



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Aflibercept *rch*

Proprietary Product Name: Zaltrap, Aflitiv,  
Lidaveg

Sponsor: Sanofi-Aventis Australia Pty

**July 2013**

**TGA** Health Safety  
Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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## I. Introduction to product submission

### Submission details

<i>Type of Submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	5 March 2013
<i>Active ingredient:</i>	Aflibercept <i>rch</i>
<i>Product Names:</i>	Zaltrap, Aflitiv, Lidaveg
<i>Sponsor's Name and Address:</i>	Sanofi-Aventis Australia Pty 12-24 Talavera Road Macquarie Park NSW 2113
<i>Dose form:</i>	Injection concentrate
<i>Strengths:</i>	100 mg/4 mL and 200 mg/8 mL
<i>Container:</i>	Vial
<i>Pack sizes:</i>	1 and 3
<i>Approved Therapeutic use:</i>	Zaltrap/Aflitiv/Lidaveg in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen. [See clinical trials for results of Zaltrap/Aflitiv/Lidaveg in combination with FOLFIRI <sup>1</sup> . Other combinations have not been evaluated].
<i>Route of administration:</i>	Intravenous infusion

<sup>1</sup> A chemotherapy regimen that includes **f**olinic acid (FOL), **f**luorouracil (F) and **i**rinotecan (IRI)

<i>Dosage (abbreviated):</i>	<p>The recommended dose, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen.</p> <p>The FOLFIRI regimen used in the VELOUR study was irinotecan 180 mg/m<sup>2</sup> intravenous infusion over 90 minutes and folinic acid (dl racemic) 400 mg/m<sup>2</sup> intravenous infusion over 2 h at the same time on day 1 using a Y line, followed by 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup> intravenous bolus, followed by 5 FU 2400 mg/m<sup>2</sup> continuous intravenous infusion over 46 h.</p> <p>The treatment cycles are repeated every 2 weeks.</p> <p>Treatment should be continued until disease progression or unacceptable toxicity occurs.</p>
<i>ARTG Numbers:</i>	195234, 195939, 195970, 195974, 195975, 195976

## Product background

Aflibercept is a novel, targeted antiangiogenic agent. It is a recombinant human (rch) protein derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the constant (Fc) portion of human immunoglobulin G1 (IgG1). Aflibercept acts as a soluble decoy receptor that binds to VEGF-A, with higher affinity than its native receptors, as well as the related ligands placental growth factor (PlGF) and VEGF-B. By acting as a ligand trap, aflibercept (also known as VEGF-Trap) prevents binding of endogenous ligands to their receptors, blocking receptor mediated signalling.

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register the product for the indication: "*aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen*". Thus, the proposal is for second line use, alongside other agents, in the setting of MCRC.

The sponsor considers the antiangiogenic mechanisms of action to be direct anti-cancer activity and potentiation of chemotherapy *via* prevention of new tumor vessel growth, regression of existing tumor vessels, vascular normalisation, direct effects on tumor cell function, offsetting of effects of chemotherapy induction of VEGF levels, and inhibition of VEGF repression of dendritic cell function.

While this application is evaluated as for a new biological entity, a different presentation and usage for aflibercept was registered in Australia in March 2012 as Eylea, aflibercept (rch) 40 mg/mL solution for intravitreal injection pre-filled syringe (Bayer as sponsor), with the indication *treatment of neovascular (wet) age-related macular degeneration (wet AMD)* and a recommended dose of 2 mg (50 µL) once per month for 3 months then once per 2 months.

## Regulatory status

Zaltrap/Lidaveg/Aflitiv received initial registration on the Australian Register of Therapeutic Goods on 2 April 2013.

At the time this application was under consideration, a similar application was approved in the USA (August 2012) and was under review in Canada, Switzerland and the European

Union [(EU) (a positive opinion was issued by the Committee for Medicinal Products for Human use (CHMP) on 15 November 2012)].

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

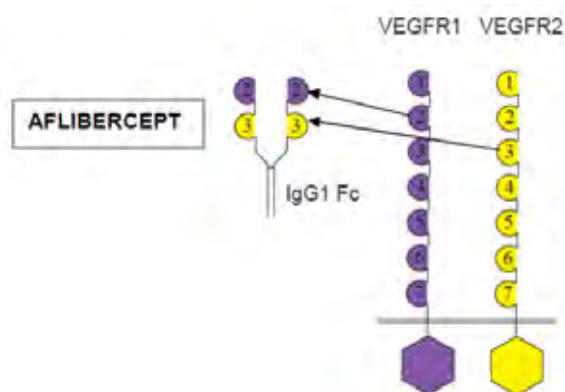
## II. Quality findings

### Drug substance (active ingredient)

#### Structure

Aflibercept is a recombinant protein consisting of sequences derived from human VEGF receptor extracellular domains fused to the Fc portion of human IgG1. The extracellular domain sequences come from two different VEGF receptors, VEGFR1 (also known as Flt-1) and VEGFR2 (also known as KDR or Flk-1). Each of the VEGF receptors are composed of seven Ig domains in their extracellular regions, with Ig domains 2 and 3 contributing the majority of the binding energy for VEGF. Thus, the amino acid sequence of a single aflibercept subunit comprises Ig domain 2 from VEGFR1, fused to Ig domain 3 from VEGFR2, which is in turn fused to the Fc domain fragment of IgG1. There are no extraneous linker sequences between any of the peptide domains. The drug substance has the following structure:

**Figure 1. Structure of aflibercept**



Aflibercept is a dimeric glycoprotein with a protein molecular weight of 96.9 kDa ( $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$ , 2 x 431 amino acids). It contains approximately 15% glycosylation to give a total molecular weight of 115 kDa. All five putative N-glycosylation sites on each polypeptide chain predicted by the primary sequence can be occupied with carbohydrate and exhibit some degree of chain heterogeneity, including heterogeneity in terminal sialic acid residues, except at the single unsialylated site associated with the Fc domain.

The disulfide bond structure of aflibercept determined by peptide mapping matches the known disulfide patterns of the VEGFR1 (Ig domain 2), VEGFR2 (Ig domain 3) and the IgG Fc domain. The C-terminus lacks the predicted lysine residue on the Fc moiety as expected.

## **Manufacture**

The manufacturing of aflibercept drug substance involves growth of a suspension culture of Chinese Hamster Ovary cells (CHO K1) engineered to express aflibercept. The recombinant product is secreted into the culture medium and subsequently purified by chromatographic (Protein A affinity, cation exchange, anion exchange and hydrophobic interaction chromatography), virus inactivation/filtration, concentration/diafiltration and membrane filtration techniques.

Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

## **Physical and chemical properties**

Product-related impurities include aggregates, truncated species, deamidated variants, charged variants and oxidised forms. The first four forms of impurity are controlled at drug substance release. Omission of controlling oxidised form at drug substance release is well justified.

## **Physicochemical and biochemical properties of aflibercept**

Data were provided in the dossier.

## **Specifications**

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use have been provided. Appropriate validation data were submitted in support of the test procedures.

## **Stability**

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

The real time data submitted support a shelf life of "24 months, stored at  $\leq -20^{\circ}\text{C}$ , protected from light" for aflibercept drug substance stored in polycarbonate bottles or Biosystems Celsius Pak (bag).

## **Drug product**

### **Formulation(s)**

Aflibercept drug product is a sterile, clear, colourless to pale yellow solution and is supplied in two presentations of 100 mg/4 mL and 200 mg/8 mL, both manufactured from the same bulk solution at 25 mg/mL of aflibercept. The drug product is formulated in 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 20% sucrose, 0.1% polysorbate 20, and pH 6.0 to 6.2. The solution is packaged in type 1, clear borosilicate glass vial closed with a gold flanged cap with tear-off lid and inserted sealing disc, polytetrafluoroethylene (Flurotec) coated. An overfilling is introduced to ensure extractability of the nominal volume from the vial. The target fill volume is 4.4 mL for the 100 mg/4 mL presentation and 8.4 mL for the 200 mg/8 mL presentation.

- The vial capacity for the 100 mg/4 mL presentation is 5 mL and the tear-off lid is blue. The package size is 1 and 3 vials.

- The vial capacity for the 200 mg/8 mL presentation is 10 mL and the tear-off lid is orange. The package size is 1 vial.

Prior to infusion, the concentrate solution is diluted with 0.9% NaCl or 5% dextrose to a final aflibercept concentration of 0.6-8 mg/mL.

### **Manufacture**

The manufacturing process involves thawing of drug substance, dissolving/mixing of the drug substance with formulation buffer, pre-filtration, final sterilisation by filtration and filling/sealing.

### **Specifications**

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product are described.

### **Stability**

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate the product is not photostable.

The real time data submitted support a shelf life of 36 months and “Store at 2°C to 8°C (Refrigerate. Do not Freeze). Protect from light”.

Chemical and physical in-use stability of aflibercept, diluted in saline or 5% dextrose at 0.6-8.0 mg/mL, has been demonstrated for up to 24 h at 2-8°C or for up to 8 h at 25°C.

### **Biopharmaceutics**

Biopharmaceutic data are not required for this product because the administration route is for intravenous (IV) infusion.

### **Advisory committee considerations**

This application was not submitted for advice to the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

### **Quality summary and conclusions**

The administrative, product usage, chemical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. The following evaluations were completed:

- Primary evaluation
- Endotoxin safety
- Viral/Transmissible Spongiform Encephalopathy (TSE) safety
- Container safety
- Sterility

There is no outstanding Module 3 issue.



## Recommendation

The Module 3 evaluator(s) recommend that the proposed products should be approved. Recommendations were also made in relation to conditions of registration, including for batch release conditions and testing, and Certified Product Details (CPD). Details of these are beyond the scope of this AusPAR.

# III. Nonclinical findings

## Introduction

### General comments

The overall quality of the nonclinical dossier was adequate. All pivotal safety related studies were conducted under Good Laboratory Practice (GLP) conditions. A safety pharmacology study examining effects of aflibercept on cardiovascular parameters in rodents was non-GLP compliant; nevertheless, the study was well documented, and cardiovascular parameters were also examined as part of GLP-compliant general repeat-dose toxicity studies in monkeys. Reports for several non-pivotal, non-GLP repeat-dose toxicity studies in mice and rats were of poor quality in some respects: no group means were calculated, clinical signs and histopathological findings were not tabulated, nor incidences per dose group calculated; the absence of group summary data (such that the results were not presented in a clear and concise manner) is at odds with the EU guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1). The pivotal toxicology studies were conducted with drug substance manufactured using the commercial process.

## Pharmacology

### Primary pharmacology

#### *Rationale and mechanism of action*

Vascular endothelial growth factor (VEGF or VEGF-A) plays a critical role in angiogenesis, which is necessary for tumour growth and proliferation. Aflibercept is a 115 kDa recombinant dimeric protein created by fusing two binding domains from VEGF receptors (the second Ig domain of VEGFR receptor 1 [VEGFR-1] and the third Ig domain of VEGFR-2) with the Fc region of a human immunoglobulin G1 (IgG1). It is designed to act as a soluble decoy receptor for VEGFR ligands.

#### *In vitro studies*

*In vitro*, aflibercept was shown to bind to human VEGF-A with subpicomolar affinity (dissociation constant (Kd) for VEGF-A165, 0.497 pM; Kd for VEGF-A121, 0.360 pM). High affinity was also found for the related angiogenic molecule, PlGF-2 (placental growth factor 2; Kd value, 38.8 pM), which acts through VEGFR-1. Binding to aflibercept occurs with higher affinity than to the ligands' endogenous receptors (compared with respective Kd values for VEGF-A binding to VEGFR-1 and VEGFR-2, 10–30 pM and 75–760 pM<sup>2</sup> and approximately 170 pM for PlGF-2 binding to VEGFR-1<sup>3</sup>). Aflibercept also showed specific

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<sup>2</sup> Robinson C.J. and Stringer S.E. The splice variants of vascular endothelial growth factor (VEGF) and their receptors. *J. Cell Sci.* 2001;114:853–865.

<sup>3</sup> Sawano A., Takahashi T., Yamaguchi S., Aonuma M. and Shibuya M. Flt-1 but not KDR/ Flk-1 tyrosine kinase is a receptor for placental growth factor, which is related to vascular endothelial growth factor. *Cell Growth Differ.* 1996;7:213–221.

and measurable binding interactions with VEGF-B (Kd 1.92 pM), but not to human VEGF-C or VEGF-D.

Aflibercept also displayed affinity for PlGF-1 (placental growth factor 1; Kd value, 392 pM); in this case, though, affinity is below that for the endogenous receptor (170 pM for binding to VEGFR-1<sup>2</sup>). The drug's affinity was similar for animal compared with human VEGF isoforms among the species tested (mouse, rat, rabbit; Kd 0.471-0.775 pM). Binding studies were not performed with monkey VEGF as its amino acid sequence is identical to human VEGF.

