the placebo arm (2% difference). Female patients in the aflibercept arm had a higher incidence of epistaxis (29% vs. 27%) and hypertension (44% vs. 39%) than male patients. Hemorrhage was slightly more frequent in women than in men (40.8% versus 35.8%) in the aflibercept arm.

Proteinuria was reported in more men than women in both the aflibercept arm (64% vs. 59%) and the placebo arm (45% vs. 35%). Renal failure events were more frequently reported in men than in women in the aflibercept arm (4% vs. 2%). The incidence of renal failure in the placebo arm was 2% for both genders.

Table 98 - VELOUR: Non-fatal Grade 3-4 AEs (by PT) by gender (incidence ≥ 2%)

PT	Females (n,%)		Males (n,%)	
	Placebo/FOLFIRI N= 259	Aflibercept/FOLFIRI N= 245	Placebo/FOLFIRI N= 346	Aflibercept/FOLFIRI N= 366
Diarrhea	21 (8)	38 (16)	26 (8)	80 (22)
Neutropenia	71 (27)	78 (32)	62 (18)	75 (20)
Hypertension	5 (2)	48 (20)	4 (1)	69 (19)
Fatigue	25 (10)	27 (11)	22 (6)	50 (14)
Stomatitis	18 (7)	30 (12)	10 (3)	48 (13)
Asthenia	5 (2)	12 (5)	13 (4)	19 (5)
Decreased appetite	6 (2)	2 (1)	5 (1)	19 (5)
Febrile neutropenia	5 (2)	7 (3)	5 (1)	19 (5)
Pulmonary embolism	5 (2)	11 (4)	16 (5)	16 (4)
Dehydration	2 (2)	10 (4)	6 (2)	15 (4)
Proteinuria	0	3 (1)	0	15 (4)
Abdominal pain	11 (4)	15 (6)	3 (1)	12 (3)
Pneumonia	3 (1)	1 (<1)	1 (<1)	10 (3)
Vomiting	10 (4)	8 (3)	11 (3)	9 (2)
Nausea	11 (4)	4 (2)	7 (2)	7 (2)
Deep vein thrombosis	6 (2)	4 (2)	5 (1)	9 (2)
Palmar-plantar erythrodysesthesia	0	8 (3)	3 (1)	9 (2)
Sepsis	2 (1)	1 (<1)	2 (1)	6 (2)
Weight decreased	2 (1)	7 (3)	3 (1)	9 (2)
Headache	1 (<1)	3 (1)	1 (<1)	7 (2)
Upper abdominal pain	4 (2)	4 (2)	2 (1)	3 (1)
Back pain	8 (3)	4 (2)	3 (1)	3 (1)
Intestinal obstruction	7 (3)	5 (2)	4 (1)	2 (1)
Neutropenic infection	2 (1)	4 (2)	4 (1)	2 (1)
Neutrophil counts decreased	2 (1)	4 (2)	3 (1)	5 (1)
Syncope	4 (2)	5 (2)	5 (1)	5 (1)
Thrombocytopenia	3 (1)	4 (2)	2 (1)	2 (1)
Urinary tract infection	1 (<1)	4 (2)	4 (1)	1 (<1)

The overall incidence of Grade 3-4 AEs in the aflibercept arm was similar in both men and women (84.1% and 83.1% respectively).

Grade 3-4 infections in the aflibercept arm were reported at a higher incidence rate in men (15%) than in women (9%). Infections from the respiratory tract, such as pneumonia, were slightly more frequent in men.

Grade 3-4 decreased appetite was reported in more men than women in the aflibercept arm (5% versus 1%). However, weight decrease was reported at a similar incidence in men and women (2% versus 3%) in the aflibercept arm.

The incidence of Grade 3-4 AEs in the gastrointestinal SOC was higher in male patients (40% versus 35%) in the aflibercept arm. In the placebo arm, the incidences of Grade 3-4

gastrointestinal AEs were higher in women (28%) than in men (20%). Diarrhea was more frequently reported in men (22%) than in women (16%) in the aflibercept arm while the incidence of Grade 3-4 diarrhea was 8% in both men and women in the placebo arm.

Grade 3-4 hypertension was reported at a similar incidence rate in men and women.

Age

Table 99 summarizes the most frequent adverse events in patients ages 65 and older compared to patients younger than 65. Median age at diagnosis was 61 years old in the placebo arm, and 62 years old in the aflibercept arm. There were 39% patients in the placebo arm and 33% patients in the aflibercept arm who were 65 years of age or older.

Table 99 - VELOUR: AEs by PTs in the geriatric group (incidence ≥ 2%)

PT	≥ 65 y.o. (n, %) N= 438		< 65 y.o. (n, %) N= 778	
	Placebo/FOLFIRI N=233	Aflibercept/FOLFIRI N=205	Placebo/FOLFIRI N= 372	Aflibercept/FOLFIRI N=406
Neutropenia	57 (24)	54 (26)	76 (20)	99 (24)
Diarrhea	23 (10)	50 (24)	24 (6)	78 (17)
Hypertension	4 (2)	40 (20)	5 (1)	77 (19)
Fatigue	21 (9)	28 (14)	26 (7)	49 (12)
Stomatitis	13 (6)	26 (13)	15 (4)	52 (13)
Asthenia	8 (3)	16 (8)	10 (3)	15 (4)
Dehydration	1 (<1)	15 (7)	7 (2)	10 (2)
Decreased appetite	5 (2)	12 (6)	6 (2)	9 (2)
Pulmonary embolism	7 (3)	9 (4)	14 (4)	18 (4)
Febrile neutropenia	4 (2)	9 (4)	6 (2)	17 (4)
Proteinuria	0	8 (4)	0	10 (2)
Abdominal pain	7 (3)	7 (3)	7 (2)	20 (5)
Weight decreased	2 (1)	7 (3)	3 (1)	9 (2)
Pneumonia	1 (<1)	7 (3)	0	1 (<1)
Neutropenic infection	4 (2)	4 (2)	2 (1)	2 (<1)
Ascites	2 (1)	4 (2)	2 (1)	1 (<1)
Dyspnea	2 (1)	4 (2)	3 (1)	1 (<1)
lethargy	3 (1)	5 (2)	2 (1)	3 (1)
Sepsis	3 (1)	5 (2)	1 (<1)	2 (<1)
Syncope	2 (1)	4 (2)	0	0
Vomiting	3 (1)	4 (2)	18 (5)	13 (3)
Disease progression	0	4 (2)	3 (1)	4 (1)
Palmar-plantar erythrodysesthesia	1 (<1)	4 (2)	2 (1)	13 (3)
Deep vein thrombosis	7 (3)	3 (1)	4 (1)	10 (2)
Anemia	4 (2)	2 (1)	1 (<1)	6 (1)

Grade 3 or 4 gastrointestinal disorders were reported with a higher incidence in the ≥65 category than the <65 category in the aflibercept arm (43% versus 36%). The most frequently observed event was diarrhea, which occurred in 24% of the patients in the ≥65 category and 17% in the <65 category.

Metabolism and nutrition disorders (SOC) were reported with a higher incidence in the ≥ 65 category than the < 65 category in the aflibercept arm (44% vs. 35%, all Grades). Incidence rates between age categories in the placebo arm were similar (27% vs. 26%). Dehydration was reported more frequently in the aflibercept arm and in more patients aged ≥ 65 years than < 65 years (15% vs. 6% in the aflibercept arm and 2% versus 4% in the placebo arm). This difference was also observed in the incidence of Grade 3-4 dehydration (7% in the older patients and 2% in the younger patients in the aflibercept arm). Grade 3-4 asthenia was also more frequent in the aflibercept-treated older patients.

Cardiac disorders were reported at similar incidence between the 2 treatment arms in patients ≥ 65 years (7% in the aflibercept arm and 5% in the placebo arm). Incidence of hypertension was not influenced by age in the aflibercept arm with 42% of the patients < 65 years and 39% of the patients ≥ 65 years old.

In the aflibercept arm, Grade 4 neutropenia (lab dataset, Table 100) was more frequent in the patients 65 years and older (20% vs. 10% in the younger patients), as were Grade 2 hemoglobin levels (22% vs. 16%). Besides these two parameters, hematologic toxicity was similar between age groups. Aflibercept did not increase hematologic toxicity in patients 65 years of age and older, but the addition of aflibercept to FOLFIRI increased the overall hematologic toxicity in patients younger than 65 years of age.

