Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Aflibercept *rch*

Proprietary Product Name: Zaltrap/Aflitiv/Lidaveg

Sponsor: Sanofi-Aventis Australia Pty Ltd

Date of CER: 28 June 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. List of abbreviations

Abbreviation	Meaning
ADR	adverse drug reaction
AE(s)	adverse event(s)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATE	arterial thromboembolic event
BSA	body surface area
BUN	Blood urea nitrogen
CI	confidence interval
CR	Complete response
CRF(s)	case report form(s)
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	electronic case report form
ELISA	enzyme linked immunosorbent assay
EP	evaluable population

Abbreviation	Meaning
FDA	Food and Drug Administration
FOLFIRI	Irinotecan/bolus-infusion-5-Fluorouracil/Leucovorin
folfiri	Irinotecan/bolus-infusion-5-Fluorouracil/Leucovorin
G-CSF	Granulocyte colony stimulating factor
HLT	high level term
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IP	investigational product
IRB	Institutional review boards
IRC	independent review committee
ITT	intent-to-treat
IV	intravenous
iv	intravenous
IVRS	interactive voice response system
LDH	Lactate dehydrogenase
LOQ	limit of quantification
LV	Leucovorin
MCRC	metastatic colorectal cancer, metastatic colorectal cancer
MedDRA	medical dictionary for regulatory activities
NCI	National Cancer Institute
NCI-CTCAE	national cancer institute common terminology criteria for adverse events
NE	Not evaluable
ORR	objective response rate

Abbreviation	Meaning
OS	Overall survival
PCSA	potentially clinically significant abnormality
PD	Progressive disease
PFS	progression free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RR	response rate
SAE(s)	serious adverse event(s)
SAP	Statistical analysis plan
SD	Stable disease
SD	standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse events
ULN	upper limit of normal
UPCR	Urine protein-creatinine ratio
VEGF	Vascular endothelial growth factor
VTE	venous thromboembolic event
WBC	White blood cell
WHO	World Health Organization

2. Clinical rationale

The sponsor's covering letter states that aflibercept "has demonstrated antitumor and antiangiogenic activity as a single-agent and in combination with various chemotherapies in a variety of tumor models". It also states that aflibercept "provides an important novel

therapeutic option for patients with MCRC who have received prior oxaliplatin-based chemotherapy, and is the only targeted agent that has demonstrated an OS benefit in this setting".

Comment: The sponsor's clinical rationale is acceptable. Colorectal cancer is a major health concern in Australia. Bowel cancer (which includes cancers of the colon, the rectosigmoid junction, and the rectum) is the second most common cancer diagnosed in males (after prostate cancer) and in females (after breast cancer). The risk of bowel cancer is relatively rare in persons aged less than 45 years, but increases sharply with age in patients aged 45 years and over (AIHW, 2010). In 2007, the risk of developing bowel cancer was 1 in 26 to age 75, and 1 in 12 to age 85 (AIHW, 2010). During the 26 year period from 1982-2007 the incidence of bowel cancer in Australia increased in males and remained relatively constant in females. In 1982 the age-standardised incidence rates were 67 males and 50 females per 100,000 population compared with 75 males and 55 females per 100,000 population in 2007 (AIHW, 2010).

In 2007, bowel cancer accounted for 10% of all deaths from invasive cancer in Australia making it the second most common cause of death after lung cancer (AIHW and AACR, 2012). Approximately 25% of patients will have advanced disease at presentation and, in spite of locally effective surgery, another 25% of patients will relapse post-operatively (Clarke, 2002). While patients diagnosed with early-stage disease generally have a favourable prognosis, patients with distant metastatic disease (Stage IV) have very poor outcomes with only about 5% surviving 5 years (Harrison's, 16th Edition, 2005).

Guidance

There were no pre-submission meetings between the sponsor and the TGA for this application. The sponsor stated that that the application was consistent with the Pre-submission Planning Form lodged on 30 December 2011.

Contents of the clinical dossier

Scope of the clinical dossier

The submission included a complete data package provided to support the registration of the NCE aflibercept for the proposed indication. In addition to hard copies, the submission was also provided in electronic format (CD). The CD was comprehensive and facilitated evaluation of the large data package. The submission contained the following clinical information:

Module 5

16 clinical pharmacology studies, including 15 that provided pharmacokinetic data and 12 that provided pharmacodynamic data (including PK/PD analyses).

5 population pharmacokinetic analyses.

1 pivotal efficacy/safety study (VELOUR).

9 other supportive safety studies (with efficacy data relating to indications other than that being proposed).

additional tables and figures from the pivotal study to support the integrated Summary of Clinical Safety provided in Module 2.

12 bioanalytical and analytical method studies.

Module 1:

Electronic lodgement cover sheet, letter of application, comprehensive table of contents; application forms, medicine information documents and labelling (including proposed Australian PI and CMI, label mock-up and specimens), information about the experts, overseas

regulatory statement (including proposed European Summary of Product Characteristics), justification for not providing pharmaceutical studies, statement regarding no paediatric development plan, proposed Risk Management Plan for Australia.

Module 2:

Clinical Overview, Clinical Summary (including Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy, Summary of Clinical Safety), literature references, synopses of individual studies).

Paediatric data

The sponsor indicated that no paediatric development program is proposed for aflibercept, "since the intended indication for use in metastatic colorectal cancer is only relevant to an adult population".

This is acceptable.

Good clinical practice

The studies were performed in compliance with Good Clinical Practice.

3. Pharmacokinetics

3.1. Overview of studies providing pharmacokinetic data

3.1.1. Studies with PK data

3.1.1.1. Non-compartmental analysis (NCA)

The submission included PK data (NCA) following aflibercept iv from 2272 patients from 13, Phase 1 and 2 studies, and 3, Phase 3 clinical efficacy and safety studies (see Table 1, below). There were 2 additional studies with PK data following aflibercept administered subcutaneously (TED6113, TED6114), but these two studies have not been evaluated as the route of administration (sc) is not considered to be relevant to the proposed route (iv) of administration. None of the PK studies assessing aflibercept iv had deficiencies precluding them from evaluation.

Table 1: Summary of studies with pharmacokinetic data.

Study	Dose and Regimen	Subjects
PK – Phase 1 single-agent studies		
TED 6115	0.3, 1 to 5, 7 mg/kg IV q2w, and 4 mg/kg SC q2w	57: 47 (IV q2w), 10 (SC q2w)
TED 6116 (ext)	0.3, 1 to 5, 7 mg/kg IV q2w, and 4 mg/kg SC q2w	40: 36 (IV q2w), 4 (SC q2w)
PK and PK/PD – Phase 2 single-agent studies		
ARD6122	2 mg/kg and 4 mg/kg IV q2w	215
ARD6123	4 mg/kg IV q2w	96
ARD6772	4 mg/kg IV q2w	16

Study	Dose and Regimen	Subjects
EFC6125	4 mg/kg IV q2w	58
PK and PK/PD – Phase 1 combination studies		
TCD6117	FOLFOX4 - 2, 4, and 5 mg/kg IV q2w	32: 4, 18, 10
TCD6118	Irinotecan/LV5FU2 - 2, 4, 5, and 6 mg/kg IV q2w	65: 4, 39, 10, 12
TCD6120	Cohort 1: VT75 - 2, 4, 5, 6, 7, and 9 mg/kg IV q3w	54
	Cohort 2: VTC - 4, 5, and 6 mg/kg IV q3w	30
	Cohort 3: VT100 - 4, 5, and 6 mg/kg IV q3w	31
	Cohort 4: V-pemetrexed – 6 mg/kg IV q3w	19
TCD6119	TCF - 2, 4, and 6 mg/kg IVq3w	44: 9, 14, 21
TCD6121	Cohort 1: GV – 4 and 6 mg/kg IV q2w	32
	Cohort 2: GEV – 1, 2, and 4 mg/kg IV single dose	29
PK and PD – Phase 1 studies, single-agent, healthy subjects		
PDY6655	2 mg/kg IV or SC at 6 weeks interval	40 (20 per sequence)
PDY6656	1, 2, and 4 mg/kg IV single-dose	48 (36 aflibercept)
PK and PK/PD – Phase 3 combination studies		
VELOUR (MCRC)	FOLFIRI – 4 mg/kg IV q2w	1216 (611 aflibercept)
VANILLA (MPC)	Gemcitabine – 4 mg/kg IV q2w	541 (270 aflibercept)
VITAL (NSCLC)	Docetaxel – 6 mg/kg IV q3w	905 (452 aflibercept)

SC: subcutaneous; IV: intravenous; q2w: every 2 weeks; VT75: aflibercept + docetaxel 75 mg/m^2; VTC: aflibercept + docetaxel 75 mg/m^2 +cisplatin 75 mg/m^2; V-pemetrexed: aflibercept and pemetrexed 500

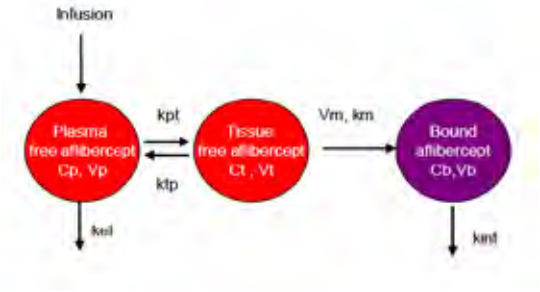
mg/m2; q3w: every 3 weeks; LV5FU2: 5 fluorouracil/leucovorin; MCRC = metastatic colorectal cancer; MPC = metastatic pancreatic cancer; NSCLC = non-small cell lung cancer.

3.1.1.2. Population pharmacokinetic data

The submission also included 5 population-pk studies. The population-pk model developed in healthy subjects (study POH0251) was used to model the PK data in the subsequent population-PK analyses in patients (POH0253/POH0263, POH0262, POH0274, POH0265). The population-pk analyses in patients were contained in sequential studies with each study building on the one preceding it. The data from the population-pk study in healthy subjects (POH0251) and in patients (POH0265/amendment 01) have been evaluated. However, the data from the 4 other population-pk studies in patients have not been evaluated in detail as the results were consistent with those from study POH0265. This is not surprising, given the considerable overlapping of data from shared studies in the population-pk analyses in patients. Relevant data from population-pk analyses in patients from studies POH0265 have been included in the body of the CER (The methodology, results, and conclusions for the population-pk analyses were extensively described in the study reports, and satisfied the relevant TGA adopted guideline for reporting the results of these types of analyses (CHMP/EWP/185990/06)).

In the population-pk analysis in healthy subjects (POH0251), the best structural model involved two compartments for free aflibercept and one for bound aflibercept, with Michaelis-Menten type binding of free aflibercept to VEGF from the peripheral compartment (see Figure 1, below). Free aflibercept in plasma distributes first to tissues and then binds to VEGF. Binding to VEGF follows the law of mass action characterized by non-linearity with Michaelis-Menten constants. Bound aflibercept is assumed to be directly eliminated through cellular internalization, and not through dissociation. The sponsor stated that the model developed in this study is the first mechanism-based population-pk model for an anti-VEGF drug.

Figure 1: Study POH0251 - Proposed structural model for free and bound aflibercept (2 compartments for free aflibercept in red, 1 compartment for bound aflibercept in purple) with binding to VEGF occurring in the peripheral compartment.



Cp = plasma concentration of free aflibercept; Cb = bound aflibercept concentration; Vp = central volume of distribution of free aflibercept; Vb = distribution volume of bound aflibercept; Vt = peripheral volume of distribution for free aflibercept; kel = first order elimination rate constant of free aflibercept from central compartment; ktp and kpt = first order tissue to plasma (tp) and plasma to tissue (pt) rate constants between central and peripheral compartments; kint= first order bound aflibercept internalization rate constant; Vm = maximum binding capacity; km = concentration of free aflibercept corresponding to half of maximum binding capacity.

3.1.1.3. Analyses of free and bound aflibercept

In order to characterize the PKs of aflibercept, two analytes were quantified in healthy subjects and in patients. These analytes were free aflibercept and pharmacologically inert bound aflibercept (VEGF:aflibercept complex in a ratio 1:1). Free aflibercept is available to bind to VEGF in the circulation and the tissues. The bound complex reflects the amount of VEGF produced in the body bound to aflibercept and presumably neutralized. The submission included 12 bioanalytical and analytical studies used to validate assay methods for the determination of free and bound aflibercept concentrations in human plasma samples, free endogenous VEGF concentrations in human plasma, and anti-aflibercept antibodies in human serum. Free and bound aflibercept in human plasma was quantified using validated enzyme-linked immunosorbent assays (ELISA) as was free VEGF. The limit of quantitation (LOQ) of free aflibercept in plasma was initially 31.3 ng/mL (for studies TED6115/TED6116) then lowered to 15.6 ng/mL for subsequent studies. The limit of quantitation of bound aflibercept was 31.5 ng/mL for all clinical studies.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated. The summary includes integrated data from healthy subjects and patients with cancer.

3.3. Overview - PK parameters in patients

The population-pk study in patients (POH0265), showed that the PKs of free aflibercept were best described by a two-compartment model, with inter-individual variability on clearance and volumes of distribution, and with combined residual error. In the final model typical clearance and central volume of distribution were 0.0425 L/h and 4.47 L respectively for a male subject. The terminal half-life was 139 hours (6 days). The study estimated the PKs for free aflibercept for a typical male patient based on the final model (see Table 2, below).

Table 2: Study POH0625 – PK parameters for free aflibercept in a typical patient.

	CL (L/h)	V_{ss} (L)	$t_{½z}$ (h)	Cycle 1			Steady State		
				Cmax (µg/mL)	Ctrough (µg/mL)	$AUC_{0-\tau}$ (µg*h/mL)	$Cmax_{ss}$ (µg/mL)	$Ctrough_{ss}$ (µg/mL)	AUC_{ss} (µg*h/mL)
4 mg/kg q2w	0.0425	7.77	139	59.1	5.33	5238	65.6	6.55	6306
6 mg/kg q3w				88.6	3.45	8766	92.4	3.76	9459

Typical patient: male 67 kg; normalized ALB 0.769; normalized ALK 0.816; normalized TP 0.866;CLCR 75.9= mL/min.
τ = 336h for 4 mg/kg q2 weeks and 504 h for 6 mg/kg q3 weeks

The pivotal Phase 3 efficacy and safety study was VELOUR [EFC10262]). In this study, aflibercept 4 mg/kg was administered in combination with FOLFIRI q2w to patients with metastatic colorectal cancer. The submission included PK data from this study, in addition to PK data from two other Phase 3 studies (VANILLA [EFC10547], and VITAL [EFC10261]). In these two additional Phase 3 studies, aflibercept was administered in combination with chemotherapeutic agents for metastatic pancreatic cancer (VANILLA) and locally advanced or metastatic non-small cell lung cancer (VITAL). PK results from the three Phase 3 studies are summarized below in Table 3.

Table 3: Summary of free and bound PK parameters (mean and CV%) in Phase 3 studies.

		Free aflibercept						Bound
Studies	N	Cmax (µg/mL)	AUC 0-τ [a] (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)	Vss (L)	t½z (day)	CLb (L/day)
VANILLA 4 mg/kg, q2w (+Gemcitabine)	204 176	68.9 (35) -	227 (21) -	280 (28) -	1.02 (27) -	7.45(16) -	5.98(32) -	- 0.189(10)
VITAL 6mg/kg, q3w (+Docetaxel)	370 326	101(17) -	428(28) -	498(49) -	0.955(28) -	7.62(18) -	6.82(55) -	- 0.186(10)
VELOUR 4 mgkg, q2w (+FOLFIRI)	500 460	67.4(19) -	245(20) -	302(25) -	1.04(33) -	7.76(14) -	6.04(27) -	- 0.179(11)

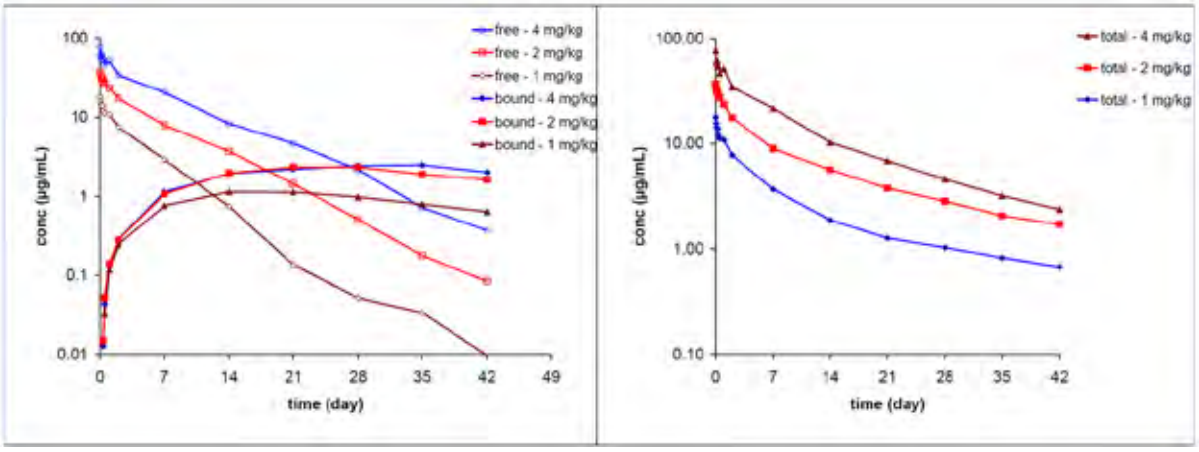
a : τ = 336h for 4 mg/kg q2 w and 504 h for 6 mg/kg q3w

Comment: The PKs of free and bound aflibercept were similar in VELOUR and VANILLA following administration of aflibercept 4 mg/kg q2w in combination with FOLFIRI and gemcitabine respectively. However, free aflibercept Cmax and AUC values were higher in VITAL following aflibercept 6 mg/kg q3w in combination with docetaxel. Bound aflibercept clearance was similar in the three studies despite differences in dosing schedule and combination chemotherapeutic agents. The PK parameters estimated in the population-pK analysis for a typical patient are consistent with those from the Phase 3 studies.

3.3.1. Concentration-time profiles following iv administration

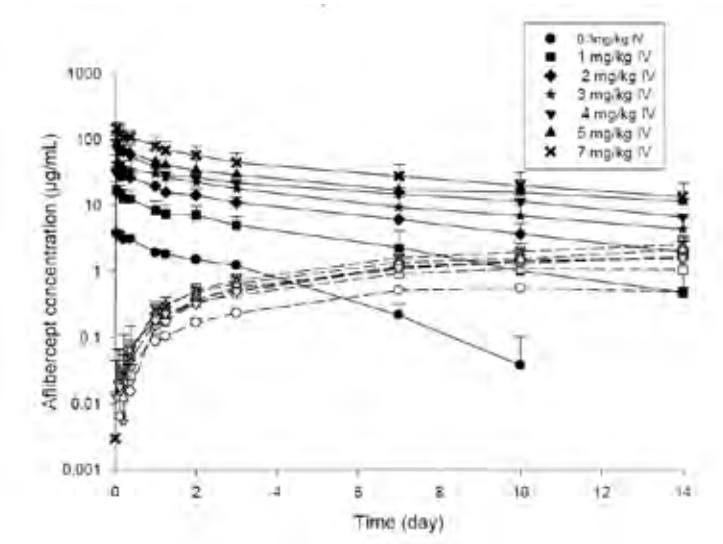
In healthy male subjects (study PDY6656), free aflibercept plasma concentration-time profiles were bi-phasic following single iv doses of aflibercept 1, 2, and 4 mg/kg with concentrations detectable up to 35 days in a majority of subjects at the 1 mg/kg dose and up to the last sampling time (42 days post-infusion) at the 2 and 4 mg/kg doses. The mean plasma concentration-time curves for free, bound, and total aflibercept from study 6656 following single aflibercept doses of 1, 2, and 4 mg/kg are provided below in Figure 2. The curves for bound aflibercept following 2 mg/kg and 4 mg/kg were superimposable, suggesting that binding is maximal at doses of ≥ 2 mg/kg. The curves for total aflibercept and free aflibercept were approximately dose proportional for doses of 1, 2, and 4 mg/kg. The PK parameters for free and bound aflibercept in healthy subjects from studies PDY6656 and PDY6655 are summarized in the dossier.

Figure 2: Study PDY6656 - aflibercept concentration-time profiles; free and unbound aflibercept (µg/mL) left-panel, and total aflibercept (µg/mL) right-panel.



In patients with relapsed or refractory solid tumours, or non-Hodgkin's lymphoma (study TED6115), free aflibercept plasma concentration time profiles following iv administration were also biphasic, with concentrations detectable up to 7 days in the patients treated at the lowest dose (0.3 mg/kg) and up to 14 days in all patients treated at higher doses (1 to 7 mg/kg). Free aflibercept was detectable at the end of the dosing period suggesting that all available endogenous VEGF was bound to aflibercept. The bound aflibercept plasma concentration time profiles suggest that maximal bound aflibercept concentrations were reached following doses ≥ 2g/kg, with no significant increases occurring at doses > 2 kg/kg. These results suggest that complete ligand binding occurs at doses ≥ 2.0 mg/kg. The mean plasma concentration-time curves (log-linear scale) for free and bound aflibercept by iv dose are provided below in Figure 3. The PK parameters for free and bound aflibercept in patients with cancer in study TED6115 are summarized in the dossier.

Figure 3: Study TED6115 - Mean (SD) free (solid lines) and bound (dotted lines) aflibercept PK profiles (log scale).



3.3.2. Absorption

The submission proposes that aflibercept be administered by iv infusion. Consequently, data relating to absorption and absolute bioavailability are not applicable.

Comment: The sponsor provided an acceptable justification for not providing an absolute bioavailability study. The sponsor stated that aflibercept "is intended for administration as an

intravenous infusion and therefore there is no requirement to provide absolute bioavailability study as it can be assumed to be 100% bioavailable. This is in accordance with the requirements of the *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM, June 2004) Appendix 15. No bioequivalence studies were submitted comparing clinical study formulations with the formulation proposed for marketing. However, from data provided in the submission it appears that the formulation used in the clinical studies is the same as that proposed for marketing. Two concentrations (nominal) are being proposed for approval (100 mg/4 mL and 200 mg/8 mL), and the sponsor indicates that both presentations are manufactured from the same bulk sterile solution (25 mg/mL). Consequently, the sponsor considered that no bioequivalence study comparing the two solution strengths were required.

3.3.3. Distribution

In patients, the population estimate of steady state volume of distribution (Vss) from the population-pk analysis was 7.77 L (study POH0265). This value is consistent with the mean (CV%) Vss of 7.76 L (14.1) in patients (n=500) from the pivotal efficacy and safety study (VELOUR).

Comment: The Vss is marginally greater than the estimated blood volume of about 5 L (equivalent to about 3 L of plasma) in a 70 kg person (Shargel and Yu, 1999). This suggests that aflibercept is not widely distributed to the tissues.

3.3.4. Metabolism

No metabolism studies were conducted. The sponsor states the expected metabolism of aflibercept and the VEGF: aflibercept complex is degradation to small peptides and individual amino-acids.

Comment: The sponsor's justification for not undertaking metabolism studies is acceptable. The relevant TGA adopted clinical guidelines relating to the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004) states that "the main elimination pathway should be identified. However, for therapeutic proteins this could be predicted, to a large extent, from the molecular size and specific studies may not be necessary". Aflibercept has a molecular weight of approximately 115,000 Daltons, and because of its large size would not be expected to undergo glomerular filtration. Consequently, it can be predicted that elimination mechanisms other than renal excretion are more important in the clearance of aflibercept (e.g., cellular internalization of the bound complex followed by catabolism).

3.3.5. Excretion

In cancer patients (TED6115), single iv dose data showed that mean free aflibercept clearance decreased from 1.95 L/day at a dose of 0.3 mg/kg to 1.13 L/day at a dose of 2 mg/kg, and then remained relatively stable over the dose range 2 to 7 mg/kg. In this study the elimination half-life increased from 1.7 days at a dose of 0.3 mg/kg to 6.2 days at a dose of 3 mg/kg and then stabilised at about 5.5 to 7.4 days over the dose range 3 to 7 mg/kg. Dose dependent clearance was also observed in healthy male subjects in study PDY6656. The sponsor states that the non-linear clearance of free aflibercept is explained by target-mediated drug disposition (TMDD)resulting from saturable binding of free aflibercept to endogenous VEGF.

The population-pk study in cancer patients (POH0625) showed that for a typical male patient treated with aflibercept 4 mg/kg, iv free aflibercept clearance was 1.02 L/day and terminal half-life was 5.8 days. These results are consistent with those from VELOUR that showed that in patients treated with aflibercept 4 mg/kg q2w (n=500) the mean (CV%) clearance was 1.04 (33) L/day, and the elimination half-life was about 6 (27) days.

The population-pk study in cancer patients (POH625) also showed that typical clearance values for free aflibercept were about 5-fold higher than for bound aflibercept (0.878 and 0.182 L/day, respectively). The maximum binding capacity was 0.761 mg/day, and the concentration of aflibercept corresponding to half the maximum binding capacity was 1.71 µg/mL. The data from

VELOUR for bound aflibercept clearance were consistent with that from the population-pk study and showed that mean unbound aflibercept clearance was about 6-fold greater than mean bound clearance (1.04 and 0.179 L/day, respectively). In study TED6115 (cancer patients), mean elimination half-life of bound aflibercept was 21.6±6.9 days (CV%=32) assessed in 14 patients (12 in the iv and 2 in the sc treatment group). In the population-pk study in healthy subjects (POH0251), the estimated terminal half-life for bound aflibercept was 25 days.

Comment: Free aflibercept showed non-linear clearance at doses less than 2 mg/kg (study TED6115), most likely due to binding with high affinity to endogenous VEGF until all the binding sites are occupied. The sponsor observes that the non-linear, dose-dependent clearance of aflibercept is consistent with TMDD. Drugs displaying TMDD bind with high affinity to their pharmacological target such that this interaction is reflected in the pharmacokinetic properties of the drug. Free aflibercept clearance was linear over the dose range 2 to 7 mg/kg (study TED6115), suggesting that once endogenous VEGF binding sites are fully occupied then free aflibercept undergoes non-saturable clearance presumably via catabolism. Based on population-pk modelling (study POH0251), the sponsor postulates that free aflibercept is eliminated through two pathways: non-saturable elimination from central compartment and saturable binding to VEGF, followed by internalization of bound aflibercept, which is the dominant elimination pathway.

3.3.6. Dose proportionality

In study TED6115 (cancer patients), dose proportionality of aflibercept administered as a single-agent was evaluated between doses of 0.3 to 7 mg/kg. In this study, free aflibercept (Cycle 1) as assessed by AUC_{inf} was more than dose proportional over the dose range 0.3 mg to 7 mg. Non-linearity was more marked over the lower dose range of 0.3 to 2 mg/kg than the higher dose range of 2 to 7 mg/kg. In study PDY6656 (healthy subjects), free aflibercept AUC_{inf} was also more than dose proportional over the dose range 1 to 4 mg/kg. In study TED6115 (cancer patients), bound aflibercept concentrations increased with dose between 0.3 and 2 mg/kg as assessed by AUC_{last}, then reached a plateau between 1 and 7 mg/kg, suggesting that free aflibercept was present in a sufficient amount to bind all endogenous VEGF at doses ≥ 2 mg/kg. The data from study TED6115 suggests that bound aflibercept concentrations are limited by VEGF levels.

3.3.7. Steady state and accumulation ratio

In study TED6116 (cancer patients), free aflibercept steady state trough concentrations measured throughout treatment in the q2w dosing schedule were similar to those measured after the first dose in the range 0.3 to 4.0 mg/kg iv (see Table 4, below). These results suggest that steady state free aflibercept was reached after the first dose. Significant accumulation of free aflibercept between baseline and steady state was not observed in the dose range 0.3 to 3 mg/kg iv, but accumulation from baseline to steady state (ratio 1.3 to 1.8) was noted for the higher dose range of 4 to 7 mg/kg iv. Free aflibercept trough concentrations increased with dose at baseline and steady state. Bound aflibercept steady state trough concentrations were reached between 1 and 2 months after the first infusion. Bound aflibercept steady state trough concentration increased in the dose range 0.3 to 1 mg/kg iv, then plateaued between 1 and 7 mg/kg iv. Moderate to high inter-individual variability (CV%) was observed in bound aflibercept steady state trough concentration in the dose range 1 to 7 mg/kg iv. As a consequence of the increase of free aflibercept concentrations with dose, and the plateau effect observed for bound aflibercept concentrations, the free/bound aflibercept ratio increased with dose. In the q2w schedule, free aflibercept concentrations were higher than bound aflibercept concentrations throughout treatment at doses ≥ 3 mg/kg.

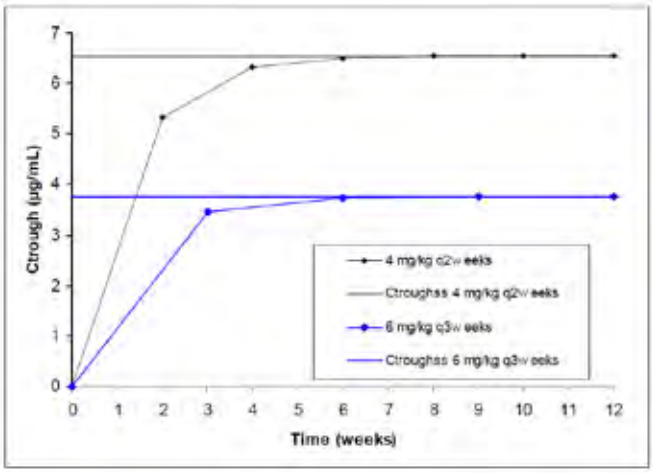
Table 4: Study TED6116, mean (CV%) free and bound aflibercept trough concentrations and free/bound ratios.

Dose	No. of patients	Free aflibercept (µg/mL)		Bound aflibercept (µg/mL)		Free/bound ratio	
		Baseline	Steady state	Baseline	Steady state	Baseline	Steady state
0.3 mg/kg IV	3	0.008 (141)	0	0.726 (14)	1.00 (2)	0.008 (141)	0
1 mg/kg IV	5	1.08 (73)	1.18 (122)	1.97 (35)	3.53 (60)	0.481 (61)	0.262 (106)
2 mg/kg IV	6	2.33 (114)	3.18 (90)	2.60 (52)	3.73 (24)	0.688 (101)	0.843 (83)
3 mg/kg IV	5	9.53 (9)	9.39 (21)	2.75 (2)	5.81 (77)	3.47 (11)	2.17 (55)
4 mg/kg IV	6	9.39 (100)	12.0 (52)	3.45 (51)	3.79 (29)	3.33 (83)	3.88 (32)
5 mg/kg IV	2	11.5 [a]	17.0 (34)	3.35 [a]	4.77 (24)	3.43 [a]	4.09 (59)
7 mg/kg IV	10	14.9 (78)	26.3 (63)	4.46 (41)	5.65 (41)	3.45 (75)	4.68 (59)

a = only 1 value.

Based on the population-pk analysis (POH0265), in a typical patient at 4 mg/kg q2w and 6 mg/kg q3w, the accumulation ratios for free aflibercept ($AUC_{ss}/AUC_{0\text{-}336h}$ and $AUC_{ss}/AUC_{0\text{-}504h}$, respectively) were 1.2 and 1.1, respectively. After 4 mg/kg q2w, estimated time to steady state was 70 days which corresponds to pre-dose of the 6th aflibercept administration, with 81% of $C_{trough.ss}$ reached at the end of the first dose. For the 6 mg/kg q3w regimen, time to steady state was 84 days which corresponds to pre-dose of the 5th aflibercept, administration with 92% of $C_{trough.ss}$ reached at the end of the first dose (see Figure 4, below).

Figure 4: Study POH0625 - Predicted free aflibercept C_{trough} versus time after administration of 4 mg/kg q2w or 6 mg/kg q3w.