In *in vitro* functional studies, aflibercept blocked VEGF-A165-dependent phosphorylation of VEGFR-2 expressed in human umbilical vein endothelial cells (HUVEC). Complete inhibition of phosphorylation was observed at  $\geq 1:1$  molar ratio of aflibercept to VEGF-A165. Aflibercept inhibited VEGFR-2 phosphorylation when it was induced by VEGF-A (concentration causing 50% inhibition (IC<sub>50</sub>) 3.15 nM), but not when it was induced by VEGF-C (up to 8.7 nM, confirming that aflibercept does not bind to VEGF-C).

Calcium mobilisation induced by binding of VEGF165 (50 pM) to VEGFR-2 in HUVECs was blocked by aflibercept (IC<sub>50</sub>: 1.2-1.7 nM). Aflibercept also inhibited VEGF165-driven proliferation of human dermal microvascular endothelial cells (HDMEC) with an IC<sub>50</sub> of 192 pM. Aflibercept inhibited the angiogenic outgrowth of branching microvessles (decreased the number of microvessles formed) from rat aorta rings cultured *ex vivo*, with IC<sub>50</sub> values of 121 pM (in the presence of 10 ng/mL VEGF-A) and 42 pM (in the absence of exogenous factors).

Aflibercept (0.85 pM to 50 nM) together with VEGF165 (10 nM) did not cause complement-dependent or antibody-dependent cell-mediated cytotoxicity in HUVECs or in several tumour cell lines, suggesting that aflibercept activity is not mediated by complement or antibody activation, but rather solely through binding and sequestration of VEGF and some of its ligands.

#### ***In vivo formation of VEGF-aflibercept complex***

Administration of 1-25 mg/kg (but not 0.5 mg/kg) subcutaneous (SC) to severe, combined immunodeficiency (SCID) mice on Days 7, 10 and 13 after implantation of rat C6 glioma tumours, caused a significant reduction of tumour burden. At these active doses, concentrations of free aflibercept in the circulation (up to 190 µg/mL at 25 mg/kg) were higher than the concentration of VEGF/aflibercept complexes (which plateaued at approximately 1 µg/mL at  $\geq 2.5$  mg/kg).

Administration of 2.5-25 mg/kg (but not  $\leq 1$  mg/kg) twice SC to SCID mice starting 12 days after implantation of human A673 rhabdomyosarcoma tumours, caused significant inhibition of tumour growth. At these active doses, concentrations of free aflibercept in the circulation (up to 182 µg/mL at 25 mg/kg) were higher than the concentration of mouse VEGF/aflibercept complexes (which plateaued at approximately 1 µg/mL at  $\geq 2.5$  mg/kg), suggesting the majority of endogenous VEGF was captured. Human VEGF/aflibercept complexes plateaued at 10 fold lower levels than mouse complexes.

These findings suggest that assays of free and bound aflibercept could estimate the proportion of bioavailable VEGF that is bound and neutralised at a given dose of aflibercept, thus estimating if the dose being used is in the efficacious range.

#### ***In vivo antitumour activity of aflibercept as a single agent***

The antitumour activity of aflibercept was studied in mice implanted with various cancers (Table 1). At  $\geq 25$  mg/kg (and in several instances at lower doses), aflibercept was active against all the colon cancer models tested, that is, early and advanced stage C51, advanced stage HT-29, advanced stage COLO 205, and early and advanced stage HCT 116. As expected, activity of aflibercept was greater at higher doses, and effective doses were higher for tumours in advanced stages. The 25 mg/kg dose in mice (75 mg/m<sup>2</sup>) active

against even advanced stage colon cancer models is 60% the expected dose in humans (4 mg/kg or 132 mg/m<sup>2</sup>) on a body surface area basis.

A single administration of aflibercept (25 mg/kg SC) reduced the vessel density of several established types of tumours grown subcutaneously in male SCID mice (compared with control), that is, rat C6 glioma (80%), U87 human glioblastoma (57%), and 786-0 human renal cell carcinoma (60%).

**Table 1. *In vivo* antitumour efficacy of aflibercept as single agent**

Tumour type	Tumour model	Tumour growth delay (T-C)* in days	log cell kill *	Aflibercept doses (mg/kg)	Study
Ovarian	Advanced stage SK-OV-3	41.5 - 46.3	3.8 - 4.2	2.5 - 40	IVV0051
	Advanced stage A2780	24.6 - 30.8	1.4 - 2.5	2.5 - 40	IVV0051
	Advanced stage NIH:OVCAR-3	19 - 44.5	0.9 - 2.0	2.5 - 40	IVV0051
Melanoma	Early stage B16	8.8 - 19.8	2.4 - 5.4	2.5 - 40	IVV0051
	Advanced stage B16	2.9 8.6	0.9 - 2.6	2.5 - 40	IVV0051
	Advanced stage A375	6.2 - 9.5	1.2 & 1.9	40 & 120	IVV0051
		1 - 1.9	0.2 & 0.4 (inactive)	4 & 10	IVV0051
	Advanced stage LOX	5.2	0.6 (inactive)	40	IVV0051
Prostate	Advanced stage DU 145	13.3 - 54.6	1.1 - 4.7	2.5 - 40	IVV0051
	Advanced stage PC-3	3.6	0.3 (inactive)	40	IVV0051
Breast	Advanced stage UISO BCA-1	16.2 - 29.9	1.1 - 2.1	10 - 40	IVV0051
		0.3	0.1 (inactive)	2.5	IVV0051
	Early stage MA13/C	12.1 - 12.7	1.3 - 1.5	10 - 40	1119
		5.2	0.6 (inactive)	2.5	1119
Pancreas	Early stage	22.1 - 38.1	1.1 - 2.1	2.5 - 40	IVV0051

Tumour type	Tumour model	Tumour growth delay (T-C)* in days	log cell kill *	Aflibercept doses (mg/kg)	Study
	BxPC3				
	Advanced stage BxPC3	25.8	1.3	40	IVV0051
	Advanced stage PANC-1	1 - 2.9	0.2 - 0.4 (inactive)	2.5 - 40	IVV0051
Gastric	Advanced stage MKN-45	15.4 - 38.2	1.1 - 2.8	2.5 - 40	IVV0051
	Advanced stage Hs746T	4.1 - 4.9	1.1 & 1.3	10 & 40	IVV0051
		1.8	0.5 (inactive)	2.5	IVV0051
	Advanced stage SNU-5	14.8 - 27.3	1.4 - 2.5	2.5 - 40	IVV0051
Colon	Early stage C51	5.4 - 20.7	1.1 - 4.2	2.5 - 40	IVV0051
	Advanced stage C51	4.7 - 7.9	1.2 & 2.0	25 & 40	IVV0051
		0.5 - 0.9	0.2 & 0.1 (inactive)	2.5 & 10	IVV0051
	Advanced stage HT-29	8.8 - 27.2	0.7 - 2.2	2.5 - 40	IVV0051
	Advanced stage COLO 205	16 - 27.4	0.9 - 1.6	10 - 40	IVV0080
	Early stage HCT 116	13.2 - 25.2	1.3 - 2.5	2.5 - 40	IVV0051
	Advanced stage HCT 116	12.9 - 22.1	0.9 - 1.6	10 - 40	IVV0081
		8.1	0.6 (inactive)	4	IVV0081
	Lung	Advanced stage NCI-H460	13.2 - 17.0	2.7 - 3.4	10 - 40
2.1			0.4 (inactive)	2.5	IVV0109
Advanced stage A549		15.6 - 19.3	1.4 - 1.7	10 - 40	IVV0109
		3.5	0.3	2.5	IVV0109

Tumour type	Tumour model	Tumour growth delay (T-C)* in days	log cell kill *	Aflibercept doses (mg/kg)	Study
			(inactive)		
	Advanced stage SHP-77	36 - 41.1	3.7 - 4.3	10 - 40	IVV0109
		2.5	0.3 (inactive)	2.5	IVV0109
Neuroblastoma	Advanced stage SK-N-MC	36.6	2.5	40	IVV0051
	Advanced stage SK-N-AS	26.7	0.6 (inactive)	40	IVV0051
Rhabdomyosarcoma	Advanced stage RH-30	23.7	1.9	40	IVV0051
Ewing's Sarcoma	Advanced stage TC-71	19.6	3.7	40	IVV0051
	Advanced stage SK-ES-1	25.5	3.2	40	IVV0051
Fibrosarcoma	Advanced stage HT-1080	0.5 - 2.4	0 - 0.2 (inactive)	4 - 40	IVV0082
Lymphoma	Advanced stage NAMALWA	12.1 - 12.9	2.1 - 2.3	10 - 40	IVV0051
	Advanced stage WSU-DLCL2	13.3	2.0	40	IVV0051

\* activity at the doses stated. Aflibercept was considered inactive if the log cell kill is <0.7 and highly active if the log cell kill is >2.8.

Administration of aflibercept SC on days 13, 16 and 19 post-implantation at doses of 10-40 mg/kg (but not ≤2.5 mg/kg) decreased tumour volume and ascites produced by the growth of implanted murine renal cell carcinoma (RENCA) cells in the kidney of mice.

Treatment with 10, 40 mg/kg aflibercept (but not 4 mg/kg) twice a week for 4 weeks in transgenic mice with islet cell carcinomas (Rip1Tag 2 mice; with transgenic expression of the large T-antigen in the β-cells of the pancreas) significantly increased the life span (survival) of the animals. Treatment with 4, 10, 40 mg/kg aflibercept twice a week for 3 weeks in these transgenic mice significantly reduced the number of animals with macroscopically visible nodules, as well as the intra-tumoural vascularisation in the pancreatic carcinomas.

The antitumour efficacy of aflibercept was tested against a wide spectrum of rodent and human tumour models. The tumour growth delay and the log cell kill (calculated taking into account the tumour growth delay and the tumour doubling time). Aflibercept was

considered inactive if the log cell kill was  $\leq 0.6$  and highly active if it was  $\geq 2.9$ . Aflibercept was active against a range of tumour models, and was inactive (or active at higher doses) against some advanced tumours (melanomas, prostate adenocarcinoma, mammary adenocarcinoma, pancreatic carcinoma, gastric adenocarcinoma, colon carcinoma and adenocarcinoma, lung cancer, neuroblastoma, and fibrosarcoma).

Aflibercept was inactive against the following tumour models, even at a dose of 40 mg/kg: advanced stage LOX melanoma, advanced stage PC-3 prostate tumour, advanced stage PANC-1 pancreas tumour, advanced stage SK-N-AS neuroblastoma, and advanced stage HT-1080 fibrosarcoma.

#### ***In vivo antitumour activity of aflibercept in combination with chemotherapy***

The effect of the administration of aflibercept in combination with other anti-cancer drugs was evaluated in several tumour models in mice. Combination of aflibercept with oxaliplatin was synergistic in inhibiting growth of C51 mouse colon adenocarcinomas. Combination of aflibercept with 5-fluorouracil (5-FU; a fluoropyrimidine antimetabolite) was synergistic in inhibiting the growth of early mammary MA13/C tumours. Combining aflibercept with irinotecan (topoisomerase I inhibitor) was synergistic against human HCT 116 colon carcinoma over several dose levels. Aflibercept displayed enhanced antitumour activity at several dose levels when combined with docetaxel and paclitaxel. There was some overlap of host toxicity in animals receiving aflibercept in combination with docetaxel.

**Table 2. *In vivo* antitumour activity of aflibercept in combination with chemotherapy**

Combined drugs (with aflibercept)	Tumour models grafted in mice	Combination Results	Study
Oxaliplatin	Mouse colon adenocarcinoma C51	Synergistic activity	IVV0103
5-Fluorouracil	Mouse mammary adenocarcinoma MA13/C	Synergistic activity	1119
Docetaxel	Mouse melanoma B16	Enhanced activity	1119
Irinotecan	Human colon carcinoma HCT 116	Synergistic activity	IVV0043
Paclitaxel	Human ovarian adenocarcinoma OVCAR-3	Enhanced activity	Hu <i>et al.</i> , 2005

#### **Safety pharmacology and secondary pharmacodynamics**

Aflibercept was shown not to bind to human VEGF-C or VEGF-D. In an immunohistochemical study examining potential cross-reactivity, no specific staining was found for aflibercept ( $\leq 25 \mu\text{g/mL}$ ) against a panel of 33 normal human tissues. The Fc region of the aflibercept molecule did not mediate any complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*.

Aflibercept had no effect on respiration in rats following IV administration ( $\leq 250 \text{ mg/kg}$  over 30 min). There was no evidence of particular central nervous system (CNS) toxicity in the repeat-dose toxicity studies; lethargy in rats (at  $\geq 2 \text{ mg/kg}$  SC administered three times weekly) and reduced activity in monkeys ( $\geq 3 \text{ mg/kg}$  IV once weekly) were observed, but

occurred at doses beyond the maximum tolerated dose (MTD; based on body weight loss or substantial inhibition of body weight gain).