Table 100 - VELOUR: Hematologic toxicity (lab data) by age group

Parameter	≥ 65 (n, %) N= 438		< 65 (n, %) N= 778	
	Placebo/FOLFIRI N=233	Aflibercept/FOLFIRI N=205	Placebo/FOLFIRI N= 372	Aflibercept/FOLFIRI N=406
Hb g/dL				
Grade 1	140 (60)	128 (62)	231 (62)	236 (58)
Grade 2	67 (29)	46 (22)	80 (22)	63 (16)
Grade 3	7 (3)	5 (2)	14 (4)	15 (4)
Grade 4	3 (1)	0	2 (1)	3 (1)
PLT $\times 10^9/L$				
Grade 1	80 (34)	76 (37)	98 (26)	164 (41)
Grade 2	10 (4)	13 (6)	12 (3)	22 (5)
Grade 3	3 (1)	5 (2)	3 (1)	5 (1)
Grade 4	1 (<1)	5 (2)	6 (2)	6 (1)
ANC $\times 10^9/L$				
Grade 1	27 (12)	23 (11)	8 (2)	47 (12)
Grade 2	40 (17)	32 (16)	58 (16)	86 (21)
Grade 3	49 (21)	42 (20)	66 (18)	99 (24)
Grade 4	32 (14)	40 (20)	32 (9)	42 (10)

Table 101 summarizes the AEs that occurred in at least three patients in the 75 years or older population. Although numbers are small, it does not appear that the combination of aflibercept and FOLFIRI was more toxic in this age group.

Table 101 - VELOUR: AEs by PTs, patients ≥ 75 years old (in at least 3 subjects).

PT	≥ 75 y.o. (n, %) N= 70	
	Placebo/FOLFIRI N=37	Aflibercept/FOLFIRI N=33
Neutropenia	10 (27)	9 (27)
Diarrhea	5 (14)	9 (27)
Dehydration	0	4 (12)
Hypertension	0	4 (12)
Fatigue	2 (5)	3 (9)
Sepsis	1 (3)	3 (9)
Stomatitis	6 (16)	2 (6)

Body mass index (BMI)

The applicant's pre-specified PK analysis found a relationship between aflibercept free concentration and efficacy. Because VELOUR was conducted using mg/kg dosing and the FDA clinical pharmacology review analyses suggested that weight-based dosing increased inter-patient variability in aflibercept exposure, in this section, a clinical analysis of the differences in toxicities observed according to body mass index (BMI) will be summarized.

To calculate the BMI, the following formula (using baseline data) was applied:

$$\frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

Patients were classified following the CDC and NIH guidelines in three categories: underweight and normal weight (BMI less than 25), overweight (BMI between 25 and 29.9), and obese (BMI ≥ 30). Data were available from 602 and 608 (99.5%) of patients in the safety population in the placebo and aflibercept arms, respectively. Table 102 summarizes the BMI demographics of the safety population in the VELOUR trial: 39% and 40% of patients in the placebo arm and aflibercept arm were overweight, and 18% and 19% of patients in the placebo arm and aflibercept arm were obese.

Table 102 - VELOUR: BMI demographics

	Placebo/FOLFIRI (n, %) N=602	Aflibercept/FOLFIRI (n, %) N=608
Mean BMI (95%CI)	26.24 (25.84 - 26.64)	26.37 (25.98 - 26.76)
Median BMI (range)	25.82 (14.56 - 56.06)	25.94 (13.39 - 48.71)
BMI < 25	260 (43)	252 (41)
BMI 25- <30	233 (39)	243 (40)
BMI ≥ 30	109 (18)	113 (19)

Table 103 summarizes the AEs with an incidence of ≥ 2% (regardless of the outcome) by BMI status. In the placebo arm, neutropenia (reported as an AE) was 10% more frequent in underweight and normal weight patients than in obese patients. Fatigue was also markedly

increased in underweight/normal weight patients. Pulmonary embolism, although infrequent overall, was incrementally increased as weight increased.

In the aflibercept arm, diarrhea and hypertension were increased in obese patients. As observed in the placebo arm, the incidence of pulmonary embolism increased as weight increased.

Table 103 - VELOUR: Grade 3-4 AEs (by PT) by BMI status

PT	Placebo/FOLFIRI (n, %) N=602			Aflibercept/FOLFIRI (n, %) N=608		
	Underweight/ Normal (N=260)	Overweight (N=233)	Obese (N=109)	Underweight/ Normal (N=252)	Overweight (N=243)	Obese (N=113)
Neutropenia	68 (26)	47 (20)	17 (16)	63 (25)	57 (24)	31 (27)
Diarrhea	17 (7)	21 (9)	9 (8)	49 (19)	40 (16)	29 (26)
Hypertension	2 (1)	4 (2)	3 (3)	47 (19)	44 (18)	26 (23)
Fatigue	30 (12)	11 (5)	6 (6)	39 (15)	24 (10)	14 (12)
Stomatitis	16 (6)	9 (4)	3 (3)	39 (15)	27 (11)	12 (11)
Asthenia	6 (2)	8 (3)	4 (4)	18 (7)	9 (4)	4 (4)
Febrile neutropenia	6 (2)	2 (1)	2 (2)	14 (6)	8 (3)	4 (4)
Dehydration	4 (2)	4 (2)	0	13 (5)	8 (3)	5 (4)
Abdominal pain	9 (3)	2 (1)	3 (3)	9 (4)	12 (5)	6 (5)
Decreased appetite	9 (3)	1 (<1)	1 (1)	11 (4)	7 (3)	3 (3)
Vomiting	9 (3)	7 (3)	5 (5)	8 (3)	6 (2)	3 (3)
Palmar-plantar erythrodysesthesia	1 (<1)	1 (<1)	1 (1)	8 (3)	8 (3)	1 (1)
Pulmonary embolism	5 (2)	9 (4)	7 (6)	5 (2)	12 (5)	11 (10)
Intestinal obstruction	6 (2)	4 (2)	2 (2)	4 (2)	4 (2)	0
Nausea	7 (3)	6 (3)	5 (5)	4 (2)	4 (2)	3 (3)
Pneumonia	1 (<1)	3 (1)	0	5 (2)	4 (2)	2 (2)
Ascites	3 (1)	1 (<1)	0	4 (2)	1 (<1)	0
Headache	0	1 (<1)	1 (1)	5 (2)	3 (1)	2 (2)
Proteinuria	0	0	0	5 (2)	8 (3)	5 (4)
Sepsis	2 (1)	1 (<1)	2 (2)	5 (2)	3 (1)	0
Weight decreased	4 (2)	1 (<1)	0	6 (2)	6 (2)	4 (4)
Deep vein thrombosis	4 (2)	4 (2)	3 (3)	3 (1)	9 (4)	1 (1)
Back pain	4 (2)	3 (1)	4 (4)	3 (1)	2 (1)	2 (2)
Device related infection	3 (3)	2 (1)	2 (2)	2 (1)	1 (<1)	3 (3)
Syncope	2 (1)	3 (1)	4 (4)	3 (1)	5 (2)	2 (2)
Hyperbilirubinemia	3 (1)	1 (<1)	2 (2)	3 (1)	0	0
Ileus	4 (2)	1 (<1)	0	2 (1)	0	0
Peripheral neuropathy	0	1 (<1)	2 (2)	2 (1)	2 (1)	2 (2)
Neutropenic infections	4 (2)	1 (<1)	2 (2)	2 (1)	3 (1)	1 (1)
Abdominal upper pain	2 (1)	2 (1)	2 (2)	0	5 (2)	2 (2)

Table 104 summarizes the Grade 3-4 AEs by HLT. In the aflibercept arm, the incidence of diarrhea and hypertension increased with increased weight; neutropenia, asthenic conditions, stomatitis, and ulcerations were observed more frequently in patients who were of normal weight or underweight.

Table 104 - VELOUR: Grade 3-4 AEs (by HLT) by BMI status

HLT	Placebo/FOLFIRI (n, %) N=602			Aflibercept/FOLFIRI (n, %) N=608		
	Underweight/ Normal (N=260)	Overweight (N=233)	Obese (N=109)	Underweight/ Normal (N=252)	Overweight (N=243)	Obese (N=113)
Neutropenias	74 (28)	49 (21)	20 (18)	71 (28)	67 (28)	34 (30)
Asthenic conditions	37 (14)	20 (9)	12 (11)	52 (21)	39 (16)	20 (18)
Vascular hypertensive disorders	2 (1)	4 (2)	3 (3)	47 (19)	44 (18)	27 (24)
Diarrhea	17 (7)	21 (9)	9 (8)	49 (19)	40 (16)	29 (26)
Stomatitis and ulcerations	18 (7)	9 (4)	3 (3)	42 (17)	30 (12)	12 (11)
General signs and symptoms NEC	13 (5)	4 (2)	3 (3)	17 (7)	5 (2)	3 (3)
Febrile disorders	7 (3)	4 (2)	2 (2)	15 (6)	9 (4)	5 (4)
Appetite disorders	9 (3)	1 (<1)	1 (1)	12 (5)	7 (3)	3 (3)
Total fluid volume decreased	4 (2)	4 (2)	0	13 (5)	8 (3)	5 (4)
GI and abdominal pains	11 (4)	4 (2)	5 (5)	9 (4)	17 (7)	7 (6)
Nausea and vomiting	13 (5)	11 (5)	6 (6)	10 (4)	9 (4)	5 (4)
GI stenosis and intestinal obstruction	13 (5)	5 (2)	2 (2)	9 (4)	5 (2)	0

Other demographic factors

The applicant conducted a subgroup analysis, showing that the overall incidence of all grade AEs was the same in patients from the different regions [North America 100%, Europe 98.6%, Rest of the World (ROW) 100%].