3.3.8. Free/bound aflibercept ratios

Based on both preclinical pharmacological data and pharmacokinetic modelling data in human subjects, the sponsor postulates that maintaining free/bound aflibercept ratios above 1 throughout the dosing interval maximizes binding of available VEGF. Elevated serum VEGF concentrations have been observed in patients with a variety of cancers compared with individuals without cancer (Salven *et al*., 1997).

The sponsor states that, from a theoretical point of view, based on the law of mass action (i.e., Kd = [free aflibercept] x [free VEGF] / [bound aflibercept] = 0.5 pM), when free aflibercept concentration is greater than bound aflibercept concentration, VEGF concentrations are lower than 0.5 pM (or 20 pg/mL). Therefore, maintaining free aflibercept concentrations higher than bound concentrations over the dosing interval is expected to maintain endogenous serum VEGF concentrations below 20 pg/mL (the median value reported Salven *et al*., 1997 in healthy subjects was 17 pg/mL). In addition, the sponsor states that non-clinical studies showed tumour regression in various models at dose levels where free aflibercept levels were in excess of bound aflibercept levels over the entire dosing interval.

In view of the theoretically attractive hypothesis that maintaining the free/bound aflibercept ratio > 1 throughout the dosing interval might be of therapeutic benefit, the sponsor measured free and unbound aflibercept trough concentrations in the Phase 1 studies as a guide for dose selection in different clinical settings. In the Phase 1 studies, the mean trough free/bound aflibercept ratio was > 1 at dose levels greater than 2 mg/kg q2w and 4 mg/kg q3w. The PK parameters for the Phase 1 studies, and trough levels and free/bound ratios at steady states are summarized in the dossier. In the Phase 2 studies, the trough free/bound ratio was > 1 throughout the dosing interval in all studies, with a higher ratio observed in study ARD6122 in patients treated with aflibercept 4 mg/kg q2w than with 2 mg/kg q2w.

3.3.9. PK modelling to support dose selection

The PK model described in POH0262 (patients) was used to simulate concentration-time courses of free and bound aflibercept for a typical patient treated with a 1-hour iv infusion of 1, 2, 4 or 6 mg/kg aflibercept q2w and q3w. After q2w and q3w administration, maximum bound aflibercept levels were reached at doses ≥4 mg/kg with similar bound levels after 4 mg/kg q2w and 6 mg/kg q3w. Simulated plasma concentration-time profiles of free and bound aflibercept as well as free/bound aflibercept ratios for the 4 mg/kg q2w and 6 mg/kg q3w dose regimens were used to compare the effects of the different dose regimens. The simulations showed that the free/bound aflibercept ratio exceeded 1 throughout all dosing intervals for 89% of the population receiving 4 mg/kg q2w and 69% of the population receiving 6 mg/kg q3w. The simulations suggest that doses of 4 mg/kg q2w are adequate to maximize binding of available endogenous VEGF in most patients, and support the selection of this dosing regimen for clinical studies in patients with MCRC.

3.3.10. Intersubject variability in pharmacokinetics

In the Phase 1 studies, total patient variability for CL and Vss was moderate with CV% ranging from about 20% to 40%. In the pivotal Phase 3 study (VELOUR), variability was moderate with CV% of 33% and 14% for CL and Vss, respectively, and 19% and 20% for Cmax and $AUC_{0\text{-}336h}$, respectively.

3.3.11. Pharmacokinetics in special populations

3.3.11.1. Hepatic impairment

No formal PK study with aflibercept in patients with hepatic impairment was submitted. However, in the population-pk study in patients with cancer (POH0625), free aflibercept clearance in a typical patient was 1.02 L/day, and hepatic impairment had no significant effects on this parameter based on increased levels of total bilirubin, aspartate amino transferase and alanine amino transferase. Patients with low serum albumin concentrations (≤0.568×ULN) or high concentrations of alkaline phosphatase (≥3.24×ULN) had 18.7% and 12.9% increase in clearance, respectively, compared with a typical patient. Descriptive statistics of the relationship between covariates reflecting hepatic impairment and mean clearance estimates of free aflibercept from the population-pk analysis are summarized below in Table 5.

Table 5: POH0625 – Descriptive statistics on individual clearance estimates of free aflibercept according to hepatic impairment; mean (CV%) [5th – 95th percentiles].

	1< BILI ≤1.5	1.5 < BILI ≤ 3	BILI ≤1 and 2.5< ALK ≤5	BILI ≤1 and ALK > 5	BILI ≤1 and 1.5<ALT or AST ≤5	BILI ≤1 and ALT or AST > 5
N	63	5	94	8	151	2
CL (L/day)	1.09(27) [0.733-1.47]	1.22(17) [0.919-1.45]	1.17(28) [0.69-1.76]	1.29(25) [0.99-1.87]	1.06(29) [0.67-1.59]	0.948-1.87

The results from VELOUR for free aflibercept PK parameters according to hepatic function based on bilirubin, transaminase, and serum alkaline phosphatase levels suggest that hepatic impairment has no significant affects of free aflibercept parameters (see Table 6, below).

Table 6: VELOUR - mean (CV%) [5th – 95th percentile] free aflibercept PK parameters according to hepatic function.

Population	N	C_{max} (µg/mL)	AUC_{0-336} (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)
BILI ≤ 1 ULN	466	67.7(20)[53.2-86.7]	245(20)[170-324]	303(25)[193-423]	1.04(33)[0.657-1.5]
1 < BILI ≤ 1.5 ULN	33	63.9(13)[52.6-80.4]	239(19)[186-304]	289(25)[199-405]	1.08(16)[0.795-1.41]
1.5 < BILI ≤ 3 ULN	1	69.1	219	241	1.37
BILI > 3 ULN	0	-	-	-	-
BILI ≤ 1 ULN and 2.5 < ALK ≤ 5 ULN	47	62.9(18)[52.1-79.4]	205(22)[138-268]	242(26)[146-334]	1.16(22)[0.797-1.59]
BILI ≤ 1 ULN and ALK > 5 ULN	5	70.1(27)[53.6-102]	198(28)[128-272]	234(38)[133-368]	1.29(30)[0.99-1.87]
BILI ≤ 1 ULN and 1.5 < AST or ALT ≤ 5 ULN	70	66.1(16)[53.2-87.1]	223(22)[147-296]	268(26)[161-386]	1.09(24)[0.715-1.5]
BILI ≤ 1 ULN and ALT or AST > 5 ULN	1	53.6	128	133	1.87

Comment: The available data in patients with hepatic impairment suggest that mild and moderate impairment do not significantly affect the PKs of free aflibercept. However, there are limited data on patients with severe hepatic impairment.

3.3.11.2. Renal impairment

No formal PK study with aflibercept in patients with renal impairment was submitted. However, data on the effect of renal impairment in cancer patients with renal impairment were available from the population-pk analysis (POH0625). Of the 1507 cancer patients in the population-pk analysis, 549 (36%) were identified with mild renal impairment (50 mL/min ≤CLCR ≤80 mL/min), 96 (6%) with moderate renal impairment (30 mL/min ≤CLCR <50 mL/min), and 5 (<1%) with severe renal impairment (CLCR <30 mL/min). The population-pk analysis showed a 6.48% decrease of free aflibercept clearance for a CLCR of 47.8 mL/min, compared with a median of CLCR of 75.9 mL/min. Mean (CV%) free aflibercept clearance was 0.633 (62%) L/day in patients with severe renal impairment, 0.803 (28%) L/day in patients with moderate renal impairment, and 0.907 (26%) L/day in with mild renal impairment, compared with 1.08 (32%) L/day in patients with normal renal function.

In the population-pk analysis, there were no significant differences in mean free aflibercept AUC_{0-336h} (µg.day/mL) values following aflibercept 4 mg/kg in patients with normal renal function (n=562), mild renal impairment (n=322), and moderate renal impairment (n=55); respective AUC_{0-336h} (µg.day/mL) values 246 (CV%=22), 235 (CV%=22), and 233 (CV%=21). Limited data in patients with severe renal failure (n=5) showed a 20% lower mean AUC_{0-336h} (µg.day/mL) compared with patients with normal renal function (n=562): AUC_{0-336h} (µg.day/mL) 198 (CV%=28) vs 246 (CV%=22), respectively.

In VELOUR, exposure to aflibercept as assessed by Cmax and AUC was similar in patients with normal renal function, mild renal impairment and moderate renal impairment, but clearance was notably lower in patients with moderate renal impairment compared with the two other groups (see Table 7, below). There were no data in VELOUR in patients with severe renal impairment.

Table 7: VELOUR - mean (CV%) [5th – 95th percentile] free aflibercept PK parameters according to renal function (CL_{CR}).

Population	N	C_{max} (µg/mL)	AUC_{0-336} (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)
CLCR < 30 mL/min	0	-	-	-	-
CLCR [30 ; 50[mL/min	10	67.3(13)[49.1-75.1]	233(18)[169.9-287]	307(25)[214-420]	0.749(25)[0.547-1.13]
CLCR [50 ; 80] mL/min	154	66.2(14)[53.1-83.8]	238(19)[167-309]	300(24)[186-423]	0.906(22)[0.613-1.25]
CLCR >80 mL/min	336	68(21)[53.2-87.6]	248(21)[175-329]	303(26)[195-427]	1.11(33)[0.755-1.57]

Comment: The submitted data suggest that exposure to free aflibercept is similar in patients with normal renal function, mild renal impairment, and moderate renal impairment. However, there are limited data in patients with severe renal impairment.

3.3.11.3. Age

There were no formal studies on the influence of age on the PKs of aflibercept. However, in the population-pk analysis (POH0265), estimated free aflibercept clearance was similar across the age groups in cancer patients. Mean (CV%) free aflibercept clearance values (L/day) were 1.01 (30%), 0.964 (37%) and 0.905 (22%) in the "< 65" (n=1038), "between 65 and 74" (n=392) and "≥ 75" (n=77) age groups, respectively. The PK parameters in the age groups in patients in VELOUR are summarized below in Table 8.

Table 8: VELOUR – mean (CV%) [5th – 95th percentile] free aflibercept PK parameters in age groups.

Population	N	C_{max} (µg/mL)	AUC_{0-336} (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)
Age < 65 years	343	67.8(15)[53.6-87.6]	247(20)[177-324]	305(25)[198-426]	1.05(26)[0.68-1.56]
65 years ≤ Age < 75 years	133	66.9(29)[52.5-84.2]	240(21)[166-318]	296(26)[190-420]	1.05(46)[0.665-1.34]
Age ≥ 75	24	65.1(11)[55.2-79.7]	239(14)[167-293]	304(19)[183-396]	0.952(20)[0.656-1.37]

Comment: The submitted data showed no significant differences in the PKs of free aflibercept across age groups. However, the number of patients in the ≥ 75 years age group was notably smaller than in the two other age groups.

3.3.11.4. Gender

In the population-pk analysis (POH0265), gender was the most significant covariate explaining the inter-individual variability in free aflibercept clearance and volume of distribution in patients with cancer. In males, free aflibercept clearance was 15.5% higher and volume of distribution was 20.6% higher than in females. The mean (CV%) aflibercept clearance was 1.09 (25%) in males and 0.894 (36%) L/day in females. In a typical patient (i.e., all covariates are the same except gender) this would lead to higher exposure in females compare to males with AUC values of 312 and 263 µg.day/mL respectively. However, in the VELOUR study where 201 patients were female and 299 were male, AUC mean (CV%) aflibercept exposure was similar in both sexes with values of 304 (26%) and 301 (25%) µg.day/mL respectively. This might be due to weight-adjusted dosing as weight was lower in females than in males with mean weights [5th-95th percentile] of 66 kg [48-92] and 82 kg [59-115], respectively. In VELOUR, mean clearance (L/day) was also marginally lower in females than in males (0.92 [CV% = 46] vs 1.12 [CV% = 21], respectively. The PK parameters in male and female patients in VELOUR are summarized below in Table 9.

Table 9: VELOUR – mean (CV%) [5th – 95th percentile] free aflibercept PK parameters in male and female patients.

Population	N	C_{max} (µg/mL)	AUC_{0-336} (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)
Male	299	64.3(14)[52.3-77.2]	246(20)[178-328]	301(25)[193-445]	1.12(21)[0.767-1.56]
Female	201	72(23)[57-89]	243(21)[170-315]	304(26)[186-420]	0.919(46)[0.61-1.26]

Comment: The submitted data suggest that the differences in the PKs of free aflibercept between male and female patients are unlikely to be clinically significant.

3.3.11.5. Race

In the population-Pk analysis (POH0625), of 1507 cancer patients, 1378 (91%) were Caucasian, 27 (2%) were Black, 75 (5%) were Asian, and 27 (2%) were "others". There were no marked differences among the races in mean (CV%) free aflibercept clearance (L/day) with the results in Caucasian, Black, Asian and "other" patients being 0.997 (32%), 0.986 (29%), 0.999 (22%) and 0.922 (22%), respectively. In VELOUR, the majority of patients were Caucasian (n=453, 90.6%) with the remainder being Asian (n=28, 5.6%) and black (n=9, 1.8%). The free aflibercept PK parameters from VELOUR are summarized below in Table 10.

Table 10: VELOUR – mean (CV%) [5th – 95th percentile] free aflibercept PK parameters; race.

Population	N	C_{max} (µg/mL)	AUC_{0-336} (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)
Caucasian	453	67.9(19)[53.7-86.6]	246(20)[170-322]	304(25)[190-422]	1.05(33)[0.677-1.5]
Black	9	71.8(24)[46.4-100]	277(28)[165-404]	358(35)[199-576]	0.916(23)[0.639-1.32]
Asian	28	58.8(10)[49.7-70.6]	209(12)[178-246]	256(20)[193-307]	0.99(20)[0.649-1.26]

Comment: The population-PK study did not identify race as a significant covariate influencing the PKs of free aflibercept. The data from VELOUR showed that free aflibercept clearance was similar across the racial groups tests, but the number of patients in the "Black" group was too small to allow meaningful conclusions to be made. Exposure to free aflibercept in the "Asian" group in VELOUR, as assessed by C_{max}, AUC_{0-336h}, and AUC_{inf} values, was lower than in the Caucasian group, but clearance in the two groups was similar.

3.3.11.6. Weight

In the population-PK analysis (POH0625), most of the 1507 patients weighed between 50 and 100 kg (n=1344, 89%). Weight increased free aflibercept clearance by 8.47% in patients with a body weight (≥99.8 kg), and volume of distribution by 16.9%. However, in VELOUR exposure to free aflibercept increased with body weight and clearance decreased eventhough dosing was based on body weight (4 mg/kg q2w) (see Table 11, below).

Table 11: VELOUR – mean (CV%) [5th – 95th percentile] free aflibercept PK parameters according to body weight.

Population	N	C_{max} (µg/mL)	AUC_{0-336} (µg.day/mL)	AUC (µg.day/mL)	CL (L/day)
Weight < 50 kg	14	56.8(7)[49.3-62.9]	185(12)[138-223]	233(19)[146-302]	0.808(25)[0.618-1.26]
Weight [50- 100[kg	446	66.7(19)[53.2-83.8]	241(19)[174-312]	298(25)[193-418]	1.03(33)[0.677-1.43]
Weight ≥ 100 kg	40	79.1(12)[67.9-95.5]	310(15)[237-396]	370(20)[262-518]	1.26(17)[0.919-1.65]

Comment: In VELOUR, free aflibercept clearance was 22% lower in patients weighing < 50 kg compared with patients weighing 50-100 kg, and 22% higher in patients weighing > 100 kg. These differences were observed despite dosing in VELOUR being adjusted based on weight (4 mg/kg q2w).

3.3.11.7. Endogenous VEGF levels; Phase III studies

Endogenous VEGF plasma levels were measured at baseline in patients from the three Phase 3 studies (VANILLA, VITAL, VELOUR), and the relationship between baseline VEGF and free aflibercept was explored. In patients with relevant data, the mean±SD VEGF concentrations (pg/mL) were 121±178, 117±305, and 75.8±132 pg/mL in VANILLA (n=75), VITAL (n=144), and VELOUR (n=356), respectively. Overall, there was no obvious relationship between free aflibercept clearance and baseline endogenous VEGF levels.

3.3.12. Pharmacokinetic interactions

3.3.12.1. PKs of aflibercept when administered in multiple agent regimens

3.3.12.1.1. Phase I studies

The 5, Phase I combination studies assessed the effect of various chemotherapeutic agents on the PKs of aflibercept. The free aflibercept PK parameters for the five, Phase 1 combination studies and the one, Phase 1 single agents study at all Cycles are summarized in the dossier. The mean (CV%) free aflibercept PK and bound parameters from the 1, Phase I single agent study (TED6115) and the five, Phase I combination studies (TCD 6117, 6118, 6119, 6120, 6121) following 4 mg/kg (Cycle 1 [C1] combination studies) are summarized below in Tables 12 and 13, respectively.

Table 12: Free aflibercept mean (CV%) PKs; combination (Cycle 1) and single agent treatments.

	Dose	n	C_{max} (µg/mL)	AUC_{inf} (µg.day/mL)	$T_{1/2.z}$ (day)	Vss (L)	CL (L/day)
TED6115	4 mg/mL (single agent)	7	97.4 (43)	293 (15)	5.51 (18)	7.88 (38)	1.10 (38)
TCD6117	4 mg/mL + FOLFOX4	18	93.5 (39)	345 (38)	4.34 (22)	4.32 (29)	0.797 (23)
TCD6118	4 mg/ml + LV5U2-CPT11	11	67.8 (31)	311 (30)	5.18 (27)	6.35 (45)	0.964 (32)
TCD6119	4 mg/mL + TC5FU	14	83.9 (16)	274 (32)	3.88 (42)	5.44 (36)	1.24 (38)
TCD6120	4 mg/mL + T75	3	130 (36)	279 (34)	4.74 (29)	4.39 (5)	0.814 (28)
TCD6120	4 mg/mL + TC	6	93.5 (49)	369 (35)	5.46 (36)	4.56 (48)	0.624 (22)
TCD6120	4 mg/mL + T100	9	81.0 (29)	275 (40)	4.63 (41)	6.28 (31)	1.09 (35)
TCD6121	4 mg/mL + Gem.	16	90.0 (25)	334 (36) [n=15]	4.78 (34)	4.88 (43) [n=15]	0.981 (66) [n=15]
TCD6121	4 mg/mL + Gem/Erlotin.	23	94.8 (39)	329 (33)	4.35 (23)	5.08 (36)	0.970 (27)

Table 13: Bound aflibercept mean (CV%) PKs; combination (Cycle 1) and single agent treatments.

Dose		n	C_{max} (µg/mL)	AUC_{Last} (µg.day/mL)	T_{max} (day) [a]	C_{Last} (µg/mL)
TED6115	4 mg/mL (single agent)	7	1.34 (45)	10.8 (38)	9.99 (3.04 - 14)	1.27 (49)
TCD6118	4 mg/ml + LV5U2-CPT11	13	1.77 (23)	15.2 (25) [b]	14 (13.9 – 29)	1.77 (23)
TCD6119	4 mg/mL + TC5FU	14	1.58 (22)	22.9 (34)	17.9 (13.9-32.0)	1.531 (26)
TCD6120	4 mg/mL + T75	3	2.06 (27)	26.7 (18)	21.0 (21.0-21.1)	2.06 (27)
TCD6120	4 mg/mL + TC	6	1.92 (19)	24.4 (13)	17.48 (13.82-21.08)	1.86 (24)
TCD6120	4 mg/mL + T100	9	2.49 (41)	35.5 (38)	14.00 (12.98-21.84)	2.11 (54)
TCD6121	4 mg/mL + Gem.	16	1.69 (29)	18.3 (53) [n=12]	14.5 (7.12-28.1)	1.69 (29)
TCD6121	4 mg/mL + Gem/Erlotin.	20	1.78 (36)	16.2 (57)	14.0 (2.00-28.4)	1.66 (24)

a = median (range). b = AUC_{0-t} (day.µg/mL).

Comment: The inter-study comparisons showed that exposures to free aflibercept following aflibercept administered at a dose of 4 mg/kg were comparable between the aflibercept single agent study (TCD6115) and the aflibercept combination studies (studies TCD 6117, 6118, 6119, 6120, 6121). However, there was a trend towards decreased clearance of free aflibercept in the majority of the combination studies compared with the single agent study. Exposure to bound aflibercept was greater in the combination studies following a dose of 4 mg/kg compared with the single agent study, while the Tmax was longer.

3.3.12.1.2. Phase 3 study (VELOUR)

The PK parameters for free aflibercept from the pivotal Phase 3 study (VELOUR) are summarized below in Table 14 and compared with the single dose data from patients with cancer treated with aflibercept from the single agent study TED6115.

Table 14: Free aflibercept comparative mean (CV%) PKs.

Dose		n	C_{max} (µg/mL)	AUC_{inf} (day.µg/mL)	$T_{1/2.z}$ (day)	Vss (L)	CL (L/day)
TED6115	4 mg/mL single dose	7	97.4 (43)	293 (15)	5.51 (18)	7.88 (38)	1.10 (38)
VELOUR	4 mg/mL + FOLFIRI q2w	500	67.4 (19)	302 (25)	6.04 (27)	7.76 (14)	1.04 (33)

Comment: The designs of studies TED6115 and VELOUR were not comparable and there was a marked imbalance in patient numbers between the two studies. Nevertheless, the PK parameters were similar in the two studies. The results suggest that the FOLFIRI regimen used in the pivotal efficacy and safety study (VELOUR) is unlikely to significantly affect the PKs of free

aflibercept. In addition, the population-pk analysis (POH0625) in patients showed that FOLFIRI had no significant affect on free aflibercept clearance.

3.3.12.2. Effects on aflibercept on other drugs

3.3.12.2.1. Effect of aflibercept on PKs of oxaliplatin (TED6117)

In study TED6117, aflibercept (1, 2, 4 mg/kg) was administered in combination with FOLFOX4 q2w in subjects with advanced solid malignancies. The PKs of total platinum following oxaliplatin 85 mg/m^2 in the aflibercept/FOLFOX4 regimen were compared with those from an earlier study in which oxaliplatin monotherapy was administered at the same dose (study INT3010). The results are summarized below in Table 15.

Table 15: Study TCD6117 - Comparative results for total platinum PKs (mean±SD, CV%).

Study	Dose (mg/m²)	Cmax (µg/mL)	CmaxN (µg/mL)	AUC(0-24h) (µg.h/mL)	AUC(0-24h)N* (µg.h/mL)
TCD6117 (n=31)	85	1.92 ± 0.40 (21%)	1.92 ± 0.40 (21%)	29.8 ± 5.5 (18%)	29.8 ± 5.5 (18%)
INT3010 (n=17)	85	2.07 ± 0.29 (14%)	2.07 ± 0.29 (14%)	26.6 ± 2.8 (10%)	26.6 ± 2.8 (10%)

Comment: The plasma concentration-time curves for total platinum in both studies showed that plasma elimination was biphasic with a rapid initial phase followed by a slow decay phase. The comparative data showed that the PKs for total platinum following oxaliplatin 85 mg/m^2 were similar in a historical monotherapy study and when administered as part of a FOLFOX4 regimen in combination with aflibercept.

3.3.12.2.2. Effect of aflibercept on PKs of cisplatin (TCD6120 and TCD 6119)

The PKs of cisplatin were assessed following doses of 75 mg/m^2 in combination with aflibercept at 4, 5 and 6 mg/kg and docetaxel at 75 mg/m^2 (TCD6120, VTC cohort), and with aflibercept at 2, 4, 6 mg/kg and docetaxel/5-FU (TCD6119). The effect of aflibercept on the PKs of total platinum when co-administered with cisplatin 75 mg/m^2 in these two studies was compared with historical PK data. The relevant combination and single dose data are summarized below in Table 16.

Table 16: Studies TCD6120 and TCD6119 – Mean±SD (CV%) total platinum plasma PKs following cisplatin 75 mg/m^2.

Study	Number of patients	C_{max} (µg/mL)	$AUC_{0\text{-}24h}$ (µg.h/mL)
TCD6120[b] (VTC cohort)	29	3.40 (16)	42.1 (21)[a] 42.1 ± 8.78[a]
TCD6119[c]	43	3.43 (15)	40.3 ± 7.50 (19)[a]
Historical data - XRP6976E/1001[d]	12		42.7 ± 5.39 (TCF) 45.8 ± 8.13 (TC)

a : $AUC_{0\text{-}24h}$

b : with docetaxel 75 mg/m²

c : with docetaxel 75 mg/m2, 5-FU 750 mg/m2

d: A pharmacokinetic interaction study of 75 mg/m² of docetaxel (RP56976, Taxotere®) plus cisplatin (75 mg/m²) and 5-FU (750 mg/m²/day for 5 days) in the treatment of patients with recurrent or metastatic solid tumors, internal clinical study report XRP6976E-1001

Comment: The results suggest that aflibercept does not affect exposure to total platinum, based on C_{max} and $AUC_{0\text{-}24h}$,when co-administered with combination regimens including cisplatin 75 mg/m^2.

3.3.12.2.3. Effect of aflibercept on the PKs of irinotecan (CPT-11) and SN-38 (study TCD6118)

In study TCD6118, PK data on irinotecan (CPT-11) and its primary metabolite (SN-38) were obtained in 38 patients during Cycle 1 following irinotecan administered at a dose of 180 mg/m^2 iv over 1 hour on Day 1 initiated just after the infusion of aflibercept. The data from

this study were compared with published PK data in which 40 patients received a total irinotecan dose of 145 mg/m² administered as a 90 minute iv infusion (Gupta *et al.*, 1997). The relevant combination and single-agent PK data are summarized below in Table 17.

Table 17: PKs of irinotecan (CPT-11) and its primary metabolite (SN-38) following irinotecan (180 mg/m² iv over 1 hour) combined with aflibercept (study TCD6118) and following irinotecan (145 mg/m² iv over 1.5 hours) administered alone (Gupta *et al.*, 1997).

Study	Analyte	tmax (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (µg.h/mL)	AUC (µg.h/mL)	t½ (h)	CL (L/h/m²)
TCD6118	CPT-11 (n=38) SN-38 (n=37)	1.25 (0.92–3.0) 1.5 (0.92–4.08)	1970 (28) 24 (40)	14.7 (32) 0.224 (64)	15.4 (32) -	5.20 (16	12.6 (28) -
Gupta *et al.*, 1997	CPT-11 (n=40) SN38	- -	1851±586 30.2±12.4	- -	11.9±5.3 0.372±0.374	8.8±4.3 -	14.6±6.4 -

TCD6118 – PK results summarized as mean (CV%) for all parameters apart from tmax which was presented as median (range). Gupta *et al.*, 1997 – PK results summarized as mean±SD.

Comment: The C_{max}, AUC, and CL values for irinotecan were similar for the two studies, but the t½ was about 3.5 hours longer in Gupta *et al.*, 1997 than in TCD6118. The exposure parameters for SN-38 are also similar for the two studies. The comparative data suggest that aflibercept has no marked effects on the PKs of irinotecan and SN-38, despite irinotecan dose differing between the two studies.

3.3.12.2.4. Effect of aflibercept on the PKs of 5-fluorouracil (5-FU)

Data on 5-FU clearance were obtained during Cycle 1 in patients from studies TCD6117, TCD6118 and TCD6119. In these studies, aflibercept was administered first followed by oxaliplatin/leucovorin (TCD6117) or irinotecan (TCD6118) or docetaxel/cisplatin (TCD6119), and then 5-FU was administered immediately after according to the following schedules: 5-FU 400 mg/m² iv bolus then 600 mg/m² iv continuous infusion over 22 hours on Day 1 and 400 mg/ m² iv bolus then 600 mg/ m² iv continuous infusion over 22 hours on Day 2 (TCD6117 and TCD6118); and 5-FU 750 mg/ m²/day iv continuous infusion from Day 1 to Day 5 (TCD6119).

The 5-FU combined with aflibercept PK data from studies (TCD6116, TCD6118, and TCD6119) were compared with the 5-FU alone data from the published literature (Terret *et al.*, 2000). In Terret *et al.* (2000), the objective of the study was to examine inter-patient and intra-patient variability of the PK parameters of 5-FU following an iv bolus dose of 5-FU 400 mg/m² followed by 600 mg/m² administered as a continuous iv infusion for 22 hours on 2 consecutive days. The relevant combination and single agent data are summarized below in Table 18.

Table 18: Mean ± SD or (CV%) or range of plasma systemic clearance of 5-FU.

Study	Regimen	n	CL (L/h)	CL (L/h/m²)
TCD6117	Aflibercept + FOLFOX4	31	145 ± 214	80.1 ± 125
TCD6118	Aflibercept + irinotecan/5-FU	38		169 ± 323

Study	Regimen	n	CL (L/h)	CL (L/h/m²)
	/leucovorin			
TCD6119	Aflibercept + docetaxel/cisplatin/ 5-FU	38	290 (77)	154 (81)
Terret *et al*., 2000	5-FU alone	21	100-350	

Comment: The sponsor states that "taking into account the high inter-individual variability of 5-fluorouracil pharmacokinetics plasma clearance of 5-FU observed after administration of FOLFOX4 (TCD6117), irinotecan/5-FU/leucovorin (TCD6118) or docetaxel/cisplatin/5-FU (TCD6119) in combination with aflibercept were in agreement with 5-FU plasma clearance previously published. This suggests that 5-FU pharmacokinetics is not affected by aflibercept co-administration". However, it is considered to be difficult to interpret the 5-FU PK data from the four studies, given the high inter-individual variability in 5-FU clearance. Consequently, it is considered that no firm conclusions can be drawn from these studies about the effect of aflibercept on the PKs of 5-FU when given in combination.

3.3.12.2.5. Effects of aflibercept on the PKs of docetaxel

The effects of aflibercept on the PKs of docetaxel were assessed in patients treated with 75 mg/m² docetaxel in combination with aflibercept at 2, 4, 5, 6, 7 or 9 mg/kg every 3 weeks (TCD6120/VT75 cohort), in patients treated with 100 mg/m² docetaxel in combination with aflibercept 4, 5 and 6 mg/kg (TCD6120/V100 cohort), in patients treated with 75 mg/m² docetaxel in combination with aflibercept 4, 5 and 6 mg/kg and cisplatin 75 mg/m² every 3 weeks (TCD6120/VTC cohort), and in patients treated with docetaxel 75 mg/m², cisplatin 75 mg/m² and 5-FU 750 mg/m² in combination with aflibercept 2, 4 and 6 mg/kg (TCD6119).

The docetaxel PK data from the two aflibercept combination studies (TCD6120 and TCD6119), were compared with docetaxel alone PK data from the published literature (Bruno *et al*., 1998; and Harvey *et al*., 2008). In Bruno *et al* (1998), data were prospectively collected from Phase 2 studies in patients with a variety of tumour types and the docetaxel starting dose was either 75 mg/m² or 100 mg/m² given as a 1-hour infusion every 3 weeks. In Harvey *et al* (2008), data were collected from a Phase 3 clinical trial in patients whose cancer had progressed after one prior chemotherapy regimen for advanced breast cancer or had recurred during or within 6 months of adjuvant chemotherapy, and who were randomly assigned to docetaxel 60, 75, or 100 mg/m² iv every 3 weeks. The relevant combination and single agent data are summarized below in Table 19.

Table 19: Docetaxel clearance mean ± SD (TCD6120, TCD6119, Harvey *et al*., 2006) and median with 5th-95th percentile (Bruno *et al*., 1998).