Increases in blood pressure were observed in monkeys given aflibercept SC (15–30 mg/kg, twice weekly), but not IV ( $\leq 30$  mg/kg once weekly). In a specialised study in mice and rats, SC administration of aflibercept increased systolic and diastolic blood pressure in both species that persisted until plasma concentrations of free aflibercept fell below 1  $\mu\text{g/mL}$ . In addition to its function as a vascular growth factor, VEGF is involved in the regulation of blood pressure by modulating available nitric oxide and prostacyclin levels to promote vasodilatation<sup>4</sup>; these results therefore presumably reflect inhibition of circulating VEGF by aflibercept.

Hypertension caused by once weekly (for 3 weeks) SC injections of aflibercept (25 mg/kg) to male rats was decreased by a diverse range of anti-hypertensives administered 3 days post-aflibercept (for 3 days): angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, alpha alpha adrenergic receptor antagonist, a nitric oxide donor, and a beta agonist. Furosemide (oral (PO), up to 4 mg/kg/day) and dl-Propranolol (intraperitoneal (IP), up to 10 mg/kg) did not decrease aflibercept-induced hypertension.

No electrocardiogram (ECG) abnormalities were observed in monkeys treated with aflibercept SC or IV. Aflibercept did not affect thrombus formation or coagulation parameters in the rabbit ( $\leq 30$  mg/kg IV). Wound healing was inhibited by aflibercept in rabbits at all doses tested (incisional and excisional models; reductions in blood vessel density, tensile strength, fibrous response and/or epidermal hyperplasia seen at  $\geq 0.3$  mg/kg IV); the finding is consistent with the known role of VEGF in wound repair (reviewed by Bao *et al*<sup>5</sup>). Aflibercept had no effect on urinalysis parameters in male mice receiving 25 mg/kg SC twice weekly for 4 weeks.

Subcutaneous injections twice weekly (2.5–25 mg/kg/administration) to male mice for 2–4 weeks caused reductions in microvessel/capillary density in the liver, pancreatic islets, thyroid, pituitary glands and adipose tissue, consistent with its pharmacological activity. Potential functional alterations of these tissues were not studied. Adrenal glands, duodenum, exocrine pancreas and retina did not have their microvessel density changed by aflibercept. Detectable effects on some of these parameters were noted at doses of aflibercept that were lower than the optimal pharmacological doses determined in tumour bearing mice.

The safety pharmacology profile of the drug is limited to well known class effects related to the inhibition of the VEGF pathway, as effects on vascular density in normal tissues, wound healing and hypertension.

## Pharmacokinetics

Free aflibercept and also VEGF-bound aflibercept, were assayed in the pharmacokinetic (PK) study. The bound form is pharmacologically inactive. Given aflibercept's protein nature, no classical biotransformation studies were conducted; this is in accordance with the relevant ICH<sup>6</sup> guideline (*Note for Guidance on Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals*; CPMP/ICH/302/95).

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<sup>4</sup> He H., Venema V.J., Gu X., Venema R.C., Marrero M.B. and Caldwell R.B. Vascular endothelial growth factor signals endothelial cell production of nitric oxide and prostacyclin through flk-1/KDR activation of c-Src. *J. Biol. Chem.* 1999;274:25130–25135.

<sup>5</sup> Bao P., Kodra A., Tomic-Canic M., Golinko M.S., Ehrlich H.P. and Brem H. The role of vascular endothelial growth factor in wound healing. *J. Surg. Res.* 2009;153:347–358.

<sup>6</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Greater than dose-proportional exposure was observed for free aflibercept in serum in rats and monkeys following SC administration. This may reflect that clearance comprises a saturable component, possibly related to VEGF binding. Slow clearance and long half-lives were observed for free aflibercept in serum following IV and SC dosing (CL: 2-3 mL/h/kg in the mouse and rat, 0.5 mL/h/kg in the monkey; half life ( $t_{1/2}$ ) approximately 40-50 h in the mouse and rat, and up to 100 h in the monkey). Bioavailability by the SC route was high in mice (94%) and monkeys (85%) and moderate in rats (33%). No sex differences in PK profiles were observed for any route/species.

With IV dosing in mice, rats and monkeys, steady-state volumes of distribution were only slightly greater than the whole blood volume, consistent with limited distribution outside of the central compartment (as is typical for large molecular weight, protein-based drugs). Results from a tissue distribution study in rats with radiolabelled iodine ( $^{125}\text{I}$ )-aflibercept, administered IV, support this. Highest tissue concentrations of radioactivity were found in the liver, followed by other highly perfused tissues. The liver (and not the kidney) was identified as having the major role in the clearance of aflibercept. Consistent with this, functional nephrectomy did not significantly affect the serum kinetics of aflibercept in rats.

Anti-aflibercept antibodies formed in mice, rats and rabbits, and less commonly in monkeys. Their development was associated with decreased drug exposure in rabbits and the rodent species, but rarely in monkeys. The aflibercept molecule contains multiple N-linked glycosylation sites. Differences in the extent of sialic acid occupancy were found to affect the drug's serum kinetics (in rats) but not its potency (assessed in *in vitro* binding and functional assays).

In mice, aflibercept formed 1:1 complexes with VEGF which remained stable in the circulation, in contrast to VEGF antibodies, which form heterogeneous, multimeric immune complexes with VEGF and are rapidly cleared. Plasma concentrations of aflibercept complex increase with aflibercept dose until most bioavailable VEGF is bound and a near maximum aflibercept complex concentration is achieved. Further increases in the aflibercept dose result in dose-related increases in free aflibercept concentrations in plasma. Free aflibercept serum concentrations (determined three days after dosing) exceeded bound complex levels at doses  $\geq 2.5$  mg/kg dose and reached levels of approximately 100  $\mu\text{g/mL}$  at a dose of 25 mg/kg, in mice. The levels of mouse VEGF:aflibercept complex increased with dose up to a concentration of 1 to 2  $\mu\text{g/mL}$  (2.5 mg/kg dose) in mice with or without human tumours and remained constant with increasing doses. Human VEGF:aflibercept complex levels in the mice bearing human tumour were approximately 0.1  $\mu\text{g/mL}$ , regardless of the dose (up to 25 mg/kg). The above findings suggest that human VEGF levels produced by the tumour (under conditions of minimal tumour burden) were modest compared to endogenous mouse tissue VEGF production. However, human VEGF production was correlated with the tumour size. In mice implanted with human tumour (A673 rhabdomyosarcoma), which grew to the size of 10% of the mouse body weight, human VEGF-aflibercept complex levels increased to around 3 fold higher the murine VEGF-aflibercept complex.

In mice implanted with murine or human tumours, effective doses ( $\geq 2.5$  mg/kg) in the inhibition of tumour growth were associated with serum free aflibercept levels exceeding steady state VEGF-aflibercept complex levels. Free aflibercept concentrations were roughly dose dependent following administration of 2.5 to 25 mg/kg aflibercept. Free aflibercept concentrations decreased to below bound complex levels at 7, 9 and 17 days following single dose administration of 2.5, 10 and 25 mg/kg doses, respectively. The elimination half-life of bound aflibercept at the 2.5 mg/kg dose was approximately 7 days.

Although endogenous VEGF production in adult human subjects is quite high (whether or not the individuals harbor tumours), human VEGF/aflibercept complex levels were directly related to tumour size when measured in mice with implanted human tumours.



Comparing the levels of free and bound aflibercept could provide guidance on when efficacious VEGF blockade is achieved.

### Pharmacokinetic drug interactions

No nonclinical studies were performed.

### Toxicology

#### Acute toxicity

Single-dose toxicity studies, performed by the IV route in rats, revealed a low order of acute toxicity for aflibercept, with no deaths observed up to the highest dose tested (500 mg/kg).

#### Repeat-dose toxicity

Subcutaneous (SC) studies were performed in mice (up to 8 weeks duration), rats (up to 13 weeks) and monkeys (up to 13 weeks), and IV studies were performed in the rabbit (2 weeks; in non-pregnant animals as a pilot study for reproductive toxicity) and monkey (up to 6 months). Aflibercept is pharmacologically active in all of these species. SC and IV doses were administered ranging from once per 2 weeks to up to 3 times weekly.

A 6-month study in rodents was found not to be feasible due to the development of anti-aflibercept antibodies. Considering this, the pre-eminence of the primate over the rodent as a relevant and feasible model for the assessment of the toxicity of the proposed product, and that there is existing experience with the pharmacological class, the reliance on the cynomolgus monkey as a single species for which there is a pivotal study is deemed to be acceptable. Group sizes were adequate; the small group size used in the monkey studies is typical, but does limit their predictive value.

#### Relative exposure

Relative systemic exposure in selected toxicity studies has been calculated based on animal:human maximum concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (AUC) for free aflibercept in plasma/serum (see Table 3, below). The human reference values used are from human population PK study POH0265, obtained from studies at the IV dose of 4 mg aflibercept to cancer patients.

**Table 3. Relative exposure to free aflibercept in selected toxicity studies**

Species	Study	Route; frequency	Dose	C <sub>max</sub> µg/mL	AUC <sub>0-14 d</sub> µg·h/mL	Exposure ratio# C <sub>max</sub> AUC	
Mouse (CD-1)	4 weeks PK01017a	SC; three times weekly	10 mg/kg	33.8	-	0.5	-
			15 mg/kg	82.2	-	1.3	-
Rat (Sprague)	13 weeks VGFT-TX-	SC; three	0.1 mg/kg	77.1	-	1.2	-

Species	Study	Route; frequency	Dose	C <sub>max</sub> µg/mL	AUC <sub>0-14 d</sub> µg·h/mL	Exposure ratio# C <sub>max</sub> AUC		
Dawley)	02006b	times weekly	0.5 mg/kg	235	-	3.6	-	
			1 mg/kg	1701	-	26	-	
			2 mg/kg	915	-	14	-	
Monkey (Cynomol- gus)	3 months VGFT-TX- 02037c	SC; twice weekly	1.5 mg/kg	31.9	-	0.5	-	
			5 mg/kg	109	-	1.7	-	
			15 mg/kg	286	-	4.4	-	
			30 mg/kg	721	-	11	-	
	3 months, juvenile VGFT-TX- 05010 /670144d	IV; once weekly	0.5 mg/kg	9.6	888	0.1	0.1	
			3 mg/kg	73.8	9648	1.1	1.5	
			30 mg/kg	830	8191 2	12. 7	13	
	6 months 670145/V GFT-TX- 05009e	IV; once per 1- 2/weeks	3 mg/kg	93.2	3768	1.4	0.6	
			10 mg/kg	305	1334 4	4.6	2.1	
			30 mg/kg	730	3232 8	11. 1	5.1	
	Human (cancer patients)	POH0265 f	IV; once/2 weeks	4 mg/kg	65.6	6306	-	-

# = calculated as animal:human values; - = no data/not applicable; a = parameters obtained on day 22; b = parameters obtained on day 83; c = parameters obtained after dosing in week 13; d = parameters obtained after dosing in week 13 (AUC over 168 h (AUC<sub>0-168 h</sub>) is multiplied by 4, accounting for dosing frequency); e = parameters obtained after dosing in week 26; dosing was once per week to week 15, then once per 2 weeks; f = C<sub>max</sub> and AUC at steady state over 14 days (AUC<sub>ss0-14d</sub>) values from the population PK study (POH0265).

## Major findings

Pronounced effects on the nasal cavity were seen with systemic administration in monkeys, along with changes in numerous additional tissues. The nasal cavity findings included atrophy/loss of the septum and/or turbinates associated with necrotising inflammation. The other principal organs targeted were bone (for example, osteocartilaginous exostoses of vertebrae; interference with growth plate maturation), kidney (increased glomerular mesangial matrix; glomerulopathy with tubular dilatation and cast formation), adrenals (decreased vacuolisation with eosinophilia of the cortex) and ovary (decreased number of maturing follicles, granulosa cells and/or theca cells). The vertebral changes were accompanied by myofibre atrophy of the overlying axial musculature along the vertebral arches or proliferation/degeneration of the microvasculature adjacent to the exostoses; kyphosis was observed in monkeys treated IV at  $\geq 10$  mg/kg/week for 13 weeks and at all dose levels ( $\geq 3$  mg/kg every 1–2 weeks) in the 6 month study. Renal histopathological changes were associated with decreased serum albumin and/or total protein and increased blood urea nitrogen and urine protein levels. Vascular alterations in various tissues (proliferation/degeneration/fibrosis in duodenum, stomach, rectum, gallbladder, pancreas, heart and/or brain) and hepatic portal inflammation and periportal necrosis were also seen. No no observed effect level (NOEL) was established for systemic toxicity in the pivotal IV study in monkeys ( $< 3$  mg/kg every 1–2 weeks).