Dehydration and decreased appetite occurred more frequently in North American or ROW patients when compared to patients from Europe. The incidence of diarrhea in aflibercept arm was similar in patients from North America (67%) and Europe (66%) but was higher in patients from ROW (76%). The same disparity was observed in the placebo arm.

Hypertension was reported more frequently in aflibercept treated patients from Europe (42%) and ROW (45%) than in those from North America (30%). This disparity was observed, but not as pronounced, in the placebo arm (Europe 13%, ROW 9%, and North America 6%).

Except for hypertension, analysis of events considered to be of special interest as VEGF-drug class events occurred less frequently in European patients compared to North American and/or ROW patients for hemorrhage (33% versus 44% and 46%, respectively, mostly accounts for bleeding from GI origin), and VTE (8% versus 13% and 11%, respectively). Incidences of ATE

were similar between the three regions (2.7% versus 3.1% and 2.2%, respectively). The same disparity was observed in placebo arm.

Acute drug reactions were more frequent in the North America population (9% in North America, 4% in Europe, and 3% in ROW).

In the aflibercept arm, the incidence of all grades proteinuria was similar in all regions: Europe 61%, ROW 63%, and North America 66%). The incidence of renal failure events was lower in the aflibercept arm in European patients (<1%) compared to North American patients (2%) and ROW patients (3%).

7.5.4 Drug-Disease Interactions

Baseline ECOG status

Table 105 summarizes the most frequent adverse events by baseline ECOG performance status. Only 12 patients per arm (2%) had baseline performance status score of 2 and the results are presented only for informative purposes.

Table 105 - VELOUR: AEs (PT) by ECOG PS (incidence ≥ 20%)

PT	PS=0 (n, %)		PS=1 (n, %)		PS=2 (n, %)	
	Placebo N= 352	Aflibercept N= 349	Placebo N= 245	Aflibercept N= 246	Placebo N= 12	Aflibercept N= 12
Diarrhea	193 (55)	242 (69)	158 (58)	174 (71)	6 (50)	7 (58)
Nausea	219 (62)	194 (56)	105 (43)	129 (52)	3 (25)	3 (25)
Stomatitis	117 (33)	180 (52)	79 (32)	123 (50)	3 (25)	3 (25)
Fatigue	136 (39)	182 (52)	97 (40)	106 (43)	3 (25)	4 (33)
Hypertension	38 (11)	162 (46)	26 (11)	86 (35)	1 (8)	4 (33)
Vomiting	130 (37)	119 (34)	70 (29)	80 (33)	2 (17)	2 (17)
Epistaxis	30 (9)	109 (31)	14 (6)	59 (24)	1 (8)	1 (8)
Decreased appetite	82 (23)	108 (31)	59 (24)	87 (35)	0	0
Dysphonia	13 (4)	104 (30)	7 (3)	49 (20)	0	2 (17)
Weight decreased	50 (14)	100 (29)	35 (14)	88 (36)	2 (17)	7 (58)
Abdominal pain	85 (24)	99 (28)	54 (22)	63 (26)	4 (33)	2 (17)
Headache	40 (11)	92 (26)	13 (5)	44 (18)	0	0
Constipation	92 (26)	85 (24)	53 (22)	51 (21)	4 (33)	1 (8)
Asthenia	43 (12)	85 (24)	34 (14)	49 (20)	3 (25)	3 (25)

The overall incidence of all grade AEs was comparable between patients with ECOG PS 0 and ECOG PS 1 with the exception of hypertensive events, which were more frequently reported in patients with ECOG PS 0 at baseline.

Increased incidence of fatigue/asthenia, epistaxis, and dysphonia was reported between ECOG PS 0 and ECOG PS 1 patients in the aflibercept arm, but not in the placebo arm. Weight decrease was observed more frequently in the ECOG PS 1 patients in the aflibercept arm when

compared to ECOG PS 0 patients. No differences in weight loss were observed between patients with ECOG PS 0 and ECOG PS 1 in the placebo arm.

Prior exposure to bevacizumab

As summarized in Section 6.1.2 and Table 22 -Table 23, an analysis of the disposition database showed discordances between the IVRS forms and the CRFs regarding the number of patients that had received prior bevacizumab. According to the IVRS forms, 70% of patients in each arm did not receive prior bevacizumab treatment; when the information from the CRFs was analyzed, 71% patients in the placebo arm and 72% patients in the aflibercept arm did not receive prior bevacizumab therapy. The analyses in this section used data derived from the CRFs (prior bevacizumab treatment in 177 patients in the placebo arm and 169 patients in the aflibercept arm). Table 106 summarizes the adverse events (PTs) with an incidence of $\geq 2\%$ by arm and prior bevacizumab exposure.

Table 106 - VELOUR: AEs (incidence $\geq 2\%$) by prior bevacizumab exposure

PT	Placebo/FOLFIRI (n, %)		Aflibercept/FOLFIRI (n, %)	
	No prior (N= 437)	Prior bevacizumab (N=177)	No prior (N=443)	Prior bevacizumab (N=169)
Diarrhea	253 (58)	89 (50)	307 (69)	116 (69)
Nausea	231 (53)	96 (54)	226 (51)	100 (59)
Fatigue	160 (37)	76 (43)	194 (44)	98 (58)
Stomatitis	146 (33)	53 (30)	221 (50)	85 (50)
Decreased appetite	101 (23)	43 (24)	126 (28)	69 (41)
Hypertension	50 (11)	15 (8)	182 (41)	70 (41)
Weight decreased	65 (15)	22 (12)	135 (30)	60 (36)
Vomiting	143 (33)	59 (33)	143 (32)	58 (34)
Neutropenia	167 (38)	38 (21)	183 (41)	55 (33)
Epistaxis	29 (7)	16 (9)	117 (26)	52 (31)
Constipation	106 (24)	43 (24)	92 (21)	45 (27)
Abdominal pain	103 (24)	40 (23)	121 (27)	43 (25)
Headache	41 (9)	12 (7)	102 (23)	34 (20)
Dyspnea	34 (8)	18 (10)	44 (10)	28 (17)
Asthenia	65 (15)	15 (8)	88 (20)	24 (14)
Back pain	53 (12)	19 (11)	52 (12)	23 (14)
Pyrexia	55 (13)	29 (16)	58 (13)	24 (14)
Abdominal pain upper	38 (9)	10 (6)	45 (10)	21 (12)
Urinary tract infection	25 (6)	12 (7)	35 (8)	21 (12)
Cough	43 (10)	15 (8)	50 (11)	18 (11)
Dyspepsia	37 (8)	19 (11)	34 (8)	16 (9)
Peripheral edema	30 (7)	14 (8)	37 (8)	15 (9)
Dizziness	34 (8)	19 (11)	22 (5)	14 (8)
Rash	21 (5)	14 (8)	28 (6)	13 (8)
Insomnia	34 (8)	11 (6)	35 (8)	12 (7)
Arthralgia	28 (6)	12 (7)	21 (5)	10 (6)
Lacrimation decreased	17 (4)	9 (5)	19 (4)	5 (3)
Hyperhidrosis	18 (4)	15 (8)	13 (3)	4 (2)

Patients with a history of prior bevacizumab exposure experienced more fatigue (in both arms, but this effect was more marked in the aflibercept arm). In the aflibercept arm, patients with prior exposure to bevacizumab more frequently experienced decrease appetite (41% vs. 18% in patients with prior exposure vs. no prior exposure respectively), decreased weight (36% vs. 30% respectively), dyspnea (15% vs. 10% respectively), and urinary tract infections (12% vs. 8% respectively). There were no differences in the incidence of hypertension with regards to prior bevacizumab exposure.

In summary, in the VELOUR study, prior exposure to bevacizumab did not increase the frequency of VEGF/R inhibition-related toxicities.

7.5.5 Drug-Drug Interactions

No formal drug-drug interactions studies were conducted for the aflibercept/FOLFIRI combination. The effect of aflibercept on the PKs of irinotecan and 5-FU were evaluated in a Phase 1 study (TCD6118), and the population PK analysis in the EFC10262/VELOUR trial assessed the effect of FOLFIRI on aflibercept PKs. Although the population PK analysis showed a minor decrease (11%) in free aflibercept clearance with the irinotecan/LV5FU2 combination used in the TCD6118 trial, Sanofi concluded that aflibercept did not affect the PKs of irinotecan or 5-FU or the FOLFIRI regimen in EFC10262/VELOUR.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies were conducted to evaluate the carcinogenicity of aflibercept.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy category for aflibercept is C. There are no studies in pregnant women. Pre-clinical studies in pregnant rabbits showed an increased incidence of external, visceral, and skeletal fetal malformations, as well as an increased abortion rate.