		N	CL (L/h)	CL (L/h/m²)
TCD6120	VT75 Cohort (i.e., docetaxel 75 mg/m²)	54	43.4±16.0	24.3±8.23
TCD6120	VT100 Cohort (i.e., docetaxel 100 mg/m²)	30	37.8 ±13.5	21.7 ± 6.59
TCD6120	VTC Cohort (i.e., docetaxel 75	29	40.6±12.5	24.3±7.92

		N	CL (L/h)	CL (L/h/m²)
	mg/m²)			
TCD6119	TCF (i.e., docetaxel 75 mg/m²)	44	58.0±16.2	30.2±8.3
Harvey *et al*., 2006	Docetaxel 75 mg/m²	[a]	43.7± 14.1	24.7 ± 7.42
Harvey *et al*., 2006	Docetaxel 100 mg/m²	[a]	43.8 ± 19.6	25.3 ± 11.0
Bruno *et al*., 1998	Docetaxel 75/100 mg/m²	640[b]	36.3 (5th – 95th percentile, 17.5 - 59.3) [b]	

a = Harvey *et al*., 2006: N not stated in the published report; stated that PK analyses were conducted at cycle 1 in 69 patients but number of patients in each of the dose groups (60, 75 and 100 mg/m²) was not stated.

b = Bruno *et al*., 1998: CL (h/L) is the median values (5th – 95th percentile); N = nearly all patients were treated with 100 mg/m².

Comment: Overall, the data for docetaxel from studies TCD6120, TCD6119, Harvey *et al* (2006), and Bruno *et al* (1998) suggest that aflibercept does not appear to have a marked effect on docetaxel clearance when administered in combination regimens including docetaxel.

3.3.12.2.6. Effect of aflibercept on the PKs of gemcitabine.

The PKs of gemcitabine and its metabolite dFdU were assessed following gemcitabine 1000 mg/m² alone (TCD6121/GV cohort) or with erlotinib 100 mg daily (TCD6121/GEV cohort) in combination with aflibercept (4 or 6 mg/kg, GV cohort; 2 or 4 mg/kg, GEV cohort). The gemcitabine and dFdU data from the combination study (TCD6121) was compared with the corresponding data from gemcitabine single-agent studies (Abbruzzese *et al*., 1991; Delaloge *et al*., 2004). In Abbruzzese *et al* (1991), gemcitabine (10 to 1000 mg/m²) was administered alone to patients with solid tumours. In Delaloge *et al* (2004), the PKs of gemcitabine and dFdU in patients with cancer and renal impairment were investigated, and the results for 9 patients with normal renal function treated with gemcitabine 500 to 1000 mg/m² were included in the data comparison. The relevant combination and single agent PK data are summarized below in Table 20.

Table 20: Clearance of gemcitabine mean (CV%) and Cmax (dose normalized) dFdU.

Study	Regimen	CL (L/h/m²)	dFdU Cmax ([ng/mL]/[mg/m²])
TCD6121 (day 1)	Gemcitabine 1000 mg/m² + aflibercept 4 mg/kg	153 (90) [n=14]	36.7 (20) [n=19]
TCD6121 (day1)	Gemcitabine 1000 mg/m² + aflibercept 6 mg/kg	128 (49) [n=11]	39.8 (13) [n=12]
TCD6121 (day 1)	Gemcitabine 1000 mg/m² + aflibercept 2 mg/kg + erlotinib 100 mg	92.6 (65) [n=4]	38.4 (26) [n=6]

Study	Regimen	CL (L/h/m²)	dFdU Cmax ([ng/mL]/[mg/m²])
TCD6121 (day 1)	Gemcitabine 1000 mg/m² + aflibercept 4 mg/kg + erlotinib 100 mg	122 (41) [n=19]	36.2 (27) [n=21]
Abbruzzese *et al* (1991)	Gemcitabine 1000 mg alone	408.4 (123) [n=5]	31.3 (53) [n=5]
Abbruzzese *et al* (1991)	Gemcitabine 1000 mg alone	255 (91) [n=3] *	-
Delaloge *et al* (2004)	Gemcitabine 500-1000 mg alone	114 (19.3) [n=9]	37 (16) [n=9]

* = mean gemcitabine clearance estimated without two outliers.

Comment: The sponsor states that "gemcitabine clearance and dFdU dose normalized C_{max} observed in these studies were similar to those reported in literature indicating aflibercept did not modify gemcitabine and dFdU pharmacokinetics". However, it is considered that the results for gemcitabine clearance do not allow firm conclusions to be drawn about the effect of aflibercept on the PKs of gemcitabine, although it is noted that the results for dFdU C_{max} (dose normalized) was consistent across the studies.

3.3.12.2.7. Effects of aflibercept on the PKs of erlotinib

The PKs of erlotinib were evaluated following single oral administration of erlotinib 100 mg in combination with aflibercept at 2 and 4 mg/kg and gemcitabine 1000 mg/m² (study TCD6121). These data were compared with data from the published literature (Rahkit *et al*., 2008; Herbst *et al*., 2005). In Rahkit *et al* (2008), the PKs of erlotinib 100 mg were assessed with and without ketoconazole, and the data from assessment without ketoconazole were used in the comparison. In Herbst *et al* (2005), the PKs of erlotinib 100 mg were assessed in patients with NSCLC. The relevant PK data are summarized below in Table 21.

Table 21: Erlotinib mean (CV%) and mean ± SD C_{max} and $AUC_{0\text{-}24h}$.

Study	Regimen	n	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (µg.mL/h)
TCD121	Erlotinib 100 mg + gemcitabine 1000 mg/m² + aflibercept 2/4 mg/kg	28	802 (55)	12.6 (50)
Rahkit *et al* 2008	Erlotinib 100 mg alone	12	804 ± 358	11.84 ± 4.8
Herbst *et al* 2005	Erlotinib 100 mg alone	5	943 ± 660	13.2 ± 11.8

Comments: Overall, the data showed that aflibercept (2 and 4 mg/kg) had no marked effects on exposure to erlotinib in the presence of gemcitabine.

3.3.12.2.8. Effects of aflibercept on the PKs of pemetrexed

The PKs of pemetrexed were assessed following single dose pemetrexed 500 mg/m^2 in combination with aflibercept 6 mg/kg (study TCD6120). These data were compared with pemetrexed (single agent) data from the published literature (Hanauske *et al.,* 2001; Dy *et al,*. 2005). In Hanauske *et al* (2001), the PKs of pemetrexed given at various dose (including 600 mg/m^2) in patients with cancer were reviewed. In Dy *et al* (2005), the effects of pemetrexed and gemcitabine on each others PKs when administered alone were investigated. The relevant combination and single agent PK data from the studies are summarized below in Table 22.

Table 22: Erlotinib mean (CV%) and mean ± SD C_{max} and $AUC_{0\text{-}24h}$.

Study	Regimen	n	CL (L/h)	CL (L/h/m^2)
TCD6120	Premetrexed 500 mg/m^2 + aflibercept 6 mg/kg	19	5.14 (34)	2.81 (34)
Hanauske *et al* 2001	Premetrexed 600 mg/m^2, single agent	20	-	2.40
Dy *et al* 2005	Pemetrexed 500 mg/m^2, single agent	12	5.95 (32)	2.89 (25)

Comment: The data suggest that aflibercept 6 mg/kg has no significant effects on the PKs of premetrexed (500 or 600 mg/m^2).

3.4. Evaluator's overall conclusions on pharmacokinetics

- Overall, the PKs of aflibercept at the proposed dose of 4 mg/kg iv q2w have been reasonably well characterized in healthy subjects and patients with advanced cancer, and the PKs are comparable in the two subject groups. In addition, data from VELOUR and the population-pk analysis (POH0625) indicate that the proposed FOLFIRI regimen did not affect the PKs of aflibercept 4 mg/kg when co-administered in patients with cancer. In the following description of the PKs of aflibercept, the results refer to patients with cancer unless otherwise stated.
- In the population-pk analysis in healthy male subjects (POH0251), the best structural population-pk model involved two compartments for free aflibercept and one for bound aflibercept, with Michaelis-Menten type binding of free aflibercept to VEGF from the peripheral compartment. This model was used in the population-pk analysis in patients (POH0625) to describe the PKs of free aflibercept. Based on its mechanism of action, the sponsor considers that aflibercept demonstrates target mediated drug disposition (TMDD) characterized by dose-dependent, saturable, high-affinity binding of aflibercept to its pharmacologic target (VEGF).
- After a single iv dose of aflibercept (0.3 to 7 mg/kg), the concentration-time profile of free aflibercept was biphasic, with concentrations detectable up to 7 days in the 3 patients treated at the lowest dose (0.3 mg/kg), and up to 14 days in all patients treated at higher doses (study TED6115). Detectable free aflibercept at the end of the dosing interval suggests that all available endogenous VEGF had been bound to aflibercept following the administered doses. After the first dose of aflibercept 4 mg/kg iv administered over 1-hour (n=7), the mean (CV%) free aflibercept Cmax and AUC_{inf} values were 97.4 (43) µg/mL and 293 (15) µg.day/mL, respectively. The median tmax following the 4 mg/kg infusion occurred almost immediately after the end of the 1-hour infusion.

- Free aflibercept exposure (AUC_{inf}) was more than dose proportional (i.e., non-linear) over the range 0.3 to 2 mg/kg, and approximately dose proportional (i.e., linear) over the range 2 to 7 mg/kg (TED6115). Population-pk analysis (POH0253) showed a dose proportional increase of free aflibercept Cmax and AUC from 2 to 9 mg/kg. In study TCD6115, bound aflibercept concentrations were similar following doses ranging from 2 to 7 mg/kg, suggesting that saturation of VEGF binding sites occurs following a dose of 2 mg/kg with little further binding at doses > 2 mg/kg. The sponsor postulates that maintaining aflibercept free/bound ratios > 1 throughout the dosing interval maximizes binding of available VEGF. Simulations conducted using the population-pk model for aflibercept 4 mg/kg q2w showed that the aflibercept free/bound ratio was > 1 throughout all dosing intervals for 89% of the population (POH0262).
- At a dose of aflibercept 4 mg/kg iv q2w (n=6), the mean (CV%) free aflibercept trough concentration was 9.39 (100) µg/mL after the first dose and 12.0 (52) µg/mL at steady state indicating an accumulation ratio of 1.3 (study TED6116). This accumulation ratio was similar to that estimated in the population-pk analysis (POH0265) for free aflibercept after 4 mg/kg q2w (ratio = 1.2; $AUC_{ss}/AUC_{0\text{-}336h}$). After 4 mg/kg q2w, the estimated time to steady state was 70 days which corresponds to predose of the 6th aflibercept administration, and $C_{trough,ss}$ values were reached at the end of the first dose in 81% of patients (POH0625).
- In the population-pk analysis (POH0265), the volume of distribution (Vss) for free aflibercept was 7.8 L (central volume of distribution 4.5 L, peripheral volume of distribution 3.3 L) for a typical patient (male, median weight 67 kg). This value was similar to the mean (CV%) Vss in patients (n=7) of 7.9 (38) L following 4 mg/kg iv (study TED6115). The Vss indicates that aflibercept does not undergo significant tissue distribution.
- The mean clearance of free aflibercept was dose-dependent over the range 0.3 to 2 mg/kg (1.95 and 1.13 L/day, respectively), and was stable over the range 2.0 to 7.0 mg/kg (study TED5115). Dose dependent non-linear clearance of free aflibercept over the dose range 0.3 to 2.0 mg/kg iv suggests saturable binding of endogenous VEGF, while linear clearance over the dose range 2.0 to 7.0 mg suggests non-saturable clearance such as catabolism.
- The mean (CV%) clearance of free aflibercept following 4 mg/kg iv (n=7) was 1.10 L/day (study TED6115), and this value was consistent with the estimated from the population-pk analysis of 1.02 L/day (POH0265). The mean free aflibercept terminal half-life increased from 1.7 days at 0.3 mg/kg iv to 3.8 days at 2 mg/kg iv and then, remained relatively stable (5 to 7 days) over the 2 to 9 mg/kg iv dose range (TED6115). In the population-pk analysis (POH0265), the free aflibercept terminal half-life estimated was 5.8 days.
- No studies assessing the metabolism of aflibercept were included in the submission. The absence of metabolic studies is considered to be acceptable as free and bound aflibercept are proteins and it can be anticipated that these large molecular weight products will undergo catabolism to small peptides and individual amino-acids.
- No formal studies investigating the effects of renal impairment on the PKs of aflibercept were included in the submission. However, as the MW of free aflibercept is 115 Da it is unlikely that free (or bound) aflibercept will be renally eliminated. In the population-pk analysis (POH0625), there were no significant differences in free aflibercept mean $AUC_{0\text{-}336h}$ values in patients with normal renal status, mild renal impairment, and moderate renal impairment treated with 4 mg/kg iv, while limited data in patients with severe renal failure showed a 20% lower mean $AUC_{0\text{-}336h}$ compared with patients with normal renal function. In VELOUR, exposure to free aflibercept as assessed by Cmax and AUC was similar in patients with normal renal function, mild renal impairment, and moderate renal impairment, but clearance was notably lower in patients with moderate renal impairment compared with the two other groups.

- No formal studies investigating the effects of hepatic impairment on the PKs of aflibercept were included in the submission. However, the population-pk analysis (POH0625) suggests that mild and moderate hepatic impairment does not significantly influence the PKs of free aflibercept, but there are no data in patients with severe hepatic impairment.
- In the population-pk analysis (POH0625), age had no significant influence on the Pks of free aflibercept, while sex was identified as the most significant covariate explaining inter-individual variability in free aflibercept clearance and volume of distribution with 15.5% and a 20.6% higher values, respectively, being observed in males than in females However, data from VELOUR suggests that the differences in the PKs between males and females are unlikely to be clinical significant. In the population-pk analysis (POH0625), increased weight increased free aflibercept clearance and volume of distribution. In the population-pk analysis (POH0625), race did not appear to affect free aflibercept clearance, but in VELOUR exposure to free aflibercept was lower in "Asians" compared with "Caucasians".
- There were no formal PK drug-drug interaction studies between aflibercept and other drugs. However, data from the clinical studies in which aflibercept 4 mg/kg iv was combined with various chemotherapeutic agents (including oxaliplatin, cisplatin, 5-FU, irinotecan, docetaxel, pemetrexed, gemcitabine and erlotinib) suggest that the PKs of free aflibercept were not significantly modified by these agents. However, there was a trend towards decreased clearance of free aflibercept in most of the combination studies. In VELOUR, the clearance, elimination half-life, Vss and exposure (AUC_{inf}) of free aflibercept following 4 mg/mL combined with FOLFIRI were similar to those following administration of aflibercept as a single agent in study TED6115,
- The data from the clinical studies showed that aflibercept had no significant impact on the PKs of oxaliplatin, cisplatin, irinotecan (and its SN-38 metabolite), docetaxel, erlotinib and pemetrexed. Although the sponsor stated that aflibercept did not significantly modify the PKs of gemcitabine and 5-FU, it is considered that the submitted data do not allow firm conclusions to be drawn regarding these interactions.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Pharmacodynamic (PD) data were provided in the following studies:

- **Studies PDY6655 and PDY6656:** The primary objective of these two studies was to evaluate the effects of aflibercept on blood pressure in healthy male subjects, and the secondary objectives included evaluation of the effects of aflibercept on a number of associated parameters (e.g., RAAS, non-invasive haemodynamics, renal function). The data from study PDY6656 included information on endpoints following treatment with aflibercept (1, 2, and 4 mg/kg iv) and placebo in a total of 48 subjects. The PD data from study PDY6656 have been evaluated (below). The data from study PDY6655 have not been evaluated as there was no information on the aflibercept dose proposed for approval (4 mg/kg iv), and the study did not include a placebo control.
- **Study TES10897:** The primary objective of the study was to compare the effects of aflibercept 6 mg/kg and placebo on the QT interval corrected according to Fridericia formula (QTcF) in cancer patients (84 evaluable for PDs). The study also included a PK/PD analysis on the relationship between exposure to free aflibercept and change from baseline in the QTcF interval. The PD, PK/PD and safety data from this study relating to the QT interval have been evaluated and are presented below under *Effect of aflibercept on QTc interval in patients (study TES10897)*).

4.2. Cardiovascular PDs in healthy subjects (study PDY6656)

The primary pharmacodynamic objective of this single-centre, randomized, double-blind, placebo-controlled, sequential ascending dose study was to evaluate the effects of single iv doses of aflibercept in healthy male subjects on blood pressure. Secondary pharmacodynamic objectives included the assessment of the effects of single iv doses of aflibercept in healthy male subjects on the renin angiotensin aldosterone system (RAAS), on haemodynamics assessment by non-invasive methods, on endothelium integrity with markers of endothelium dysfunction, and on renal function.

4.2.1. Primary pharmacodynamic endpoint (24-hour mean SBP measured by ABPM)

The primary endpoint was the 24-hour mean systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring (ABPM) over 24-hour periods, excluding data measured after antihypertensive therapy. The primary PD response was established from the SBP data of 24-hour ABPM assessed at baseline, then on Days 2, 4, 8, 15, 22, 29, 36, and 43 after aflibercept or placebo infusion. The primary analysis consisted of an analysis of covariance (ANCOVA) of the maximum effect (Emax) in the 24-hour mean SBP, with terms for treatment and baseline value. There were 12 subjects in each of the four treatment groups (placebo and aflibercept 1, 2, and 4 mg/kg).

Increases in the 24-hour mean SBP were observed following aflibercept at 1, 2, and 4 mg/kg iv, and were most marked following the highest dose. The placebo-corrected increase in the 24-hour mean SBP observed with the 4 mg/kg dose reached a peak of +14.54 mmHg at week 2, and was still significantly increased 6 weeks after administration (+5.47 mm Hg). The Emax analysis is summarized below in Table 23.

Table 23: Study PDY6656 – ANCOVA on Emax of the change from baseline in mean 24-hour ambulatory SBP (mm Hg).

Treatment	Mean[a] difference vs placebo	Mean[b] change	Placebo mean[b] change	P-value	95% CI	
					Lower	Upper
1 mg/kg – Placebo	5.16	9.47	4.31	0.0232	0.74	9.58
2 mg/kg – Placebo	4.90	9.21	4.31	0.0272	0.58	9.22
4 mg/kg – Placebo	10.27	14.58	4.31	<.0001	5.77	14.78

a Mean difference = LSM (Treatment) minus LSM (Placebo); b Mean is LSM

Dose effects (repeated measure analysis): The repeated measures ANCOVA analysis on change from baseline in 24-hour mean SBP showed that placebo-subtracted increases were observed at each of the three dose levels. The estimated placebo-corrected difference with 4 mg/kg was 8.53 mmHg (95% CI: 4.81, 12.25), and this difference was approximately 2-fold greater than for the two lowest dose.

Determination of time course: Maximum increases in 24-hour mean SBP were achieved at Day 16, irrespective of dose. The placebo-corrected increase with 4 mg/kg at Day 16 was 14.54 mmHg (95% CI: 10.14, 18.95), p <0.0001, and the increase with this dose was still significant at Day 44 (5.47 mm Hg [95% CI: 1.28, 9.66], p = 0.0118).

Comment: The results of the statistical analysis on Emax of the change from baseline in mean 24-hour ambulatory SBP showed a significant difference for each of the aflibercept doses versus placebo. The placebo-subtracted increase was similar for both the 1 and 2 mg/kg doses, while the placebo-subtracted increase for the 4 mg/kg dose was about 2-fold greater than both lower doses. Repeated measures ANCOVA showed that placebo-subtracted 24-hour mean SBP was significantly increased for each aflibercept dose, with similar increases being observed for the 1 and 2 mg/kg and the increase for the 4 mg/kg dose being about 2-fold greater than for the 2 lowest doses. The maximum mean placebo-subtracted significant increase in 24-hour SBP from was observed at day 16 for the 4 mg/kg iv dose and the effects were still significant at day 44.

4.2.2. Main secondary pharmacodynamic endpoints

The main secondary PD endpoints included markers of RAAS. Blood samples were taken on Days -1, 2, 3, 8, 15, 22, 29, 36, and 43 at the same clock-time throughout the study. Plasma active renin concentrations were lower in aflibercept treated subjects than in placebo treated subjects. The repeated measures analysis demonstrated that the decreases in plasma active renin concentrations were significant for each aflibercept dose compared with placebo and the effect was not dose dependent. Plasma aldosterone concentrations were lower in aflibercept treated subjects than in placebo treated subjects. The repeated measures analysis demonstrated that the decreases in plasma aldosterone concentrations were statistically significantly lower than placebo in the 2 mg/kg dose group only. Plasma angiotensin concentrations were highly variable and numerous values were missing and/or below the LOQ in this assay. No conclusions can be drawn about the effects of aflibercept on plasma angiotensin. Overall, the data suggest that hypertension associated with aflibercept administration is caused by a renin independent mechanism.

4.2.3. Other secondary pharmacodynamic endpoints.

Increases in the 24-hour mean ambulatory DBP with aflibercept compared with placebo were consistent with the increases observed in the 24-hour mean ambulatory DBP. Increases in clinical supine SBP, DBP and MAP in the aflibercept groups compared with placebo were consistent with those observed in 24-hour ABPMs. Aflibercept had no significant effect on pulse pressure, suggesting main that the main effects of the drug are on small arteries. The HR repeated measures analysis showed that aflibercept reduced heart rate compared with placebo with the difference being statistically significant at the 4 mg/kg dose.

Aflibercept had no marked effects on venous occlusion plethysmography parameters (venous capacity, arterial flow reserve, venous capacity). Pulse wave analysis showed that aflibercept increased radial mean pressure and aortic mean pressure), but did not significantly increase pulse wave velocity.

No statistically significant differences between placebo and aflibercept were observed for endothelium dysfunction markers (plasma endothelin, plasma E-selectin, plasma cGMP concentrations and urinary nitrates excretion). The inter-subject variability for all markers was high.

Aflibercept had no significant effects on renal function markers (proteinuria; microalbuminuria; sodium, potassium or chloride excretion; or creatinine clearance). However, the inter-subject variability in renal function markers was high.

Higher plasma free VEGF concentrations were observed in aflibercept treated subjects from 2 weeks following administration, irrespective of the dose, with high levels still being present at the end of the 6-week study period. However, further investigations are ongoing in order to exclude a possible artefact accounting for the increased amounts of VEGF.

4.3. Effect of aflibercept on QTc interval in patients (study TES10897)

This Phase 1 study included patients with solid malignancies treated with single agent docetaxel 75 mg/m^2 (or less) q3w. Patients were randomized to receive double-blind treatment with either aflibercept 6 mg/kg over 1 hour iv or matching placebo, followed immediately by docetaxel 75 mg/m^2 administered over 1 hour.

The primary objective of this study was to assess the effect on the QTcF interval (QTc Fridericia) of aflibercept versus placebo, in cancer patients. The secondary objectives of this study were to assess the effects of aflibercept versus placebo: on heart rate (HR); QT, QTcB (Bazett's correction), and QTcN (population specific correction formula) intervals; and clinical safety. The secondary objectives also included assessment of the PKs of aflibercept (administered q3w) at Cycle 1 and Cycle 3.

The main ECG analyses were performed on the evaluable patient population, defined as all randomized and treated patients who had at least two valid QT measurements (at baseline, and during the first 3 cycles). Analysis of the ECG was based on (triplicate) recordings extracted by the central ECG core lab from the 12-lead ECG Holter, at the following time points: Cycle 1, pre-dose (baseline) at T(-1.5h), T(-1h) and T(-0.5h); Cycle 1, post-dose at T0.5h, T1h (end of aflibercept/placebo infusion), T2h, T3h, T4h, T6h; Cycle 3, pre-dose at T(-0.5h); and Cycle 3, post-dose at T0.5h, T1h (end of aflibercept/placebo infusion), T2h, T3h, T4h, T6h.

The primary analysis was the least square mean (LSM) difference calculated on the QTcF change from baseline over the interval T1h (end of infusion) to T3h (2h post end of infusion), on Cycle 3, Day 1. The secondary analyses were: LSM difference calculated on the QTcF change from baseline over the interval T0.5h (midpoint during the infusion) to T6h (5h post end of infusion) on Cycle 3, Day 1; estimate and 1-sided 95% confidence interval of the largest time-matched mean difference among all timepoints at Cycle 3 (QTcF); all QTcF analyses performed at Cycle 3, were also performed at Cycle 1; estimate and 2-sided 90% confidence intervals (CIs) in mean QTcF change from baseline, at all individual post-baseline time points in Cycle 1, and all time points in Cycle 3.

The PD results for the repeated measures analyses for mean change from baseline between T1h and T3h for Cycle 3 (primary analysis) are summarized below in Table 24. In the longer interval (T0.5h and T6h), QTcF LSM (se) difference of the change from baseline for cycle 3 (secondary analysis) was 2.2 (4.07) ms (90% CI: -4.6, 9.0) in the EP population.

Table 24: Study TES1087 - Repeated measures analysis for mean change from baseline between T1h and T3h for Cycle 3 only; EP population.

	Placebo (N=43)		Aflibercept (N=41)			90% CI of LS Mean Difference	
Change from baseline in ECG parameters	Number	LS Mean (se)	Number	LS Mean (se)	LS Mean Difference[a] (se)	Lower	Upper
QTcF (ms)	31	3.0 (3.04)	28	6.3 (3.26)	3.4 (4.51)	-4.2	10.9
HR (bpm)	31	-1.0 (2.04)	28	-3.1 (2.16)	-2.0 (3.07)	-7.2	3.1
QTcN (ms)	31	3.1 (2.96)	28	5.3 (3.17)	2.3 (4.38)	-5.1	9.6
QTcB (ms)	31	3.2 (3.18)	28	2.9 (3.40)	-0.3 (4.68)	-8.1	7.5
QT (ms)	31	3.3 (4.96)	28	11.3 (5.33)	8.0 (7.47)	-4.6	20.5

a LS Mean Difference = LS mean of Aflibercept - LS mean of placebo. Note: LS = Least Square; CI = Confidence Interval. The LS mean is estimated using ANCOVA model with fixed terms of treatment, gender, actual palonosetron use, and with baseline measurement as covariate and subject nested within treatment-by-gender as a random term.

The study included a PK/PD analysis assessing the relationship between free aflibercept exposure and the QT interval (i.e., baseline adjusted QTcF changes and log free aflibercept concentration plasma). A linear mixed effects model was employed with the QTcF changes as the dependent variable and the corresponding aflibercept log plasma concentration as the independent variable. At cycle 1, the slope of the relationship was – 0.013 (95%CI: -0.044, 0.019), or a 1 msec QTcF decrease per 100 µg/mL increase in free aflibercept concentration. At cycle 3, the slope of the relationship is + 0.048 (95% CI: 0.013, 0.082), or a 5 msec increase per 100 µg/mL increase in free aflibercept concentration.

The results for patients with on-treatment abnormalities in Cycles 1 or 3 in the safety population are summarized in the dossier. The safety population consisted of all patients who were randomized and received at least one dose of double-blind study medication and analyzed as per treatment actually received.

Comment: The sponsor states that study TES10897 was conducted to meet the requirements of the ICH E14 note for guidance for "clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-arrhythmic drugs" taking into account "the specificities of

[aflibercept] and its intended use in cancer patients". The choice of placebo/docetaxel as the control agent for aflibercept/docetaxel is considered to be appropriate as docetaxel does no appear to be associated with QT prolongation (no mention in approved PI), although it has been associated with heart when used in combination with certain other oncological drugs. The sponsor argues that, based on the preclinical cardiovascular toxicity studies and data from bevacizumab, a biological with a similar mechanism of action, it was considered that no standalone safety pharmacology study on the cardiovascular system was needed with aflibercept, and no *in vitro* tests (hERG channel or purkinje fiber assays) were conducted.

In TES10897, the primary analysis endpoint was the LSM difference calculated on the QTcF change from baseline over the interval T1h (end of infusion) to T3h (2h post end of infusion), on Cycle 3, Day 1. There were 59 patients who had Cycle 3 post-baseline ECG, and the primary analysis in these patients showed that the QTcF LSM (se) difference of the change from baseline on Day 1 in the time interval T1h to T3h (aflibercept 6 mg/kg minus placebo) was +3.4 (4.51) ms, and the upper 90% CI was 10.9 ms. The QTcF was prolonged (>450 ms male, >470 ms female) in 7 (15.9%) patients in the placebo/docetaxel arm and 6 (14.0%) patients in the aflibercept/docetaxel arm, and > 480 ms in no patients in placebo/docetaxel arm and 1 (2.3%) patients in the aflibercept/docetaxel arms. No patients no patients in either treatment arm had QTcF values ≥500 ms during the study. Overall, the data from this study suggest that aflibercept is unlikely to be associated with clinically significant QTcF prolongation.

4.4. PK/PD analyses relating to efficacy and safety (VELOUR)

4.4.1. Overview

VELOUR was the pivotal Phase 3 efficacy and safety study. It included PK/PD analyses exploring efficacy and safety outcomes in 500 patients with data on free aflibercept concentrations and 400 patients with data on bound aflibercept concentrations. The methodology of these analyses were provided in the "Statistical Analysis Plan for PK/PD and Immunogenicity Analyses" (dated 23 March 2011), and the results were included in the CSR.

4.4.2. PK parameters used in the PK/PD analyses

The PK parameters were derived from the population-pk analysis (POH0265) of free and bound aflibercept. The PK parameters for free aflibercept used in the PK/PD analyses were: AUC for first cycle; cumulative AUC until last aflibercept/placebo administration + 90 days or death or cut-off date (for overall survival) or date of progression (for progression-free survival) based on tumour assessment by the Independent Review Committee (IRC), whichever comes first (Cumulative AUC) divided by the number of cycles; cumulative AUC until cycle 2 or death or cut-off date (for overall survival) or date of progression (for progression-free survival) based on tumour assessment by the IRC, whichever comes first; clearance (CL); and Cmax at cycle 1. The free aflibercept PK parameters derived from VELOUR in the population-pk analysis are summarized in the dossier. The PK parameter for bound aflibercept used in the PK/PD analysis was clearance (CL).

4.4.3. Efficacy and safety endpoints used in the PK/PD analyses

The efficacy endpoints in the PK/PD analyses were overall survival, and progression–free survival. The safety endpoints in the PK/PD analyses are summarized below in Table 25. Due to the low incidence (<5 events in the PK population) of arterial thromboembolic event and headache grade 3-4, no modelling could be performed for these events.

Table 25: VELOUR - Selected toxicities; PK population free aflibercept.

	Aflibercept/Folfiri (N=500)	
Selected toxicity (All grades)	Overall	Cycles 1,2
Dysphonia	129 (25.8%)	97 (19.4%)
Arterial thromboembolic event	12 (2.4%)	1 (0.2%)
Venous thromboembolic event	46 (9.2%)	6 (1.2%)
Haemorrhage	189 (37.8%)	83 (16.6%)
Hypertension	202 (40.4%)	114 (22.8%)
Proteinuria (grade ≥ 2)	48 (9.6%)	15 (3.0%)
Renal failure (grades 3, 4)	13 (2.6%)	8 (1.6%)
Diarrhoea (grades 3, 4)	92 (18.4%)	34 (6.8%)
Headache (grades 3, 4)	9 (1.8%)	4 (0.8%)
Stomatitis and ulceration (HLT)	268 (53.6%)	149 (29.8%)
Infections and infestations (SOC)	225 (45.0%)	70 (14.0%)

4.4.4. Statistical methods

The PK/PD relationships between the safety parameters and the PK parameters were analyzed using both univariate and logistic regression modelling. The multivariate analyses including covariates of age, gender, region, ECOG PS, prior bevacizumab, location of primary disease, prior hypertension and number of metastatic organs involved, and keeping the most significant PK parameter at the 10% significance level from the univariate analyses. The PK/PD relationships between the efficacy parameters (OS, PFS) and the PK parameters were analyzed by univariate and multivariate proportional hazard regression modelling. For multivariate analyses a stepwise procedure was used for inclusion and deletion of covariates. The significance level for variable entry or removal at each step was 15%.