Mice and rats treated with aflibercept SC commonly and rapidly developed anti-aflibercept antibodies, leading to decreased drug exposure. The kidney was identified as the principal target organ for toxicity in the two rodent species, with glomerulonephritis routinely observed. This finding is consistent with deposition of circulating antigen-antibody complexes in the glomerulus. Other findings in treated mice and/or rats included vascular changes (haemorrhage, congestion and/or dilatation) in various tissues (kidney, liver, lungs and gastrointestinal tract), and changes in teeth (broken, thickened and altered colour) and bone (osteoporosis of femur).

Anti-aflibercept antibodies developed in monkeys at low frequency only in short-term studies (4–13 weeks; SC and IV routes), but their development was more common in the 6-month IV study (39% of treated animals). Animals are poor models for immunogenicity in humans; the potential immunogenicity of the drug therefore requires particular clinical focus.

## Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were included in the submission. Their omission is acceptable in accordance with the ICH guideline on *Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals*; CPMP/ICH/302/95) and justified on the basis that as a large protein the drug is not expected to interact directly with DNA or other chromosomal material, that chronic rodent studies are not feasible due to immunogenicity, and that the drug does not have growth factor activity and did not display immunosuppressant activity in the general repeat-dose toxicity studies.

## Reproductive toxicity

No specialised fertility study was conducted. Relevant data were obtained, though, as part of the 6 month IV general repeat-dose toxicity study in monkeys. In that study, females showed absent or irregular menses, associated with profound reductions in ovarian hormones (oestradiol, progesterone, and inhibin B) and increases in follicle stimulating hormone (FSH) levels, at all dose levels tested ( $\geq 3$  mg/kg). Ovarian weight was reduced, accompanied by compromised luteal development and reduction of maturing follicles. Uterine and vaginal atrophy were also found. Following recovery, all aflibercept-treated

females exhibited normal ovarian folliculogenesis and presence of medium-to-large-sized corpora lutea; uterine and vaginal atrophy were also reversed. There were no aflibercept-related effects on male reproductive hormone levels (FSH, luteinising hormone (LH) and testosterone). Decreased sperm motility and increased sperm abnormalities were evident at all doses; these effects were considered consequential upon fertility, but were seen to be fully reversible after the treatment-free phase. NOAELs for effects on male and female fertility were not established in the study (relative exposure at the lowest observed effect levels (LOELs), 724).

Specialised reproductive toxicity studies conducted by the sponsor covered embryofetal development only. These were conducted in a single species (rabbit), and involved IV administration once every 3 days during the period of organogenesis. Placental transfer was demonstrated by the finding of free aflibercept in the amniotic fluid of pregnant rabbits. Abortions and increased post-implantation loss were seen with dosing at 45 and 60 mg/kg. Maternotoxicity was evident at  $\geq 15$  mg/kg (as transient body weight loss). Treatment-related external and visceral fetal abnormalities, including malformations, were observed at all dose levels studied ( $\geq 3$  mg/kg); skeletal malformations and variations were observed at 60 mg/kg and the incidence of incomplete ossification was increased at  $\geq 3$  mg/kg. Such effects are unsurprising given the critical role played by angiogenesis in fetal development. No NOEL was established for effects on embryofetal development. Plasma C<sub>max</sub> and AUC values for free aflibercept at the lowest dose tested (3 mg/kg IV) were 56.1  $\mu\text{g/mL}$  and 1935  $\mu\text{g}\cdot\text{h/mL}$ , respectively. These are 0.8 times and 0.3 times the C<sub>max</sub> and AUC, respectively, in patients after IV administration of 4 mg aflibercept (Clinical Study POH0265).

No pre-/postnatal development study was conducted. Excretion of aflibercept in milk was not investigated in animals.

### ***Pregnancy classification***

The sponsor has proposed Pregnancy Category D.<sup>7</sup> This categorisation is considered appropriate based on the drug's anti-angiogenic activity and the demonstration of teratogenicity in the rabbit.

### **Local tolerance**

In a specialised study, no irritation or other local reactions attributable to aflibercept or the vehicle were found following IV, IM and SC administration in the rabbit; the study was adequately conducted.

### **Paediatric use**

The product is not proposed for use in children and adolescents. A repeat-dose toxicity study in juvenile monkeys (13 weeks duration; IV administration) revealed findings similar to those seen in mature animals, with the skeletal system a particular target of the drug.

### **Nonclinical summary and conclusions**

- The sponsor has conducted adequate nonclinical studies on the pharmacodynamics (PD), PK and toxicity of aflibercept according to the relevant guidelines. All pivotal safety-related studies were conducted according to GLP.

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<sup>7</sup> Use in pregnancy Category D is defined as: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

- Pharmacodynamic studies with aflibercept revealed high affinity for mouse, rat, rabbit and human forms of VEGF-A, and to the related angiogenic molecules, PlGF-1 and mouse and human PlGF-2, but not to human VEGF-C and VEGF-D. Aflibercept inhibited VEGF-dependent receptor phosphorylation and subsequent calcium mobilisation, and vessel proliferation, in a complement- and antibody- independent fashion.
- Secondary PD studies with aflibercept revealed high specificity. It did not bind to human VEGF-C or VEGF-D and did not exhibit cross-reactivity against a panel of human tissues. The Fc region of the molecule did not mediate complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity in vitro. Safety pharmacology examinations revealed increased blood pressure in rodents and monkeys and inhibition of wound healing in rabbits following systemic administration. Hypertension caused by aflibercept in rats was decreased by a diverse range of anti-hypertensives. In mice, aflibercept caused reductions in microvessel density in several organs, and no effects in urinalysis.
- The antitumour efficacy of aflibercept was tested against a wide spectrum of rodent and human tumour models. At  $\geq 25$  kg/kg (and in several instances at lower doses), aflibercept was active against all the colon cancer models tested, that is, early and advanced stage C51, advanced stage HT-29, advanced stage COLO 205, and early and advanced stage HCT 116. Aflibercept was inactive against the following tumour models, even at a dose of 40 mg/kg: advanced stage LOX melanoma, advanced stage PC-3 prostate tumour, advanced stage PANC-1 pancreas tumour, advanced stage SK-N-AS neuroblastoma, and advanced stage HT-1080 fibrosarcoma.
- Pharmacokinetic studies in rabbits and monkeys indicated a long half-life for free aflibercept (non-VEGF-bound) in plasma. A major role was identified for the liver and not the kidney in the systemic clearance of aflibercept.
- A PK study revealed that aflibercept forms an inert 1:1 complex with VEGF that remains stable in the circulation (where it can be measured). At active antitumour doses, the concentration of free aflibercept exceeds the concentration of bound aflibercept, suggesting that aflibercept complex levels could provide guidance on when efficacious VEGF blockade is achieved. Endogenous production of VEGF was high in normal adult mice and patients. Therefore, although human VEGF/aflibercept complex levels were directly related to tumour size, tumour-derived VEGF represented a minority of total body VEGF under conditions of minimal tumour burden.
- Aflibercept displayed a low order of acute toxicity in rats by the IV route.
- Pivotal repeat-dose toxicity studies were conducted in the cynomolgus monkey only; chronic studies in rodents were not feasible due to the development of anti-aflibercept antibodies, which decreased drug exposure. The pivotal monkey studies involved IV administration every 1–2 weeks for 6 months. Tissues identified as targets for toxicity in studies involving systemic administration (involving higher exposure) were bone, kidney, adrenals, ovary, and the nasal cavity.
- No studies on genotoxicity or carcinogenicity were submitted.
- Effects consequent on male and female fertility were seen in monkeys treated with aflibercept IV (decreased sperm motility and increased abnormalities; irregular and absent menses associated with hormonal changes). In an embryofetal development study in rabbits, treatment with aflibercept (administered IV) produced abortions, increased post-implantation loss and caused fetal malformations (external, visceral and skeletal), variations and impairment of ossification.
- Aflibercept was immunogenic in the laboratory animal species, though markedly less so in monkeys compared with rodents or rabbits. In monkeys, this rarely affected PK.

## Conclusions and recommendation

- The scope of the nonclinical data set is consistent with EU/ICH guidelines for a protein-based drug.
- The nonclinical data provide evidence of efficacy.
- Increased blood pressure with aflibercept, identified following systemic administration in animals, was reduced by commonly used antihypertensives.
- Findings in the repeat-dose toxicity studies were largely attributable to the drug's pharmacological action, disrupting the role of VEGF in microvascular maintenance. Bone, kidney, adrenals, ovary and nasal cavity were identified as the target organs for toxicity, and are predicted to occur in patients treated with Zaltrap based on the existence of a small multiple of the maximum anticipated human exposure at  $\geq 3$  mg/kg ( $\geq 1.1$  times the clinical AUC) in monkeys, and at the NOEL established in the rat (0.1 mg/kg, that is, 1.2 times the clinical AUC).
- Given the limited predictivity of animals, assessment of the potential immunogenicity of aflibercept relies on clinical data.
- The absence of genotoxicity and carcinogenicity studies is acceptable; no particular concern for such effects is held.
- Teratogenicity was observed in the rabbit, beginning at a non-maternotoxic dose. No NOEL was established for adverse effects on embryofetal development, the large exposure multiple at the LOEL notwithstanding. Considering these findings and given the pharmacological class (anti-angiogenic agent), placement in Pregnancy Category D is justified and the inclusion of appropriate precautionary statements in the Product Information document is warranted.
- There are no nonclinical studies investigating the potential toxicological interactions between aflibercept and irinotecan and/or fluoropyrimidine agents. However, according to the ICH guideline S9, nonclinical studies evaluating the combination is not usually warranted if the human toxicity profile of each medicine has been characterised. The registration of the products for the proposed indication is approvable only if the human toxicity profiles of aflibercept, irinotecan and fluoropyrimidine agents have been adequately characterised.
- The PI document should be amended as directed.<sup>8</sup>

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 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 metastatic colorectal cancer (MCRC) who have received prior oxaliplatin-based chemotherapy, and is the only targeted agent that has demonstrated an OS benefit in this setting".

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<sup>8</sup> Details of recommended revisions to the proposed PI are beyond the scope of this AusPAR.

**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<sup>9</sup>). 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<sup>10</sup>). 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<sup>11</sup>). 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 Principles of Internal Medicine, 16<sup>th</sup> Edition, McGraw-Hill, 2005).

## Guidance

There were no pre-submission meetings between the sponsor and the TGA for this application.

## Contents of the clinical dossier

The submission included a complete data package provided to support the registration of the new chemical entity 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 PK data and 12 that provided PD data (including PK/PD analyses).
- 5 population PK 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:

<sup>9</sup> Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2010. Cancer in Australia: an overview, 2010. Cancer Series no. 60. Cat. No. CAN 56. Canberra: AIHW

<sup>10</sup> AIHW, 2012 Cancer incidence projections: Australia, 2011 to 2020. Cancer Series no. 66. Cat. No. CAN 62. Canberra.

<sup>11</sup> Clarke S. New treatments for advanced and metastatic colorectal cancer. *Aust Prescriber* 2002;25:111-3.

Electronic lodgement cover sheet, letter of application, comprehensive table of contents; application forms, medicine information documents and labelling (including proposed Australian PI and consumer medicine information (CMI), label mock-up and specimens), information about the experts, overseas regulatory statement (including proposed European Summary of Product Characteristics (SmPC)), justification for not providing pharmaceutical studies, statement regarding no paediatric development plan, proposed Risk Management Plan (RMP) 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.

### Pharmacokinetics

#### Overview of studies providing pharmacokinetic data

The submission included PK data (non-compartmental analyses; NCA) following aflibercept IV from 2272 patients from 13 Phase I and II studies, and 3 Phase III clinical efficacy and safety studies (see Table 4, below). There were 2 additional studies with PK data following aflibercept administered SC (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 4. Summary of studies with pharmacokinetic data.**

Study	Dose and Regimen	Subjects
<b>PK – Phase I single-agent studies</b>		
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)
<b>PK and PK/PD – Phase II single-agent studies</b>		
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
<b>PK and PK/PD - Phase I combination studies</b>		
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 IV q3w	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
<b>PK and PD - Phase I studies, single-agent, healthy subjects</b>		
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)
<b>PK and PK/PD - Phase III combination studies</b>		
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<sup>2</sup>; VTC: aflibercept + docetaxel 75 mg/m<sup>2</sup> + cisplatin 75 mg/m<sup>2</sup>; V-pemetrexed: aflibercept and pemetrexed 500 mg/m<sup>2</sup>; q3w: every 3 weeks; LV5FU2: 5 fluorouracil/leucovorin; MCRC = metastatic colorectal cancer; MPC = metastatic pancreatic cancer; NSCLC = non-small cell lung cancer.