Fertility was also impaired in cynomolgus monkeys, where ovarian function and follicular development impairment following aflibercept dosing was observed.

7.6.3 Pediatrics and Assessment of Effects on Growth

Colorectal carcinoma is a disease of adulthood, and its incidence increases with age. In pediatrics, colorectal carcinoma is usually associated with conditions such as familial

adenomatous polyposis and ulcerative colitis. The diagnosis of polyp syndrome is often made in the first or second decade of life, long before the risk of intestinal neoplasia.

In the SEER report from 2004-2008 (<http://seer.cancer.gov/statfacts/html/colorect.html>), 0.1% of all colorectal cancers were diagnosed under the age of 20 (around 1 per million people younger than 20 years, or fewer than 100 cases annually).

In this application, Sanofi requested a waiver of the requirement to assess aflibercept in all pediatric age groups because studies would be impossible or highly impracticable. This reviewer agrees with the request and recommends granting the applicant a waiver for aflibercept in the second line metastatic colorectal carcinoma indication.

A Phase 1 dose-escalation pediatric study conducted by the Children's' Oncology Group [under a separate (IND 100137)] determined that the recommended pediatric dose is 2.5 mg/kg, below the optimal biological dose of 4 mg/kg. DLTs in the pediatric group were VEGF/R inhibition related (hemorrhage and tumor hemorrhage). Currently, there are no pediatric studies ongoing.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no expected drug abuse potential for aflibercept. There were no events of overdose in the trials submitted. Doses up to 9 mg/kg have been studied in Phase 1 trials (2.25 times the dose used in the pivotal study, VELOUR).

7.7 Additional Submissions / Safety Issues

In this section, Sanofi's 120-day update (data cut-off January 25, 2012) will be reviewed. This information (submitted on May 25, 2012) provided 11 additional months of follow-up to the VELOUR study. At the time of the original data cut-off (February 7, 2011), 97% of patients in the VELOUR study discontinued treatment (see Table 30) and 149 patients (24%) in the placebo arm and 207 patients (34%) in the aflibercept arm were alive.

As of January 25, 2012, all patients in the placebo arm and all but one patient in the aflibercept arm discontinued treatment. Nineteen additional deaths in the placebo arm were reported: four patients died from toxicity-related causes within 30 days of receiving the placebo/FOLFIRI regimen and 13 patients died from disease progression. In the aflibercept/FOLFIRI, 31 new deaths were reported: 14 patients from toxicity-related causes within 30 days of receiving study drugs and 15 patients from disease progression.

Overall, the toxicity profile emerging from this subset of patients who were still on treatment at the time of the original data cut-off was consistent with what was observed in the final analysis of the VELOUR study. Additional events of interest observed in the aflibercept arm were

intestinal fistula in one patient, renal failure in two patients, nephrotic syndrome in one patient, myocardial infarctions in three patients, and congestive heart failure in one patient. In the placebo arm, there was one colonic fistula, an intestinal perforation, and one patient with renal failure. There were 7 events of pulmonary embolism in each arm.

In conclusion, the 120-day safety update was consistent with the results summarized in the complete study report that is the basis of this application. No new safety signals were identified with further follow-up.

In addition, Sanofi submitted the summary and narratives for study EFC10688 (AFFIRM), a randomized, Phase 2 study in first-line mCRC of the combination of mFOLFOX6 vs. aflibercept/mFOLFOX6. As in the VELOUR study, the safety profile was typical of an agent targeting VEGF, and enhancement of the backbone regimen toxicity was observed, including stomatitis, diarrhea, palmar-plantar erythrodysesthesia, infections, and neutropenia. In this study, although patients in the aflibercept arm had an increased 12-month PFS (25.8% [95% CI 17.2% to 34.4%] vs. 21.2% [95% CI 12.2% to 30.3%] in the aflibercept/mFOLFOX6 and mFOLFOX6 respectively), this difference was not statistically significant, with a stratified HR of 1.003 (95% CI 0.73 to 1.36). The OS HR was 0.97 (95% CI 0.65 to 1.44).

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

Chen, H. X., Cleck, J. Adverse effects of anticancer agents that target the VEGF pathway N. Nat. Rev. Clin. Oncol. 2009, 6, 465–477
Ellis L. and Hicklin D. VEGF targeted therapy: mechanisms of anti-tumor activity. Nature Reviews Cancer, 2008 , August V8, 579-591
Eremina V., Jefferson JA., Kowaleska J., Hochster H., Hass M., et al. VEGF inhibition and renal thrombotic microangiopathy. N. Engl J Med. 2008 Mar 13;358(11):1129-36.
Giles F. The vascular endothelial growth factor (VEGF) signaling pathway: a therapeutic target in patients with hematologic malignancies. The Oncologist, 2001, October V6, suppl 5, 32-39
Hapani S., Chu D., Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol 2009; 10: 559–68
Hinchey J., Chaves C., Appignani B., Breen J., Pao L. et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996 Feb 22;334(8):494-500.
Ito Y., Arahata Y., Goto Y., Hirayama M., Nagamitsu M. et al. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. Am J Neuroradiol 1998, Mar 19 (3): 415-7.
Izzedine H., Massard C., Spano JP., Goldwasser F., Khayat D. et al. VEGF signaling inhibition-induced proteinuria: Mechanisms, significance and management. Eur. J. of Cancer 2010, 46:439-448
Johnson D., Fehrenbacher L., Novotny W., Herbst R., Nemunaitis J. et al. Randomized Phase II Trial Comparing Bevacizumab Plus Carboplatin and Paclitaxel With Carboplatin and Paclitaxel Alone in Previously Untreated Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. J. Clin. Oncol. 2004, V22, No 11: 2184-2191
Mukherjee P, McKinstry RC. Reversible posterior leukoencephalopathy syndrome: evaluation with diffusion-tensor MR imaging. Radiology. 2001; 219:756–65.
Ranpura V., Pulipati B., Chu D., Zhu X., Wu S. Increased Risk of High-Grade Hypertension With Bevacizumab in Cancer Patients: A Meta-Analysis American J. of Hypertension, 2010 May V23 N5: 460-468
Roodhart J., Marlies H. Langenberg H., Witteveen L., Voest E. The Molecular Basis of Class Side Effects Due to Treatment with Inhibitors of the VEGF/VEGFR Pathway Current Clinical Pharmacology, 2008, 3, 132-143.
Sandler A., Gray R., Perry M., Brahmer J., Schiller J. Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer. N Engl J Med 2006; 355:2542-2550.
Scappaticci F., Fehrenbacher L., Cartwright T., hainsworth J., Heim W. et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J. Surg. Oncol 2005, 3:173-80.
Scappaticci F., Skillings J., Holden S., Gerber H., Miller K. et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J. Natl. Cancer Inst. 2007 Aug 15; 99(16):1232-9.

Schmiegel W., Pox C., Arnold D., Porschen R., Rödel C. et al. Colorectal carcinoma: the management of polyps, (neo) adjuvant therapy, and the treatment of metastases. Dtsch Arztebl Int. 2009 Dec;106 (51-52): 843-8.

Wagner AD., Arnold D., Grothey AA., Haerting J., Unverzagt S. Anti-angiogenic therapies for metastatic colorectal cancer. Cochrane Database Syst Rev. 2009 Jul 8;(3): CD005392.

Wasif Saif M., Elfiky A., Salem R. Gastrointestinal Perforation Due to Bevacizumab in Colorectal Cancer. ChBAnnals of Surgical Oncology 2007 14(6):1860–1869.

9.2 Labeling Recommendations

This section reflects the significant changes in the clinical sections of the label at the time of this review. Further changes may be discussed in an addendum to this review after negotiations with the company take place.

Section 1: Indications and Usage

Original language

ZALTRAP in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen.

Proposed language

ZALTRAP, in combination with a FOLFIRI chemotherapy regimen, is indicated for patients with metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

FDA reason to change to FOLFIRI instead of irinotecan-fluoropyrimidine-based chemotherapy is to reflect the study in which the indication was based. The change to the population further clarified that patients should have been treated and progressed after an oxaliplatin-containing regimen; sanofi's statement may include patients who received an oxaliplatin-based regimen more than 6 months before or as part of adjuvant therapy, in which case oxaliplatin may still be a drug of choice.

Section 2: Dosage and Administration

This section has been modified to follow the current labeling guidance.

(b) (4)

(b) (4)

Extensive editing to the indications for drug preparation and storage for clarity, consistency and accuracy were proposed. Current microbiology studies support only the storage of diluted aflibercept up to 4 hours.