4.4.5. Results – PK/PD safety endpoints

- No PK parameters of free aflibercept were found to be significantly correlated (at 10% level) with dysphonia, venous thromboembolic event, renal failure (grade 3, 4), diarrhoea (grade 3-4), stomatitis and ulceration (HLT), infection and infestation (SOC) at cycles 1 and 2.
- A total of 114 out of 500 patients (22.8%) experienced any grade hypertension during cycles 1 and 2. The occurrence of hypertension during cycles 1 and 2 was significantly correlated with free aflibercept Cmax, AUC of first cycle, AUC extrapolated, and cumulative AUC at Cycles 1 and 2. The effect of AUC of first cycle (most significant prognostic factor in the univariate analysis) remained significant in the multivariate analysis, after adjusting for baseline/demographic covariates. The same conclusion could be drawn when adding endogenous VEGF as a covariate in the model.
- A total of 15 out of 500 patients (3%) experienced proteinuria grade ≥ 2 during cycles 1 and 2. Free aflibercept cumulative AUC at cycles 1 and 2 was the significant factor associated with proteinuria grade ≥ 2 during cycles 1 and 2, and all other PK parameters were not statistically significant ($p > 0.85$). However, an increase of 2000 µg.h/mL corresponded to a 51% decrease ($p=0.0006$, univariate analysis) in the odds of experiencing proteinuria. This relationship was opposite to that expected.
- A total of 83 out of 500 patients (16.6%) experienced any grade haemorrhage during cycles 1 and 2. Occurrence of haemorrhage was significantly correlated with free aflibercept AUC extrapolated and cumulative AUC at Cycles 1 and 2. For cumulative AUC at cycles 1 and 2 (most significant factor), an increase of 1000 µg.h/mL was associated with a 19% increase in the odds of experiencing haemorrhage. The effect of cumulative AUC at Cycles 1 and 2 (most significant prognostic factor in the univariate analysis) remained significant in the multivariate analysis, after adjusting for baseline/demographic covariates. The same conclusion can be drawn when adding endogenous VEGF as a covariate in the model.

- Bound aflibercept clearance was not found to be significant for any safety endpoint, except for diarrhoea (grade 3-4) and venous thromboembolic event at the 10% level (p=0.0779 and p=0.0936, respectively).

4.4.6. Results – PK/PD efficacy endpoints

Overall survival (OS) was significantly correlated with decreased free aflibercept clearance (p=0.0147), as well as increased Cmax (p=0.0005), increased AUC extrapolated (p<0.0001), increased AUC at first cycle (p<0.0001) and increased average AUCcumOS (p<0.0001). A significant relationship was also found with decreased bound aflibercept clearance (p<0.0001). For average AUC_{cumOS}, an increase of 1000 μg.h/mL was associated with a 13% increase in the survival hazard rate.

- Similar results to those observed with OS were also observed for progression free survival (PFS): PFS was significantly correlated with decreased free aflibercept clearance (p<0.0001), as well as increased AUC extrapolated (p<0.0001), increased average AUCcumPFS (p<0.0001) and AUC of first cycle (p<0.0001) were significantly correlated with higher PFS. Decreased bound aflibercept clearance was also correlated with a higher PFS (p=0.0048).
- For OS and PFS, the results of multivariate analyses for AUC extrapolated were consistent with those of the univariate analyses. When adding endogenous VEGF at baseline in the multivariate model (356 patients) the relationship between AUC extrapolated and OS and PFS efficacy endpoints remained significant, with a hazard ratio estimate in the same range as without VEGF in the model.

Comment: The occurrence of any grade hypertension was correlated with free aflibercept PK parameters, with an increase in the C_{max} and AUC being associated with an increase in the odds of experiencing hypertension. Similar results for the analyses were observed after adjusting for baseline/demographic characteristics. The occurrence of proteinuria (grade ≥ 2) was correlated only with the PK parameter of AUC_{cum} for cycles 1 and 2, but the PK/PD relationship for this parameter was the opposite of that expected. The occurrence of haemorrhage was correlated with two free aflibercept PK parameters (AUC extrapolated and cumulative AUC at cycles 1 and 2). No relationship was found between any PK parameters and the occurrence of dysphonia, venous thromboembolic event, renal failure (grade 3-4), diarrhea (grade 3-4), stomatitis and ulceration (HLT), or infection and infestation (SOC). Change in bound aflibercept clearance was not significantly associated with any safety endpoint, except for diarrhea (grade 3-4) and venous thromboembolic events.

With respect to efficacy outcomes of OS and PFS, a significant relationship was found with all of the free aflibercept PK parameters, and with bound aflibercept clearance. Decrease in clearance and increase in AUC or C_{max} was associated increased overall survival and progression free survival probability.

4.5. Evaluator's overall conclusions on pharmacodynamics

- Study PDY6656 showed that aflibercept administered as a single, 4 mg/kg iv dose to healthy male subjects had a marked effect on 24-hour mean systolic blood pressure (ABPM). The maximum effect on systolic blood pressure measured from day 3 after administration was observed at day 16, and the effect was still significant at day 44. Increases in 24-hour mean diastolic blood pressure (ABPM) were consistent with those seen for systolic blood pressure. The RAAS data suggest that hypertension following aflibercept administration is caused by a renin independent mechanism. The effect of aflibercept on increasing blood pressure is not unexpected as this is a known class effect for VEGF inhibitors. Study TES10897 in patients with cancer showed that increases in the QTcF observed with aflibercept are unlikely to be clinically significant.

- PK/PD analyses of safety outcomes based on data from VELOUR showed that hypertension was associated with increased free aflibercept exposure based on Cmax and AUC levels, and diarrhea (grade 3-4), and venous thromboembolic events were associated with bound aflibercept clearance. PK/PD analyses of efficacy outcomes based on data from VELOUR showed that increases in AUC or Cmax (free aflibercept) and decreases in clearance (bound aflibercept) were associated with both increased overall survival and progression-free survival.

5. Dosage selection for the pivotal studies

5.1. Study TCD6118 (Phase 1, dose-escalation, sequential cohorts)

The aflibercept dose selected for the pivotal Phase 3 study (VELOUR) was based on the findings of the Phase 1, dose-escalation, sequential cohort study (TCD6118) in which aflibercept (2, 4, 5, and 6 mg/kg) was administered in combination with 5-FU, leucovorin, and irinotecan (LV5U2-CPT11) in patients with solid tumours. The primary objective of the study was to determine dose-limiting (DLT) toxicities, and to establish the "recommended Phase 2 dose" (RP2D) of aflibercept to be administered in combination with standard fixed doses of LV5U2-CPT11.

Aflibercept was administered by iv infusion over 1 hour and was immediately followed by irinotecan, 180 mg/m^2 iv over 60 minutes on Day 1, together with leucovorin 200 mg/m^2 (or elvorine 100 mg/m^2) iv over 2 hours on Day 1 via Y-line, followed by 5-FU 400 mg/m^2 iv bolus then 600 mg/m^2 iv continuous infusion over 22 hours on Day 1, followed by leucovorin 200 mg/m^2 (or elvorine 100 mg/m^2) iv over 2 hours on Day 2, followed by 5-FU 400 mg/m2 iv bolus then 600 mg/m^2 iv continuous infusion over 22 hours on Day 2. In the absence of study withdrawal criteria, treatment was given once every 2 weeks and patients were followed from the date of informed consent until last aflibercept dose + 90 days.

Part 1 was designed as a multicentre (1 centre each, France and Belgium), open-label, dose-escalation study of aflibercept plus LV5FU2-CPT11 to determine the RP2D of aflibercept. Sequential cohorts of 3 to 6 patients, each with advanced solid malignancies, were treated with successively higher doses of aflibercept plus LV5FU2-CPT11 every 2 weeks in the absence of study withdrawal criteria. The RP2D was defined as the highest dose at which 0 or 1 of 3 to 6 patients experienced DLT during the first 2 cycles of treatment. Demonstration of acceptable safety for each dose level in the single agent study TED6115 was a prerequisite for enrolling patients into the corresponding dose level cohort in Part 1 of study TCD6118. The dose escalation schedule in study TCD6118 was aflibercept 2 mg/kg (n=4), 4 mg/kg (n=12), 5 mg/kg (n=10), and 6 mg/kg (n=12).

The DLTs observed during the DLT observation period at the 5 mg/kg and 6 mg/kg dose levels were stated by the sponsor to be most probably related to the chemotherapy, while the DLTs observed at the 4 mg/kg dose level were considered to be most likely related to VEGF blockade. The observed DLTs did not appear to be dose dependent. Based on the observed DLTs in Cycles 1 and 2, it is clear that the RP2D dose could not be based solely on these DLTs as the observed toxicities did not appear to be dose dependent. In a previous study (TED6115), dose escalation had been stopped at 7 mg/kg. Consequently, no higher dose than 7 mg/kg was investigated in study TCD6118. The DLTs in Part 1 of study TCD6118 are summarized below in Table 26.

Table 26: Study TCD6118 – Dose limiting toxicities; Part 1.

	Dose escalation		Subsequent patients	
Aflibercept dose level (mg/kg)	Patients with DLT/patients evaluable for DLT (n/n)	Dose limiting toxicities	Patients with DLT/patients evaluable for DLT (n/n)	Dose limiting toxicities
2	0/3[a]	None	0	None
4	0/4	None	2/6 0/2[d]	G3 proteinuria > 2 weeks Acute nephrotic syndrome and TMA
5	2[b]/6	G3 stomatitis [b] G3 esophagitis reflux	0/4	None
6	1/6	Febrile neutropenia	2[c]/6	G3 stomatitis G3 abdominal pain due to subocclusion

a excluding patient not evaluable for DLT due to known leuconeutropenia of ethnic origin.

b patient received 5-FU day 1 infusion at cycle 2 in 1 hour instead of 24 hours. Grade 3 stomatitis not considered as DLT.

c not considered as DLTs, considered to be linked to chemotherapy and underlying disease

d 2 additional patients treated before Part 2 of the study was opened

G=grade, n=number, TMA=thrombotic microangiopathy

For Part 2 of study TCD6118, the 4 mg/kg dose of aflibercept was selected as the RP2D. However, as discussed above this dose was not selected on the basis of DLTs as no dose-dependent DLTs were observed for the dose-escalations 2, 4, 5 and 6 mg/kg. Therefore, the 4 mg/kg dose was stated by the sponsor to be the optimum dose based on:

- an aflibercept free/bound ratio >1 during the 2 week period, approaching a ratio of 1 at the end of the cycle for all patients;
- the high level of efficacy in the heavily pretreated study population. Of the patients evaluable for response, partial responses were seen at all dose levels with the majority being observed in the 4 mg/kg group (i.e., 1/4 [2 mg/kg], 5/11 [4 mg/kg], 1/10 [5 mg/kg], 2/10 [6 mg/kg]);
- an acceptable safety profile with no apparent dose effect being observed for clinical TEAEs; and
- no cumulative toxicity observed.

Comment: The submission included no formal dose response studies in patients with MCRC. The dose of aflibercept (4 mg/kg) chosen for the pivotal Phase 3 study (VELOUR) was based on the findings from Part 1 of study TCD6118. The sponsor stated that the data from Part 2 (extension phase) of study TCD6118 confirm the "feasibility of the combination regimen", including aflibercept at a dose of 4 mg/kg (27 patients were treated with 417 cycles). Furthermore, the sponsor noted that 7 patients out of 42 with MCRC in the study showed objective partial response and 27 had stable disease as the best response category (i.e., 81% with disease control), confirming the activity of aflibercept combined with LV5U2-CPT11 in the pretreated MCRC population. Despite the sponsor's support for the 4 mg/kg dose based on study TCD6118, it is considered that the optimum dose of aflibercept for the proposed indication has not been adequately characterized in the submitted data.

6. Clinical efficacy

6.1. VELOUR/EFC10262 - pivotal study for MCRC - 2nd line treatment

6.1.1. Study design, objectives, locations and dates

The submission included one, pivotal Phase 3 efficacy and safety study provided to support the proposed indication. This was a prospective, multinational, multicentre, randomized (1:1), double-blind, parallel-arm study of aflibercept versus placebo in patients with metastatic colorectal cancer (MCRC) being treated with irinotecan/bolus-infusion-5-FU/leucovorin (FOLFIRI = folfiri), following disease progression while on or after completion of treatment with an oxaliplatin based regimen. The study was sponsored by Sanofi-Aventis, France. The results of the study were presented at the 12th ESMO-World Congress on Gastrointestinal Cancer, Barcelona 2010, (Van Cutsem *et al*, 2011). However, the full study report had not been published at the date of submission.

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

The **secondary objectives** were: to compare progression free survival (PFS) in the two treatment arms; to evaluate overall response rate (ORR), as per response evaluation criteria in solid tumours (RECIST), in the two treatment arms; to evaluate the safety profile in the two treatment arms; to assess immunogenicity of iv aflibercept; to assess the PKs of iv aflibercept and to perform a population-pk evaluation.

The co-ordinating investigator was located at the University of Florida (USA), Department of Medicine (Hematology/Oncology). The study took place in 28 countries (including Australia) at 176 active centres. The first patient was enrolled on 19 November 2007, the data cut-off date was 7 February 2011 (at 863rd patient's death), and the date of the Clinical Study Report (CSR) was 23 August 2011. The protocol and its 5 amendments were submitted to all relevant independent ethics committees (IECs) and/or institutional review boards (IRBs) for review and written approval. The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws, regulations, and applicable guidelines of the countries in which the study was conducted. Informed patient consent was obtained prior to the conduct of any study-related procedures.

Comment: The study design is considered satisfactory. The sponsor stated that the FOLFIRI regimen was chosen because of its "worldwide recognition as a standard regimen for the treatment of patients with MCRC by the medical oncology community". Second-line therapy of MCRC is accepted in most centres for patients with good performance status, and the choice of agents depends on earlier lines of treatment with FOLFIRI being an acceptable second line option (Van Cutsem *et al*., 2011). The use of first line oxaliplatin is consistent with the approved Australian indication relating to treatment of advanced colorectal cancer.

In Australia, bevacizumab is approved for the treatment of MCRC in combination with fluoropyrimidine-based chemotherapy. Therefore, the more clinically relevant comparison would have been aflibercept/FOLFIRI compared with bevacizumab/FOLFIRI for second-line treatment for patients previously treated with oxaliplatin, rather than aflibercept/FOLFIRI compared with placebo/FOLFIRI. However, the sponsor stated that "at the time the study was initiated no data were available in the second-line setting after an oxaliplatin based therapy for the combination of FOLFIRI and bevacizumab, which therefore precluded conducting the trial with bevacizumab as active comparator". The sponsor's statement is acceptable.

6.1.2. Inclusion and exclusion criteria

The study included adult patients aged 18 years or older with histologically or cytologically proven adenocarcinoma of the colon or rectum, with metastatic disease not amenable to potentially curative treatment (i.e., inoperable), and one and only one prior chemotherapeutic regimen for metastatic disease that had to be an oxaliplatin containing regimen. To be eligible for randomization, patients with MCRC were to have progressed during or after discontinuation of a prior oxaliplatin-based chemotherapy for metastatic disease or progressed within 6 months following adjuvant therapy with an oxaliplatin containing regimen. Patients with measurable or non-measurable disease (as per RECIST) were eligible. Patients were to have adequate haematological, renal and hepatic function, no uncontrolled hypertension, and no brain metastasis at baseline. Patients who received prior therapy with irinotecan were excluded, but prior treatment with a biologic agent in combination with the prior line of chemotherapy was allowed, and prior use of bevacizumab was subject to stratification at randomization. The inclusion and exclusion criteria are summarized in the dossier. The study also included criteria for removing patients from the study based on disease progression; unacceptable toxicity not manageable by symptomatic therapy, cycle delay of dose modification; intercurrent illness; loss to follow-up; unblinding by the investigator; or patient's decision.

Comment: The inclusion and exclusion are considered to be satisfactory for oncology studies in patients with advanced metastatic disease being treated with second-line therapy. The exclusion criteria were extensive.

6.1.3. Study treatments

Patients received either aflibercept 4 mg/kg or placebo infused iv over 1 hour, followed immediately by the folfiri regimen, with treatment being repeated every 2 weeks (q2w), with a plus or minus 2-day treatment window being permitted.

The folfiri regimen was:

- irinotecan 180 mg/m^2 iv infusion in 500 mL D5W over 90 minutes and dl leucovorin 400 mg/m^2 iv infusion over 2 hours, at the same time, in bags using a Y-line, followed by;
- 5-FU 400 mg/m^2 iv bolus given over 2-4 minutes, followed by;
- 5-FU 2400 mg/m^2 continuous iv infusion in 500 mL D5W (recommended) over 46 hours.

BSA was calculated prior to each treatment cycle from body weight recorded prior to the start of each treatment cycle, and height recorded at baseline. The Dubois and Dubois equation was the preferred method of calculating (i.e., BSA m^2 = weight in kg 0.425 x height in cm 0.725 x 0.007184). In case were the BSA was >2.0 m^2, actual doses of irinotecan and 5-FU were adjusted to a maximum BSA of 2.0 m^2 for safety reasons.

Patients were to receive treatment until disease progression, unacceptable toxicity, patient refusal to continue or investigator decision to stop treatment. Patients were to be followed for the duration of treatment, and for survival until death or study cut-off date, whichever came first. After the data cut-off for primary analysis of OS, patients who were still receiving study treatment or alive patients who had completed study treatment and were experiencing ongoing serious adverse events (SAEs) or new and/or ongoing related adverse events (AEs), were to be respectively followed for safety purposes up to stabilization or resolution for a maximum of 9 months after the study cut-off date (Protocol Amendment 5).

Premedications included: for cholinergic adverse effects (including early diarrhoea), unless contraindicated 0.25 to 1 mg iv or sc atropine; antiemetics according to hospital practice; granulocyte-colony stimulating factor (G-CSF) recommended in accordance with American Society of Clinical Oncology guidelines (Smith *et al*., 2006). Following implementation of Protocol Amendment 4 on 11 February 2010, it was recommended that investigators initiate

treatment with G-CSF on occurrence of a first episode of grade ≥3 neutropenia and implement secondary prophylaxis for subsequent treatment cycles.

Dose adjustments (according to the worst grade toxicity) and/or cycle delays were permitted in cases of toxicity; dose adjustments were to be made according to the worst grade toxicity (graded according to NCI-CTC AE v3.0). Once a dose had been decreased, re-escalation was not permitted for that patient. Delays of up to 2 weeks were permitted in cases of unresolved toxicity at the time of planned re-administration (administration of aflibercept/placebo could be omitted for one cycle). New cycles could not begin until study drug-related toxicities were adequately resolved.

The protocol specified that only one dose reduction for aflibercept/placebo from 4 mg/kg to 2 mg/kg was allowed and listed the actions to be taken according to the type of toxicity. The protocol specified 2 dose reductions for irinotecan and 5-FU based on worst toxicity during the previous cycle: i.e., irinotecan/bolus 5-FU/infusional 5-FU initial (180/400/2400) → level 1 reduction (150/320/2000) → level 2 (120/240/1500).

Permitted concomitant treatments included all supportive measures (including blood transfusions and erythropoietin) consistent with optimal patient care, C-GSF, anti-hypertension medications, anti-diarrhoeal medications, atropine sulfate, antiemetics, benzodiazepines, analgesics, and heparins.

Non-permitted concomitant treatments included systemic cancer agents other than those being investigated, other investigational therapies or devices, concomitant radiotherapy, and anticonvulsants that are CYP3A4 inducers.

6.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was overall survival (OS), defined as the time interval from the date of randomization to the date of death due to any cause. Once disease progression was documented, patients were to be followed every 2 months for survival status, until death or until the study cut-off date, whichever came first.

The secondary efficacy endpoints were: *progression free survival (PFS)*, defined as the interval from the date of randomization to the date of first observation of disease progression or the date of death due to any cause, whichever came first; and *objective response* (complete response [CR] and partial response [PR]) according to RECIST criteria version 1.0 (see Appendix A for quick reference to RECIST).

Tumour assessment was to be conducted within 21 days before randomization, and then every 6 weeks until progression. Assessment were also to occur during the follow-up phase in cases of early study treatment discontinuation (i.e., prior to documented progression). First occurrence of response was to be confirmed by a second imaging performed at least 4 weeks later. The same imaging techniques were to be used from baseline to disease progression to maintain consistency. Ultrasound was not permitted for evaluation of tumour progression.

Independent imaging third party review was initiated following implementation of Protocol Amendment 2 on 23 April 2008. The independent review committee (IRC) was blinded to randomization. Third party review of PFS event was considered to be the main PFS analysis. Objective response rate (ORR) was also calculated using measurements made by the IRC. For patients who died before implementation of Amendment 2 or who denied consent for IRC review, the investigators' information was used in the PFS analysis. Only patients who consented to third party review were included in the analyses of ORR (i.e., patients who died before implementation of Amendment 2 or who denied consent were excluded).

Comment: The primary and secondary efficacy endpoints of OS and PFS are consistent with those described in the relevant TGA adopted EMEA guideline as being "acceptable" in confirmatory Phase 3 therapeutic confirmatory trials for evaluating anticancer medicinal products (CPMP/EWP/205/95/Rev.3/Corr.2). In addition, the ORR is an acceptable secondary

efficacy endpoint for the pivotal study. The inclusion of independent review of the imaging data (blinded to randomization) strengthens the endpoint analyses based on these data due to interpretation being less subject to observer bias.

6.1.5. Randomization and blinding methods

Randomization (1:1) was stratified according to prior therapy with bevacizumab (yes vs no), and baseline Eastern cooperative oncology group performance status (ECOG PS) (0 vs 1 vs 2) (see Appendix B for ECOG PS criteria). Treatment allocation was performed by Interactive Voice Response System (IVRS). Patients who were in a blinded follow-up phase of a double-blind controlled study with bevacizumab at the time of randomization could still be randomized in VELOUR. In such cases, stratification for prior bevacizumab was to be "yes". Patients, investigators, and other persons responsible for study conduct and data analyses were blinded to treatment assignment. Aflibercept and placebo were supplied in indistinguishable sealed vials in identical boxes corresponding to individual patient kits.

6.1.6. Analysis populations

Three analysis populations were defined (randomized, efficacy and safety); see Table 27 below.

Table 27: VELOUR – Summary of the analysis populations.

	Placebo/Folfiri	Aflibercept/Folfiri	All
Randomized population	614 (100%)	612 (100%)	1226 (100%)
Efficacy populations			
Intent-to Treat (ITT)	614 (100%)	612 (100%)	1226 (100%)
Evaluable Patient population[a]	530 (86.3%)	531 (86.8%)	1061 (86.5%)
Safety population	605	611	1216

a For response rate only. Note: For the safety population, patients are tabulated according to treatment actually received. Patients who received at least one dose of aflibercept are counted in the aflibercept/FOLFIRI treatment group, whatever the randomization group. For efficacy populations, patients are tabulated according to their randomized treatment.

The intent-to-treat (ITT) population was the primary population for the analysis of efficacy (OS and PFS), and included all patients who gave informed consent and for whom there was confirmation of successful allocation of a randomization number. All analyses using this population were based on treatment assigned by IVRS. In this study, the ITT included all randomized patients.

The evaluable population (EP) was used for assessment of tumour response rate. It included all randomized patients with measurable disease at study entry, as per IRC evaluation, with at least one valid post-baseline tumour evaluation. Patients who died due to progressive disease (PD), or who had documented radiological progressive disease before the first protocol scheduled post-baseline imaging evaluation were not excluded. All analyses using the EP population were based on randomized treatment assigned by IVRS. Only those patients who consented to third party review were part of the EP analysis.

The safety population comprised the subset of the ITT population that took at least one dose of study treatment (aflibercept, placebo or FOLFIRI). Analyses in this population were based on treatment actually received.

6.1.7. Sample size

For the primary endpoint of OS, the expected median survival time in the control arm (placebo/folfiri) was 11 months. A 20% risk reduction in the aflibercept/folfiri arm compared with the placebo/folfiri arm was expected (i.e., HR of 0.80, corresponding to a median OS improvement from 11 months in the control placebo/folfiri arm to 13.75 months in the test aflibercept/folfiri arm). Assuming that survival times would be exponentially distributed in both treatment arms, a total of 863 deaths was required to detect with 90% power a 20% risk

reduction in the aflibercept/folfiri arm relative to the placebo/folfiri arm, using a two-sided, log-rank test at a significance level of 0.0499. The calculation took into account the stopping boundaries for overwhelming efficacy at two interim analyses of OS (at 36.5% and 65% of 863 deaths) 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)-spending function at the first interim analysis. 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 1200 patients (600 in each arm) were required to achieve the targeted number of events.

6.1.8. Statistical methods

6.1.8.1. Primary analysis (OS)

In the primary analysis of OS, the two treatment arms were compared in the ITT population using a log-rank test stratified by the factors specified at the time of randomization by the IVRS (i.e., prior therapy with bevacizumab [yes vs no] and ECOG PS [0 vs 1 vs 2]). The estimates of the hazard ratio (HR) and corresponding confidence interval (CI) at the (1-α)% level (α being the two-sided nominal significance level: α=0.0466 at final analysis) were provided using a Cox Proportional Hazard Model (CPHM) stratified by the same factors as those used for the log-rank test. The median OS, probabilities of surviving at 3, 6, 9, 12, 18, 24, and 30 months, and CIs were presented by treatment arm using Kaplan-Meier estimates. The cut-off date for the analysis of OS was to be the time when the 863rd death had occurred.

OS subgroup analyses were also undertaken with respect to the following demographic / baseline characteristics and prognostic factors: ECOG PS (according to IVRS); prior bevacizumab (according to IVRS); age; gender; race; location of primary tumour; number of metastatic organs (as per IRC); liver metastasis (as per IRC evaluation); prior hypertension and geographical region. For each parameter, a CPHM was used for the overall population, including the parameter, treatment effect and the treatment by parameter interaction. Within each selected subgroup, the treatment effect HR and its (1-α)% CIs were estimated using a CPHM on patients of that subgroup (α being the same as in the primary analysis, α=0.0466). For each subgroup and for the overall population, HRs and (1-α)% CIs were displayed using forest plots. A multivariate analysis of OS was also performed using a CPHM with the covariates described above.

6.1.8.2. Secondary efficacy analyses (PFS and RR)

PFS was analyzed in the ITT population, and was based on the IRC evaluation. However, since IRC review was not in place at the start of the study, investigator assessments were used for patients who died prior to the implementation of IRC review, and for those patients who did not give consent for third party IRC review. If death or progression was not observed, the patient was censored at the date of last valid tumour assessment without evidence of progression, or at the study cut-off date whichever came first, regardless of initiation of further anti-tumour therapies.

PFS was analyzed using the Kaplan-Meier method, and treatment arms were compared using the log-rank test stratified by the factors determined at randomization (IVRS) at a 2-sided, 0.0001 significance level. The estimates of the HR and corresponding 99.99% CI were provided using a CPHM stratified by the same factors, and 95% CIs for the HR were also provided. The final PFS analysis was conducted at the time of the second interim analysis for OS when 561 deaths had occurred. Assuming a median PFS time in the control arm of 4 months, it was considered that an improvement in a range of 2 to 2.5 months in median PFS could reasonably reflect a clinically meaningful treatment benefit in OS. Based on a predicted 845 PFS events, allocation of an alpha of 0.0001 to the final PFS analysis would allow the statistical evaluation to be consistent with a meaningful clinical judgment. Three sensitivity analyses of PFS were undertaken.

The RR, based on the IRC evaluation, was analyzed in the EP and was summarized using descriptive statistics and 95% CIs. Best overall response (CR, PR, SD, PD, NE) was summarized using descriptive statistics.

6.1.8.3. Other comments

Multiplicity of endpoints was handled by splitting the overall alpha level between OS and PFS: PFS was tested at a 2-sided, 0.0001 level and OS was tested at a 2-sided, 0.0499 level. The RR was to be tested only after either OS or PFS tested positive.

No changes to the statistical analyses of the data were made after the study blind was broken.

6.1.9. Interim analyses

Two interim analyses of OS were planned to be performed by an independent external statistician, and to be reviewed by the DMC independently of sponsor involvement. The results of these interim analyses were reviewed by the DMC and the recommendation was to continue the study.

The initial protocol specified one formal interim analysis to be undertaken when 561 death events (65% of the 863 planned) had occurred, using a two-sided nominal significance level of 0.0107 based on an O'Brien-Fleming alpha spending function. Early stopping of the study for efficacy was to be considered if the O'Brien Fleming efficacy boundary was met. The final PFS analysis was performed at the time of this interim OS analysis.

At the request of the DMC, an additional interim analysis of OS was performed, prior to that specified in the initial protocol, in order to provide an early evaluation of the benefit-risk ratio. This analysis was undertaken when 315 death events (i.e., 36.5% of the 863 planned) had occurred (Protocol Amendment 3). A futility boundary was planned for that analysis, based on a Gamma(-5) b-spending function. The boundary would be crossed if the HR was ≥ 1.084 in favour of the placebo/folfiri arm at the predicted 36.5% information fraction. The corresponding conditional power under the alternative hypothesis at that time was 0.327. In order to maintain the integrity of the trial (penalty for type-I error), a stopping boundary for possible overwhelming efficacy was also planned using the O'Brien-Fleming alpha spending function. The two-sided nominal significance level for efficacy at this interim analysis was 0.00042.

For both interim analyses, the primary analysis was the comparison of OS between treatment groups using the log-rank test procedure stratified by the same factors as for the final analysis. The HR estimate and corresponding (1-α)% CI were provided using a CPHM stratified by the same 2 factors (α=0.00042 for first interim analysis, α=0.0107 for second interim analysis). Using a group sequential approach with an O'Brien Fleming Alpha-spending function and an overall two-sided α level of 0.0499, the two-sided nominal significance level to be used at the final analysis of OS was 0.0466.

6.1.10. Participant flow

A total of 1401 patients signed informed consent forms, and 175 of these patients were screening failures and were not randomized. The submitted CSR summarized the results of analyses made on 1226 patients who were randomized between 19 November 2007 and 16 March 2010 (614 to placebo/folfiri; 612 patients to aflibercept/folfiri). Of the 1216 randomized patients, 5 in each treatment arm were not treated. These included 4 patients who were ineligible, 2 patients who withdrew consent or did not wish to continue, 2 patients who developed an illness or exacerbation of an existing illness, one patient for whom reimbursement of supportive care by "medical aid" was denied, and one patient who experienced rapid disease progression before treatment could be given. Patient disposition in the ITT population is summarized below in Table 28. Stratification as per IVRS based on baseline ECOG and prior bevacizumab was well balanced between the two randomized treatment groups (see Table 29, below).

In accordance with the protocol, the cut-off date for survival was the date when the 863rd patient death occurred (i.e., 7 February 2011). At this time, 598 patients (97.4%) in the placebo arm and 593 patients (96.9%) in the aflibercept arm had discontinued study treatment, while 11 and 14 patients, respectively, continued to receive treatment. The main reason for treatment discontinuation was disease progression, which occurred with greater frequency in the placebo/folfiri arm (71.2%) than in the aflibercept/folfiri arm (49.8%), and AEs, which occurred with greater frequency in the aflibercept/folfiri arm (26.6%) than in the placebo/folfiri arm (12.1%).

Table 28: VELOUR – Patient disposition; ITT population.

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

Table 29: VELOUR - Patients randomized by stratification factor (as per IVRS); ITT population

Stratification factors	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
ECOG PS [n(%)]			
0	350 (57.0%)	349 (57.0%)	699 (57.0%)
1	250 (40.7%)	250 (40.8%)	500 (40.8%)
2	14 (2.3%)	13 (2.1%)	27 (2.2%)
Prior Bevacizumab [n(%)]			
Yes	187 (30.5%)	186 (30.4%)	373 (30.4%)
No	427 (69.5%)	426 (69.6%)	853 (69.6%)

6.1.11. Major protocol violations/deviations

Important protocol deviations were defined as important selection criteria deviations or randomization and drug dispensing irregularities.