### **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 Clinical Evaluation Report (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<sup>12</sup>)).

### Evaluator's overall conclusions on pharmacokinetics

- Overall, the PKs of aflibercept at the proposed dose of 4 mg/kg IV every 2 weeks (q2w) have been reasonably well characterised 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) characterised 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 h (n=7), the mean (coefficient of variation (CV%)) free aflibercept C<sub>max</sub> and AUC over zero to infinity values were 97.4 (43) µg/mL and 293 (15) µg.day/mL, respectively. The median t<sub>max</sub> following the 4 mg/kg infusion occurred almost immediately after the end of the 1 h infusion.
- Free aflibercept exposure (AUC<sub>inf</sub>) was more than dose proportional (that is, non-linear) over the range 0.3 to 2 mg/kg, and approximately dose proportional (that is, linear) over the range 2 to 7 mg/kg (TED6115). Population-pk analysis (POH0253) showed a dose proportional increase of free aflibercept C<sub>max</sub> 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 maximises binding of available VEGF. Simulations conducted using the population-PK model for aflibercept 4 mg/kg q2w showed that the aflibercept

<sup>12</sup> Details of a separate extensive evaluation of the population-PK studies have not been included in this AusPAR or in the extract from the Clinical Evaluation Report at Attachment 2.

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 ( $C_{\text{trough}}$ ) was 9.39 (100)  $\mu\text{g/mL}$  after the first dose and 12.0 (52)  $\mu\text{g/mL}$  at steady state (SS) 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;  $\text{AUC}_{\text{ss}}/\text{AUC}_{0-336\text{h}}$ ). After 4 mg/kg q2w, the estimated time to steady state was 70 days which corresponds to predose of the 6<sup>th</sup> aflibercept administration, and  $C_{\text{trough,ss}}$  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 at steady state (Versuss) 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%) Versuss in patients (n=7) of 7.9 (38) L following 4 mg/kg IV (study TED6115). The Versuss 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 molecular weight of free aflibercept is 115 daltons 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  $\text{AUC}_{0-336\text{h}}$  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  $\text{AUC}_{0-336\text{h}}$  compared with patients with normal renal function. In VELOUR, exposure to free aflibercept as assessed by  $C_{\text{max}}$  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 clinically 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,  $V_{ss}$  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.

## Pharmacodynamics

### Studies providing pharmacodynamic data

Pharmacodynamic 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 (for example, renin angiotensin aldosterone system (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. 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 in the clinical evaluation report (CER; see Attachment 2).

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

### Overview

VELOUR was the pivotal Phase III 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 clinical study report (CSR).

The safety endpoints in the PK/PD analyses are summarised below in Table 5. 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 5. VELOUR - Selected toxicities; PK population free aflibercept.**

Selected toxicity (All grades)	Aflibercept/FOLFIRI (N=500)	
	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%)

The results for the PK/PD overall survival efficacy analyses are summarised in Table 6.

**Table 6. VELOUR: Overall Survival (OS) PK/PD (efficacy analyses).**

	Free aflibercept (N=500)	Bound aflibercept (N=460)
Univariate analyses	C <sub>max</sub> (per 10µg/mL)	Clearance (per 1mL/h)
	HR=0.821 95%CI=(0.735,0.918) p=0.0005	HR= 1.320 95%CI= (1.153,1.510) p < 0.0001
	Clearance (per 10 mL/h)	
	HR= 1.052 95%CI= (1.010,1.096) p= 0.0147	
	AUC <sub>extrapolated</sub> (per 1000µg h/mL)	
	HR = 0.803 95%CI= (0.754,0.855) p <0.0001	
	AUC <sub>cum OS</sub> (per 1000 µg h/mL)	
HR = 0.869 95%CI= (0.818,0.924) p <0.0001		
AUC <sub>0-336</sub> (per 1000 µg h/mL)		
HR = 0.750 95%CI= (0.684,0.822) p <0.0001		
Multivariate analysis	AUC <sub>extrapolated</sub> (per 1000µg h/mL)	Clearance (per 1mL/h)
	HR = 0.788 95%CI= (0.736,0.844) p <0.0001	HR= 1.394 95%CI= (1.213,1.603) p <0.0001
Multivariate analysis adding endogenous VEGF as a covariate	N=356	N=323
	AUC <sub>extrapolated</sub> (per 1000µg h/mL)	Clearance (per 1mL/h)
	HR = 0.779 95%CI= (0.718,0.845) p <0.0001	HR= 1.343 95%CI= (1.140,1.583) p =0.0004

The results for the PK/PD progression free survival efficacy analyses are summarised in Table 7:

**Table 7. VELOUR: Progression Free Survival PK/PD (efficacy) analyses.**

	Free aflibercept (N=500)	Bound aflibercept (N=460)
Univariate analyses	Clearance (per 10 mL/h)	Clearance (per 1mL/h)
	HR = 1.118 95%CI= (1.069,1.168) p <0.0001	HR = 1.229 95%CI= (1.065,1.417) p =0.0048
	AUC extrapolated (per 1000 µg.g/mL)	
	HR = 0.822 95%CI= (0.768,0.879) p <0.0001	
	AUCD-336 (per 1000 µg.h/mL)	
	HR = 0.779 95%CI= (0.702,0.865) p <0.0001	
Multivariate analyses	AUCcum PFS (per 1000 µg.g/mL)	
	HR = 0.890 95%CI= (0.839,0.944) p = 0.0001	
	AUC extrapolated (per 1000 µg.g/mL)	Clearance (per 1mL/h)
Multivariate analyses adding endogenous VEGF as a covariate	HR = 0.814 95%CI= (0.761,0.872) p <0.0001	HR = 1.234 95%CI= (1.069,1.426) p = 0.0042
	N=356	N=323
	AUC extrapolated (per 1000 µg.g/mL)	Clearance (per 1mL/h)
	HR = 0.833 95%CI= (0.769,0.901) p <0.0001	HR = 1.149 95%CI= (0.977,1.352) p = 0.0926

### 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 h mean systolic blood pressure (measured by ambulatory blood pressure monitoring (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 h 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 diarrhoea (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 (OS) and progression free survival (PFS).

### Dose selection for the pivotal trials

#### Study TCD6118 (Phase I, dose-escalation, sequential cohorts)

The aflibercept dose selected for the pivotal Phase II study (VELOUR) was based on the findings of the Phase I, 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 toxicities(DLT), and to establish the "recommended Phase II dose" (RP2D) of aflibercept to be administered in combination with standard fixed doses of LV5U2-CPT11.

Aflibercept was administered by IV infusion over 1 h and was immediately followed by irinotecan, 180 mg/m<sup>2</sup> IV over 60 minutes on Day 1, together with leucovorin 200 mg/m<sup>2</sup> (or elvorine 100 mg/m<sup>2</sup>) IV over 2 h on Day 1 *via* Y-line, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus then 600 mg/m<sup>2</sup> IV continuous infusion over 22 h on Day 1, followed by leucovorin

200 mg/m<sup>2</sup> (or elvorne 100 mg/m<sup>2</sup>) IV over 2 h on Day 2, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus then 600 mg/m<sup>2</sup> IV continuous infusion over 22 h 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 plus 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 summarised below in Table 8.

**Table 8. Study TCD6118 – Dose limiting toxicities; Part 1.**

Aflibercept dose level (mg/kg)	Dose escalation		Subsequent patients	
	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 <sup>a</sup>	None	0	None
4	0/4	None	2/6 0/2 <sup>d</sup>	G3 proteinuria > 2 weeks Acute nephrotic syndrome and TMA
5	2 <sup>b</sup> /6	G3 stomatitis <sup>b</sup> G3 esophagitis reflux	0/4	None
6	1/6	Febrile neutropenia	2 <sup>c</sup> /6	G3 stomatitis G3 abdominal pain due to subocclusion

a excluding patient not evaluable for DLT due to known leuconetropenia 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 (that is, 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 treatment emergent adverse events (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 III 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 (that is, 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 characterised in the submitted data.

## Efficacy

### VELOUR/EFC10262. Pivotal study for MCRC second line treatment

The submission included one, pivotal Phase III efficacy and safety study provided to support the proposed indication. This was a prospective, multinational, multicentre, randomised (1:1), double-blind, parallel-arm study of aflibercept versus placebo in patients with 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 12<sup>th</sup> ESMO-World Congress on Gastrointestinal Cancer, Barcelona 2010, (Van Cutsem *et al*, 2011<sup>13</sup>). However, the full study report had not been published at the date of submission.

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

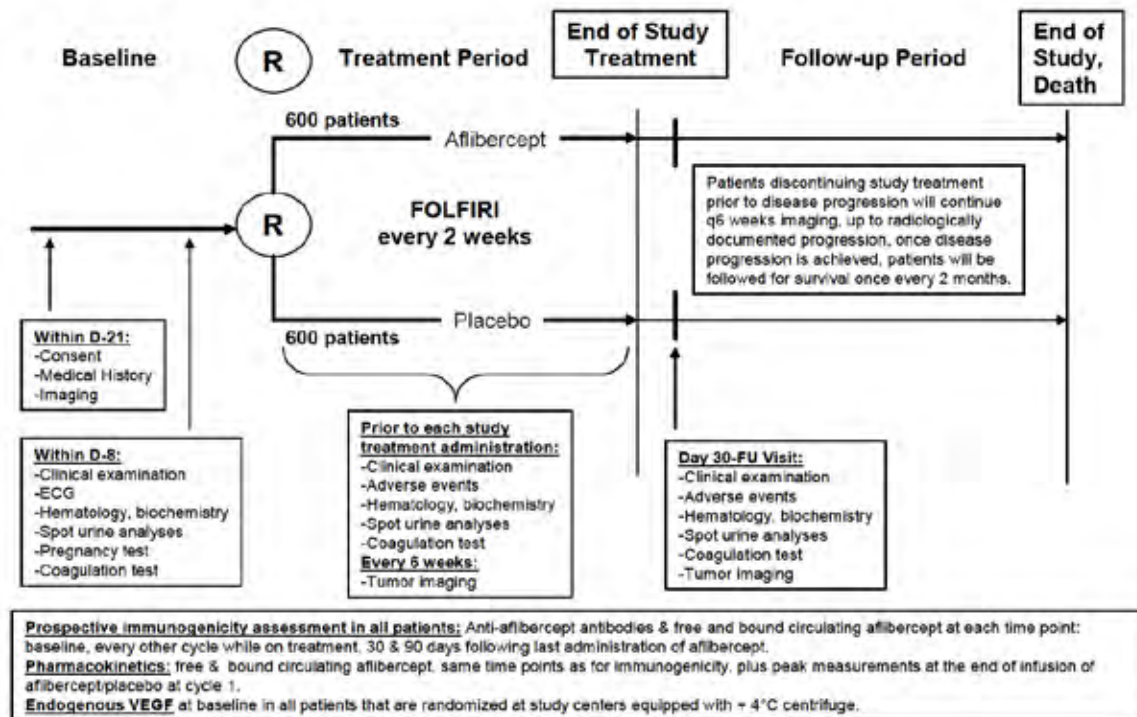
The **secondary objectives** were: to compare PFS in the two treatment arms; to evaluate overall objective response rate (ORR), as per response evaluation criteria in solid tumours (RECIST; see definition in Appendix A of Attachment 2 of this AusPAR), in the two treatment arms; to evaluate the safety 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 study design is summarised in Figure 2.

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<sup>13</sup> See Van Cutsem E *et al*. Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status. *JCO* May 20, 2011 vol. 29 no. 15, 2011-2019.



Figure 2. VELOUR Study design.

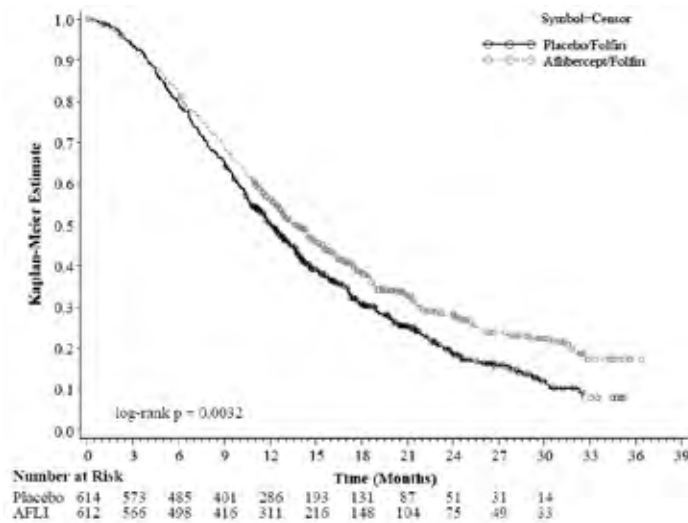


**Comment:** The study design is considered satisfactory. The sponsor stated that the FOLFIRI regimen was chosen because of its “worldwide recognition as a standard regimen for the treatment of patients with MCRC by the medical oncology community”. Second line therapy of MCRC is accepted in most centres 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 afibercept/FOLFIRI compared with bevacizumab/FOLFIRI for second line treatment for patients previously treated with oxaliplatin, rather than afibercept/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.