Section 4: Contraindications

<div>(b) (4)</div>
<p>FDA guidance states that contraindications should be based on actual events and not hypothetical concerns. FDA changed the contraindications to none.</p>
Section 5: Warnings and Precautions
<p>This section has been modified to follow the current labeling guidance, and for clarity and consistency.</p>
<p>In subsection 5.6, Proteinuria, language was modified to reflect current practice of medicine in the U.S., so proteinuria will be monitored by urine dipstick analysis and/or urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria during aflibercept therapy.</p>
<div>(b) (4)</div>
Section 6: Adverse reactions
<p>This section was modified for clarity. In subsection 6.1, Clinical Trials Experience,</p>
<div>(b) (4)</div>
<p>(b) (4) FDA edited the label to state the fact that the most frequent adverse reactions leading to permanent discontinuation in $\geq 1\%$ of patients treated with ZALTRAP/FOLFIRI regimen were asthenia/fatigue, infections, diarrhea, dehydration, hypertension, stomatitis, venous thromboembolic events, neutropenia, and proteinuria.</p>
<p>Information that was redundant was deleted.</p>
Section 14: Clinical Studies
<p>This section was modified for clarity. Clarifications were made regarding the exploratory nature of the subgroup analyses.</p>
Section 17: Patient Counseling
<p>This section was modified for clarity.</p>
Patient Information
<p>Aflibercept will be administered in oncology clinics or hospitals. Before receiving aflibercept, all patients will have signed informed consent documents, and had extensive counseling information with their physicians and health care team. The clinical team</p>

considers that the information that patients will receive before starting treatment with aflibercept is sufficient and no PPI is needed. Additionally, not including a PPI is consistent with the labeling of bevacizumab, the other drug targeting the VEGF pathway approved by FDA.

9.3 Advisory Committee Meeting

Aflibercept is a fusion molecule that inhibits the VEGF pathway. This application was submitted to approve aflibercept in the second line setting of metastatic colorectal carcinoma. Although aflibercept is a new molecular entity, the aflibercept mechanism of action is through the same pathway as bevacizumab, an anti-VEGF monoclonal antibody approved for patients in combination with irinotecan-containing chemotherapy. The pivotal trial analyzed in this review was a well-designed, placebo-controlled Phase 3 trial comparing aflibercept/FOLFIRI vs. placebo/FOLFIRI with overall survival as the primary endpoint. The safety profile of aflibercept is similar to the known bevacizumab toxicity. For these reasons, no advisory committee meeting was held for this application.

9.4 Additional Tables and Figures

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Table 107 - Study Flow Chart

Evaluation	Baseline Phase		Treatment			Post study treatment Follow-up until death	
	Within 21 days before randomization	Within 8 days before randomization	First cycle within 3 days after randomization				
			Before each cycle	Every 6 weeks	30-day FU visit (end of treatment)		
Informed Consent (a)	X						
Inclusion/Exclusion Criteria		X (b)					
Clinical Examination (c)		X	X		X		
Demography (d)	X						
Past Medical/Surgical History (e)	X		R A N D O M I Z E D A S S I G N M E N T				
Prior Anticancer Treatment (f)	X						
Prior/Concomitant Medication (g)	X			X		X	X
Aflibercept/placebo (h)				X			
FOLFIRI				X			
Imaging evaluation (i)	X				X	X	X
Adverse Events (j)				X		X	X
Hematology (k)		X		X		X	
Biochemistry (k)		X		X		X	
Urine analyses (l)		X		X		X	
Coagulation test (m)		X	X		X		
Pregnancy Test (n)		X					
12-Lead EKG		X					
Immunogenicity (o)			On day 1 of cycle 1, prior to, and at the end of aflibercept/placebo infusion, then every other cycle			X	
Pharmacokinetics (p)							
Endogenous VEGF level (q)			On day 1 of cycle 1, prior to aflibercept/placebo infusion				
Post study treatment anticancer therapy						X	

- a) Before any protocol study procedure
- b) Time between biological work-up at baseline and first infusion was not to exceed 8 days. If time exceeded 8 days, biological tests were to be repeated prior to first administration of study treatment.
- c) Including examination of major body systems, height (at baseline visit only), ECOG PS, body weight and blood pressure.
- d) Including age, sex, and race.
- e) Including cancer diagnosis (primary tumor characteristics and metastatic sites), other prior medical and surgical history.
- f) Including previous surgery for cancer, radiotherapy, chemotherapy, and potential investigational antitumor therapy.
- g) Any prior treatment received within 21 days before study entry (stopped, or ongoing) was to be recorded. Concomitant medications and treatments were to be recorded from 21 days prior to the start of study treatment, at study entry, before every cycle during the study treatment period, at 30 days after the end of study treatment (30-day FU visit) and after the 30-day FU visit in case of related adverse event(s) (AE) or serious adverse event(s) (SAE).
- h) Study treatment was to start on Cycle 1 Day 1 just before FOLFIRI administration, within 3 days of randomization, and then repeated every 2 weeks.
- i) Abdomino-pelvic CT scan or MRI and chest X-ray (or chest CT or MRI scan in case of thoracic target lesion) and other exams, as clinically indicated, were to be performed to assess disease status at baseline, then every 6 weeks during study treatment, and at the end of study treatment (30-day FU visit). If patients discontinued study treatment without documented disease progression, then tumor assessments were to continue to be performed every 6 weeks until disease progression was documented. The same imaging method was to be used at each assessment. For RR analysis, a CR or a PR was considered as a confirmed response, if response was confirmed by a subsequent imaging assessment, as per RECIST criteria.
- j) AEs were to be recorded regardless of seriousness and relationship with study treatment. Whenever possible, symptoms were to be reported as a single syndrome or diagnosis. Laboratory abnormalities were to be recorded as AE only if they were serious, and/or if they led to study treatment modification (dose reduction, cycle delay, infusion temporarily interrupted), or study treatment discontinuation. Signs/symptoms that were present, or occurred, from the time the patient signed the ICF to first study drug administration were to be recorded as AEs, at cycle 1, with actual starting date of the event, if present at the time of first administration of study treatment. SAEs were to be recorded from the time the patient signed the informed consent. During the treatment period AEs were to be collected at each visit up to the 30-day FU visit. During the FU period –ie, after the 30-day FU visit–, only related ongoing, or new related, AEs were to be recorded. SAEs, regardless of relationship with study treatment, ongoing at the end of study treatment, were to be followed during the FU period until resolution or stabilization.
- k) Including hematology (hemoglobin, WBC, ANC, platelet count), biochemistry (sodium, chloride, potassium, magnesium, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, total bilirubin, total protein, albumin.
- l) Urinalysis: dipstick (WBC, RBC); urinary protein, urinary creatinine and UPCR were to be calculated on morning urine spot. During study treatment, 24-hour urine collection was to be performed to quantify proteinuria when UPCR >1; in case UPCR >2 or in case a proteinuria from renal origin (according to urine protein electrophoresis) was associated with hematuria then LDH, haptoglobin, schistocytes and orosomucoid were to be measured in blood.
- m) Patients under Vitamin K antagonist therapy only: prothrombin time (expressed as international normalized ratio).
- n) Serum or urine β -hCG levels were to be measured for women of reproductive potential within 8 days of randomization
- o) Prospective evaluation of immunogenicity was to be performed in all randomized and treated patients. Serum for detection of anti-aflibercept antibodies was to be collected before infusion of aflibercept/placebo for cycle 1, then before infusion of aflibercept/placebo of each odd-numbered cycle during the treatment period, and finally 30 ± 3 days and 90 ± 7 days after the last administration of aflibercept/placebo. Simultaneously, circulating free and bound aflibercept were to be measured (see footnote p). Note that event driven evaluations were to be performed in addition to the prospective evaluation (see Section 6.3.3.3).
- p) Pharmacokinetics evaluation: in addition to measurements of free aflibercept and bound aflibercept that were performed for the prospective immunogenicity evaluation, patients were to have one additional blood sample collected at the end of infusion of aflibercept/placebo for cycle 1 for peak measurement of free and bound aflibercept.
- q) Endogenous VEGF level was to be assessed on day 1 of cycle 1 in all patients that were randomized at study sites that were equipped with a 4°C centrifuge.