There were 16 patients with at least one important selection criteria deviation (10 in the placebo/folfiri arm, 6 in the aflibercept/folfiri arm). These patients were not excluded from the ITT population or the EP population. There were 3 patients in the randomized population without histologically proven primary tumours in the colon or rectum (1 in the placebo/folfiri

arm, 2 in the aflibercept/folfiri arm). Details of selection criteria deviations were provided in the dossier.

At the time of randomization, a total of 58 patients had errors with regards to stratification data, with 27 (4.4%) patients in the placebo/folfiri arm and 31 (5.1%) patients in the aflibercept/folfiri arm having at least one stratification error. Overall, errors in stratification at randomization were reasonably well balanced between the two treatment arms.

In the randomized to placebo/folfiri arm (n=609), 605 (99.3%) patients actually received placebo/folfiri treatment compared with 4 (0.7%) patients who received aflibercept/folfiri. In the randomized to aflibercept/folfiri arm (n=607), all patients received aflibercept/folfiri treatment.

The study blind was broken at the local level for 3 patients in the placebo/folfiri arm due to adverse events (1x toxic pericarditis, 1x fractured neck of femur, 1x worsening renal calculi), and 2 patients in the aflibercept/folfiri arm (1x ileus, 1x due to disease progression). The study blind was also broken at the central level by the global safety officer for 19 patients (6 placebo/folfiri and 13 aflibercept/folfiri) for the purpose of regulatory reporting (i.e., unexpected serious adverse reactions).

Comment: Overall, it is considered that the protocol violations/deviations are unlikely to have biased the study or significantly affected the analysis of the efficacy data. The protocol violations/deviations were reasonably well balanced between the two treatment groups.

6.1.12. Baseline data

Demographics: Patient demographics were well balanced between the two treatment arms, with similar distributions of patients according to gender, age, race and geographical location. In both treatment arms, approximately 60% of patients were male. The median age of the total ITT population (n=1226) was 61.0 years (range: 19, 86), with 63.9% of patients aged < 65 years, 30.3% aged ≥ 65 but < 75 years, and 5.9% aged ≥ 75 years. In both treatment arms, more than 85% of patients were Caucasian/White.

Baseline disease characteristics: The baseline disease characteristics were well balanced between the two treatment arms. In the total ITT population (n=1226), the distribution of the primary site of disease was colon 48.2%, rectosigmoid 21.1%, rectum 28.3%, and other 0.4%, with all patients having confirmed adenocarcinoma. In the ITT population, the median time was from first diagnosis to randomization 14.3 months (range: 2.1, 325.1 months), with time data missing for 1 patient in the aflibercept/folfiri arm.

Metastatic sites at baseline: Baseline metastatic disease characteristics were well balanced between the two treatment arms. In the total ITT population (n=1226), 43.0% had 1 metastatic site at baseline and 56.4% had more than 1 metastatic site. There were 8 patients without a previous metastatic site (6 in the placebo/folfiri arm, 2 in the aflibercept/folfiri arm), and these patients were excluded from the analysis of response rate in the EP. Overall, the most frequently involved organs were the liver (72.6%), the lungs (44.7%) and the lymph nodes (28.9%).

Stratification factors: Baseline stratification factors were well balanced between the two treatment arms, as per eCRF (case report form) corrected for inconsistencies between initial reporting between the IVRs and eCRF (see Table 30, below).

Table 30: VELOUR - patients randomized by level of stratification factor (as per eCRF); ITT population.

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
ECOG PS [n(%)]			
0	354 (57.7%)	350 (57.2%)	704 (57.4%)
1	248 (40.4%)	249 (40.7%)	497 (40.5%)
2	12 (2.0%)	13 (2.1%)	25 (2.0%)
Prior Bevacizumab [n(%)]			
Yes	177 (28.8%)	169 (27.6%)	346 (28.2%)
No	437 (71.2%)	443 (72.4%)	880 (71.8%)

Note: ECOG: Eastern Cooperative Oncology Group, PS: Performance Status, CRF: Case Report Form

Prior chemotherapy: Prior chemotherapies were well balanced between the two treatment arms. In the total ITT population (n=1226), all patients had received at least one prior chemotherapy with 10.1% having received only adjuvant chemotherapy and all others advanced chemotherapy, either with or without prior neoadjuvant/adjuvant chemotherapy (17.1% and 72.8%, respectively). Prior exposure to oxaliplatin was well balanced between the 2 treatment arms with an overall median duration of 5.16 months (range: 0.1, 23.9), and only two patients (one in each treatment arm) had not received prior treatment with oxaliplatin. In the majority of patients oxaliplatin was administered as part of a combination regimen, with 99.3% (n=1218) receiving oxaliplatin with a fluoropyrimidine. In 4 patients from the placebo/folfiri arm and 2 from the aflibercept/folfiri arm, prior oxaliplatin was administered as a single agent. Overall response rates (complete plus partial response) to prior first line advanced chemotherapy were 40.9% and 44.5% in the placebo/folfiri and aflibercept/folfiri arms, respectively.

Prior surgery: Prior anti-cancer surgeries were well balanced between the two treatment arms. In the total ITT population (n=1226), 83.4% had undergone prior anti-cancer surgery; 51.8% primary tumour resection of the colon, 28.5% primary tumour resection of the rectum, and 12.2% surgical metastasis resection.

Prior radiation therapy: Prior anti-cancer radiation therapies were well balanced between the two treatment arms. In the total ITT population (n=1226), 21.4% had received prior radiation therapy, with the intent being curative in 13.0% and palliative in 9.1%.

Prior cardiovascular disease: The submission included a comprehensive summary of patients with a prior history cardiovascular disease, and these patients were well balanced between the two treatment groups. In the placebo/folfiri and aflibercept/folfiri arms, 65.3% (n=401) and 64.9% (n=397) of patients, respectively had a history of thrombovascular events and/or presence of cardiovascular risk factors. The most commonly reported prior cardiovascular disease was hypertension (43.6% [n=267] and 43.5% [n=266], placebo/folfiri and aflibercept/folfiri arms, respectively).

Baseline laboratory abnormalities: The submission included a comprehensive summary of baseline laboratory findings, including electrolytes, haematology, metabolism, and urinalysis. Baseline laboratory parameters were similar for the two treatment groups. Anaemia was the most commonly reported haematological baseline abnormality, with grade 1-2 anaemia being reported in 47.6% (n=292) of patients in the placebo/folfiri arm and 44.2% (n=270) of patients in the aflibercept/folfiri arm, with no baseline grade 3-4 anaemia being reported in either treatment arm. Thrombocytopenia grade 1 was reported at baseline in 13.1% (n=80) of patients in the placebo/folfiri arm and 12.3% (n=75) of patients in the aflibercept/folfiri arm, and no patients in either treatment arm had baseline events ≥ grade 2. Hyperbilirubinaemia grade 1-2 was reported at baseline in 7.7% (n=47) of patients in the placebo/folfiri arm and in 6.4% (n=39) of patients in the aflibercept/folfiri arm. Proteinuria (morning spot or 24-hour collection) grade 1-2 was reported at baseline in 14.6% (n=87) of patients in the placebo/folfiri arm and in 13.6% (n=82) of patients in the aflibercept/folfiri arm. Creatinine clearance was

normal in 65.3% (n=314) of patients in the placebo/folfiri arm and 67.6% (n=321) of patients in the aflibercept/folfiri arm, with respective rates for clearance ≥ 60 to ≤ 80 mL/min being 23.9% (n=115) and 25.9% (n=123), and for clearance ≥ 30 to < 60 mL/min being 10.8% (n=53) and 6.5% (n=83). There were no reports of patients in either treatment arm with creatinine clearance values < 30 mL/min, but data on creatinine clearance was missing in 22.0% (n=270) of the total ITT population.

Prior and concomitant medication: The submission included a summary of prior antihypertensive medications in patients with a history of the hypertension, and prior anticoagulant medications for patients with and without prior thrombovascular events. In patients with prior hypertension (43.6%, overall in the ITT population), anti-hypertensive medications had been used by approximately 90% of patients in both treatment arms. In patients with prior thrombovascular events (16.2% overall in the ITT population), anti-coagulant use was similar in the two treatment arms (52.1% placebo/folfiri, 61.0% aflibercept/placebo). In patients without prior thromboembolic events (83.8%, overall in the ITT population), anti-coagulant use was also similar in the two treatment arms (9.0% placebo/folfiri, 8.7% aflibercept/folfiri).

Endogenous VEGF: Endogenous VEGF was measured only at those sites equipped with a 4°C centrifuge. Consequently, data were available for only 68% (n=838) of patients in the ITT population (69.2%, n=425, placebo/folfiri; 67.5%, n=413, aflibercept/folfiri). The mean (SD) VEGF concentration was 91.8 (159.9) pg/mL in the placebo/folfiri arm and 73.9 (124.7) pg/mL in the aflibercept/folfiri arm.

6.1.13. Results for the primary efficacy outcome (overall survival)

The primary analysis demonstrated a statistically significant OS benefit in favour of aflibercept/folfiri compared with placebo/folfiri in the ITT population (see Table 31, and Figure 5, below). Median OS in the placebo/folfiri arm was 12.06 months (95.34% CI: 11.072, 13.109) and 13.50 months (95.34% CI: 12.517, 14.949) in the aflibercept/folfiri arm: HR = 0.817 (95.34% CI: 0.713, 0.937); p=0.0032, log-rank test. The analysis of OS was based on a total of 863 deaths, with 460 (74.9%) in the placebo arm and 403 (65.8%) in the aflibercept arm. The median follow-up time at the cut-off date in the ITT population was 22.28 months.

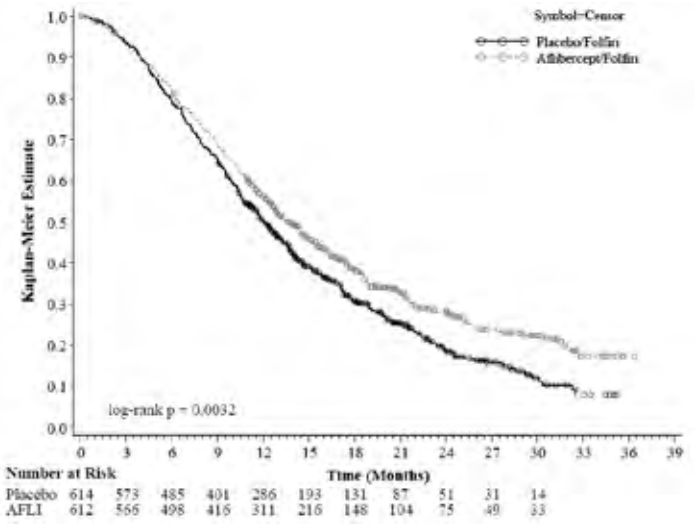
Table 31: VELOUR – Overall survival (OS) analysis (months); ITT population.

Parameter	Placebo/FOLFIRI (n=614)	Aflibercept/FOLFIRI (n=612)
Median OS (95.34% CI), months	12.06 (95.34% CI: 11.072, 13.109)	13.50 (95.34% CI: 12.517 to 14.949)
Number of death events, n/N (%)	460/614 (74.9%)	403/612 (65.8%)
Stratified log-rank test [a]	p = 0.0032	
Stratified HR (95.34% CI) [a]	HR = 0.817 (95.34% CI: 0.713, 0.937).	

Cutoff date = 7 February 2011; Median follow-up time = 22.28 in months

[a] Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS. Significance threshold is set to 0.0466 using the O'Brien-Fleming alpha spending function.

Figure 5: VELOUR- OS (months) – Kaplan-Meier curves by treatment group; ITT population



Patient censoring: In the placebo/folfiri arm, 149 patients (24.3%) were alive at the cut-off date, compared with 201 patients (32.8%) in the aflibercept/folfiri arm. Patient censoring information is provided in the dossier.

Probabilities of surviving over time: In the aflibercept/folfiri and placebo/folfiri arms, the respective probabilities of surviving were 38.5% (95.34% CI: 34.3, 42.7) vs 30.9% (95.34% CI: 26.9, 34.8) after 18 months, 28.0% (95.34% CI: 23.7, 32.4) vs 18.7% (95.34% CI: 14.9, 22.5) after 24 months, and 22.3% (95.34% CI: 17.8, 26.8) vs 12.0% (95.34% CI: 8.0 to 16.0) after 30 months.

Sensitivity analysis of overall survival (unstratified log-rank test): The results of the comparison of median survival times by unstratified log-rank test were consistent with the primary analysis: HR (unadjusted) = 0.809 (95.34% CI: 0.706, 0.927); p = 0.0019, log-rank test.

Sensitivity analysis of overall survival (multivariate Cox proportional hazards model): In a further sensitivity analysis using a multivariate Cox proportional hazards model the treatment effect of aflibercept/folfiri vs placebo/folfiri after adjusting for prognostic factors was consistent with the primary OS analysis: HR = 0.817 (95.34% CI: 0.713 to 0.936), p=0.0032. The prognostic factors in this analysis included ECOG PS (1 vs 0; 2 vs 0), prior bevacizumab status (yes vs no), age (≥ 65 vs < 65), prior hypertension status (yes vs no) and number of metastatic organs involved as per IRC (> 1 vs 0-1). Selection of the prognostic factors included in the multivariate analysis was done prior to database lock without including the treatment group, and using a stepwise procedure with a variable entry of 5% level and a variable removal at each step of 10% level. The following prognostic factors did not meet the criteria for inclusion in the final model: gender, race, region, and liver metastasis.

Subgroup analyses of overall survival by stratification factors (as per IVRS): OS favoured aflibercept/FOLFIRI over placebo/FOLFIRI for each stratification factor, with the exception of baseline ECOG PS of 2 (see Table 32, below). It is also noted that the HRs for the subgroups of prior bevacizumab, and ECOG PS 1 and 2 are not statistically significant as the 95.34% CIs includes 1. However, interactions between treatment arms and stratification factors were not significant at the 2-sided 10% level, supporting a consistent effect of treatment across the subgroups.

Table 32: VELOUR – OS (months) subgroup analyses stratification factors (as per IVRS); ITT population.

	Placebo/Folfiri Median (Months) (95.34% CI)	Aflibercept/Folfiri Median (Months) (95.34% CI)	Hazard Ratio (95.34% CI) vs Placebo/Folfiri	P-value for interaction[a]
All patients	12.1 (11.07 to 13.11)	13.5 (12.52 to 14.95)	0.817 (0.713 to 0.937)	
Prior bevacizumab				
No	12.4 (11.17 to 13.54)	13.9 (12.71 to 15.64)	0.788 (0.669 to 0.927)	0.5668
Yes	11.7 (9.82 to 13.77)	12.5 (10.78 to 15.51)	0.862 (0.673 to 1.104)	
ECOG PS				
0	14.1 (12.88 to 16.62)	16.9 (14.78 to 18.79)	0.768 (0.635 to 0.928)	0.7231
1	10.1 (9.20 to 11.53)	10.7 (9.36 to 12.35)	0.869 (0.71 to 1.063)	
2	4.4 (1.97 to 10.02)	2.8 (0.92 to 9.82)	0.978 (0.43 to 2.221)	

Cut-off date = 7 February 2011; Median follow-up time = 22.28 in months.

a Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction

Results for subgroup analyses of baseline demographic factors on OS are summarized using a forest plot. There was no evidence of treatment interaction at the 10% level between treatment groups and demographic factors, indicating a consistent treatment effect across demographic subgroups.

Results for subgroup analyses of baseline disease characteristics on OS are summarized using a forest plot. No significant interaction was observed at the 10% level except for liver metastasis only where a greater effect of treatment was observed in patients with liver metastases only compared with those with no liver metastasis or liver metastasis with other organs involved (p=0.0899). OS favoured aflibercept/folfiri over placebo/folfiri for all subgroups (i.e., HR < 1), except for the rectosigmoid/other primary tumour subgroup (HR = 1.04).

Comment: The study met its primary efficacy endpoint, demonstrating a statistically significant difference in OS in favour of aflibercept/folfiri compared with placebo/folfiri with a median difference between the two treatment arms of 1.44 months. Based on the HR for the primary analysis, there was an 18% risk reduction (HR = 0.817) of experiencing a death event in the aflibercept/folfiri arm compared with the placebo/folfiri arm. The observed results for both risk reduction and difference in median OS between the two treatment arms were inferior compared with the assumptions on which the sample size calculations were based: i.e., 20% risk reduction in aflibercept/folfiri arm compared with placebo/folfiri arm (HR = 0.80, corresponding to a median OS improvement from 11 months in the control arm to 13.75 months in the test arm). The observed results are considered to be clinically insignificant, based on the survival parameters used to calculate the sample size.

6.1.14. Results for the secondary efficacy outcomes

6.1.14.1. Progression free survival (PFS)

Analysis of PFS was based on a total of 847 events assessed by the IRC, with 454 (73.9%) in the placebo/folfiri arm and 393 (64.2%) in the aflibercept/folfiri arm. For 42 patients (26 aflibercept/folfiri, 16 placebo/folfiri) who died prior to the implementation of IRC review or who refused consent for the IRC, the investigator's tumour assessment was used. The final analysis of PFS was performed at the time of the second interim analysis of OS (cut-off date of 06 May 2010), and was conducted in the ITT population. Kaplan-Meier estimates of PFS for the two treatment arms in the ITT population were compared using a log-rank test stratified at the time of randomization (ECOG PS, 1 versus 0, 2 versus 0; prior bevacizumab, yes versus no), and are shown below in Table 33. The full summary of the PFS and the Kaplan-Meier curves for the two treatment arms are provided in the dossier.

Table 33: VELOUR – PFS (months); assessed by IRC in the ITT population.

Parameter	Placebo/FOLFIRI (n=614)	Aflibercept/FOLFIRI (n=612)
Median PFS (99.99% CI), months	4.67 (99.99% CI: 4.074, 5.552)	6.90 (99.99% CI: 5.881, 7.852)
Number of events, n/N (%)	454/614 (73.9%)	393/612 (64.2%)
Stratified log-rank test [a]	0.00007	
Stratified HR (99.99% CI) [a]	0.758 (CI: 99.99%: 0.578 to 0.995)	

Cut-off date = 06 May 2010.

a Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS.

Significance threshold is set to 0.0001.

- Of the 454 patients with an event in the placebo folfiri arm, documented disease progression accounted for 371 (81.7%) and death without disease progression accounted for 83 (18.3%). These figures differed from those in the aflibercept/folfiri arm where, of the 393 patients with an event, documented disease progression accounted for 292 (74.3%) and death without disease progression accounted for 101 (25.7%). The median time from last tumour assessment with a response different from "not evaluable" and "progressive disease" to death was 3.55 months (range: 0.2, 20.9) in the placebo/folfiri arm and 2.04 months (range: 0.2, 15.02) in the aflibercept/folfiri arm.
- In the first (#1) specified PFS sensitivity analysis, patients with documented radiological progression or death occurring more than 9 weeks (corresponding to 1.5 times the interval between assessments) after the last valid tumour assessment without progression were censored at the date of that tumour assessment, and patients who received further anti-cancer therapy without documented progression were censored at the date of the last valid tumour assessment. Estimation of PFS was based on 634 events, with 353 in the placebo/folfiri arm (57.5%) and 281 in the aflibercept/folfiri arm (45.9%). The median PFS was 4.53 months (99.99% CI: 4.074, 5.684) in the placebo/folfiri arm compared with 6.97 months (99.99% CI: 6.045, 8.509) in the aflibercept/folfiri arm. The stratified log-rank test p-value for placebo/folfiri compared with aflibercept/folfiri was <0.00001, and the stratified HR was 0.654 (99.99% CI: 0.477, 0.895).
- In the second (#2) specified sensitivity analysis, PFS was determined and analyzed using the investigators' assessment, and clinical progression was also considered to be an event, there was no statistically significant difference between the two treatment arms based on 937 events, with 485 events (79.0%) in the placebo/folfiri arm and 452 events (73.9%) in the aflibercept/folfiri arm. Median PFS was 4.50 months (99.99% CI 4.041, 5.552) in the placebo/folfiri arm compared with 6.24 months (99.99% CI 5.487, 7.195) in the aflibercept/folfiri arm. The stratified log-rank hazard ratio showed an improvement in PFS in favour of aflibercept/folfiri over placebo/folfiri (HR = 0.814; 99.99% CI: 0.63 to 1.052), but the difference was not significant at the 0.0001 level (stratified log-rank test p-value p=0.0017).

- Overall, the IRC reviewed data for 1184 patients. Discrepancies between the IRC and the investigators' assessments with regards to radiological PD status or the date of progression were reported in 273 patients (45.8%) in the placebo/FOLFIRI arm and 231 patients (39.3%) in the aflibercept/FOLFIRI arm. In particular, disagreements in the determination of PD status were reported for 142 patients (23.8%) in the placebo/FOLFIRI arm and 138 patients (23.5%) in the aflibercept/FOLFIRI arm.
- In an additional sensitivity analysis in which the PFS results were analyzed using an unstratified log-rank test, the results were consistent with the analysis using a stratified log-rank test. The HR (unadjusted) was 0.757 (99.99% CI: 0.578, 0.991) and the unstratified log-rank test p-value was 0.00005 (i.e., < 0.0001, significance threshold).
- In the pre-specified analysis by stratification factors at the time of randomization "as per IVRS", there were no statistically significant differences in PFS between the two treatment arms based on prior bevacizumab treatment. The forest plot for PFS based on baseline demographic factors, and the forest plot for PFS based on tumour assessment is provided in the dossier. In all subgroup comparisons, PFS favoured aflibercept/folfiri over placebo/folfiri. As seen for the subgroup analysis of OS, a significant interaction at the 10% level was observed between treatment arms and the liver metastasis subgroups (quantitative interaction, p=0.0076), demonstrating a greater effect of treatment in patients with liver metastases only (HR = 0.547 [99.99% CI: 0.313, 0.956]) compared with no liver metastasis or liver metastasis with other metastases (HR = 0.839 [99.99% CI: 0.617, 1.143]).

Comment: The median duration of PFS (IRC assessment) was 2.23 months longer in the aflibercept/folfiri arm than in the placebo/folfiri arm, and this increase was statistically significant. There was a 24% risk reduction (HR of 0.758) of experiencing a PFS event in the aflibercept/folfiri treatment arm compared with the placebo/folfiri treatment arm. The results of the first (#1) specified PFS sensitivity analysis supported the primary PFS analysis, but the results of the second (#2) specified PFS sensitivity analysis did not support the primary PFS analysis. An additional sensitivity analysis based on an unstratified log-rank test supported the primary PFS analysis. The subgroup analyses of PFS consistently favoured aflibercept/folfiri over the placebo/folfiri. There were no interactions at the 10% significance level between treatment and prior bevacizumab status or baseline ECOG PS score. A significant treatment by liver metastasis interaction was observed indicating a greater treatment effect in patients who had liver metastases only at baseline than in patients with no liver metastases or liver metastases with additional organ involvement (quantitative interaction p=0.0076). This interaction was also observed in the corresponding OS subgroup analysis.

6.1.14.2. Objective response rate

The evaluation of the response rate was conducted in the evaluable patient (EP) population and was based on IRC assessment (see Table 34, below). Overall, 165 patients were excluded from the EP population with a comparable number of patients being excluded from each treatment arm (placebo/folfiri 13.7%, n=84; aflibercept/folfiri 13.2%, n=81). In both treatment arms, the most common reason for exclusion was the absence of target lesions at baseline (57 [9.3%] patients in the placebo/folfiri arm; 41 [6.7%] patients in the aflibercept/folfiri arm).

Table 34: VELOUR – Overall objective response rate; EP population.

	Placebo/Folfiri (N=530)	Aflibercept/Folfiri (N=531)
Best Overall Response [n(%)]		
Complete response	2 (0.4%)	0
Partial response	57 (10.8%)	105 (19.8%)
Stable disease	344 (64.9%)	350 (65.9%)
Progressive disease	114 (21.5%)	55 (10.4%)
Not evaluable	13 (2.5%)	21 (4.0%)
Overall Response		
Responders (Complete response or Partial response)	59 (11.1%)	105 (19.8%)
95% CI[a]	8.5% to 13.8%	16.4% to 23.2%
Stratified Cochran-Mantel-Haenszel test p-value[b]		
Vs Placebo/Folfiri	-	0.0001

[a]estimated by Normal approximation
[b]Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS

Comment: The objective response rate (ORR) was statistically significantly higher in the aflibercept/folfiri arm than in the placebo/folfiri arm.

6.1.15. Further anti-cancer therapy

Overall, 730 (59.5%) patients in the ITT population went on to receive at least one further anti-cancer therapy (59.6% [n=366] of the placebo/folfiri arm; 59.5% [n=364] of the aflibercept/folfiri arm). The different types of first further therapy were comparable between the two arms, with the majority of patients receiving systemic anti-cancer therapy. In addition, the types of all further systemic anti-cancer treatments were also comparable between the two treatment groups.

Comment: Overall, more than half the patients 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.

6.2. Evaluator's conclusion on efficacy

The submission included only one efficacy study supporting registration of aflibercept for the proposed indication (VELOUR). In this pivotal study, there was a statistically significant difference in OS (the primary efficacy endpoint) in favour of aflibercept/folfiri compared with placebo/folfiri (stratified HR = 0.817 [95.34% CI: 0.713 to 0.937]; p=0.0032 log-rank test), based on 863 events and a median duration of follow-up of 22.28 months. The number of death events in the aflibercept/folfiri arm was 403 (65.8%) and 460 (74.9%) in the placebo/folfiri arm. Median OS in the aflibercept/folfiri arm (13.50 months [95.34% CI: 12.517, 14.949]) was 1.44 months longer than in the placebo/folfiri arm (12.06 months [95.34% CI: 11.072 to 13.109]).

However, while the difference in OS between the two treatment arms was statistically significant the results are considered not to be clinically significant based on the survival criteria used to calculate the sample size. The sample size was based on a 20% risk reduction in death events in the aflibercept/folfiri arm compared with the placebo/folfiri arm (HR = 0.80 corresponding to a median OS improvement from 11 months in the placebo/folfiri arm to 13.75 months in the aflibercept/folfiri arm). The observed risk reduction in the aflibercept/folfiri arm compared with the placebo/folfiri arm was 18% (c.f., 20% sample size survival criteria) and the observed difference in median OS in favour of placebo/folfiri was 1.44 months (c.f., 2.75 months sample size survival criteria). Based on the survival criteria used to calculate the sample size, it is reasonable to infer that a relative risk reduction of 20% in death events and a median difference of 2.75 months in OS in favour of aflibercept/folfiri compared with placebo/folfiri are the minimum clinically significant criteria required for this study. As aflibercept/folfiri failed to meet either of these criteria it is considered that the observed results for OS are not clinically significant.

The two secondary efficacy analyses of PFS and ORR both statistically significantly favoured the aflibercept/folfiri arm over the placebo/folfiri arm. The PFS stratified HR was 0.758 (99.9% CI: 0.578, 0.995), p=0.00007 log-rank test, and the difference in median PFS was 2.23 months in favour of aflibercept/folfiri (6.90 months [99.99% CI: 5.881, 7.852]) compared with placebo/folfiri (4.67 months [99.99% CI: 4.074, 5.552]). The ORR was 19.8% (95% CI: 16.4, 23.2) in the aflibercept/folfiri arm and 11.1% (95% CI: 8.5%, 13.8%), p=0.0001 stratified CMH test.

7. Clinical safety

7.1. Studies providing evaluable safety data

7.1.1. Pivotal safety data – VELOUR

In VELOUR, 1226 patients were randomized, and 1216 of these patients received at least one dose of study treatment and were included in the safety population (605 in the placebo/folfiri arm, 611 in the aflibercept/folfiri arm). Of the randomized patients, 5 in each treatment arm did not receive treatment and were excluded from the safety analysis, and 4 patients who were randomized to the placebo/folfiri arm received at least one dose of aflibercept and were included in the aflibercept/folfiri arm for the safety analysis.

All AEs regardless of seriousness or relationship to study treatment, from the first administration of study treatment until 30 days after the last administration of study treatment, were to be recorded. Signs and/or symptoms that were present, or occurred, from the time the patient signed the informed consent form to first study drug administration were recorded as AEs. During the treatment period AEs were systematically collected at each visit up to the 30-day visit. During the follow-up period after the 30-day visit, treatment related ongoing AEs, new treatment related AEs, and SAEs ongoing at the end of study treatment (regardless of relationship to study treatment), were followed until resolution or stabilization. The type, severity, seriousness and relationship to study treatment of TEAEs were recorded, and event severity was assessed according to National Cancer Institute Common Terminology Criteria (NCI-CTC), version 3.0.

Laboratory safety tests (including complete blood counts, serum chemistries, urine analyses and other tests as clinically indicated) were to be obtained prior to the first study drug administration, at every visit before treatment administration and at the 30-day follow-up visit. Laboratory safety tests were carried out according to standard operating procedures by the local laboratories. Laboratory abnormalities were assessed according to NCI-CTCAE criteria, version 3.0.

Assessment of vital signs (including systolic and diastolic blood pressure, and body weight) and ECOG performance status was conducted as part of the clinical examination within 8 days before randomization, before each treatment cycle, and at the 30-day follow-up visit. Vital signs or ECG abnormalities were to be recorded as AEs only if considered medically relevant by the investigator.

7.1.2. Supportive safety data - Summary of Clinical Safety (SCS)

The submission included a Summary of Clinical Safety (SCS) located in Module 2.7.4 of the dossier. This summary included a total of 2073 patients exposed to aflibercept from Phase 1, 2, and 3 clinical studies, including 611 from VELOUR (see Table 35, below). The cut-off date for the SCS was 07 February 2011. It appears that, as the result of a presubmission meeting between the sponsor and the FDA in July 2011, it was agreed that the text of the Integrated Summary of Safety (ISS), generally located in Module 5, would be identical to the SCS and be presented only in Module 2, with supporting tables, appendices, and datasets being provided in Module 5.

The safety data from the single-agent Phase 1 and 2 studies and the Phase 1 combination chemotherapy studies provided in the SCS (see Table 35, below) have been examined, and safety data from the individual studies have been included in the synopses of these studies. The safety data from these Phase 1 and 2 studies are consistent with the safety data from the pivotal Phase 3 study VELOUR and the two Phase 3 supportive safety studies (VANILLA and VITAL), and no new or unexpected signals were observed in these studies. In view of the overall similarity of the safety data from the Phase 1, 2 and 3 studies the review of the supportive safety data provided in the section on *Supportive Phase 3 studies (VANILLA and VITAL)*, below, of this CER focuses on safety data from the Phase 3 studies (VANILLA and VELOUR).

The SCS also included a brief review of safety data from other sources including 7 ongoing Sanofi and Regenero sponsored studies and 16 NCI sponsored studies. The safety data from these other sources appeared to be consistent those in the sponsor's primary safety set for this submission (i.e., 2073 patients exposed to aflibercept). The submission also included an integrated safety summary (ISS) of reversible posterior leukoencephalopathy syndrome (RPLS) in all studies undertaken with aflibercept as of 28 July 2011 (i.e., ~ 3759 exposed patients). This ISS is reviewed under *Other safety data*, below, in this CER.