The Kaplan-Meier curves for the primary objective (OS) is shown below (intention to treat (ITT) population)

**Figure 3. VELOUR.-OS (months) Kaplan-Meier curves by treatment group; ITT population.**



### 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/folfin compared with placebo/folfin (stratified hazard ratio (HR) = 0.817 [95.34% confidence interval (CI): 0.713 to 0.937]; probability value (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/folfin arm was 403 (65.8%) and 460 (74.9%) in the placebo/folfin arm. Median OS in the aflibercept/folfin arm (13.50 months [95.34% CI: 12.517, 14.949]) was 1.44 months longer than in the placebo/folfin 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/folfin arm compared with the placebo/folfin arm (HR = 0.80 corresponding to a median OS improvement from 11 months in the placebo/folfin arm to 13.75 months in the aflibercept/folfin arm). The observed risk reduction in the aflibercept/folfin arm compared with the placebo/folfin arm was 18% (compared with 20% sample size survival criteria) and the observed difference in median OS in favour of placebo/folfin was 1.44 months (compared with 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/folfin compared with placebo/folfin are the minimum clinically significant criteria required for this study. As aflibercept/folfin 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/folfin arm over the placebo/folfin 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/folfin (6.90 months [99.99% CI: 5.881, 7.852]) compared with placebo/folfin (4.67 months [99.99% CI: 4.074, 5.552]). The ORR was 19.8% (95% CI: 16.4, 23.2) in the aflibercept/folfin arm and 11.1% (95% CI: 8.5%, 13.8%), p=0.0001 stratified Cochran-Mantel-Haenszel (CMH) test.

## Safety

### Studies providing evaluable safety data

#### *Pivotal safety data – VELOUR*

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

#### *Supportive safety data. Summary of clinical safety*

The submission included a Summary of Clinical Safety (SCS). This summary included a total of 2073 patients exposed to aflibercept from Phase I, II, and III clinical studies, including 611 from VELOUR (see Table 9, below). The cut-off date for the SCS was 07 February 2011.

The safety data from the single-agent Phase I and II studies and the Phase I combination chemotherapy studies provided in the SCS (see Table 9, 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 I and II studies are consistent with the safety data from the pivotal Phase III study VELOUR and the two Phase III 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 I, II and III studies the review of the supportive safety data focuses on safety data from the Phase III 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 National Cancer Institute (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 (that is, 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 (that is, approximately 3759 exposed patients). This ISS is reviewed in the CER.

**Table 9. 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
Associated chemotherapy (if applicable)	FOLFIRI	ARD6122	TCD6118	ILV5FU2	SUPPORTIVE for safety	SUPPORTIVE for safety
		ARD6123	TCD6121	Gemcitabine		
		ARD6772	TCD6121	Gemcitabine/erlotinib		
		EFC6125	TCD6119	TCF	Docetaxel 75 mg/m <sup>2</sup>	Gemcitabine
			TCD6120	Docetaxel 75 mg/m <sup>2</sup>		
			TCD6120	Docetaxel/cisplatin		
			TCD6120	Docetaxel 100 mg/m <sup>2</sup>		
		TCD6120	Pemetrexed			
Aflibercept schedule & dose	4 mg/kg q2w	0.3 to 7.0 mg/kg q2w	2.0 to 8.0 mg/kg q2w 2.0 to 9.0 mg/kg q3w		8.0 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

### Extent of exposure

- In VELOUR, the pivotal study (pivotal safety data), there were 1226 randomised 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/fofiri arm received a total of 6127 treatment cycles, with a median of 8 cycles (range: 1 to 67), and patients in the aflibercept/fofiri 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/fofiri arm, and 21.4 weeks (range: 2, 105) in the aflibercept/fofiri arm.
- In VANILLA (metastatic pancreatic cancer), exposure was generally similar in both the aflibercept/gemcitabine and placebo/gemcitabine treatment arms. The median relative dose intensity (RDI) was higher in the placebo/gemcitabine arm than in the aflibercept/gemcitabine arm (0.91 versus 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.

### Other safety data

The submission included an integrated safety summary (ISS) of cases of RPLS reported or known to the sponsor as of 28 July 2011. The ISS included 17 cases (13 females and 4 males) in approximately 3759 patients exposed to aflibercept, giving an overall incidence of approximately 0.5%. Overall, the mean age was 60.5 years (standard deviation (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 II study with modified FOLFOX6. There was one case from a dose-escalating phase I 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).

### Meta-analysis

The Summary of Clinical Safety included a meta-analysis of TEAEs of interest by pooling the data for the TEAEs of special interest from the three, Phase III 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 are summarised in Table 10, below.

**Table 10. Meta-analysis (VELOUR/VANILLA/VITAL). Pooled TEAEs of special interest; safety population.**

	Placebo (n=1329)	Aflibercept (n=1333)	Odds Ratio (95% CI)
Hypertension (all Grades)	105 (7.9%)	447 (33.5%)	5.74 (4.74, 7.55)
Hypertension (Grade 3 or 4)	21 (1.6%)	194 (14.6%)	8.27 (5.46, 13.85)
Haemorrhage (all Grades)	184 (14.6%)	421 (31.6%)	2.63 (2.20, 3.24)
Haemorrhage (Grade ≥ 3)	20 (1.5%)	41 (3.1%)	1.56 (0.92, 2.74)
Cardiac dysfunction (all Grades)	3 (0.2%)	9 (0.7%)	2.93 (0.82, 13.41)
Cardiac dysfunction (Grade 3 or 4)	1 (<0.1%)	6 (0.5%)	4.52 (0.72, 114.5)
Arterial thromboembolic events (all Grades)	22 (1.7%)	30 (2.3%)	1.33 (0.76, 2.35)
Arterial thromboembolic events (Grade 3 or 4)	13 (1.0%)	22 (1.7%)	1.27 (0.65, 2.66)
Venous thromboembolic events (all Grades)	95 (7.1%)	95 (7.1%)	0.97 (0.72, 1.31)
Venous thromboembolic events (Grade 3 or 4)	85 (6.4%)	81 (6.1%)	0.69 (0.51, 0.97)
Fistula GI or non -GI origin (all Grades)	3 (0.2%)	14 (1.1%)	4.57 (1.42, 20.01)
Gastrointestinal perforation (all Grades)	4 (0.3%)	10 (0.8%)	2.44 (0.78, 8.99)
Gastrointestinal perforation (Grades 3 or 4)	3 (0.2%)	10 (0.8%)	2.51 (0.70, 11.02)

	Placebo (n=1329)	Aflibercept (n=1333)	Odds Ratio (95% CI)
Compromised wound healing (all Grades)	5 (0.4%)	7 (0.5%)	1.36 (0.42, 4.71)
Compromised wound healing (Grades 3 or 4)	0	3 (0.2%)	NA
Osteonecrosis (all Grades)	1 (< 0.1%)	3 (0.2%)	2.92 (0.31, 76.89)
Osteonecrosis (Grade 3 or 4)	1 (< 0.1%)	1 (< 0.1%)	0.75 (0.02, 27.25)
RPLS - No data	-	-	-
Acute drug reaction (all Grades)	46 (3.5%)	58 (4.4%)	1.23 (0.83, 1.84)
Acute drug reaction (Grade 3 or 4)	7 (0.5%)	9 (0.7%)	0.96 (0.34, 2.64)

#### Evaluator's overall conclusions on clinical safety

- The key safety data in the submission are derived from the pivotal Phase III efficacy and safety study (VELOUR). It is considered that this study has demonstrated that the overall safety profile of aflibercept/fofiri is inferior to that of placebo/fofiri in patients with MCRC. In addition, the supportive safety data from Phase I, II, and III 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/fofiri and 605 with placebo/fofiri. The median duration of exposure was longer in the aflibercept/fofiri arm than in the placebo/fofiri arm (21.4 weeks [range: 2, 105] versus 18.1 weeks [range: 2, 135]), as was the median number of treatment cycles (9 [range: 1, 50] versus 8 [range: 1, 67]). However, the median number of aflibercept/placebo infusions was lower in the aflibercept/fofiri arm than in the placebo/fofiri arm (7.0 [range: 1, 35] versus 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/fofiri versus 99.2%, aflibercept/fofiri). TEAEs (all Grades) occurring in  $\geq 20\%$  of patients in at least one treatment arm and more commonly in the aflibercept/fofiri arm than in the placebo/fofiri arm were diarrhoea (69.2% versus 56.5%), stomatitis (50.1% versus 32.9%), fatigue (47.8% versus 39.0%), hypertension (41.2% versus 10.7%), neutropenia (39.0% versus 33.9%), decreased appetite (31.9% versus 23.8%), weight decreased (31.9% versus 14.4%), epistaxis (27.7% versus 7.4%), abdominal pain (26.8% versus 23.6%), dysphonia (25.4% versus 3.3%), and headache (22.3% versus 8.8%). Other TEAEs occurring in  $\geq 20\%$  of patients in both treatment arms, but with similar frequencies were nausea, vomiting, alopecia, and constipation.
- Risk-ratios (aflibercept/fofiri relative to placebo/fofiri) were greater than 1 for a number of frequently occurring TEAEs. The most notable increased risks associated

with aflibercept/fofiri relative to placebo/fofiri were dysphonia (risk ratio (RR) = 7.67 [95% CI: 4.88, 12.06]) and proteinuria (RR=6.93 [95% CI: 3.48, 13.81]). TEAEs with RR  $\geq 3$  to  $< 4$  were hypertension, epistaxis, rhinorrhoea, and dehydration, and TEAEs with RR  $\geq 2$  to  $< 3$  were skin hyperpigmentation, proctalgia, haemorrhoids, palmar-plantar erythrodysesthesia syndrome, headache, oropharyngeal pain, weight decreased and rectal haemorrhage.

- TEAEs (Grade  $\geq 3$ ) were reported more frequently in the aflibercept/fofiri arm than in the placebo/fofiri arm (83.5% versus 62.5%). TEAEs (Grade  $\geq 3$ ) reported in  $\geq 2\%$  more patients in the aflibercept/fofiri arm than in placebo/fofiri arm were neutropenia (25.0% versus 22.0%), diarrhoea (19.3% versus 7.8%), hypertension (19.1% versus 1.5%), stomatitis (12.8% versus 4.6%), fatigue (12.6% versus 7.8%), urinary tract infection (9.2% versus 6.1%), asthenia (5.1% versus 3.0%), abdominal pain (4.4% versus 2.3%), dehydration (4.3% versus 1.3%), proteinuria (2.9% versus 0%), and palmar-plantar erythrodysesthesia syndrome (2.8% versus 0.5%). The most marked differences ( $\geq 5\%$ ) 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/fofiri arm than in the placebo/fofiri arm (95.6% versus 90.9%), as were treatment-related TEAEs (Grade  $\geq 3$ ) (73.8% versus 46.9%). The most frequently reported treatment-related TEAEs (all Grades) and TEAEs (Grade  $\geq 3$ ) were similar to the corresponding all causality TEAEs (all Grades) and TEAEs (Grade  $\geq 3$ ).
- Total deaths on-treatment (that is, within 30 days of last dose) occurred more frequently in the aflibercept/fofiri arm than in the placebo/fofiri arm (4.9%, n=30 versus 3.1%, n=19), as did deaths on-treatment due to identified AEs (2.3%, n=14 versus 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/fofiri arm than in the placebo/fofiri arm (2.6%, n=16 versus 1.0%, n=6). Of these deaths, 6 (1%) in the aflibercept/fofiri arm were considered treatment-related by investigators compared with 3 (0.5%) in the placebo/fofiri 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/fofiri arm were: 1 x neutropenic infection; 1x lobar pneumonia; and 1x interstitial lung disease.
- Serious adverse events (SAEs; all Grades) were reported more frequently in patients in the aflibercept/fofiri arm than in the placebo/fofiri arm (48.1% versus 32.7%), as were SAEs (Grade  $\geq 3$ ) (41.6% versus 28.28%). SAEs (Grade  $\geq 3$ ) occurring in  $\geq 2\%$  of patients in at least one of the treatment arms, and more frequently in the aflibercept/fofiri arm than in the placebo/fofiri arm, were diarrhoea (5.6% versus 2.0%), febrile neutropenia (3.1% versus 2.0%), pulmonary embolism (3.1% versus 2.0%), dehydration (2.9% versus 0.8%) and disease progression (2.6% versus 2.3%). Treatment-related SAEs (Grade  $\geq 3$ ) were also reported more frequently in the aflibercept/fofiri arm than in the placebo/fofiri arm (31.8% versus 15.4%).
- TEAEs (all Grades) resulting in permanent treatment discontinuation occurred notably more frequently in patients in the aflibercept/fofiri arm than in the placebo/fofiri arm (26.8% versus 12.1%), and the majority of patients in both treatment arms permanently discontinued treatment due to TEAEs (Grade  $\geq 3$ ) (20.3%, aflibercept/fofiri versus 8.8%, placebo/fofiri). The most frequently reported TEAEs (all Grades) grouped according to event similarity and leading to permanent treatment discontinuation (aflibercept/fofiri versus placebo/fofiri) were: fatigue/asthenia (3.7% versus 1.3%); infections and infestations system organ class (SOC) (3.4% versus 1.7%); diarrhoea (2.3% versus 0.7%); myelosuppression including neutropenia,

thrombocytopenia, anemia and febrile neutropenia (2.0% versus 1.0%); pulmonary embolism (1.1% versus 1.2%); proteinuria including nephrotic syndrome (1.7% versus 0%); and deep vein thrombosis including deep vein thrombosis (DVT), subclavian vein thrombosis, vena cava thrombosis, and thrombophlebitis (1.3% versus 0.3%).