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Table 108 - VELOUR: Sanofi OS analysis excluding site 036007

Time to Event or Censoring	Placebo/Folfiri (N=606)	Aflibercept/Folfiri (N=597)
Overall		
Number of death events, n/N(%)	453/606 (74.8%)	394/597 (66.0%)
25% quantile overall survival (95.34% CI) (months)	6.83 (6.275 to 7.589)	7.69 (6.538 to 8.476)
Median overall survival (95.34% CI) (months)	12.06 (11.039 to 13.076)	13.50 (12.485 to 14.850)
75% quantile overall survival (95.34% CI) (months)	21.42 (19.154 to 22.998)	25.59 (21.947 to 31.704)
Number of patients at risk		
3 months	565	551
6 months	480	484
9 months	396	405
12 months	281	303
18 months	129	143
24 months	51	72
27 months	31	48
30 months	14	33
Survival probability (95.34% CI)		
3 months	0.934 (0.914 to 0.954)	0.929 (0.908 to 0.950)
6 months	0.793 (0.761 to 0.826)	0.816 (0.785 to 0.848)
9 months	0.655 (0.616 to 0.693)	0.686 (0.648 to 0.724)
12 months	0.501 (0.460 to 0.542)	0.561 (0.520 to 0.601)
18 months	0.310 (0.270 to 0.350)	0.382 (0.339 to 0.424)
24 months	0.190 (0.151 to 0.228)	0.277 (0.233 to 0.321)
27 months	0.160 (0.122 to 0.199)	0.238 (0.194 to 0.283)
30 months	0.122 (0.081 to 0.162)	0.223 (0.177 to 0.268)
Stratified Log-Rank test p-value ^a vs Placebo/Folfiri	-	0.0047
Stratified Hazard ratio (95.34% CI) ^a vs Placebo/Folfiri	-	0.822 (0.716 to 0.944)

Table 109 - VELOUR: Sanofi PFS analysis excluding site 036007

Time to Event or Censoring	Placebo/Folfiri (N=606)	Aflibercept/Folfiri (N=597)
Overall		
Number of events, n/N(%)	447/606 (73.8%)	383/597 (64.2%)
Median PFS (99.99% CI) (months)	4.70 (4.074 to 5.684)	6.90 (5.848 to 8.049)
Number at risk		
3 months	350	408
6 months	169	238
9 months	93	97
12 months	45	41
18 months	9	6
Probability of surviving (99.99% CI)		
3 months	0.664 (0.587 to 0.742)	0.791 (0.724 to 0.859)
6 months	0.393 (0.308 to 0.478)	0.570 (0.483 to 0.657)
9 months	0.256 (0.175 to 0.337)	0.315 (0.223 to 0.408)
12 months	0.146 (0.075 to 0.216)	0.164 (0.082 to 0.245)
18 months	0.043 (0.000 to 0.091)	0.045 (0.000 to 0.101)
Stratified Log-Rank test p-value ^a vs Placebo/Folfiri	-	0.00019
Stratified Hazard ratio (99.99% CI) ^a vs Placebo/Folfiri	-	0.769 (0.584 to 1.012)
Cutoff date = 6 MAY 2010		

Table 110 - VELOUR: Radiotherapy received before randomization (ITT population)

Radiotherapy site	Placebo/FOLFIRI	Aflibercept/FOLFIRI
ABDOMEN	1	2
BLADDER	1	0
BONE	12	9
BRAIN / CNS	0	1
COLON	2	0
COLON / RECTUM	6	10
HEAD / NECK	1	2
ILIAC CREST	1	0
LEFT LUNG	1	1
LIVER	8	7
LUNGS	1	0
LYMPH NODES - INGUINAL	0	1
LYMPH NODES - INTRA ABDOMINAL	1	1
LYMPH NODES - PARA AORTIC	0	1
LYMPH NODES - REGIONAL	1	3
MEDIASTINUM	0	1

OTHER	1	3
PELVIS	57	40
PERITONEUM	0	1
RECTO SIGMOID	3	2
RECTUM	51	60
SKIN	0	1
THORAX	3	1

Table 111 - VELOUR: Listing of randomized patients with erroneous IVRS "prior bevacizumab" strata

Placebo/FOLFIRI	Aflibercept/FOLFIRI
152001009	203001019
203001015	203001025
203002007	203001030
36003011	203001032
56001003	203001038
56003014	203002008
56003015	36003002
56003029	36004006
56004009	56003018
56004012	56003023
56004015	56003026
616004006	56003027
616007008	56004001
642004002	56004013
710004009	56006006
76004001	616006006
826005009	76004002
826011004	76004003
840017004	76004004
	76004007
	804006004
	826005010
	840014003
	840094001

Table 112 - VELOUR: Listing of randomized patients with erroneous IVRS "no prior bevacizumab" strata

Placebo/FOLFIRI	Aflibercept/FOLFIRI
208003006	203001036
36007013	300002002
380002006	300005004
76001009	36005010
840001001	528002003
840006002	76006001
840006010	840012001
840044001	
840047001	

Table 113 - VELOUR: Listing of randomized patients with erroneous IVRS ECOG status strata

Error	Placebo	Aflibercept
IVRS ECOG=0, CRF ECOG≠0	724001004 724001007 724001008 724007003	528001011 56004004 616001008 643004001 724001010 724002003 826004006 840010002
IVRS ECOG=1, CRF ECOG≠1	56003003 56003005 56003012 56003014 710004008 724003002 840084002	203001002 203001018 203001036 578003004 710005001 826005001 840006007 840072002 840096001
IVRS ECOG=2, CRF ECOG≠2	724002001 826009011	

Table 114 - VELOUR: Medical/Surgical pre-existing conditions (by SOC, ITT population)

SOC	Placebo/FOLFIRI (n, %) N=614	Aflibercept/FOLFIRI (n, %) N=612
# Patients with pre-existing conditions	538 (88)	513 (84)
Blood and lymphatic system disorders	41 (7)	26 (4)
Cardiac disorders	6 (1)	2 (<1)
Congenital, familial and genetic disorders	6 (1)	10 (2)
Ear and labyrinth disorders	14 (2)	13 (2)
Endocrine disorders	35 (6)	31 (5)
Eye disorders	28 (5)	24 (4)
Gastrointestinal disorders	240 (39)	231 (38)
General disorders and administration site conditions	101 (16)	88 (14)
Hepatobiliary disorders	40 (7)	38 (6)
Immune system disorders	21 (3)	31 (5)
Infections and infestations	82 (13)	75 (12)
Injury, poisoning and procedural complications	33 (5)	51 (8)
Investigations	27 (4)	24 (4)
Metabolism and nutrition disorders	47 (8)	38 (6)
Musculoskeletal and connective tissue disorders	120 (20)	126 (21)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	64 (10)	49 (8)
Nervous system disorders	208 (34)	186 (30)
Pregnancy, puerperium and perinatal conditions	4 (<1)	1 (<1)
Psychiatric disorders	92 (15)	82 (13)

Renal and urinary disorders	64 (10)	65 (11)
Reproductive system and breast disorders	56 (9)	57 (9)
Respiratory, thoracic and mediastinal disorders	94 (15)	96 (16)
Skin and subcutaneous tissue disorders	44 (7)	37 (6)
Social circumstances	5 (1)	7 (1)
Surgical and medical procedures	289 (47)	274 (45)
Vascular disorders	20 (3)	15 (2)

Table 115 - VELOUR: Concomitant use of non-cancer drugs at baseline (by therapeutic drug class, ITT population)

Therapeutic class	Placebo/FOLFIRI (n=614)		Aflibercept/FOLFIRI (n=612)	
	N	%	N	%
ANALGESICS	257	42	233	38
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	165	27	169	28
DRUGS FOR ACID RELATED DISORDERS	145	24	161	26
OPHTHALMOLOGICALS	110	18	129	21
PSYCHOLEPTICS	122	20	111	18
STOMATOLOGICAL PREPARATIONS	114	19	110	18
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	114	19	110	18
ANTITHROMBOTIC AGENTS	96	16	108	18
BETA BLOCKING AGENTS	98	16	99	16
CALCIUM CHANNEL BLOCKERS	89	14	90	15
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	76	12	85	14
LIPID MODIFYING AGENTS	75	12	75	12
VITAMINS	69	11	71	12
ANTI-ACNE PREPARATIONS	60	10	59	10
PSYCHOANALEPTICS	59	10	64	10
ANTIDIARR.,INTEST. ANTIINFL./ANTIINFECT. AGENTS	66	11	56	9
DRUGS USED IN DIABETES	68	11	57	9
CARDIAC THERAPY	57	9	53	9
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	58	9	58	9
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	44	7	54	9
NASAL PREPARATIONS	39	6	55	9
LAXATIVES	88	14	52	8
DIURETICS	65	11	48	8
CORTICOSTEROIDS FOR SYSTEMIC USE	46	7	51	8
VASOPROTECTIVES	41	7	52	8
MINERAL SUPPLEMENTS	49	8	43	7
ANTIBACTERIALS FOR SYSTEMIC USE	40	7	43	7
OTOLOGICALS	43	7	44	7
ANTIEMETICS AND ANTINAUSEANTS	48	8	37	6
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	36	6	37	6

OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS	39	6	36	6
OTHER GYNECOLOGICALS	35	6	34	6
ANTIHISTAMINES FOR SYSTEMIC USE	23	4	38	6
ANTIANEMIC PREPARATIONS	34	6	33	5
ANTIEPILEPTICS	36	6	33	5
UROLOGICALS	39	6	31	5
THYROID THERAPY	33	5	29	5
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	23	4	29	5
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	15	2	28	5
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	31	5	25	4
COUGH AND COLD PREPARATIONS	28	5	23	4
ALL OTHER THERAPEUTIC PRODUCTS	21	3	23	4
ANESTHETICS	26	4	19	3
OTHER DERMATOLOGICAL PREPARATIONS	24	4	17	3
ANTIBIOTICS AND CHEMOTHER. FOR DERMATOLOGICAL USE	15	2	17	3
ANTI-PRURITICS, INCL. ANTIHIST., ANESTHET., ETC.	10	2	16	3
ENDOCRINE THERAPY	11	2	16	3
OTHER NERVOUS SYSTEM DRUGS	13	2	18	3
ANTIGOUT PREPARATIONS	16	3	10	2
UNSPECIFIED HERBAL	18	3	14	2
ANTI-HYPERTENSIVES	15	2	11	2
EMOLLIENTS AND PROTECTIVES	12	2	12	2
ANTI-PARKINSON DRUGS	7	1	11	2
APPETITE STIMULANTS	5	1	10	2
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	6	1	10	2
THROAT PREPARATIONS	9	1	10	2
ANTIFUNGALS FOR DERMATOLOGICAL USE	5	1	7	1
ANTIMYCOTICS FOR SYSTEMIC USE	4	1	6	1
ANTISEPTICS AND DISINFECTANTS	7	1	8	1
BILE AND LIVER THERAPY	4	1	6	1
DIGESTIVES, INCL. ENZYMES	5	1	6	1
DRUGS FOR TREATMENT OF BONE DISEASES	7	1	7	1
ECTOPARASITICID., INCL. SCABICID., INSECT. AND REPELL.	4	1	4	1
GENERAL NUTRIENTS	4	1	6	1
MUSCLE RELAXANTS	5	1	6	1
ANTI-PROTOZOALS	2	0	5	1
CONTRAST MEDIA	2	0	6	1
MEDICATED DRESSINGS	3	0	4	1
PERIPHERAL VASODILATORS	3	0	6	1
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	2	0	6	1
ANTIVIRALS FOR SYSTEMIC USE	4	1	2	0

TONICS	4	1	0	0
	1	0	0	0
ALL OTHER NON-THERAPEUTIC PRODUCTS	2	0	2	0
ANABOLIC AGENTS FOR SYSTEMIC USE	0	0	1	0
ANTHELMINTICS	1	0	0	0
ANTIHEMORRHAGICS	1	0	2	0
ANTIMYCOBACTERIALS	0	0	1	0
ANTINEOPLASTIC AGENTS	1	0	3	0
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	3	0	3	0
DIAGNOSTIC AGENTS	2	0	2	0
IMMUNOSTIMULANTS	2	0	2	0
IMMUNOSUPPRESSANTS	1	0	0	0
OTHER DRUGS FOR DISORD. OF THE MUSCULO-SKELET.SYST	1	0	3	0
OTHER HEMATOLOGICAL AGENTS	1	0	0	0
OTHER RESPIRATORY SYSTEM PRODUCTS	2	0	1	0
PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES	1	0	3	0
VACCINES	2	0	1	0

Table 116 - VELOUR: AEs (all Grades) by PT with an incidence of 2-4%

PT	Placebo/FOLFIRI N=605		Aflibercept/FOLFIRI N=611	
	N	%	N	%
LACRIMATION INCREASED	26	4	24	4
UPPER RESPIRATORY TRACT INFECTION	22	4	23	4
PARAESTHESIA	25	4	23	4
MUSCULOSKELETAL PAIN	19	3	27	4
MYALGIA	20	3	27	4
PERIPHERAL SENSORY NEUROPATHY	18	3	22	4
FEBRILE NEUTROPENIA	10	2	26	4
THROMBOCYTOPENIA	15	2	25	4
FLATULENCE	15	2	22	4
DISEASE PROGRESSION	17	3	19	3
ANAEMIA	18	3	20	3
DRY MOUTH	21	3	20	3
RHINITIS	16	3	18	3
DRY SKIN	16	3	19	3
DEEP VEIN THROMBOSIS	13	2	18	3
DYSPHAGIA	10	2	16	3
CHILLS	11	2	16	3
INFLUENZA	12	2	20	3
BONE PAIN	12	2	21	3
ANXIETY	15	2	17	3
DEPRESSION	13	2	16	3
DYSURIA	15	2	19	3
HYPOTENSION	11	2	18	3
PNEUMONIA	9	1	21	3

	Placebo/FOLFIRI N=605		Aflibercept/FOLFIRI N=611	
MOUTH ULCERATION	9	1	21	3
TOOTHACHE	5	1	19	3
LOWER RESPIRATORY TRACT INFECTION	16	3	12	2
CHOLINERGIC SYNDROME	20	3	11	2
HAEMATURIA	18	3	10	2
INTESTINAL OBSTRUCTION	12	2	10	2
ASCITES	13	2	13	2
DEVICE RELATED INFECTION	15	2	12	2
NEUTROPHIL COUNT DECREASED	10	2	13	2
CONJUNCTIVITIS	10	2	13	2
GASTROESOPHAGEAL REFLUX DISEASE	13	2	11	2
ORAL CANDIDIASIS	10	2	12	2
PAIN	13	2	11	2
HYPERSENSITIVITY	15	2	11	2
ORAL CANDIDIASIS	10	2	12	2
POLYNEUROPATHY	10	2	11	2
PRODUCTIVE COUGH	11	2	12	2
PRURITUS	12	2	11	2
PHLEBITIS SUPERFICIAL	10	2	13	2
NEUTROPENIC INFECTION	8	1	11	2
SYNCOPE	9	1	10	2
VISION BLURRED	9	1	12	2
ORAL PAIN	6	1	14	2
INFLUENZA LIKE ILLNESS	7	1	11	2
NON-CARDIAC CHEST PAIN	8	1	15	2
BRONCHITIS	8	1	15	2
CYSTITIS	9	1	13	2
SINUSITIS	4	1	10	2
NECK PAIN	8	1	14	2
CONFUSIONAL STATE	9	1	10	2
NAIL DISORDER	9	1	11	2
HAEMOPTYSIS	1	0	10	2
ABDOMINAL DISCOMFORT	2	0	11	2
ANAL FISSURE	3	0	12	2
OESOPHAGITIS	2	0	10	2
PHARYNGITIS	2	0	11	2
POST PROCEDURAL HAEMORRHAGE	2	0	10	2
URINE PROTEIN/CREATININE RATIO INCREASED	0	0	10	2
ABDOMINAL DISTENSION	16	3	7	1
MUSCLE SPASMS	20	3	9	1
LEUKOPENIA	14	2	9	1
DYSPNOEA EXERTIONAL	10	2	9	1
ABDOMINAL PAIN LOWER	10	2	9	1
SALIVARY HYPERSECRETION	11	2	8	1
FALL	13	2	6	1
MUSCULOSKELETAL CHEST PAIN	13	2	7	1

Table 117 - VELOUR: Urinalysis abnormalities, safety population (copied from the submission)

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Proteinuria (morning spot or 24H) [n/N(%)]		
N	579	584
Grade 1	199/579 (34.4%)	219/584 (37.5%)
Grade 2	41/579 (7.1%)	113/584 (19.3%)
Grade ≥3	7/579 (1.2%)	50/584 (8.6%)
UPCR [n/N(%)]		
N	575	582
[0-1]	535/575 (93.0%)	449/582 (77.1%)
[1-2]	29/575 (5.0%)	68/582 (11.7%)
[2-3]	6/575 (1.0%)	39/582 (6.7%)
>3	5/575 (0.9%)	26/582 (4.5%)
Dipstick RBC [n/N(%)]		
N	586	586
+	118/586 (20.1%)	153/586 (26.1%)
++	58/586 (9.9%)	47/586 (8.0%)
+++	50/586 (8.5%)	55/586 (9.4%)
Dipstick WBC [n/N(%)]		
N	586	586
+	139/586 (23.7%)	138/586 (23.5%)
++	56/586 (9.6%)	55/586 (9.4%)
+++	60/586 (10.2%)	79/586 (13.5%)

Table 118 - VELOUR: SMQs

<i>SMQ (Narrow Search)</i>	<i>Placebo/FOLFIRI (N=605)</i>			<i>Aflibercept/FOLFIRI (N=611)</i>		
	<i>Events</i>	<i># pts</i>	<i>(%)</i>	<i>Events</i>	<i># pts</i>	<i>(%)</i>
(1) Acute renal failure	1	1	0.17	8	8	1.31
(3) Bradyarrhythmias (incl conduction defects and disorders of sinus node function) *	0	0	0	6	6	0.98
(2) Gingival disorders *	26	4	0.66	120	25	4.09
(4) Disorders of sinus node function *	0	0	0	5	5	0.82
(1) Hypertension *	132	65	10.74	1035	253	41.41
(3) Ischaemic cerebrovascular conditions *	0	0	0	8	4	0.65
(1) Shock	1	1	0.17	7	5	0.82
(3) Gallbladder related disorders *	1	1	0.17	15	5	0.82
(2) Embolic and thrombotic events, arterial *	3	2	0.33	22	8	1.31
(1) Severe cutaneous adverse reactions	0	0	0	8	3	0.49
(2) Haemorrhage laboratory terms	0	0	0	5	3	0.49
(2) Myocardial infarction	0	0	0	6	3	0.49