7.1.3. Table 35: Summary of integrated safety database.

	Pivotal phase 3 study	Single-agent Phase 1 and Phase 2 studies	Phase 1 Combination with chemotherapy		Phase 3 studies in other indications	
Indication	MCRC	Solid tumors Ovary-NSCLC	Solid tumors		NSCLC	MPC
Study #	EFC10262	TED6115/6116	TCD6117	FOLFOX	EFC10261	EFC10547
		ARD6122	TCD6118	HILV5FU2	SUPPORTIVE for safety	SUPPORTIVE for safety
Associated chemotherapy (if applicable)	FOLFIRI	ARD6123	TCD6121	Gemcitabine		
		ARD6772	TCD6121	Gemcitabine/erlotinib	Docetaxel 75 mg/m²	Gemcitabine
		EFC6125	TCD6119	TCF		
			TCD6120	Docetaxel 75 mg/m²		
			TCD6120	Docetaxel/cisplatin		
			TCD6120	Docetaxel 100 mg/m²		
			TCD6120	Pemetrexed		
Aflibercept schedule & dose	4 mg/kg q2w	0.3 to 7.0 mg/kg q2w	2.0 to 6.0 mg/kg q2w 2.0 to 9.0 mg/kg q3w		6.0 mg/kg q3w	4.0 mg/kg q2w
Number of treated patients	1216 (611 aflibercept)	Pooled data: 404 (overall) including 258 at 4 mg/kg	336		905 (452 aflibercept)	541 (270 aflibercept)
Total number of patients exposed to aflibercept			2073			

NSCLC: non small-cell lung cancer; MCRC: Metastatic colorectal cancer ; MPC: metastatic pancreatic cancer; FOLFOX: oxaliplatin/5FU/leucovorin; FOLFIRI: irinotecan / 5-FU combination; TCF: docetaxel/cisplatin/5FU; q2w: every 2-week regimen; q3w: every 3-week regimen

7.2. VELOUR – pivotal study, pivotal safety data.

7.2.1. Extent of exposure

- In this study, there were 1226 randomized patients and 1216 of these patients received at least one dose of study treatment and were included in the safety population (605 in the placebo arm, 611 in the aflibercept arm). Patients in the placebo/folfiri arm received a total of 6127 treatment cycles, with a median of 8 cycles (range: 1 to 67), and patients in the aflibercept/folfiri arm received a total of 6362 treatment cycles, with a median of 9 cycles (range: 1 to 50). The median duration of exposure was 18.1 weeks (range: 2, 135) in the placebo/folfiri arm, and 21.4 weeks (range: 2, 105) in the aflibercept/folfiri arm. Information on treatment exposure by cycle in the safety population is provided in the dossier.
- More placebo infusions were received in patients in the placebo/folfiri arm (6035 infusion) than aflibercept infusions in patients in the aflibercept/arm (5632 infusions), with the

respective median number of infusions in the two treatment arms being 8.0 (range: 1, 67) and 7.0 (range: 1, 35). The median duration of exposure to placebo in the placebo/folfiri arm was similar to that of aflibercept in the aflibercept/folfiri arm (18 weeks [range: 2, 135] vs 17.9 weeks [range: 2, 85], respectively). The median relative dose intensity (RDI) for placebo was greater in the placebo/folfiri arm than for aflibercept in the aflibercept/folfiri arm (92% [range: 20, 110] vs 83% [range: 10, 110], respectively), as was the total cumulative dose (32 mg/kg [range: 0.6, 266.4] vs 28 mg/kg [range: 3.8, 140.0], respectively). Information on treatment exposure by number of infusions is summarized in the dossier.

- Exposure to irinotecan in the two treatment arms: The median number of irinotecan infusions and the median duration of exposure to irinotecan were higher in the aflibercept/folfiri arm than in the placebo/folfiri arm. Patients in the aflibercept/folfiri arm received a median of 9 infusions (range: 1, 50) over a period of 21.0 weeks (range: 2, 105), compared with a median of 8 infusions (range: 1, 67) over a period of 18.1 weeks (range: 2, 135) in the placebo/folfiri arm. Conversely, the median actual dose intensity and relative dose intensity for irinotecan were higher in the placebo/folfiri arm (82.1 mg/m^2/week and 91%, respectively) than in the aflibercept/folfiri arm (75.6 mg/m^2/week and 84%, respectively).
- Exposure to 5-FU in the two treatment arms: The median number of 5-FU infusions and the median duration of exposure to 5-FU were higher in the aflibercept/folfiri arm than in the placebo/folfiri arm. Patients in the aflibercept/folfiri arm received a median of 9 infusions (range: 1, 50) over a period of 21 weeks (range: 2, 105), compared with a median of 8 infusions (range: 1, 67) over a period of 18.1 weeks (range: 2, 135) in the placebo/folfiri arm. Conversely, the median actual dose intensity and the median relative dose intensity for 5-FU, were higher in the placebo/folfiri arm (1276.38 mg/m^2/week and 91%, respectively) than in the aflibercept/folfiri arm (1165 mg/m^2/week and 83%, respectively).
- Cycle delays and dose modifications: Cycles were considered to be delayed if the interval between cycles was > 16 days, and delays were experienced by 73.6% (895/1216) of treated patients. Cycle delays were reported more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (77.7%, n=475 vs 69.4%, n=420), and delays lasting more than 7 days were more frequent in the aflibercept/folfiri arm (365 patients, 59.7%) than in the placebo/folfiri arm (59.7%, n=365 vs 42.6%, n=258).
- Dose modifications included dose reductions and dose omissions: Dose modifications were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (16.7%, n=102 vs 4.8%, n=29). The majority of patients underwent either a dose reduction (57 patients) or a dose omission (52 patients), with 21 patients having both dose omissions and reductions.
- Irinotecan dose modifications were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (37.2%, n=227 vs 22.6%, n=127). In both treatment arms, the majority of irinotecan modifications were dose reductions only. Similarly, 5-FU dose modifications were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (39.1%, n=239 vs 21.7%, n=231). In both treatment arms, the majority of 5-FU modifications were dose reductions only.

Comment: Patients in the placebo/folfiri arm received a lower median number of study treatment cycles than in the aflibercept/folfiri arm, but a lower number of aflibercept infusions were administered in the aflibercept/folfiri arm than placebo infusions in the placebo/folfiri arm. This difference was due to higher frequencies of dose reductions, dose admissions and permanent treatment discontinuations due to adverse events in the aflibercept/folfiri arm than in the placebo/folfiri arm. Similarly, irinotecan and 5-FU dose modifications (predominantly

dose reductions only) due to adverse events were more frequently observed in the aflibercept/folfiri arm than in the placebo/folfiri arm.

7.2.2. Adverse events

7.2.2.1. Overview

Treatment-emergent adverse events (TEAEs) in all categories occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (see Table 36, below).

Table 36: VELOUR – Overview of patients with at least one TEAE; safety population.

n(%)	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Patients with any TEAE	592 (97.9%)	606 (99.2%)
Patients with any grade 3-4 TEAE	378 (62.5%)	510 (83.5%)
Patients with any grade 3-4 related TEAE	284 (46.9%)	451 (73.8%)
Patients with any serious TEAE	198 (32.7%)	294 (48.1%)
Patients with any serious related TEAE	93 (15.4%)	194 (31.8%)
Patients with any TEAE with a fatal outcome[a]	29 (4.8%)	37 (6.1%)
Any patient who permanently discontinued due to TEAE	73 (12.1%)	164 (26.8%)

n(%) = number and percentage of patients with at least one TEAE
TEAE: Treatment-Emergent Adverse Event
(a) based on AE reported start date

7.2.2.2. Adverse events

7.2.2.2.1. System Organ Class (SOC) with most frequently reported TEAEs (PT)

At the SOC level, the most frequently reported TEAEs (all grades) occurring in ≥ 20% of patients in at least one of the two treatment arms (aflibercept/folfiri vs placebo/folfiri) by decreasing order of frequency in the aflibercept/folfiri arm were gastrointestinal disorders (93.5% vs 86.1%), general disorders and administration site conditions (71.5% vs 62.5%), respiratory, thoracic and mediastinal disorders (58.8% vs 35.5%), vascular disorders (48.9% vs 22.6%), skin and subcutaneous tissue disorders (47.8% vs 43.3%), infections and infestations (46.2% vs 32.7%), nervous system disorders (45.8% vs 37.4%), blood and lymphatic disorders (44.2% vs 38.3%), investigations (31.9% vs 19.3%), metabolism and nutrition disorders (38.1% vs 26.4%), and musculoskeletal and connective tissue disorders (34.0% vs 31.2%). All of the previously listed SOCs occurred more commonly in the aflibercept/folfiri arm than in the placebo/folfiri arm. The most commonly reported TEAEs occurring in at least 5% of patients in either of the two treatment groups by primary SOC and preferred term are summarized in the dossier.

At the SOC level, TEAEs (Grade ≥ 3) occurring in ≥ 10% of patients in at least one of the two treatment arms (aflibercept/folfiri vs placebo/folfiri) were gastrointestinal disorders (38.0% vs 23.0%), blood and lymphatic disorders (29.3% vs 24.1%), vascular disorders (23.7% vs 5.1%), general disorders and administration site conditions (21.9% vs 14.5%), and infections and infestations (12.3% vs 6.9%).

7.2.2.2.2. TEAEs (all grades) most frequently reported (≥ 20% of patients)

In both treatment arms, nearly all patients experienced at least one TEAE (606 patients, 99.2%, aflibercept/folfiri vs 592 patients, 97.9%, placebo/folfiri). The most frequently reports TEAEs (all grades), regardless of relationship to study treatment, occurring in ≥ 20% of patients in at least one of two treatment arms (aflibercept/folfiri vs placebo/folfiri) by decreasing order of frequency in the aflibercept/folfiri arm were diarrhoea (69.2% vs 56.5%), nausea (53.4% vs 54.0%), stomatitis (50.1% vs 32.9%), fatigue (47.8% vs 39.0%), hypertension (41.2% vs 10.7%), neutropenia (39.0% vs 33.9%), vomiting (32.9% vs 33.4%), decreased appetite (31.9% vs 23.8%), weight decreased (31.9% vs 14.4%), epistaxis (27.7% vs 7.4%), abdominal pain (26.8% vs 23.6%), alopecia (26.8% vs 30.1%), dysphonia (25.4% vs 3.3%), headache (22.3% vs 8.8%), and constipation (22.4% vs 24.6%). All TEAEs occurring in ≥ 20% of patients in either

treatment arm were reported more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm, except nausea, vomiting, alopecia, and constipation.

7.2.2.2.3. Risk-Ratios for TEAEs (all grades)

Risk-ratios were provided for the most frequently occurring TEAEs (i.e., ≥ 5% in either of the two treatment arms, with a difference between arms of ≥ 2%). TEAEs (all grades) with risk-ratios ≥ 2 in decreasing order of frequency are summarized below in Table 37. The complete summary of the risk-ratios is provided in the dossier.

Table 37: VELOUR - Most frequent TEAEs * (all grades) by risk-ratio; safety population.

Preferred term	Placebo/Folfiri (N=605)		Aflibercept/Folfiri (N=611)		Risk Ratio (95% CI)
Dysphonia	20	(3.3%)	155	(25.4%)	7.67 (4.88 to 12.06)
Proteinuria	9	(1.5%)	63	(10.3%)	6.93 (3.48 to 13.81)
Hypertension	65	(10.7%)	252	(41.2%)	3.84 (2.99 to 4.92)
Epistaxis	45	(7.4%)	169	(27.7%)	3.72 (2.73 to 5.06)
Rhinorrhoea	11	(1.8%)	38	(6.2%)	3.42 (1.77 to 6.63)
Dehydration	18	(3.0%)	55	(9.0%)	3.03 (1.80 to 5.09)
Skin Hyperpigmentation	17	(2.8%)	50	(8.2%)	2.91 (1.70 to 4.99)
Proctalgia	11	(1.8%)	32	(5.2%)	2.88 (1.47 to 5.66)
Haemorrhoids	13	(2.1%)	35	(5.7%)	2.67 (1.42 to 4.99)
Palmar-Plantar Erythrodysaesthesia Syndrome	26	(4.3%)	67	(11.0%)	2.55 (1.65 to 3.96)
Headache	53	(8.8%)	136	(22.3%)	2.54 (1.89 to 3.42)
Oropharyngeal Pain	19	(3.1%)	46	(7.5%)	2.40 (1.42 to 4.04)
Weight Decreased	87	(14.4%)	195	(31.9%)	2.22 (1.77 to 2.78)
Rectal Haemorrhage	15	(2.5%)	32	(5.2%)	2.11 (1.16 to 3.86)

MedDRA 13.1; All grades, regardless of relationship to IP;

* Any TEAE with a frequency ≥ 5% in any arms with a difference of frequency between arms ≥ 2%

7.2.2.2.4. TEAEs (Grade ≥ 3)

TEAEs grade ≥ 3 were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (83.5%, n=510 vs 62.5%, n=378). TEAEs ≥ grade 3 reported in ≥ 2% more patients in the aflibercept/folfiri arm than in placebo/folfiri arm were neutropenia (25.0% vs 22.0%), diarrhoea (19.3% vs 7.8%), hypertension (19.1% vs 1.5%), stomatitis (12.8% vs 4.6%), fatigue (12.6% vs 7.8%), urinary tract infection (9.2% vs 6.1%), asthenia (5.1% vs 3.0%), abdominal pain (4.4% vs 2.3%), dehydration (4.3% vs 1.3%), proteinuria (2.9% vs 0%), and palmar-plantar erythrodysaesthesia syndrome (2.8% vs 0.5%). The most marked differences (≥ 5%) were reported for hypertension (17.6%), diarrhoea (11.5%), and stomatitis (8.2%).

7.2.2.2.5. Treatment-related TEAEs

Treatment-related TEAEs (all grades) were reported in 95.6% (n=584) of patients in the aflibercept/folfiri arm and 90.9% (n=550) in the placebo/folfiri arm. The most frequently reported treatment-related TEAEs (all grades), occurring in ≥ 20% of patients in at least one of the two treatment arms (aflibercept/folfiri arm vs the placebo/folfiri arm) and in decreasing order of frequency in the aflibercept/folfiri arm were diarrhea (62.7% vs 49.4%), nausea (48.3% vs 50.1%), stomatitis (46.8% vs 29.8%), fatigue (41.6% vs 32.6%), neutropenia (37.5% vs 31.2%), hypertension (36.5% vs 7.8%), vomiting (27.2% vs 28.3%), alopecia (25.2% vs 27.1%), epistaxis (24.2% vs 6.0%), decreased appetite (23.6% vs 17.4%), and dysphonia (22.7% vs 3.3%). The most frequently reported treatment-related TEAEs (all grades) were similar to the most frequently reported all causality TEAEs (all grades).

Treatment-related TEAEs (grade ≥ 3) were reported in 73.8% (n=451) of patients in the aflibercept/folfiri arm and 46.9% (n=284) of patients in the placebo/folfiri arm. The most frequently occurring treatment-related TEAEs (grade ≥ 3), reported in ≥ 2% of patients in the aflibercept/folfiri arm vs the placebo/folfiri arm and in decreasing order of frequency in the aflibercept/folfiri arm were neutropenia (24.4% vs 20.2%), hypertension (17.5% vs 1.2%), diarrhoea (16.9% vs 6.9%), stomatitis (12.3% vs 4.1%), fatigue (11.3% vs 6.4%), asthenia (4.3% vs 2.3%), pulmonary embolism (3.9% vs 2.8%), febrile neutropenia (3.3% vs 1.5%), dehydration (3.1% vs 1.0%), proteinuria (2.9% vs 0.0%), decreased appetite (2.8% vs 1.0%), palmar-plantar erythrodysaesthesia syndrome (2.6% vs 0.5%) and vomiting (2.0% vs 3.0%).

7.2.2.2.6. Adverse reactions

The SCS included a summary of adverse drug reactions (ADRs), based on the VELOUR safety population, and defined as any TEAE having ≥ 2% greater incidence (all grades) in the aflibercept/folfiri treatment group compared with the placebo/folfiri arm.

7.2.3. Deaths and serious adverse events

7.2.3.1. Deaths

Death during the treatment period (i.e., from start of treatment up to 30 days after last dose), or during the follow-up period (i.e., death > 30 days after last dose) are summarized below in Table 38.

Table 38: VELOUR – Deaths; safety population.

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Total number of deaths [n(%)]	452 (74.7%)	403 (66.0%)
Cause of death [n(%)]		
Adverse event	4 (0.7%)	14 (2.3%)
Disease progression	436 (72.1%)	369 (60.4%)
Other reason	12 (2.0%)	20 (3.3%)
Number of deaths within 30 days from last dose [n(%)]	19 (3.1%)	30 (4.9%)
Cause of death [n(%)]		
Adverse event	4 (0.7%)	14 (2.3%)
Disease progression	13 (2.1%)	14 (2.3%)
Other reason	2 (0.3%)	2 (0.3%)
Deaths more than 30 days from last dose due to adverse event [n(%)]	0	0
Deaths within 60 days from first dose [n(%)]	16 (2.6%)	20 (3.3%)
Cause of death [n(%)]		
Adverse event	1 (0.2%)	4 (0.7%)
Disease progression	13 (2.1%)	13 (2.1%)
Other reason	2 (0.3%)	3 (0.5%)

The proportion of patients who experienced fatal AEs in the context of disease progression within 30 days of last study treatment was similar in the two treatment arms (14 patients, 2.3%, aflibercept/folfiri; 12 patients, 2.0%, placebo/folfiri). Fatal AEs reported in this context in the aflibercept/folfiri vs placebo/folfiri arms, respectively, were disease progression (12 patients, 2.0% vs 11 patients, 1.8%), intestinal obstruction (1 patient, 0.2% vs no patients), ileal perforation (1 patient, 0.2% vs no patients), and ileus (no patients vs 1 patient, 0.2%).

Overall, 22 patients experienced fatal AEs within 30 days of study treatment in other context than disease progression. The proportion of fatal AEs reported in this context was higher in the aflibercept/folfiri arm than the placebo/folfiri arm (16 patients, 2.6% vs 6 patients, 1.0%). In each of the SOCs in which death was reported, the proportion of patients experiencing an AE in the aflibercept/folfiri arm was greater than or equal to the proportion of patients in the placebo/folfiri arm. The most frequently reported causes of death in both treatment arms were

SOC infections and infestations (4 patients. 0.7%, aflibercept folfiri vs 3 patients, 0.5%, placebo/folfiri).

Of the fatal AEs reported within 30 days of study treatment in other context than disease progression, 6 (1.0%) in the aflibercept/folfiri arm were considered treatment-related by investigators compared with 3 (0.5%) in the placebo/folfiri arm. The 6 treatment-related deaths in the aflibercept/placebo arm were: 2x neutropenic infection (1x rectal abscess, 1x intestinal mucositis); 1x unknown cause; 1x hypovolaemic shock (diarrhoea and vomiting); 1x duodenal ulcer haemorrhage; and 1x pulmonary embolism. The 3 treatment-related deaths in the placebo/folfiri arm were: 1 x neutropenic infection; 1x lobar pneumonia; and 1x interstitial lung disease.

7.2.3.2. Other serious adverse events (serious TEAEs)

SAEs (all grades) occurred more commonly in the aflibercept/folfiri arm than in the placebo/folfiri arm (48.1%, n=294 vs 32.7%, n=198). Similarly, SAEs (grade ≥ 3) occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (41.6%, n=254 vs 28.8%, n=174). The SAE results are summarized below in Table 39.

Of the SAEs (all grades) occurring in ≥ 2% of patients in at least one of the two treatment arms, with an incidence ≥ 2% in the aflibercept/folfiri arm compared with the placebo/folfiri arm were febrile neutropenia, dehydration, and diarrhoea. Of the SAEs (grade ≥ 3) occurring in ≥ 2 % of patients in at least one of the two treatment arms, events occurring more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm were diarrhoea, febrile neutropenia, pulmonary embolism, dehydration and disease progression, with the only exception being pyrexia.

Table 39: VELOUR - Serious TEAE(s) by Primary SOC and PT (≥2% frequency for PT); safety population.

	Placebo/Folfiri (N=605)		Aflibercept/Folfiri (N=611)	
Primary system organ class Preferred term n(%)	All Grades	Grades ≥3	All Grades	Grades ≥3
Any class	198 (32.7%)	174 (28.8%)	294 (48.1%)	254 (41.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	15 (2.5%)	13 (2.1%)	40 (6.5%)	36 (5.9%)
Febrile neutropenia	6 (1.0%)	6 (1.0%)	19 (3.1%)	19 (3.1%)
METABOLISM AND NUTRITION DISORDERS	11 (1.8%)	8 (1.3%)	30 (4.9%)	24 (3.9%)
Dehydration	7 (1.2%)	5 (0.8%)	24 (3.9%)	18 (2.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18 (3.0%)	16 (2.6%)	36 (5.9%)	27 (4.4%)
Pulmonary embolism	12 (2.0%)	12 (2.0%)	19 (3.1%)	19 (3.1%)
GASTROINTESTINAL DISORDERS	68 (11.2%)	61 (10.1%)	124 (20.3%)	98 (16.0%)
Diarrhoea	14 (2.3%)	12 (2.0%)	44 (7.2%)	34 (5.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	42 (6.9%)	28 (4.6%)	44 (7.2%)	31 (5.1%)
Pyrexia	15 (2.5%)	3 (0.5%)	10 (1.6%)	2 (0.3%)
Disease progression	14 (2.3%)	14 (2.3%)	16 (2.6%)	16 (2.6%)

Note : Adverse Events are reported using MedDRA version MEDDRA13.1 and graded using NCI CTC Version 3.0.
TEAE = Treatment Emergent Adverse Events
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in aflibercept/FOLFIRI group for all grades.

7.2.4. TEAEs leading to permanent treatment discontinuation

TEAEs (all grades) resulting in permanent treatment discontinuation occurred notably more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (26.8%, n=164 vs 12.1%, n=73), and the majority of patients in both treatment arms permanently discontinued treatment due to TEAE grade ≥ 3 events (n=124, 20.3% vs n=53, 8.8%, respectively). TEAEs (all grades) leading to permanent treatment discontinuation and occurring in ≥ 1% more patients in the aflibercept/folfiri arm than in the placebo/folfiri arm were: hypertension (2.3% vs 0%); diarrhoea (2.3% versus 0.7%); fatigue (2.1% vs 1.0%); asthenia

(1.6% vs 0.3%); and proteinuria (1.5% vs 0%). TEAEs occurring in ≥ 0.5% of patients leading to permanent treatment discontinuation are summarized in the dossier.

TEAEs (all grades) grouped according to similarity of events and most frequently leading to permanent treatment discontinuation (aflibercept/folfiri vs placebo/folfiri) were: fatigue/asthenia (23 patients, 3.7% vs 8 patients, 1.3%); infections and infestations SOC (21 patients, 3.4% vs 10 patients, 1.7%), diarrhoea (14 patients, 2.3% vs 4 patients, 0.7%); myelosuppression including neutropenia, thrombocytopenia, anemia and febrile neutropenia (12 patients, 2.0% vs 6 patients, 1.0%); pulmonary embolism (7 patients, 1.1% vs 7 patients, 1.2%); proteinuria including nephrotic syndrome (10 patients. 1.7% vs no patients); and deep vein thrombosis including DVT, subclavian vein thrombosis, vena cava thrombosis, and thrombophlebitis (8 patients, 1.3% vs 2 patients, 0.3%).

7.2.5. TEAEs leading to cycle delay and/or dose modification

Cycle delay: TEAEs (all grades) leading to at least one cycle delay occurred notably more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (70.0%, n=428 vs 54.4%, n=329). TEAEs (any grade) resulting in cycle delay and reported in ≥ 2.0% more patients in the aflibercept/folfiri arm than in the placebo/folfiri arm were: hypertension (10.8% vs 0.8%); diarrhoea (12.1% vs 5.0%); stomatitis (8.5% vs 3.1%); fatigue (9.0% vs 5.3%); neutropenia (36.2% vs 33.4%); decreased appetite (4.4% vs 1.7%); proteinuria (3.4% vs 1.2%); abdominal pain (2.5% vs 1.0%); thrombocytopenia (3.3% vs 2.0%); and urinary tract infection (2.0% vs 1.0%).

Dose modifications (reductions or omissions): TEAEs (all grades) leading to dose modifications occurred notably more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (50.4%, n=308 vs 26.8%, n=162). TEAES (any grade) resulting in dose modifications and reported in ≥ 2% more patients in the aflibercept/folfiri arm than in the folfiri/placebo arm were: diarrhoea (16.2% vs 6.4%); stomatitis (11.9% vs 5.0%); hypertension (6.2% vs 0.3%); proteinuria (4.1% vs 0.5%); palmar-plantar erythrodysaesthesia syndrome (2.9% vs 0.3%); and fatigue (4.4% vs 2.1%).

7.2.6. TEAEs - VEGF class effects

The study included an assessment of grouped AEs considered to be known risks for agents targeting the VEGF pathway. The results of this assessment are summarized below in Table 40. The results showed increased risks in the aflibercept/folfiri arm compared with the placebo/folfiri arm for hypertension, fistula from gastrointestinal origin, haemorrhage, fistula from other origin than gastrointestinal, arterial thromboembolic events, and venous thrombolic events. In terms of patient numbers, the most important of these risks were hypertension, haemorrhage, and venous thromboembolic events and each of these are discussed in more detail below.

Table 40: VELOUR – Grouped TEAEs (all grades) by risk ratio; safety population.

Grouped terms	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)	RR (95% CI)
Acute drug reaction	26 (4.3%)	26 (4.3%)	0.99 (0.58 to 1.69)
Arterial thromboembolic event	9 (1.5%)	16 (2.6%)	1.76 (0.78 to 3.95)
Cardiac dysfunction	0	2 (0.3%)	NC (NC)
Fistula from gastrointestinal origin	2 (0.3%)	7 (1.1%)	3.47 (0.72 to 16.62)
Fistula from other origin than gastrointestinal	1 (0.2%)	2 (0.3%)	1.98 (0.18 to 21.78)
Gastrointestinal perforation	3 (0.5%)	3 (0.5%)	0.99 (0.20 to 4.89)
Haemorrhage	115 (19.0%)	231 (37.8%)	1.99 (1.64 to 2.41)
Hypertension	65 (10.7%)	253 (41.4%)	3.85 (3.01 to 4.94)
Osteonecrosis	0	2 (0.3%)	NC (NC)
Venous thromboembolic event	44 (7.3%)	57 (9.3%)	1.28 (0.88 to 1.87)
Wound healing	5 (0.8%)	3 (0.5%)	0.59 (0.14 to 2.47)

MedDRA 13.1
NC: not calculated

Hypertension: The risk of hypertension (all grades) was about 4-fold higher in the aflibercept/folfiri arm relative to the placebo/folfiri arm. The observed difference in incidence between the two treatment arms remained about 30% regardless of pre-existing hypertension status. The risk of hypertension grade ≥ 3 TEAEs was about 13-fold higher in the aflibercept/folfiri arm than in the placebo/folfiri arm: RR = 12.98 (95%CI: 6.65, 25.33); 19.3% (n=118) vs 1.5% (n=9), respectively. All but 1 patient in the aflibercept/folfiri arm with grade ≥ 3 hypertension had grade 3 rather than grade 4 events; grade 3 events were defined as requiring more than one drug or more intensive therapy than previously, and grade 4 events as having life-threatening consequences. Permanent treatment discontinuation due to hypertension was reported notably more frequently in the aflibercept/folfiri arm (29 patients, 4.7%) than in the placebo/folfiri arm (1 patient, 0.2%), as were dose delays (66 patients, 10.8% vs 5 patients, 0.8%) and dose reductions (38 patients, 6.2% vs 2 patients, 0.3%).

Haemorrhage: The risk of experiencing at least one haemorrhagic event (all grades) was about 2-fold higher in the aflibercept/folfiri arm relative to the placebo/folfiri arm. The risk of experiencing haemorrhagic grade ≥ 3 events was marginally higher in the aflibercept/folfiri arm (18 patients, 2.9% vs 10 patients, 1.7%). The most frequently reported haemorrhagic event (all grades) was epistaxis (169 patients, 27.7%, aflibercept/folfiri vs 45 patients, 7.4% placebo/folfiri). Other haemorrhagic events (all grades) occurring in ≥ 1% of patients in the aflibercept/folfiri arm (vs placebo/folfiri arm) were: rectal haemorrhage (5.2% vs 2.5%); haemoptysis (1.6% vs 0.2%); post-procedural haemorrhage (1.6% vs 0.3%); haematuria (1.6% vs 3.0%); contusion (1.3% vs 1.2%); haemorrhoidal haemorrhage (1.1% vs 0.3%); haematochezia (1.3% vs 1.0%); vaginal haemorrhage (1.0% vs 0.3%); and gingival bleeding (1.0% vs 0.2%). The only haemorrhagic grade ≥ 3 events to be reported in ≥ 2 patients in the aflibercept/folfiri arm (vs placebo/folfiri) were: post-procedural haemorrhage (4 patients, 0.7% vs 1 patient, 0.2%); and gastrointestinal haemorrhage (3 patients, 0.5% vs no patients). The majority of patients in both treatment arms required no change in treatment related to haemorrhagic events (203 patients, 87.9% aflibercept/folfiri vs 107 patients, 93.0%. placebo/folfiri), but the proportion of patients permanently discontinuing treatment in the aflibercept/folfiri arm due to haemorrhagic events was greater than in the placebo/folfiri arm (12 patients, 2.0% vs 1 patient, 0.2%).

Venous thrombolic events (VTEs): The risk of experiencing a VTE (all grades) was 1.28-fold higher in the aflibercept/folfiri arm than in the placebo/folfiri arm. The majority of VTEs in both treatment arms were grade ≥ 3 events (48 patient, 7.9% aflibercept/folfiri vs 38 patients, 6.3% placebo/aflibercept). The most commonly reported VTE in both treatment arms was pulmonary embolism (28 patients, 4.7% aflibercept/folfiri vs 21 patients, 3.5% placebo/folfiri), and all of

these events were grade ≥ 3. The only other VTE occurring in ≥ 1% of patients in both treatment arms was deep vein thrombosis (18 patients, 2.9% aflibercept/folfiri vs 13 patients, 2.1% placebo/folfiri), and nearly all of these events were grade ≥ 3 (13/18, aflibercept/folfiri vs 11/13, placebo/folfiri). There was one fatal VTE (pulmonary embolism) in 1 patient in the aflibercept/folfiri arm. Permanent discontinuations due to VTEs occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (4.3%, n=25 vs 2.6%, n=16).

7.2.7. Laboratory tests

7.2.7.1. Haematology

Laboratory haematological abnormalities (leukopenia, neutropenia, anaemia, thrombocytopenia) were reported frequently in both treatment arms during the study. Thrombocytopenia (all grades), neutropenia (all grades) and leukopenia (all grades) were all reported more frequently in the aflibercept/folfiri arm than in the placebo/aflibercept arm, while the converse was observed for anaemia. The haematological abnormality with the highest incidence of grade 3 or 4 events was neutropenia (N=221/603 patients, 36.7%, aflibercept/folfiri vs N=176/597 patients, 29.5%, placebo/folfiri).

The incidence of neutropenic complications (all grades and grade ≥ 3) was greater in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (see Table 41, below). All 18 patients in the placebo/folfiri arm experienced only 1 episode, while in the aflibercept/folfiri arm 35 (87.5%) patients experienced 1 episode and 5 (12.5%) patients experienced 3 episodes. The median time to onset of neutropenic complications was 44 days (range: 2, 212) in the placebo/aflibercept arm and 48 days (range: 10, 341) in the aflibercept/folfiri arm. There was 1 fatal outcome associated with neutropenic complications in both treatment arms. The majority of patients in both treatment arms with neutropenic complications required no change in treatment or were managed by dose delays or dose reductions rather than permanent treatment discontinuation.

Table 1: VELOUR - Neutropenic complications (TEAEs, PT); safety population.

	Placebo/Folfiri (n=605)		Aflibercept/Folfiri (n=611)	
	All Grades	Grades ≥3	All Grades	Grades ≥3
All	**18 (3.0%)**	**17 (2.8%)**	**40 (6.5%)**	**35 (5.7%)**
Neutropenic colitis	0	0	1 (0.2%)	1 (0.2%)
Febrile neutropenia	10 (1.7%)	10 (1.7%)	26 (4.3%)	26 (4.3%)
Neutropenic infection	8 (1.3%)	7 (1.2%)	11 (1.8%)	6 (1.0%)
Neutropenic sepsis	0	0	3 (0.5%)	3 (0.5%)

7.2.7.2. Clinical chemistry

7.2.7.2.1. Liver function

Liver function abnormalities: the main outcomes are summarized below in Table 42. Both ALT (all grades) and AST (all grades) were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm, and the majority of abnormalities in both

arms were grade 1 events. The incidence of increased serum alkaline phosphatase was similar in the two treatment arms, as was the incidence of increased total bilirubin.