- TEAEs (all Grades), leading to at least one cycle delay occurred notably more frequently in patients in the aflibercept/fofiri arm than in the placebo/fofiri arm (70.0% versus 54.4%). TEAEs (all Grades) resulting in cycle delay and reported in  $\geq 2.0\%$  more patients in the aflibercept/fofiri arm than in the placebo/fofiri arm were neutropenia (36.2% versus 33.4%), diarrhoea (12.1% versus 5.0%), hypertension (10.8% versus 0.8%), fatigue (9.0% versus 5.3%), stomatitis (8.5% versus 3.1%), decreased appetite (4.4% versus 1.7%), proteinuria (3.4% versus 1.2%), thrombocytopenia (3.3% versus 2.0%), abdominal pain (2.5% versus 1.0%), and urinary tract infection (2.0% versus 1.0%).
- TEAEs (all Grades) leading to dose modifications occurred notably more frequently in patients in the aflibercept/fofiri arm compared with the placebo/fofiri arm (50.4% versus 26.8%). TEAEs (any Grade) reported in  $\geq 2\%$  more patients in the aflibercept/fofiri arm than in the fofiri/placebo arm and resulting in dose modifications were diarrhoea (16.2% versus 6.4%), stomatitis (11.9% versus 5.0%), hypertension (6.2% versus 0.3%), fatigue (4.4% versus 2.1%), proteinuria (4.1% versus 0.5%), and palmar-plantar erythrodysesthesia syndrome (2.9% versus 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/fofiri relative to placebo/fofiri) 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  $\leq 1$  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/fofiri arm, while 2 (0.3%) cases in the aflibercept/fofiri arm were reported for each of these events. 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/fofiri 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/fofiri versus 29.5%, N=176/597, placebo/fofiri). The incidence of neutropenic complications was greater in patients in the aflibercept/fofiri arm than in the placebo/fofiri arm, and nearly all of these events in both treatment arms were Grade  $\geq 3$  (5.7% versus 2.8%, respectively).
- Laboratory clinical chemistry abnormalities (all Grades) for liver function tests of increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) were reported more frequently in patients in the aflibercept/fofiri arm than in the placebo/fofiri arm, and the events were predominantly Grade 1 and 2 in both treatment arms (ALT all Grades 47.3% versus 37.1%, AST all Grades 57.5% versus 50.2%). Increased total bilirubin (all Grades) occurred with similar frequencies in the aflibercept/fofiri and placebo/fofiri arms (22.8% versus 23.2%, respectively), as did



increased serum alkaline phosphatase (all Grades) (70.8% versus 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/fofiri arm (1.1%) and the placebo/fofiri 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/fofiri 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 hepatotoxicity in the aflibercept/fofiri arm compared with the placebo/fofiri arm.
- Increased creatinine levels (all Grades) occurred more frequently in the aflibercept/fofiri arm than in the placebo/fofiri arm (22.6%, N=136/601 versus 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% versus N=3/596, 0.5%, respectively). The percentage of patients with increased creatinine clearance values on treatment were about 2% greater in the aflibercept/fofiri arm compared with the placebo/fofiri arm for < 50 mL/min (15.3% versus 13.1%) and ≥ 50 to ≤ 80 mL/min (46.8% versus 44.6%). Renal failure events were reported in 2.9% of patients in the aflibercept/fofiri arm and 2.1% of patients in the placebo/fofiri arm. Overall, the results suggest that the risks of renal impairment were marginally increased in the aflibercept/fofiri arm compared with the placebo/fofiri arm.
- Patients in the aflibercept/fofiri arm did not appear to be at an increased risk of developing anti-aflibercept antibodies compared with patients in the placebo/fofiri arm (1.5% versus 3.4%, respectively), or neutralising antibodies (0.2% versus 0.4, respectively). Hypersensitivity reactions (TEAEs all Grades, grouped) occurred in 2.5% of patients in the placebo/fofiri arm compared with 1.8% of patients in the aflibercept/fofiri, 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/fofiri arm compared with the placebo/fofiri arm. There was no systematic investigation of ECG changes in VELOUR, but the PD 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.

## Benefit-risk assessment

### 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/fofiri compared with placebo/fofiri (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/fofiri arm than in patients in the aflibercept/fofiri arm (74.9%, N=460/614 versus 65.8%, N=403/612). The median OS in the aflibercept/fofiri arm (13.50 months [95.34% CI: 12.517, 14.949])

was 1.44 months longer than in the placebo/fulfiri 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/fulfiri arm compared with the placebo/fulfiri arm (HR = 0.80 corresponding to a median OS improvement from 11 months in the placebo/fulfiri arm to 13.75 months in the aflibercept/fulfiri arm). The observed risk reduction in the aflibercept/fulfiri arm compared with the placebo/fulfiri arm was 18% (compare with 20% sample size survival criteria), and the observed difference in median OS in favour of placebo/fulfiri was 1.44 months (compare with 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/fulfiri compared with placebo/fulfiri are the minimum clinically significant criteria required for this study. As aflibercept/fulfiri 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/fulfiri arm over the placebo/fulfiri 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/fulfiri (6.90 months [99.99% CI: 5.881, 7.852]) compared with placebo/fulfiri (4.67 months [99.99% CI: 4.074, 5.552]). The ORR was 19.8% (95% CI: 16.4, 23.2) in the aflibercept/fulfiri 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/fulfiri arm compared with the placebo/fulfiri 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/fulfiri arm.

### Assessment of risks

The pivotal study (VELOUR) showed that the risks of treatment with aflibercept/fulfiri (n=611) were greater than those with placebo/fulfiri (n=605). While TEAEs (all Grades) were reported in nearly all patients in both treatment arms (99.2%, aflibercept/fulfiri versus 97.9%, placebo/fulfiri), almost all clinically important risks occurred more frequently in the aflibercept/fulfiri arm than in the placebo/fulfiri 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/fulfiri arm than in the placebo/fulfiri arm (that is, 70% versus 54.4%, cycle delay; 50.4% versus 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/fulfiri arm than in the placebo/fulfiri arm (26.6% versus 12.1%).

The most commonly occurring TEAEs (all Grades) and laboratory events\* (all Grades) reported in  $\geq 20\%$  of patients in either treatment arm, and more frequently with aflibercept/fulfiri than with placebo/fulfiri, in order of decreasing frequency were leucopenia\* (78.3% versus 72.4%), diarrhoea (69.2% versus 56.5%), neutropenia\* (67.8% versus 56.3%), proteinuria\* (62.2% versus 40.7%), AST increased\* (57.5% versus 50.2%), stomatitis (50.1% versus 32.9%), fatigue (47.8% versus 39.0%), thrombocytopenia\* (47.4% versus 33.8%), ALT increased\* (47.3% versus 37.1%), hypertension (41.2% versus 10.7%), decreased appetite (31.9% versus 23.8%), weight decreased (31.9% versus 14.4%), epistaxis (27.7% versus 7.4%), abdominal pain (26.8% versus 23.6%), dysphonia (25.4% versus 3.3%), and headache (22.3% versus 8.8%). Other

TEAEs occurring in  $\geq 20\%$  of patients and with similar frequencies in both treatment arms were nausea, vomiting, alopecia, and constipation.

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

Risk ratios (aflibercept/fofiri:placebo/fofiri) were greater than 1 for a number of frequently occurring TEAEs. The most notably increased risks associated with aflibercept/fofiri relative to placebo/fofiri 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  $\geq 3$  to  $< 4$  were hypertension, epistaxis, rhinorrhoea, and dehydration, and TEAEs with RRs  $\geq 2$  to  $< 3$  were skin hyperpigmentation, proctalgia, haemorrhoids, palmar-plantar erythrodysesthesia 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 (approximately 4 fold increase) and haemorrhage (approximately 2 fold increase) were statistically significantly greater in the aflibercept/fofiri arm compared with the placebo/fofiri arm. In addition, a fatal duodenal ulcer haemorrhage considered to be treatment-related occurred in one patient in the aflibercept/fofiri 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/fofiri treatment arm. Risk ratios  $\leq 1$  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/fofiri arm, while each of these events occurred in 2 (0.3%) patients in the aflibercept/fofiri 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 approximately 3759 patients exposed to aflibercept, giving an overall incidence of approximately 0.5%.

Total deaths on-treatment (i.e., within 30 days of last dose) occurred more frequently in the aflibercept/fofiri arm than in the placebo/fofiri arm (4.9%, n=30 versus 3.1%, n=19, respectively), as did deaths on-treatment due to identified AEs (2.3%, n=14 versus 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/fofiri arm than in the placebo/fofiri arm (2.6%, n=16 versus 1.0%, n=6). Of these deaths, 6 (1%) in the aflibercept/fofiri arm were considered treatment-related by investigators compared with 3 (0.5%) in the placebo/fofiri 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/fofiri 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/fofiri 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 versus 29.5%, placebo/fofiri). The incidence of neutropenic complications was greater in patients in the aflibercept/fofiri arm than in the placebo/fofiri arm, and nearly all of these events in both treatment arms were Grade  $\geq 3$  (5.7% versus 2.8%, respectively).

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

Patients in the aflibercept/fofiri arm did not appear to be at an increased risk of developing anti-aflibercept antibodies compared with patients in the placebo/fofiri arm (1.5% versus 3.4%, respectively), or neutralising antibodies (0.2% versus 0.4%). Hypersensitivity reactions (TEAEs all Grades, grouped) occurred in 2.5% of patients in the placebo/fofiri arm compared with 1.8% of patients in the aflibercept/fofiri, 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  $\geq 65$  years experienced the following TEAEs (all Grades)  $\geq 5\%$  more frequently than patients aged  $< 65$  years: diarrhoea (73.7% versus 67.0%); weight decreased (41.0% versus 27.3%); asthenia (22.0% versus 16.5%); dehydration (14.6% versus 6.2%); and dizziness (9.3% versus 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/fofiri treatment, but these are not considered to be significant. There were no meaningful data on the risks of aflibercept/fofiri in the different racial groups, due to relatively small numbers of patients in all groups apart from Caucasian/White.

### **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/fofiri arm compared with the placebo/fofiri arm, while demonstrating a notably inferior safety profile for the aflibercept/fofiri arm compared with the placebo/fofiri arm.

### **Recommendation regarding authorisation**

#### **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.

#### **Reasons for recommendation to reject**

The single pivotal study has failed to establish that aflibercept/fofiri provides a clinically significant benefit in OS compared with placebo/fofiri. In addition, the benefit-risk

balance for aflibercept/fofiri is unfavourable as the pivotal study failed to establish a clinically significant improvement in OS in the aflibercept/fofiri arm compared with the placebo/fofiri arm, while demonstrating that the safety profile of aflibercept/fofiri is notably inferior to that of placebo/fofiri.

There was a statistically significant difference in OS (the primary efficacy endpoint) in favour of aflibercept/fofiri compared with placebo/fofiri (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/fofiri arm there were 403 (65.8%) death events compared 460 (74.9%) in the placebo/fofiri arm. The median OS in the aflibercept/fofiri arm (13.50 months [95.34% CI: 12.517, 14.949]) was 1.44 months longer than in the placebo/fofiri 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/fofiri compared with aflibercept/fofiri, 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/fofiri 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/fofiri arm than in the placebo/fofiri 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/fofiri compared with placebo/fofiri, it is considered that these results can not offset the failure of aflibercept/fofiri to establish a clinically significant OS benefit compared with placebo/fofiri.