(1) Cerebrovascular disorders	2	1	0.17	8	4	0.65
(2) Central nervous system haemorrhages and cerebrovascular conditions	2	1	0.17	8	4	0.65
(2) Parkinson-like events	1	1	0.17	42	4	0.65
(1) Hyponatraemia/SIADH	0	0	0	9	3	0.49
(2) Infectious biliary disorders *	2	2	0.33	8	6	0.98
(1) Extravasation events (injections, infusions and implants)	8	2	0.33	19	6	0.98
(1) Cardiac failure	0	0	0	3	2	0.33
(1) Asthma/bronchospasm	2	1	0.17	6	3	0.49
(2) Cytopenia and haematopoietic disorders affecting more than one type of blood cell	0	0	0	2	2	0.33
(2) Toxic-septic shock conditions	1	1	0.17	5	3	0.49
(1) Convulsions	0	0	0	2	2	0.33
(1) Pseudomembranous colitis	0	0	0	2	2	0.33
(1) Pulmonary hypertension	0	0	0	4	2	0.33
(1) Osteonecrosis	0	0	0	16	2	0.33
(1) Cardiac arrhythmias	6	5	0.83	14	14	2.29
(2) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	6	5	0.83	14	14	2.29
(1) Angioedema	61	7	1.16	147	18	2.95
(1) Haemorrhages	607	115	19.01	2408	231	37.81
(2) Haemorrhage terms (excl laboratory terms) *	607	115	19.01	2407	230	37.64
(2) Gastrointestinal ulceration *	14	4	0.66	23	10	1.64
(2) Gastrointestinal perforation *	11	7	1.16	75	17	2.78
(1) Oropharyngeal disorders *	1093	232	38.35	2407	364	59.57
(1) Agranulocytosis	40	18	2.98	96	41	6.71
(1) Periorbital and eyelid disorders *	15	3	0.5	24	7	1.15
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	941	222	36.69	2131	349	57.12
(1) Torsade de pointes/QT prolongation	0	0	0	1	1	0.16
(1) Rhabdomyolysis/myopathy	6	1	0.17	12	2	0.33
(4) Liver neoplasms, benign (incl cysts and polyps) *	0	0	0	8	1	0.16
(1) Dyslipidaemia *	0	0	0	18	1	0.16
(4) Conduction defects *	0	0	0	1	1	0.16
(4) Ventricular tachyarrhythmias	0	0	0	1	1	0.16
(2) Torsade de pointes, shock-associated conditions	1	1	0.17	2	2	0.33
(2) Hypovolaemic shock conditions	1	1	0.17	2	2	0.33
(1) Acute central respiratory depression	1	1	0.17	2	2	0.33
(1) Psychosis and psychotic disorders	1	1	0.17	2	2	0.33
(1) Noninfectious meningitis	24	1	0.17	48	2	0.33
(1) Ischaemic colitis	2	1	0.17	4	2	0.33
(1) Renovascular disorders	4	1	0.17	6	2	0.33

(2) Gastrointestinal haemorrhage *	84	30	4.96	255	56	9.17
(2) Hearing impairment	14	4	0.66	42	7	1.15
(1) Extrapyrimal syndrome	7	3	0.5	48	5	0.82
(1) Gastrointestinal perforation, ulceration, haemorrhage or obstruction	131	59	9.75	386	92	15.06
(2) Oropharyngeal infections *	114	24	3.97	150	38	6.22
(3) Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias)	6	5	0.83	8	8	1.31
(2) Thrombocytopenia	51	17	2.81	49	26	4.26
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	4905	498	82.31	5288	536	87.73
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	5115	501	82.81	5599	538	88.05
(2) Gastrointestinal nonspecific inflammation	39	14	2.31	77	21	3.44
(1) Hyperglycaemia/new onset diabetes mellitus	68	4	0.66	94	6	0.98
(2) Oropharyngeal allergic conditions *	12	2	0.33	6	3	0.49
(1) Embolic and thrombotic events	204	45	7.44	327	62	10.15
(4) Supraventricular tachyarrhythmias	6	5	0.83	7	7	1.15
(1) Taste and smell disorders *	382	37	6.12	666	48	7.86
(1) Conjunctival disorders *	34	13	2.15	44	17	2.78
(2) Embolic and thrombotic events, venous *	201	44	7.27	305	55	9
(1) Haematopoietic cytopenias	611	232	38.35	742	268	43.86
(1) Depression and suicide/self-injury	86	16	2.64	73	20	3.27
(2) Depression (excl suicide and self injury)	86	16	2.64	73	20	3.27
(1) Haemodynamic oedema, effusions and fluid overload *	516	62	10.25	831	76	12.44
(1) Hearing and vestibular disorders	38	12	1.98	88	15	2.45
(3) Bile duct related disorders *	7	4	0.66	5	5	0.82
(2) Leukopenia	560	228	37.69	691	260	42.55
(1) Peripheral neuropathy	286	59	9.75	478	70	11.46
(1) Accidents and injuries	153	32	5.29	210	36	5.89
(4) Hepatitis, non-infectious	1	1	0.17	2	1	0.16
(1) Haemolytic disorders	1	1	0.17	5	1	0.16
(1) Anaphylactic reaction	1	1	0.17	1	1	0.16
(1) Ischaemic heart disease	34	8	1.32	26	8	1.31
(3) Haemorrhagic cerebrovascular conditions *	2	1	0.17	2	1	0.16
(2) Shock-associated circulatory or cardiac conditions (excl torsade de pointes)	1	1	0.17	1	1	0.16
(2) Anaphylactic/anaphylactoid shock conditions	1	1	0.17	1	1	0.16
(2) Hypoglycaemic and neurogenic shock conditions	1	1	0.17	1	1	0.16
(1) Biliary disorders	58	18	2.98	43	18	2.95
(1) Noninfectious encephalopathy/delirium	2	2	0.33	3	2	0.33
(1) Corneal disorders	1	1	0.17	3	1	0.16

(1) Eosinophilic pneumonia	1	1	0.17	1	1	0.16
(2) Vestibular disorders	24	8	1.32	46	8	1.31
(3) Liver related investigations, signs and symptoms	126	39	6.45	139	39	6.38
(1) Lacrimal disorders *	208	29	4.79	193	28	4.58
(2) Gastrointestinal obstruction *	23	21	3.47	36	20	3.27
(2) Functional, inflammatory and gallstone related biliary disorders	58	18	2.98	41	17	2.78
(3) Drug related hepatic disorders - severe events only	52	16	2.64	82	15	2.45
(1) Hepatic disorders	136	46	7.6	156	43	7.04
(2) Drug related hepatic disorders - comprehensive search	136	46	7.6	156	43	7.04
(2) Gastrointestinal nonspecific dysfunction	171	67	11.07	234	60	9.82
(4) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	51	15	2.48	72	13	2.13
(2) Malignancy related conditions *	50	13	2.15	19	11	1.8
(1) Malignancies *	57	16	2.64	25	13	2.13
(1) Thrombophlebitis	4	4	0.66	11	3	0.49
(2) Malignant or unspecified tumours *	6	3	0.5	6	2	0.33
(3) Cholestasis and jaundice of hepatic origin	45	11	1.82	21	7	1.15
(3) Site unspecified biliary disorders *	45	11	1.82	21	7	1.15
(2) Other ischaemic heart disease	34	8	1.32	20	5	0.82
(3) Liver-related coagulation and bleeding disturbances *	3	2	0.33	1	1	0.16
(1) Acute pancreatitis	2	1	0.17	0	0	0
(1) Systemic lupus erythematosus	9	1	0.17	0	0	0
(2) Tumour markers *	1	1	0.17	0	0	0
(2) Dystonia	6	2	0.33	6	1	0.16
(1) Skin neoplasms, malignant and unspecified	2	1	0.17	0	0	0
(1) Interstitial lung disease	9	4	0.66	2	2	0.33
(3) Biliary system related investigations, signs and symptoms	49	14	2.31	21	7	1.15
(1) Retroperitoneal fibrosis	18	7	1.16	4	3	0.49
(1) Lens disorders	28	2	0.33	0	0	0
(1) Retinal disorders	18	5	0.83	20	1	0.16

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

/s/

SANDRA J CASAK
07/05/2012

STEVEN J LEMERY
07/05/2012

I agree with primary recommendations of the clinical review. Also refer to the secondary CDTL review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125418

Applicant: sanofi aventis

Stamp Date: February 3, 2012

Drug Name: Aflibercept

NDA/BLA Type:

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA - 351(a)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Not needed, single dose proposed.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 EFC10262 (VELOUR): A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer (MCRC)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Treated with Irinotecan / 5-FU Combination (FOLFIRI) after failure of an oxaliplatin based regimen. Indication: Aflibercept is indicated in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				Adequacy to be determined by the clin/pharm team
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver request.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Not relevant
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Sandra J. Casak	03/28/2012
Reviewing Medical Officer	Date
Steven J. Lemery	03/28/2012
Clinical Team Leader	Date

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

/s/

SANDRA J CASAK
03/29/2012

STEVEN J LEMERY
03/30/2012