Table 2: VELOUR – Liver function abnormalities on-treatment; safety population.

	Placebo/Folfiri			Aflibercept/Folfiri		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
ALT	221/595 (37.1%)	13/595 (2.2%)	0/595	284/600 (47.3%)	15/600 (2.5%)	1/600 (0.2%)
AST	296/590 (50.2%)	9/590 (1.5%)	1/590 (0.2%)	339/590 (57.5%)	16/590 (2.7%)	2/590 (0.3%)
Alk.P	411/594 (69.2%)	38/594 (6.4%)	0/594	424/599 (70.8%)	29/599 (4.8%)	0/599
Bili.T	138/595 (23.2%)	13/595 (2.2%)	3/595 (0.5%)	137/600 (22.8%)	8/600 (1.3%)	2/600 (0.3%)

In VELOUR, there were 7 patients in each treatment arm with potential Hy's law criteria for drug-related hepatotoxicity (1.1% in the aflibercept/folfiri arm and 1.2% in the placebo/folfiri arm). These patients had ALT or AST >3xULN and bilirubin >2xULN during the treatment period, and all had liver metastases. In the placebo/folfiri arm, 5/7 patients had ALT and total bilirubin elevated in the same cycle compared with 3/7 patients in the aflibercept/folfiri arm.

In VANILLA, there were 16 (5.9%) patients in the placebo/gemcitabine arm with potential Hy's law criteria compared with 19 (7.0%) patients in the aflibercept/gemcitabine arm, while in VITAL there was 1 (0.2%) patient in the placebo/docetaxel arm with potential Hy's law criteria compared with 3 (0.7%) patients in the aflibercept/docetaxel arm.

In VELOUR, TEAE hepatobiliary disorders (SOC, all grades) were reported in 3.9% (n=24) of patients in the aflibercept/folfiri arm and 5.0% (n=30) of patients in the placebo/aflibercept arm, and the corresponding results for SOC (grade ≥ 3) events were 1.6% (n=10) and 2.0% (n=12), respectively. There was 1 case of hepatic failure reported in the placebo/aflibercept arm.

7.2.7.2.2. Renal function

Creatinine levels and creatinine clearance results:. Increased creatinine levels (all grades) occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (N=136/601, 22.6% vs N=106/596, 18.1%, respectively), while the incidence of grade 3 or 4 events did not notably differ between the two treatment arms (N=0/601, 0% vs N=3/596, 0.5%, respectively). Creatinine clearance < 50 mL/min occurred marginally more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (N=92/601, 15.3% vs N=78/596, 13.1%, respectively), as did creatinine clearance ≥ 50 to ≤ 80 mL/min (N= 281/601, 46.8% vs N=266/596, 44.6%). The mean (SD) creatinine clearance values (worst values) were similar in the aflibercept/folfiri and the placebo/folfiri arms: 75.7 (27.4) and 78.9 (28.9) mL/min, respectively.

Renal failure events (defined as grade 3 or 4 AEs referring to renal failure, grade 3 or 4 creatinine increase as per laboratory values, or calculated creatinine clearance <30 mL/min) were reported in 2.9% (n=18) of patients in the aflibercept/folfiri arm compared with 2.1% (n=13) of patients in the placebo/folfiri arm, with the majority of events being low creatinine levels. The median time to onset of renal failure events was 66 and 67 days in the placebo/folfiri

and aflibercept/folfiri arms, respectively. The median duration of the longest episode was also similar between the two treatment arms, 14 days and 11 days in the placebo/folfiri and aflibercept/folfiri arms, respectively. Of the total number of patients with renal failure (n=31), 28 patients (N=12/13, 92.3%, placebo/folfiri; N=16/18, 88.9%, aflibercept/folfiri) had the event concomitantly or following AEs that may have contributed to the development of renal failure such as vomiting, diarrhoea, dehydration, sepsis including complicated neutropenia, or obstructive uropathy. Renal failure was reported as recovered in the majority of patients in both treatment arms (N=14/18, 77.8%, aflibercept/folfiri; N=7/11, 53.8%, placebo/folfiri). One (1) patient in the aflibercept/folfiri arm and 4 patients in the placebo/folfiri arm did not recover from renal failure before death due to either disease progression or infection. Information about recovery was not available for 5 patients in the placebo arm.

Proteinuria (reports of proteinuria as TEAEs including grade 4 or nephrotic syndrome, spot tests of morning urine samples, or 24-hour collection) was reported in 62.7% (n=380) of patients in the aflibercept/folfiri arm and 40.7% (n=246) of patients in the placebo/folfiri arm. In most cases these events were grade 1 or 2 in severity, but grade 3 or 4 events were reported in 7 (1.2%) patients in the placebo/folfiri arm and 48 (7.9%) patients in the aflibercept/folfiri arm (including 2 patients [0.3%] with grade 4 proteinuria or nephrotic syndrome). In the placebo/folfiri arm, 10 (1.7%) patients had one proteinuria event leading to dose modification or treatment discontinuation compared with 62 (10.1%) patients in the aflibercept/folfiri arm. No patients in the placebo/folfiri arm permanently discontinued treatment due to proteinuria compared with 36 (5.9%) patients in the aflibercept/folfiri arm.

7.2.7.2.3. Other clinical chemistry parameters

Overall, for most clinical chemistry parameters, the incidence of on-treatment abnormalities were higher in the aflibercept/folfiri arm than in the placebo/folfiri arm.

7.2.8. Immunogenicity

In the aflibercept/folfiri arm, 8 (1.5%) patients had positive response for anti-aflibercept antibody (ADA) at least once post-baseline, and 1 (0.2%) patient had neutralizing ADA. In the placebo/folfiri arm, 18 (3.4%) patients) had positive response for ADA at least once post-baseline, and 2 (0.4%) patients had neutralizing ADA. Among ADA positive patients, 4 and 10 were positive at baseline in the aflibercept/folfiri and placebo/folfiri arms, respectively. The results are summarized below in Table 43.

Table 43: VELOUR – Antibody status; patient treated and evaluable for antibody assessment.

	Placebo/Folfiri		Aflibercept/Folfiri	
	Baseline status		Baseline status	
	Negative or missing (N=515)	Positive (N=11)	Negative or missing (N=516)	Positive (N=5)
At any time post-baseline				
ADA Negative	507 (96.4%)	1 (0.2%)	512 (98.3%)	1 (0.2%)
ADA Positive (drug specific)	8 (1.5%)	10 (1.9%)	4 (0.8%)	4 (0.8%)
neutralizing Ab	0	2 (0.4%)	0	1 (0.2%)
not neutralizing Ab	8 (1.5%)	8 (1.5%)	4 (0.8%)	3 (0.6%)
90 days after last dose				
ADA Negative	236 (44.9%)	2 (0.4%)	234 (44.9%)	1 (0.2%)
ADA Positive (drug specific)	4 (0.8%)	1 (0.2%)	0	3 (0.6%)
neutralizing Ab	0	0	0	0
not neutralizing Ab	4 (0.8%)	1 (0.2%)	0	3 (0.6%)

Note : Baseline status = cycle 1 predose

In all clinical studies, of the patients with data evaluable for immunogenicity, 3.8% (63/1671) treated with aflibercept exhibited a positive low titre response at any time during treatment compared with 3.2% (35/1105) treated with placebo, with the respective positive results for neutralizing antibody being 1.3% (n=17) and 0.2% (n=2), respectively. Most of the samples

positive in the ADA assay exhibited only the minimum assay titre (30), and none of the patients with a positive assay response exhibited a high titre (>500) or a greater than 4-fold increase in the titre in subsequent samples. The sponsor postulated that 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 a treatment-emergent immune response to aflibercept, since the level of low titre ADA assay responses in the aflibercept treated patients was similar to that observed in the placebo treated patients. The sponsor also stated that immunogenicity did not appear to have a functional impact on aflibercept, but no relevant data could be identified supporting this statement.

7.2.9. Vital signs

Blood pressure was measured for all patients before each treatment cycle. The proportion of patients with potentially clinical significant increases in blood pressure was notably higher in the aflibercept/folfiri arm than in the placebo/folfiri arm (see Table 44, below). ECG was systematically performed at baseline and during study treatment only when clinically indicated. Therefore, there was no analysis of this parameter in VELOUR.

Table 44: VELOUR – Potentially clinical significant changes in blood pressure.

Vital Signs Test/PCSA Criteria	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Systolic Blood Pressure (mmHg) [n/N(%)]		
≤ 95 mmHg and decrease from baseline ≥ 20 mmHg	30/586 (5.1%)	21/588 (3.6%)
≥ 160 mmHg and increase from baseline ≥ 20 mmHg	46/586 (7.8%)	162/588 (27.6%)
Diastolic Blood Pressure (mmHg) [n/N(%)]		
≤ 45 mmHg and decrease from baseline ≥ 10 mmHg	3/586 (0.5%)	5/588 (0.9%)
≥ 110 mmHg and increase from baseline ≥ 10 mmHg	5/586 (0.9%)	35/588 (6.0%)

7.2.10. Special groups

7.2.10.1. Male/Female

7.2.10.1.1. TEAES (all grades)

In the aflibercept/folfiri arm, TEAEs (all grades) were reported in 100%(245/245) and 98.6% (361/366) of female and male patients, respectively. The most notable differences between the sexes was the increased incidence in females compared with males of the SOCs of infections and infestations (51.0% vs 42.9%) and skin and subcutaneous disorders (56.3% vs 42.1%), and the increase incidence of metabolism and nutrition disorders in males compared with females (41.8% vs 32.7%).

The main reason for the increased risk of infections and infestations (SOC) in females compared with males in the aflibercept/folfiri arm related to the higher incidence of urinary tract infections (16.7% vs 4.1%, respectively). Infections and infestations (SOC) did not markedly differ between females and males in the placebo/folfiri arm (34.4% vs 31.5%, respectively), and although urinary tract infections in this arm were higher in females compared with males (8.1% vs 4.6%, respectively) the difference was not as marked as in the aflibercept/folfiri arm.

The main reason for the increased risk of skin and subcutaneous tissue disorders (SOC) in females compared with males related primarily to the higher incidence of alopecia (35.0% vs 21.0%, respectively). Skin and subcutaneous tissue disorders (SOC) did not markedly differ between females and males in the placebo/folfiri arm (43.1% vs 43.6%, respectively).

The main reason for the increased risk of metabolism and nutrition disorders (SOC) in males compared with females related to the higher incidence of decreased appetite (35.5% vs 26.5%). There was no marked difference between metabolism and nutrition disorders (SOC) in male and female patients in the placebo/aflibercept arm (27.7% vs 24.7%, respectively).

7.2.10.1.2. TEAES (grades 3 and 4)

Grade 3 or 4 TEAEs were reported in 84.1% (206/245) and 83.1% (304/366) of female and male patients, respectively, in the aflibercept/folfiri arm. At the SOC level, conversely to TEAEs (all grade), infections and infestations in the aflibercept/folfiri arm were reported at a slightly higher incidence in males (14.8%) than in females (8.6%). There was no obvious cause for the disparity between sexes in the aflibercept/folfiri arm, although pneumonia was reported more frequently in males compared with females (2.7% vs 0.4%). Skin and subcutaneous tissue disorders (SOC) were reported more frequently in females than in males in the aflibercept/folfiri arm (5.3% vs 3.0%, respectively), and the difference was predominantly due to a higher incidence of palmar-plantar erythrodysaesthesia syndrome in females compared with males (3.3% vs 2.5%).

Metabolism and nutrition disorders (SOC) were reported more frequently in males than in females in the aflibercept/folfiri arm (10.7% vs 7.8%) due primarily to decreased appetite (5.2% vs 0.8%, respectively). While no difference was reported between male and female patients for TEAEs (all grades) for gastrointestinal disorders (SOC), the incidence of TEAEs (grade 3 or 4) for this SOC was greater in males than in females (40.2% vs 34.7%, respectively). Conversely, in the placebo/folfiri arm, the incidence of TEAEs (grade 3 or 4) for this SOC was higher in females than in males (27.7% vs 19.7%, respectively). In the aflibercept/folfiri arm, grade 3 or 4 diarrhoea was more frequently reported in males than in females (21.5% vs 15.5%, respectively), while lower incidences were reported in the placebo/folfiri arm with no notably difference between males and females (7.5% vs 8.1%, respectively). In the aflibercept/folfiri arm, the incidence of grade 3 or 4 vomiting was similar in males and female (2.5% vs 3.3%, respectively), and were comparable with those in the placebo/folfiri arm for males and females (3.2% vs 3.9%, respectively).

7.2.10.1.3. Race

Nearly all patients in the safety population were Caucasian/White (87.3%, 1062/1216), with the rest of the patients being Black (3.5%, 43/1216), Asian/Oriental (7.1%, 86/1216) or Other (2.1%, 25/1216). Consequently, no meaningful conclusions can be drawn regarding safety differences among the racial groups due to the small patient numbers in the non Caucasian/White groups.

7.2.10.1.4. Age

TEAEs were compared in patients in the aflibercept/placebo arm aged < 65 years (n=406) with patients aged ≥ 65 years (n=205). TEAEs (all grades) were experienced by 99.0% (402/406) of patients aged < 65 years compared with 99.5% (204/205) of patients aged ≥ 65 years.

In the aflibercept/folfiri arm, the incidence of TEAEs (all grades) reported in ≥ 5% of patients in either age group and ≥ 5% more patients in the ≥ 65 years compared with the < 65 years age group were: diarrhoea (73.7% vs 67.0%); weight decreased (41.0% vs 27.3%); asthenia (22.0% vs 16.5%); dehydration (14.6% vs 6.2%); and dizziness (9.3% vs 4.2%).

In the aflibercept/folfiri arm, TEAEs (all grades) reported in ≥ 5% of patients in either age group and ≥ 5% more patients in the < 65 years compared with the ≥ 65 years age group were: stomatitis (52.5% vs 45.4%); fatigue (50.2% vs 42.9%); vomiting (35.5% vs 27.8%); headache (24.4% vs 18.0%); abdominal pain (13.3% vs 3.4%); aphthous stomatitis (6.7% vs 1.5%); palmar-plantar erythrodysaesthesia syndrome (12.8% vs 7.3%); skin hyperpigmentation (9.9% vs 4.9%); and pain in extremity (7.4% vs 2.0%).

In the aflibercept/folfiri arm, TEAEs (grade ≥ 3) were experienced by 80.5% (327/406) of patients aged < 65 years compared with 89.3% (183/205) of patients aged ≥ 65 years. TEAEs (grade ≥3) reported in ≥ 5% of patients in either age group and ≥ 5% more patients in the ≥ 65 years compared with the < 65 years age group were diarrhoea (24.4% vs 16.7%) and

dehydration (7.8% vs 2.5%). No other marked differences in TEAEs (grade ≥ 3) between the two age groups were observed in the aflibercept/folfiri arm.

7.2.11. Other groups

Renal impairment: There were no specific studies in patients with renal impairment. In VELOUR, patients were excluded if the serum creatinine was > 1.5x ULN, or if the serum creatinine was 1.0 to 1.5x ULN and the creatinine clearance was < 60 mL/min. In VELOUR, there were no marked differences in the TEAEs between patients with baseline creatinine clearance > 80 mL/min and ≥ 50 mL/min to < 80 mL/min. The number of patients with creatinine clearance < 50 mL/min was too small to allow meaningful comparisons to be made with the two other groups. The incidence of hypertension was similar in patients in the aflibercept/folfiri arm in the ≥ 50-80 mL/min and the > 80 mL/min groups (40.6% vs 41.6%, respectively). There was a higher incidence of renal failure events during study treatment in patients in the ≥ 50-80 mL/min group compared with the > 80 mL/min group in both treatment arms (4.7% vs 0.9%, aflibercept/folfiri; 3.4% vs 1.0%, placebo/folfiri).

Hepatic impairment: There were no specific studies in patients with hepatic impairment. In VELOUR, patients were excluded if total bilirubin was > 1.5xULN or transaminases were > 3xULN (or 5xULN if liver metastases were present). The SCS included a pooled summary of TEAEs from the three Phase 3 studies (VELOUR, VANILLA, VITAL) based on baseline liver function tests. The results showed that patients in the aflibercept group with transaminases > 3xULN compared with patients with transaminases > 1.5 to ≤ 3xULN experienced more frequent decreased appetite (44.8% vs 34.7%), weight decreased (44.4% vs 25.8%), dehydration (17.2% vs 10.5%), and dizziness (17.2% vs 4.0%). The observed differences between the two baseline transaminase groups with aflibercept were not seen with placebo. As regards the TEAEs of specific interest, the only notable differences were higher incidences of haemorrhage and arterial thromboembolic events with aflibercept compared with placebo in patients in the transaminases > 1.5 and ≤ 3xULN groups compared with the >3xULN group (i.e., haemorrhage 32.3% vs 24.1%; ATE 4.8% vs 3.1%). As regards liver function tests, there was an increased incidence of approximately 10% for all parameters (transaminases, bilirubin, and alkaline phosphatase) observed in patients treated with aflibercept in the transaminases >3xULN groups compared with the >1.5 and ≤ 3xULN group, and a similar trend was observed in patients treated with placebo.

7.3. Supportive phase 3 studies (VANILLA and VITAL)

7.3.1. Extent of exposure

- In VANILLA (metastatic pancreatic cancer), exposure was generally similar in both the aflibercept/gemcitabine and placebo/gemcitabine treatment arms. The median RDI was higher in the placebo/gemcitabine arm than in the aflibercept/gemcitabine arm (0.91 vs 0.85).
- In VITAL (NSCLC), exposure was generally lower in the placebo/docetaxel arm than in the aflibercept/docetaxel arm. However, actual dose intensity and RDA were similar in the two treatment arms.

7.3.2. Adverse events – TEAEs

7.3.2.1. VANILLA (metastatic pancreatic cancer)

The percentage of patients who experienced at least one TEAE (all grades) in the aflibercept/gemcitabine arm was 98.5% (N=266/270) compared with 94.8% (N=257/271) in the placebo/gemcitabine arm. Notable differences were observed between the two treatment arms in the following SOCs (placebo/gemcitabine vs aflibercept/gemcitabine) with higher incidences being observed in the aflibercept/gemcitabine arm: vascular disorders (19.2% vs

42.6%); nervous system disorder (17.7% vs 33.3%); respiratory, thoracic and mediastinal disorders (20.7% vs 37.8%); renal and urinary disorders (8.1% vs 17.8%); blood and lymphatic system disorders (35.8% vs 45.2%); and investigations (26.9% vs 39.3%).

The most frequently reported TEAEs (all grades) with more than 10% difference between the two treatment arms (placebo/gemcitabine vs aflibercept/gemcitabine) and a greater incidence in the aflibercept/gemcitabine arm were: hypertension (6.3% vs 35.9%); dysphonia (2.3% vs 19.3%); weight decrease (15.9% vs 30.0%); epistaxis (1.8% vs 14.4%); and headache (7.0% vs 18.9%). The other most frequently reported TEAEs with more than 5% difference between the two treatment arms (placebo/gemcitabine vs aflibercept/gemcitabine) were stomatitis and ulceration (6.3% vs 15.9%), and nausea (46.1% vs 38.1%). All other TEAEs (all grades) were observed at similar frequencies in patients in both treatment arms.

TEAEs (grade ≥ 3) were observed more frequently in patients in the aflibercept/gemcitabine arm than in the placebo/gemcitabine arm (79.3% vs 67.2%). In the aflibercept/gemcitabine arm, the most common TEAEs (grade ≥ 3) observed in ≥ 2% of patients and with a higher incidence than in the placebo/gemcitabine arm were hypertension, asthenic conditions (HLT), gastrointestinal and abdominal pains (HLT), infections and infestations (SOC), vomiting, nausea, pulmonary embolism, weight decrease, and musculoskeletal and connective tissue pain and discomfort (HLT).

7.3.2.2. VITAL (NSCLC)

The percentage of patients who experienced at least one TEAE (all grades) was 94.9% (N=430/453) in the placebo/docetaxel arm and 98.5% (N=445/452) in the aflibercept/docetaxel arm. At the SOC level, the most frequently reported TEAEs (placebo/docetaxel vs aflibercept/docetaxel) were gastrointestinal disorders (49.9% vs 70.6%), general disorders and administration site conditions (60.9% vs 65.5%), respiratory, thoracic and mediastinal disorders (49.0% vs 62.4%), skin and subcutaneous tissue disorders (44.6% vs 47.6%), and nervous system disorders (36.6% vs 40.7%). The most frequently reported TEAEs with more than 10% difference between the treatment arms (placebo/docetaxel vs aflibercept/docetaxel) and occurring with a greater incidence in the aflibercept/docetaxel arm were: stomatitis and ulceration (15.5% vs 42.9%); weight decrease (7.7% vs 24.3%); hypertension (5.1% vs 21.0%); epistaxis (6.2% vs 20.4%), and dysphonia (3.5% vs 18.4%). The other most frequently reported TEAEs occurring in 5% more patients in the aflibercept/docetaxel arm compared with the placebo/docetaxel arm were: infections; decreased appetite; headache; lacrimation increased; and oedema (HLT). Other TEAEs were observed at similar frequencies in both treatment arms.

The most frequently reported TEAEs (grade ≥ 3) with a higher frequency in the aflibercept/docetaxel arm than in the placebo/docetaxel arm were: asthenic conditions (HLT, 15.5% vs 6.4%); stomatitis and ulceration (HLT, 9.1% vs 0.7%); hypertension (7.3% vs 0.9%), diarrhoea (4.2% vs 2.4%); decreased appetite (2.7% vs 1.3%); and dehydration (2.2% vs 0.7%). Other TEAE grade ≥3 events were observed at similar frequencies in both treatment arms.

7.3.3. Deaths

7.3.3.1. VANILLA (metastatic pancreatic cancer)

Death occurred more commonly in the aflibercept/gemcitabine arm (74.1%, n=200) than in the placebo/gemcitabine arm (65.7%, n=178). The frequency of death within 30 days of the last dose was marginally higher in the aflibercept/gemcitabine arm than in the placebo/gemcitabine arm (18.5% vs 15.5%), and the main cause of death in this time interval in both treatment arms was disease progression (11.1% and 13.3%, respectively). Deaths due to AEs and for "other reasons" (irrespective of relationship to treatment) occurring within 30 days of the last dose not in the context of progressive disease were observed in 12 patients in the placebo/gemcitabine arm (4.4%) and 15 patients in the aflibercept/gemcitabine arm (5.6%). In terms of SOC, the main known causes of death in the aflibercept/gemcitabine arm were nervous system disorders

(4 patients) and gastrointestinal disorders (3 patients). These deaths included 4 due to haemorrhage (1 cerebral, and 3 gastrointestinal). No deaths from haemorrhage were observed in the placebo/gemcitabine arm. All other AEs leading to death occurred with a similar frequency in both treatment arms. A total of 4/15 deaths in the aflibercept/gemcitabine arm and 2/14 deaths in the placebo/gemcitabine arm were assessed as being related to study treatment.

7.3.3.2. VITAL (NSCLC)

Total deaths occurred with similar frequencies in the aflibercept/docetaxel and the placebo/docetaxel arms (74.8%, n=338 vs 75.5%, n=342, respectively). Deaths occurred more frequently in the aflibercept/docetaxel arm than in the placebo/docetaxel arm within 30 days from the last study dose (14.6% vs 6.8%, respectively), and this difference was observed whatever the cause of death. The main cause of death within 30 days of the last study dose in both study arms was progressive disease (n=35, 8.0%, aflibercept/docetaxel; n=16, 3.5%, placebo/docetaxel). Total deaths due to AEs (other than in the context of disease progression) and due to "other" reasons (unexplained deaths/sudden deaths) within 30 days of the last infusion were observed in 18 (4%) patients in the placebo/docetaxel arm and 32 (7.1%) patients in the aflibercept/docetaxel arm.

The main cause of death due to AEs in both treatment arms was infection, and these deaths occurred more frequently in the aflibercept/docetaxel arm than in the placebo/docetaxel arm (2.2% vs 1.3%). Neutropenic sepsis accounted for 5 deaths in the aflibercept/docetaxel arm compared with no deaths in the placebo/docetaxel arm. Additionally, there were more deaths in the aflibercept/docetaxel arm compared with the placebo/docetaxel arm in almost all SOCs, including death/sudden death (2.2% vs 0.9%), respiratory, thoracic and mediastinal disorders (1.3% vs 0.4%), and gastrointestinal disorders/perforations (0.7% vs 0.2%). Two fatal myocardial infarctions occurred in the placebo/docetaxel arm and none in the aflibercept/docetaxel arm. Two patients in each treatment arm died due to haemorrhage (2 pulmonary haemorrhage/haemoptysis in the aflibercept/docetaxel arm, and 1 haemoptysis and gastrointestinal hemorrhage in the placebo/docetaxel arm). Half of the deaths occurring other than in the context of disease progression were assessed as related to study treatment in both the aflibercept/docetaxel arm (16/32) and the placebo/docetaxel arm (9/18).

7.3.4. SAEs (other than death)

7.3.4.1. VANILLA (metastatic pancreatic cancer)

There was a greater percentage of patients with serious TEAEs (all grades) in the aflibercept/gemcitabine arm than in the placebo/gemcitabine arm (54.8%, n=148 vs 45.0%, n=122). At least one serious TEAE (grade ≥ 3), irrespective of relationship to treatment, was experienced by 48.5% of patients in the aflibercept/gemcitabine arm compared with 40.6% of patients in the placebo/gemcitabine arm. The most frequently reported serious TEAEs (grade ≥ 3) (placebo/gemcitabine vs aflibercept/gemcitabine) were pulmonary embolism (4.1%, vs 1.5%), vomiting (1.5% vs 3.0%), abdominal pain (3.3% vs 2.2%), and disease progression (8.1% vs 13.7%).

7.3.4.2. VITAL (NSCLC)

There was a greater percentage of patients with serious TEAEs (all grades) in the aflibercept/docetaxel arm than in the placebo/gemcitabine arm (48.2%, n=218 vs 35.2%, n=159). Similarly, the incidence of serious TEAEs (grade ≥ 3) was higher in patients in the aflibercept/docetaxel arm than in the placebo/docetaxel arm (44.5% vs 31.6%), due mainly to the higher frequency of patients experiencing disease progression (6.9% vs 2.6%) and stomatitis (2.4% vs 0%).

7.3.5. Adverse events leading to permanent treatment discontinuation

7.3.5.1. VANILLA (metastatic pancreatic cancer)

The frequencies of TEAEs (all grades) and TEAES (grade ≥ 3) leading to permanent treatment discontinuation in the aflibercept/gemcitabine arm were higher than in the placebo/gemcitabine arm: 28.1% vs 11.8%; and 24.4% vs 10%, respectively. At the SOC level (TEAEs all grades), the difference between the aflibercept/gemcitabine and the placebo/gemcitabine arms was due mainly to a greater incidence of permanent treatment discontinuation from gastrointestinal disorders (4.4% vs 1.1%), hepatobiliary disorders (3.0% vs 0.7%), and renal and urinary disorders (4.4% vs 0.7%). In each of these SOCs, similar imbalances in incidence were observed between the two treatment arms for TEAEs (grade ≥ 3) leading to permanent treatment discontinuation. For both TEAEs (all grades) and TEAEs (grade ≥ 3), differences between the two treatment arms were mainly due to higher incidences in the aflibercept/gemcitabine arm compared with the placebo/gemcitabine arm of proteinuria, neutropenia, hypertension, blood alkaline phosphatase increased, and hyperbilirubinaemia.

7.3.5.2. VITAL (NSCLC)

The frequencies of TEAEs (all grades) and TEAEs (grade ≥3) leading to permanent treatment discontinuation in the aflibercept/docetaxel arm were higher than in the placebo/docetaxel arm: 27.2% vs 14.6%; and 21.7% vs 11.5%, respectively. At the SOC level (TEAEs all grades), the difference between the aflibercept/docetaxel and placebo/docetaxel arms was due mainly to a greater incidence of permanent treatment discontinuation from gastrointestinal disorders (3.8% vs 1.1%), and general disorders and administration site conditions (4.6% vs 1.5%). In each of these SOCs, similar imbalances in incidence were observed between the two treatment arms for TEAEs (grade ≥ 3) leading to permanent treatment discontinuation. For both TEAEs (all grades) and TEAEs (grade ≥ 3), differences between the two treatment arms resulting in permanent treatment discontinuation were mainly due to higher incidences in the aflibercept/docetaxel arm compared with the placebo/docetaxel arm of stomatitis, asthenia, neutropenic sepsis, diarrhoea, and hypertension.

7.3.6. Adverse events leading to cycle delay and dose modification

7.3.6.1. VANILLA (metastatic prostate cancer)

TEAEs leading to cycle delay (2 days or more) occurred more frequently in patients in the aflibercept/gemcitabine arm than in the placebo/gemcitabine arm (20.4%, 55/270 vs 17.7%, 48/271). The most frequently reported TEAEs (≥ 1% of patients) occurring in at least one of the two treatment arms (aflibercept/gemcitabine vs placebo/gemcitabine) were neutropenia (6.3% vs 3.7%), proteinuria (2.2% vs 1.1%), fatigue (1.9% vs 0.4%), hypertension (1.5% vs 0%), epistaxis (1.1% vs 0%), hyperbilirubinaemia (0% vs 1.8%), and urinary tract infection (0% vs 1.1%),

TEAEs leading to dose modifications occurred more frequently in the aflibercept/gemcitabine arm than in the placebo/gemcitabine arm (62.2%, 168/270 vs 48.0%, 130/271). The most frequently reported TEAEs (≥ 3% of patients) occurring in at least one of the two treatment arms (aflibercept/gemcitabine vs placebo/gemcitabine) were neutropenia (28.5% vs 23.6%), thrombocytopenia (16.3% vs 6.6%), hypertension (6.7% vs 1.1%), proteinuria (6.7% vs 1.1%), fatigue (4.4% vs 1.5%), and ALT increased (3.0% vs 2.2%)

7.3.6.2. VITAL (NSCL)

TEAEs leading to cycle delay (2 days or more) occurred more frequently in patients in the aflibercept/docetaxel arm than in the placebo/docetaxel arm (32.7%, 148/452 vs 17.9%, 81/453). The most frequently reported TEAEs (≥ 1% of patients) occurring in at least one of the two treatment arms (aflibercept/docetaxel vs placebo/docetaxel) were hypertension (4.9% vs 0.7%), proteinuria (4.9% vs 0.4%), fatigue (4.9% vs 1.1%), stomatitis (2.9% vs 0.2%), asthenia

(2.2% vs 0.7%), diarrhoea (1.5% vs 0.2%), neutropenia (1.5% vs 0.9%), bronchitis (1.3% vs 0.4%), pneumonia (0.9% vs 1.3%), and oedema peripheral (0% vs 1.3%).

TEAEs leading to dose modifications occurred more frequently in the aflibercept/docetaxel arm than in the placebo/docetaxel arm (27.9%, 126/452 vs 14.1%, 64/453). The most frequently reported TEAEs (≥ 1% of patients) occurring in at least one of the two treatment arms (aflibercept/docetaxel vs placebo/docetaxel) were stomatitis (5.5% vs 0.4%), neutropenia (3.8% vs 2.0%), fatigue (3.3% vs 1.1%), peripheral sensory neuropathy (2.9% vs 2.2%), diarrhoea (2.2% vs 1.3%), proteinuria (2.0% vs 0.2%), palmar-plantar erythrodysaesthesia syndrome (1.5% vs 0%), febrile neutropenia (1.5% vs 1.8%), hypertension (1.3% vs 0.4%), and asthenia (1.1% vs 0.9%).

7.3.7. TEAES of interest (grouped terms) related to VEGF inhibition

7.3.7.1. VANILLA (metastatic pancreatic cancer)

The grouped TEAEs (all grades) of interest by risk ratio are summarized below in Table 45. The risks of hypertension and haemorrhage were statistically significantly higher in the aflibercept/gemcitabine arm than in the placebo/gemcitabine arm (i.e., RR 95% CI excludes 1).

Table 45: VANILLA – Grouped TEAEs (all grades) of interest by risk ratio; safety population.

Grouped terms	Placebo/ Gemcitabine (N=271)	Aflibercept/ Gemcitabine (N=270)	RR (95% CI)
Acute drug reaction	5 (1.8%)	7 (2.6%)	1.41 (0.45 to 4.37)
Arterial thromboembolic event	5 (1.8%)	8 (3.0%)	1.61 (0.53 to 4.85)
Cardiac dysfunction	1 (0.4%)	5 (1.9%)	5.02 (0.59 to 42.67)
Fistula from gastrointestinal origin	0	1 (0.4%)	NC (NC)
Gastrointestinal perforation	0	1 (0.4%)	NC (NC)
Haemorrhage	20 (7.4%)	64 (23.7%)	3.21 (2.00 to 5.15)
Hypertension	17 (6.3%)	99 (36.7%)	5.85 (3.59 to 9.50)
Rpls	1 (0.4%)	0	0.00 (NC)
Venous thromboembolic event	30 (11.1%)	24 (8.9%)	0.80 (0.48 to 1.34)
Wound healing	0	1 (0.4%)	NC (NC)

7.3.7.2. VITAL (NSCLC)

The grouped TEAEs (all grades) of interest by risk ratio are summarized below in Table 46. The risks of hypertension and haemorrhage were statistically significantly higher in the aflibercept/docetaxel arm than in the placebo/docetaxel arm (i.e., RR 95% CI excludes 1).

Table 46: VITAL – Grouped TEAEs (all grades) of interest by risk ratio; safety population.

Grouped terms	Placebo/ Docetaxel (N=453)	Aflibercept/ Docetaxel (N=452)	RR (95% CI)
Acute drug reaction	15 (3.3%)	25 (5.5%)	1.67 (0.89 to 3.13)
Arterial thromboembolic event	8 (1.8%)	6 (1.3%)	0.75 (0.26 to 2.15)
Cardiac dysfunction	2 (0.4%)	2 (0.4%)	1.00 (0.14 to 7.08)
Fistula from gastrointestinal origin	0	4 (0.9%)	NC (NC)
Gastrointestinal perforation	1 (0.2%)	6 (1.3%)	6.01 (0.73 to 49.75)
Haemorrhage	59 (13.0%)	126 (27.9%)	2.14 (1.62 to 2.83)
Hypertension	23 (5.1%)	95 (21.0%)	4.14 (2.68 to 6.40)
Osteonecrosis	1 (0.2%)	1 (0.2%)	1.00 (0.06 to 15.97)
Venous thromboembolic event	21 (4.6%)	14 (3.1%)	0.67 (0.34 to 1.30)
Wound healing	0	3 (0.7%)	NC (NC)

7.3.8. Meta-analysis (VELOUR, VANILLA, VITAL)

The SCS included a meta-analysis of TEAEs of interest by pooling the data for the TEAEs of special interest from the three, Phase 3 studies (VELOUR, VANILLA, VITAL). The results for each of the TEAEs of interest were consistent with the results from the individual studies. The results for the meta-analysis were summarized in the dossier.

7.3.9. Other safety data

Other relevant supportive safety data from VANILLA and VITAL have been incorporated into the main text relating to VELOUR.

7.4. Other safety data

The submission included an integrated safety summary (ISS) of cases of reversible posterior leukoencephalopathy syndrome (RPLS) reported or known to the sponsor as of 28 July 2011. The ISS included 17 cases (13 females and 4 males) in ~ 3759 patients exposed to aflibercept, giving an overall incidence of ~ 0.5%. Overall, the mean age was 60.5 years (SD 12.5) with a median age of 59 years (range 34 to 76 years). The mean cycle at diagnosis was 4.8 (SD 5.3), mean day from last administration was 10.4 (SD 6.8). Twelve (12) cases were reported as having recovered, and the mean duration for these 12 cases was 13.5 days (SD 11.2). The dosing regimen of 4 mg/kg aflibercept administered every 2 weeks was background treatment 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 including 1 event each in dose escalation studies with gemcitabine, and S-1, and 1 event in a Phase 2 study with modified FOLFOX6. There was one case from a dose-escalating phase 1 study where aflibercept 5mg/kg was administered in combination with FOLFOX4. In the remaining 5 cases the dosing regimen of 6 mg/kg aflibercept administered every 3 weeks was background treatment, all in combination with cytotoxic chemotherapy: 3 in combination with pemetrexed/cisplatin and 2 in combination with docetaxel/(prednisone or prednisolone). The most common presenting symptoms included altered mental status in 10 patients, seizure in 9 patients and headache in 6 patients. Additionally, patients complained of visual hallucinations, blurred vision, falls, amnesia, nausea, vomiting, and dysarthria. Of the 17 cases, 2 were reported from studies undertaken in Australia, and both patients recovered.

7.5. Post-marketing experience

Not applicable.

7.6. Evaluator's overall conclusions on clinical safety

The key safety data in the submission are derived from the pivotal Phase 3 efficacy and safety study (VELOUR). It is considered that this study has demonstrated that the overall safety profile of aflibercept/folfiri is inferior to that of placebo/folfiri in patients with MCRC. In addition, the supportive safety data from Phase 1, 2, and 3 studies are considered to be consistent with that from VELOUR. In total, 2073 patients have been exposed to aflibercept in single-agent and combination studies included in the sponsor's safety database. The safety data discussed below are from VELOUR, unless otherwise stated.

- In VELOUR, the safety population included 1216 patients with metastatic colorectal cancer of whom 611 had been treated with aflibercept/folfiri and 605 with placebo/folfiri. The median duration of exposure was longer in the aflibercept/folfiri arm than in the placebo/folfiri arm (21.4 weeks [range: 2, 105] vs 18.1 weeks [range: 2, 135]), as was the median number of treatment cycles (9 [range: 1, 50] vs 8 [range: 1, 67]). However, the median number of aflibercept/placebo infusions was lower in the aflibercept/folfiri arm

than in the placebo/folfiri arm (7.0 [range: 1, 35] vs 8.0 [range: 1, 67]), due to more frequent cycle delays and dose modifications primarily due to TEAEs.

- TEAEs (all grades) were reported in nearly all patients in both treatment arms (97.9%, placebo/folfiri vs 99.2%, aflibercept/folfiri). TEAEs (all grades) occurring in ≥ 20% of patients in at least one treatment arm and more commonly in the aflibercept/folfiri arm than in the placebo/folfiri arm were diarrhoea (69.2% vs 56.5%), stomatitis (50.1% vs 32.9%), fatigue (47.8% vs 39.0%), hypertension (41.2% vs 10.7%), neutropenia (39.0% vs 33.9%), decreased appetite (31.9% vs 23.8%), weight decreased (31.9% vs 14.4%), epistaxis (27.7% vs 7.4%), abdominal pain (26.8% vs 23.6%), dysphonia (25.4% vs 3.3%), and headache (22.3% vs 8.8%). Other TEAEs occurring in ≥ 20% of patients in both treatment arms, but with similar frequencies were nausea, vomiting, alopecia, and constipation.
- Risk-ratios (aflibercept/folfiri relative to placebo/folfiri) were greater than 1 for a number of frequently occurring TEAEs. The most notable increased risks associated with aflibercept/folfiri relative to placebo/folfiri were dysphonia (RR = 7.67 [95% CI: 4.88, 12.06]) and proteinuria (RR=6.93 [95% CI: 3.48, 13.81]). TEAEs with RR ≥ 3 to < 4 were hypertension, epistaxis, rhinorrhoea, and dehydration, and TEAEs with RR ≥ 2 to < 3 were skin hyperpigmentation, proctalgia, haemorrhoids, palmar-plantar erythrodysaesthesia syndrome, headache, oropharyngeal pain, weight decreased and rectal haemorrhage.
- TEAEs (grade ≥ 3) were reported more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (83.5% vs 62.5%). TEAEs (grade ≥ 3) reported in ≥ 2% more patients in the aflibercept/folfiri arm than in placebo/folfiri arm were neutropenia (25.0% vs 22.0%), diarrhoea (19.3% vs 7.8%), hypertension (19.1% vs 1.5%), stomatitis (12.8% vs 4.6%), fatigue (12.6% vs 7.8%), urinary tract infection (9.2% vs 6.1%), asthenia (5.1% vs 3.0%), abdominal pain (4.4% vs 2.3%), dehydration (4.3% vs 1.3%), proteinuria (2.9% vs 0%), and palmar-plantar erythrodysaesthesia syndrome (2.8% vs 0.5%). The most marked differences (≥ 5%) between the two treatment arms were reported for hypertension (17.6%), diarrhoea (11.5%), and stomatitis (8.2%).
- Treatment-related TEAEs (all grades) were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (95.6% vs 90.9%), as were treatment-related TEAEs (grade ≥ 3) (73.8% vs 46.9%). The most frequently reported treatment-related TEAEs (all grades) and TEAEs (grade ≥ 3) were similar to the corresponding all causality TEAEs (all grades) and TEAEs (grade ≥ 3).
- Total deaths on-treatment (i.e., within 30 days of last dose) occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (4.9%, n=30 vs 3.1%, n=19), as did deaths on-treatment due to identified AEs (2.3%, n=14 vs 0.7%, n=4). Deaths on-treatment due to identified AEs or for other reasons not in the context of disease progression also occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (2.6%, n=16 vs 1.0%, n=6). Of these deaths, 6 (1%) in the aflibercept/folfiri arm were considered treatment-related by investigators compared with 3 (0.5%) in the placebo/folfiri arm. The 6 treatment-related deaths in the aflibercept/placebo arm were: 2x neutropenic infection (1x rectal abscess, 1x intestinal mucositis); 1x unknown cause; 1x hypovolaemic shock (diarrhoea and vomiting); 1x duodenal ulcer haemorrhage; and 1x pulmonary embolism. The 3 treatment-related deaths in the placebo/folfiri arm were: 1 x neutropenic infection; 1x lobar pneumonia; and 1x interstitial lung disease.
- SAEs (all grades) were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (48.1% vs 32.7%), as were SAEs (grade ≥ 3) (41.6% vs 28.28%). SAEs (grade ≥ 3) occurring in ≥ 2 % of patients in at least one of the treatment arms, and more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm, were diarrhoea (5.6% vs 2.0%), febrile neutropenia (3.1% vs 2.0%), pulmonary embolism

(3.1% vs 2.0%), dehydration (2.9% vs 0.8%) and disease progression (2.6% vs 2.3%). Treatment-related SAEs (grade ≥ 3) were also reported more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (31.8% vs 15.4%).

- TEAEs (all grades) resulting in permanent treatment discontinuation occurred notably more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (26.8% vs 12.1%), and the majority of patients in both treatment arms permanently discontinued treatment due to TEAEs (grade ≥ 3) (20.3%, aflibercept/folfiri vs 8.8%, placebo/folfiri). The most frequently reported TEAEs (all grades) grouped according to event similarity and leading to permanent treatment discontinuation (aflibercept/folfiri vs placebo/folfiri) were: fatigue/asthenia (3.7% vs 1.3%); infections and infestations SOC (3.4% vs 1.7%); diarrhoea (2.3% vs 0.7%); myelosuppression including neutropenia, thrombocytopenia, anemia and febrile neutropenia (2.0% vs 1.0%); pulmonary embolism (1.1% vs 1.2%); proteinuria including nephrotic syndrome (1.7% vs 0%); and deep vein thrombosis including DVT, subclavian vein thrombosis, vena cava thrombosis, and thrombophlebitis (1.3% vs 0.3%).
- TEAEs (all grades), leading to at least one cycle delay occurred notably more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (70.0% vs 54.4%). TEAEs (all grades) resulting in cycle delay and reported in ≥ 2.0% more patients in the aflibercept/folfiri arm than in the placebo/folfiri arm were neutropenia (36.2% vs 33.4%), diarrhoea (12.1% vs 5.0%), hypertension (10.8% vs 0.8%), fatigue (9.0% vs 5.3%), stomatitis (8.5% vs 3.1%), decreased appetite (4.4% vs 1.7%), proteinuria (3.4% vs 1.2%), thrombocytopenia (3.3% vs 2.0%), abdominal pain (2.5% vs 1.0%), and urinary tract infection (2.0% vs 1.0%).
- TEAEs (all grades) leading to dose modifications occurred notably more frequently in patients in the aflibercept/folfiri arm compared with the placebo/folfiri arm (50.4% vs 26.8%). TEAEs (any grade) reported in ≥ 2% more patients in the aflibercept/folfiri arm than in the folfiri/placebo arm and resulting in dose modifications were diarrhoea (16.2% vs 6.4%), stomatitis (11.9% vs 5.0%), hypertension (6.2% vs 0.3%), fatigue (4.4% vs 2.1%), proteinuria (4.1% vs 0.5%), and palmar-plantar erythrodysaesthesia syndrome (2.9% vs 0.3%).
- TEAEs (all grades) considered to be known risks associated with drugs targeting the VEGF pathway were separately assessed using grouped terms. Risk ratios (aflibercept/folfiri relative to placebo/folfiri) were statistically significantly higher for hypertension (RR = 3.85 [95% CI: 3.01, 4.94) and haemorrhage (RR = 1.99 [95% CI: 1.64, 2.41]), while risk ratios > 1 but not statistically significant were reported for fistula from gastrointestinal origin, fistula from other than gastrointestinal origin, arterial thromboembolic events, and venous thromboembolic events. Risk ratios ≤ 1 were reported for acute drug reaction, gastrointestinal perforation, and wound healing. Risk ratios could not be calculated for cardiac dysfunction, and osteonecrosis because of lack of events in the placebo/folfiri arm, while 2 (0.3%) cases in the aflibercept/folfiri arm were reported for each of these advents. There were no reports of RPLS in VELOUR. However, in the ISS of RPLS there were 17 cases reported in approximately 3759 patients exposed to aflibercept, giving an overall incidence of approximately 0.5%.
- Laboratory haematological abnormalities (all grades) of thrombocytopenia, neutropenia and leukopenia were all reported more frequently in the aflibercept/folfiri arm than in the placebo/aflibercept arm, while the converse was observed for anaemia. The laboratory haematological abnormality with the highest incidence of grade 3 or 4 events was neutropenia (36.7%, N=221/603, aflibercept/folfiri vs 29.5%, N=176/597, placebo/folfiri). The incidence of neutropenic complications was greater in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm, and nearly all of these events in both treatment arms were grade ≥ 3 (5.7% vs 2.8%, respectively).

- Laboratory clinical chemistry abnormalities (all grades) for liver function tests of increased ALT and increased AST were reported more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm, and the events were predominantly grade 1 and 2 in both treatment arms (ALT all grades 47.3% vs 37.1%, AST all grades 57.5% vs 50.2%). Increased total bilirubin (all grades) occurred with similar frequencies in the aflibercept/folfiri and placebo/folfiri arms (22.8% vs 23.2%, respectively), as did increased serum alkaline phosphatase (all grades) (70.8% vs 69.2%, respectively).
- Potential Hy's law cases (ALT or AST > 3xULN and bilirubin >2xULN during the treatment period) were reported in 7 patients in both the aflibercept/folfiri arm (1.1%) and the placebo/folfiri arm (1.2%), and all patients had hepatic metastases. Hepatobiliary disorders (SOC, all grades) were reported in 3.9% (n=24) of patients in the aflibercept/folfiri arm and 5.0% (n=30) of patients in the placebo/aflibercept arm, and the corresponding results for SOC (grade ≥ 3) events were 1.6% (n=10) and 2.0% (n=12), respectively. Overall, the results suggest that there was no increased risk of drug-related hepatoxicity in the aflibercept/folfiri arm compared with the placebo/folfiri arm.
- Increased creatinine levels (all grades) occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (22.6%, N=136/601 vs 18.1%, N=108/596, respectively), while the incidence of grade 3 or 4 events did not notably differ between the two treatment arms (N=0/601, 0% vs N=3/596, 0.5%, respectively). The percentage of patients with increased creatinine clearance values on treatment were about 2% greater in the aflibercept/folfiri arm compared with the placebo/folfiri arm for < 50 mL/min (15.3% vs 13.1%) and ≥ 50 to ≤ 80 mL/min (46.8% vs 44.6%). Renal failure events were reported in 2.9% of patients in the aflibercept/folfiri arm and 2.1% of patients in the placebo/folfiri arm. Overall, the results suggest that the risks of renal impairment were marginally increased in the aflibercept/folfiri arm compared with the placebo/folfiri arm.
- Patients in the aflibercept/folfiri arm did not appear to be at an increased risk of developing anti-aflibercept antibodies compared with patients in the placebo/folfiri arm (1.5% vs 3.4%, respectively), or neutralizing antibodies (0.2% vs 0.4, respectively). Hypersensitivity reactions (TEAEs all grades, grouped) occurred in 2.5% of patients in the placebo/folfiri arm compared with 1.8% of patients in the aflibercept/folfiri, with drug hypersensitivity being reported in 0.5% and 0.7% of patients respectively, and allergic oedema in 0.2% and 0% of patients, respectively.
- Changes in vital signs were characterized by notably greater increases in blood pressure from baseline in patients in the aflibercept/folfiri arm compared with the placebo/folfiri arm. There was no systematic investigation of ECG changes in VELOUR, but the pharmacodynamic study TES10897 suggests that QTcF prolongation is unlikely to be a clinically significant problem with aflibercept.
- TEAEs were generally similar in males and females, and the observed differences are unlikely to be clinically significant. No dosage changes appear to be required based on sex. There were some differences in TEAEs observed in patients aged < 65 years and ≥ 65 years, but no dosage changes appear to be required based on age.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The submission included only one efficacy study supporting registration of aflibercept for the proposed indication (VELOUR). In this pivotal study, there was a statistically significant difference in OS (the primary efficacy endpoint) in favour of aflibercept/folfiri compared with

placebo/folfiri (stratified HR = 0.817 [95.34% CI: 0.713 to 0.937]; p=0.0032 log-rank test), based on 863 events and a median duration of follow-up of 22.28 months. Death events occurred more frequently in patients in the placebo/folfiri arm than in patients in the aflibercept/folfiri arm (74.9%, N=460/614 vs 65.8%, N=403/612). The median OS in the aflibercept/folfiri arm (13.50 months [95.34% CI: 12.517, 14.949]) was 1.44 months longer than in the placebo/folfiri arm (12.06 months [95.34% CI: 11.072 to 13.109]).

While the difference in OS between the two treatment arms was statistically significant, the results are considered to be not clinically significant based on the survival criteria used to calculate the sample size. The sample size calculation was based on a 20% risk reduction in death events in the aflibercept/folfiri arm compared with the placebo/folfiri arm (HR = 0.80 corresponding to a median OS improvement from 11 months in the placebo/folfiri arm to 13.75 months in the aflibercept/folfiri arm). The observed risk reduction in the aflibercept/folfiri arm compared with the placebo/folfiri arm was 18% (c.f., 20% sample size survival criteria), and the observed difference in median OS in favour of placebo/folfiri was 1.44 months (c.f., 2.75 months sample size survival criteria). Based on the sample size survival criteria, it is reasonable to infer that a relative risk reduction of 20% and a median difference of 2.75 months OS in favour of aflibercept/folfiri compared with placebo/folfiri are the minimum clinically significant criteria required for this study. As aflibercept/folfiri failed to meet either of these survival criteria it is considered that the observed results for OS are not clinically significant.

The two secondary efficacy analyses of PFS and ORR both statistically significantly favoured the aflibercept/folfiri arm over the placebo/folfiri arm. The PFS stratified HR was 0.758 (99.9% CI: 0.578, 0.995), p=0.00007 log-rank test, and the difference in median PFS was 2.23 months in favour of aflibercept/folfiri (6.90 months [99.99% CI: 5.881, 7.852]) compared with placebo/folfiri (4.67 months [99.99% CI: 4.074, 5.552]). The ORR was 19.8% (95% CI: 16.4, 23.2) in the aflibercept/folfiri arm and 11.1% (95% CI: 8.5%, 13.8%), p=0.0001 stratified CMH test. Although the secondary efficacy analyses of PFS and ORR both statistically significantly favoured the aflibercept/folfiri arm compared with the placebo/folfiri arm, it is considered that these results do not outweigh the failure of the primary efficacy analysis of OS to demonstrate a clinically significant benefit for the aflibercept/folfiri arm.

8.2. First round assessment of risks

The pivotal study (VELOUR) showed that the risks of treatment with aflibercept/folfiri (n=611) were greater than those with placebo/folfiri (n=605). While TEAEs (all grades) were reported in nearly all patients in both treatment arms (99.2%, aflibercept/folfiri vs 97.9%, placebo/folfiri), almost all clinically important risks occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm. In addition, although the risks in both treatment arms were manageable by cycle delay or dose modifications rather than permanent treatment discontinuation, these two methods were required in notably more patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (i.e., 70% vs 54.4%, cycle delay; 50.4% vs 26.8%, dose modifications). Furthermore, despite the availability of cycle delays and dose modifications to manage risks, permanent treatment discontinuations occurred notably more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (26.6% vs 12.1%).

The most commonly occurring TEAEs (all grades) and laboratory events* (all grades) reported in ≥ 20% of patients in either treatment arm, and more frequently with aflibercept/folfiri than with placebo/folfiri, in order of decreasing frequency were leucopenia* (78.3% vs 72.4%), diarrhoea (69.2% vs 56.5%), neutropenia* (67.8% vs 56.3%), proteinuria* (62.2% vs 40.7%), AST increased* (57.5% vs 50.2%), stomatitis (50.1% vs 32.9%), fatigue (47.8% vs 39.0%), thrombocytopenia* (47.4% vs 33.8%), ALT increased* (47.3% vs 37.1%), hypertension (41.2% vs 10.7%), decreased appetite (31.9% vs 23.8%), weight decreased (31.9% vs 14.4%), epistaxis (27.7% vs 7.4%), abdominal pain (26.8% vs 23.6%), dysphonia (25.4% vs 3.3%), and headache

(22.3% vs 8.8%). Other TEAEs occurring in ≥ 20% of patients and with similar frequencies in both treatment arms were nausea, vomiting, alopecia, and constipation.

The risk of patients experiencing TEAEs (grade ≥ 3) were notably greater in the aflibercept/folfiri arm (83.5%) than in the placebo/folfiri arm (62.5%). TEAEs (grade ≥ 3) reported in ≥ 2% more patients in the aflibercept/folfiri arm than in placebo/folfiri arm were neutropenia (25.0% vs 22.0%), diarrhoea (19.3% vs 7.8%), hypertension (19.1% vs 1.5%), stomatitis (12.8% vs 4.6%), fatigue (12.6% vs 7.8%), urinary tract infection (9.2% vs 6.1%), asthenia (5.1% vs 3.0%), abdominal pain (4.4% vs 2.3%), dehydration (4.3% vs 1.3%), proteinuria (2.9% vs 0%), and palmar-plantar erythrodysaesthesia syndrome (2.8% vs 0.5%). The most marked risks (TEAEs grade ≥ 3) in the aflibercept/folfiri arm compared with the placebo/folfiri (≥ 5% difference) were hypertension (17.6% difference), diarrhoea (11.5% difference), and stomatitis (8.2% difference).

Risk-ratios (aflibercept/folfiri:placebo/folfiri) were greater than 1 for a number of frequently occurring TEAEs. The most notably increased risks associated with aflibercept/folfiri relative to placebo/folfiri were dysphonia (RR = 7.67 [95% CI: 4.88, 12.06) and proteinuria (RR=6.93 [95% CI: 3.48, 13.81]). TEAEs with RRs ≥ 3 to < 4 were hypertension, epistaxis, rhinorrhoea, and dehydration, and TEAEs with RRs ≥ 2 to < 3 were skin hyperpigmentation, proctalgia, haemorrhoids, palmar-plantar erythrodysaesthesia syndrome, headache, oropharyngeal pain, weight decreased and rectal haemorrhage.

Of the grouped TEAEs (all grades) considered to be known risks for drugs targeting the VEGF pathway, the risks of hypertension (~4-fold increase) and haemorrhage (~2-fold increase) were statistically significantly greater in the aflibercept/folfiri arm compared with the placebo/folfiri arm. In addition, a fatal duodenal ulcer haemorrhage considered to be treatment-related occurred in one patient in the aflibercept/folfiri treatment arm. Risk ratios > 1, but not statistically significant were reported for fistulae from both gastrointestinal and other than gastrointestinal origins, and arterial (ATE) and venous (VTE) thromboembolic events. In addition, a fatal VTE (pulmonary embolism) considered to be treatment related occurred in one patient in the aflibercept/folfiri treatment arm. Risk ratios ≤ 1 were reported for acute drug reaction, gastrointestinal perforation, and wound healing. Risk ratios could not be calculated for cardiac dysfunction, and osteonecrosis because no events were reported in the placebo/folfiri arm, while each of these events occurred in 2 (0.3%) patients in the aflibercept/folfiri arm. There were no reports of RPLS in VELOUR. However, in the ISS of RPLS there were 17 cases (13 females and 4 males) in ~ 3759 patients exposed to aflibercept, giving an overall incidence of ~ 0.5%.

Total deaths on-treatment (i.e., within 30 days of last dose) occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (4.9%, n=30 vs 3.1%, n=19, respectively), as did deaths on-treatment due to identified AEs (2.3%, n=14 vs 0.7%, n=4). Deaths on-treatment due to identified AEs or for other reasons not related to disease progression also occurred more frequently in the aflibercept/folfiri arm than in the placebo/folfiri arm (2.6%, n=16 vs 1.0%, n=6). Of these deaths, 6 (1%) in the aflibercept/folfiri arm were considered treatment-related by investigators compared with 3 (0.5%) in the placebo/folfiri arm. The 6 treatment-related deaths in the aflibercept/placebo arm were: 2x neutropenic infection (1x rectal abscess, 1x intestinal mucositis); 1x unknown cause; 1x hypovolaemic shock (diarrhoea and vomiting); 1x duodenal ulcer haemorrhage; and 1x pulmonary embolism. The 3 treatment-related deaths in the placebo/folfiri arm were: 1 x neutropenic infection; 1x lobar pneumonia; and 1x interstitial lung disease.

Laboratory haematological abnormalities (all grades) of thrombocytopenia, neutropenia and leukopenia were all reported more frequently in the aflibercept/folfiri arm than in the placebo/aflibercept arm, while the converse was observed for anaemia. The haematological laboratory abnormality with the highest incidence of TEAEs (grade 3 or 4) was neutropenia (36.7%, aflibercept/folfiri vs 29.5%, placebo/folfiri). The incidence of neutropenic

complications was greater in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm, and nearly all of these events in both treatment arms were grade ≥ 3 (5.7% vs 2.8%, respectively).

Patients in the aflibercept/folfiri arm did not appear to be at a significantly greater risk of hepatic or renal toxicity compared with patients in the placebo/folfiri arm. However, proteinuria defined as patients with at least one AE (nephrotic syndrome or proteinuria) or with morning spot and/or 24 hour urinalysis was reported notably more frequently in patients in the aflibercept/folfiri arm than in the placebo/folfiri arm (67.2% vs 40.7%),

Patients in the aflibercept/folfiri arm did not appear to be at an increased risk of developing anti-aflibercept antibodies compared with patients in the placebo/folfiri arm (1.5% vs 3.4%, respectively), or neutralizing antibodies (0.2% vs 0.4%). Hypersensitivity reactions (TEAEs all grades, grouped) occurred in 2.5% of patients in the placebo/folfiri arm compared with 1.8% of patients in the aflibercept/folfiri, with drug hypersensitivity being reported in 0.5% and 0.7% of patients respectively, and allergic oedema in 0.2% and 0% of patients, respectively.

Patients aged ≥ 65 years experienced the following TEAEs (all grades) ≥ 5% more frequently than patients aged < 65 years: diarrhoea (73.7% vs 67.0%); weight decreased (41.0% vs 27.3%); asthenia (22.0% vs 16.5%); dehydration (14.6% vs 6.2%); and dizziness (9.3% vs 4.2%). However, no dosage adjustment appears to be indicated based on age, but the number of patients aged > 75 years was small. There were some differences between male and female patients in the risks associated with aflibercept/folfiri treatment, but these are not considered to be significant. There were no meaningful data on the risks of aflibercept/folfiri in the different racial groups, due to relatively small numbers of patients in all groups apart from Caucasian/White.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy for the treatment of metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen is considered to be unfavourable. It is considered that the pivotal study failed to demonstrate a clinically significant improvement in OS in the aflibercept/folfiri arm compared with the placebo/folfiri arm, while demonstrating a notably inferior safety profile for the aflibercept/folfiri arm compared with the placebo/folfiri arm.

9. First round recommendation regarding authorisation

9.1. Recommendation to reject

It is recommended that the application to register aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy for the treatment of adults with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen be rejected.

9.2. Reasons for recommendation to reject

The single pivotal study has failed to establish that aflibercept/folfiri provides a clinically significant benefit in OS compared with placebo/folfiri. In addition, the benefit-risk balance for aflibercept/folfiri is unfavourable as the pivotal study failed to establish a clinically significant improvement in OS in the aflibercept/folfiri arm compared with the placebo/folfiri arm, while demonstrating that the safety profile of aflibercept/folfiri is notably inferior to that of placebo/folfiri.

There was a statistically significant difference in OS (the primary efficacy endpoint) in favour of aflibercept/folfiri compared with placebo/folfiri (stratified HR = 0.817 [95.34% CI: 0.713 to 0.937]; p=0.0032 log-rank test), based on 863 events and a median duration of follow-up of 22.28 months. In patients in the aflibercept/folfiri arm there were 403 (65.8%) death events compared 460 (74.9%) in the placebo/folfiri arm. The median OS in the aflibercept/folfiri arm (13.50 months [95.34% CI: 12.517, 14.949]) was 1.44 months longer than in the placebo/folfiri arm (12.06 months [95.34% CI: 11.072 to 13.109]).

While the pivotal study showed a statistically significant difference in OS between the two treatment arms in favour of aflibercept/folfiri compared with aflibercept/folfiri, it is considered that the observed difference is not clinically significant. The risk of experiencing an OS death event was reduced by 18% in the aflibercept/folfiri arm relative to the placebo/aflibercept arm (HR stratified = 0.817 [95.34% CI: 0.713 to 0.937]; p=0.0032 log-rank test), and the median duration of OS was 1.44 months longer in the aflibercept/folfiri arm than in the placebo/folfiri arm (13.50 months [95.34% CI: 12.517, 14.949] and 12.06 months [95.34% CI: 11.072 to 13.109], respectively). However, the observed relative risk reduction was lower, and the observed median duration difference was shorter, than the corresponding values considered to be clinically significant based on the survival criteria used to calculate the sample size (i.e., 20% risk reduction, median difference of 2.75 months). Although the secondary efficacy endpoints (PFS and the ORR) statistically significantly favoured aflibercept/folfiri compared with placebo/folfiri, it is considered that these results can not offset the failure of aflibercept/folfiri to establish a clinically significant OS benefit compared with placebo/folfiri.

10. Clinical questions

No questions

11. Second round evaluation of clinical data submitted in response to questions

Not applicable

12. References

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13. APPENDIX A. Response evaluation criteria in solid tumors (RECIST) quick reference

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to quality for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response / Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions[1]

[1] Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician. Should prevail and the progression status should be confirmed later on by the review panel (or study chairmen).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

14. Appendix B. ECOG performance status scale.

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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