### List of questions

No questions.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

A copy of the EU RMP Version 1.0 (dated 18 October 2011, with data lock point 7 February 2011) and a copy of the Australian-specific Annex (ASA) Version 1.0 (March 2012) were provided for this submission. A total of 11 important identified risks, 3 important potential risks and 5 areas of missing information, is listed as ongoing safety concerns. Routine pharmacovigilance and risk minimisation activities are proposed for all ongoing safety concerns. An abbreviated form of the Summary of the AUS RMP of the ASA is shown in Table 11.

Table 11. Summary of the Australian RMP

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
<b>Important Identified Risks</b>		
Hypertension	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Hypertension), Adverse Effects (Description of selected adverse reactions - Hypertension), Dosage and Administration, Overdosage</i> sections CMI
Proteinuria/nephrotic syndrome	Routine pharmacovigilance	Routine (labelling): PI – <i>Pharmacokinetics (Special populations – Renal Impairment), Precautions (Proteinuria), Adverse Effects (Description of selected adverse reactions – Proteinuria, Other special populations – Renal Impairment), Dosage and Administration, Overdosage</i> sections CMI
Haemorrhage	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Haemorrhage), Adverse Effects (Description of selected adverse reactions – Haemorrhage), Dosage and Administration</i> sections CMI
Arterial Thromboembolic Events (ATE)	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Arterial thromboembolic events), Adverse Effects (Description of selected adverse reactions – Arterial thromboembolic events), Dosage and Administration</i> sections CMI
Gastrointestinal	Routine	Routine (labelling):

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
perforation	pharmacovigilance	PI – <i>Precautions (Gastrointestinal perforation), Adverse Effects (Description of selected adverse reactions – Gastrointestinal perforation), Dosage and Administration</i> sections CMI
Fistula (from GI and non-GI origin)	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Fistula formation), Adverse Effects (Description of selected adverse reactions – Fistula formation), Dosage and Administration</i> sections
Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Reversible posterior leukoencephalopathy syndrome), Adverse Effects (Description of selected adverse reactions – Reversible posterior leukoencephalopathy syndrome), Dosage and Administration</i> sections CMI
Thrombotic microangiopathy (TMA)	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Proteinuria), Adverse Effects ((Description of selected adverse reactions - Proteinuria), Dosage and Administration</i> sections
Hypersensitivity reaction	Routine pharmacovigilance	Routine (labelling): PI – <i>Contraindications, Precautions (Hypersensitivity reactions), Adverse Effects (Description of selected adverse reactions – Hypersensitivity reactions), Dosage and Administration</i> sections CMI

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Wound healing complications	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Compromised wound healing), Adverse Effects (Description of selected adverse reactions – Compromised wound healing), Dosage and Administration</i> sections CMI
Increased chemotherapy-associated toxicity (within the context of concomitant chemotherapy), including neutropenia and neutropenic complications, diarrhoea and dehydration, stomatitis, and palmar plantar erythrodysesthesia (PPE) syndrome	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Neutropenia and neutropenic complications, Diarrhoea and Dehydration), Adverse Effects ((Description of selected adverse reactions - Neutropenia and neutropenic complications, Diarrhoea and Dehydration, Other special populations - Elderly), Dosage and Administration</i> sections CMI
<b>Important Potential Risks</b>		
Cardiac Dysfunction	Routine pharmacovigilance	There is no specific recommendation about Cardiac dysfunction
Osteonecrosis	Routine pharmacovigilance	There is no specific recommendation about Osteonecrosis
Venous Thromboembolic events (VTE)	Routine pharmacovigilance	Routine (labelling): PI – <i>Adverse Effects (Description of selected adverse reactions – Venous thromboembolic events)</i> section CMI
<b>Important Missing Information</b>		
Use in patients with severe renal	Routine pharmacovigilance	Routine (labelling): PI – <i>Pharmacokinetics (Special</i>



Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
impairment		<i>populations – Renal Impairment), Adverse Effects (Other special populations – Renal Impairment), Dosage and Administration (Special Populations – Renal Impairment) sections</i>
Use in patients with severe hepatic impairment	Routine pharmacovigilance	Routine (labelling): PI – <i>Pharmacokinetics (Special populations – Hepatic Impairment), Dosage and Administration (Special Populations – Hepatic Impairment) sections</i>
Use in non-Caucasian patients	Routine pharmacovigilance	Routine (labelling): PI – <i>Pharmacokinetics (Special populations – Race) section</i>
Use in children and adolescents	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Paediatric Use), Adverse Effects (Other special populations – Paediatric Population), Dosage and Administration (Special populations – Paediatric population) sections</i> CMI
Use in pregnant and lactating women, fertile males	Routine pharmacovigilance	Routine (labelling): PI – <i>Precautions (Effects on Fertility, Use in Pregnancy, Use in Lactation) sections</i> CMI

### Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified in the EU RMP by the sponsor is as follows:

**Table 12. Summary of Ongoing Safety Concerns**

<b>Important identified risks</b>	Hypertension
	Proteinuria/nephrotic syndrome
	Haemorrhage
	Arterial thromboembolic events (ATE)
	Gastrointestinal (GI) perforation
	Fistula (from GI and non-GI origin)
	Reversible posterior leukoencephalopathy syndrome (RPLS)
	Thrombotic microangiopathy (TMA)
	Hypersensitivity reactions
	Wound healing complications
	Increased chemotherapy-associated toxicity (within the context of concomitant chemotherapy), including neutropenia and neutropenic complications, diarrhoea and dehydration, stomatitis, and palmar plantar erythrodysesthesia (PPE) syndrome
<b>Important potential risks</b>	Cardiac dysfunction
	Osteonecrosis
	Venous thromboembolic events (VTE)
<b>Important missing information</b>	Use in patients with severe renal impairment
	Use in patients with severe hepatic impairment
	Use in non-Caucasian patients
	Use in children and adolescents
	Use in pregnant and lactating women, fertile males

**OPR reviewer comment:**

The above summary of the Ongoing Safety Concerns is considered acceptable, unless additional concerns are raised from the evaluation of the non-clinical and clinical aspects of the safety specifications.

**Pharmacovigilance plan**

Routine pharmacovigilance activities are proposed for all ongoing safety concerns. The proposed plan for implementing only routine pharmacovigilance activities for all ongoing

safety concerns at this stage is considered acceptable, unless additional concerns are raised by the clinical and/or non-clinical evaluator(s).

### **Risk minimisation activities**

It is concluded in Section 4.1 *Australian specific risk management plan* of the ASA that only routine risk minimisation activities will be required. These activities will be in the form of safety information, dosing recommendation and instruction for use as presented in the draft Australian PI and CMI. It is noted that a user leaflet containing information on how to prepare and administer the infusion solution (instruction for use intended for healthcare professionals) is also proposed for inclusion as a package insert.

#### ***OPR reviewer's comment:***

This is considered acceptable considering that this product will be used under the supervision of a physician experienced in the use of antineoplastic medicinal products, unless additional concerns are raised by clinical and/or non-clinical evaluator(s).

### **Risk minimisation plan**

#### ***Planned actions***

Routine risk minimisation activities in the form of the relevant information presented in the PI and CMI are proposed for all ongoing safety concerns.

#### ***OPR reviewer's comments:***

The proposed plan for implementing only routine risk minimisation activities for all ongoing safety concerns at this stage is considered acceptable, unless additional concerns are raised by the clinical and/or non-clinical evaluator(s). In regard to the proposed routine risk minimisation activities, the draft PI and CMI are considered satisfactory except for the following:

- there is no specific recommendation or information provided in the draft PI/CMI for the important potential risks of cardiac dysfunction and osteonecrosis, with no justification provided.
- there appears to be a minor error in the draft PI – *Dosage and Administration – Dosage – Dose modification/Discontinuations/Treatment delay recommendations* section, under the subheading Discontinue Zaltrap for (see PRECAUTIONS): the terms “Reversible” and “posterior leukoencephalopathy syndrome” should be one term.

It is recommended that the sponsor provides an appropriate justification as to why routine risk minimisation activities in the form of safety information provided in the PI and/or CMI is not required for the important potential risks of cardiac dysfunction and osteonecrosis.

### **Summary of recommendations**

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application, under the provision that no additional safety concerns are raised by the clinical and/or non-clinical evaluator(s):

- implementation of the RMP identified as the EU RMP Version 1.0 (dated 18 October 2011) and the ASA Version 1.0 (March 2012), and any subsequent versions, is imposed as a condition of registration.
- consideration be given to revising the draft PI and CMI as described above.

## VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Background

Aflibercept (VEGF-Trap) is a novel, targeted antiangiogenic agent. It is a recombinant protein derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). Aflibercept acts as a soluble decoy receptor that binds to VEGF-A, with higher affinity than its native receptors, as well as the related ligands placental growth factor (PlGF) and VEGF-B. By acting as a ligand trap, aflibercept prevents binding of endogenous ligands to their receptors blocking receptor mediated signalling.

### Targets and mechanism of action

Aflibercept (rch) is a fusion protein generated using recombinant DNA technology. It is a dimeric glycoprotein (97 kDa + glycosylation approximately equal to 115 kDa), composed of two human vascular endothelial growth factor (VEGF) receptor extracellular domains linked to the Fc portion of human immunoglobulin G1 (IgG1). It includes domain 2 from VEGFR-1 (Flt-1) and domain 3 from VEGFR-2 (KDR / Flk-1) (see structure in Figure 1).

Aflibercept is anti-angiogenic, acting as "a soluble decoy receptor that binds to VEGF-A, with higher affinity than its native receptors, as well as the related ligands placental growth factor (PlGF) [PlGF-1 and PlGF-2] and VEGF-B". By acting as a ligand trap, aflibercept prevents binding of endogenous ligands to their receptors.

The sponsor considers the mechanisms of action to be direct anti-cancer activity and potentiation of chemotherapy *via* "prevention of new tumor vessel growth, regression of existing tumor vessels, vascular normalisation, direct effects on tumor cell function, offsetting of effects of chemotherapy induction of VEGF levels, and inhibition of VEGF repression of dendritic cell function".

Affinity to VEGF-C and VEGF-D is low. The nonclinical evaluator reported high specificity, with no cross-reactivity against a panel of 33 normal human tissues. The Fc region of aflibercept did not mediate complement-dependent cytotoxicity or antibody-dependent cell mediated cytotoxicity *in vitro*.

### Aim of submission PM-2011-04301-3-4

The sponsor aims to register the product for the indication: "*aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer (MCR) previously treated with an oxaliplatin-containing regimen*". Thus, the proposal is for second line use, alongside other agents, in the setting of metastatic colorectal cancer.

The VEGF pathway plays an important role in angiogenesis and is considered important in the pathological angiogenesis seen in MCR.

Three biologicals are currently approved for (at least) second line treatment: bevacizumab (anti-VEGF), cetuximab (anti-EGFR) and panitumumab (anti-EGFR). The sponsor states that none of these has shown a statistically significant improvement in OS in combination with FOLFIRI when compared to FOLFIRI alone.

**Relevant TGA guidelines adopted from the EU**

- Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA/EWP/205/95 Rev 3 Corr) and its appendices 1-2
- Points to Consider on Application with 1: Meta-Analyses; 2: One Pivotal Study (CPMP/EWP/2330/99)
- Guideline on Reporting the results of Population Pharmacokinetic Analysis (CHMP/EWP/185990/06)

**Quality**

There were no objections to registration from a biochemistry / molecular biology perspective.

**Nonclinical**

Major targets for toxicity in monkeys included: nasal cavity; bone (for example, vertebral exostoses associated with kyphosis), kidneys (e.g. increased glomerular mesangial matrix; glomerulopathy with tubular dilatation and cast formation), adrenals and ovary (for example, reversible reduction in maturing follicles, with profound reduction in ovarian hormones).

There were no objections to registration from the nonclinical evaluator.

**Clinical****Overview of data**

One pivotal efficacy and safety study was submitted. This was Study EFC10262 (VELOUR), a randomised, double-blind, placebo-controlled trial. This study has been published.<sup>14</sup>

Nine supportive safety studies were submitted, with efficacy data relating to indications other than that being proposed. These included randomised, double-blind studies VANILLA (metastatic pancreatic cancer) and VITAL (NSCLC).

There were 16 clinical pharmacology studies and 5 population-PK studies.

The formulation used in preclinical and clinical development is that proposed for commercial use.

**Pharmacokinetics**

A brief summary of the PK follows:

Estimated PK parameters for free aflibercept in a typical<sup>15</sup> male patient receiving 4 mg/kg q2w are: clearance of 0.0425 L/h; steady-state volume of distribution 7.77 L; terminal half-life of 6 days; C<sub>max</sub> of 59.1 µg/L in cycle 1 rising to 65.6 at steady state; C<sub>trough</sub> of 5.33 µg/L at cycle 1 rising to 6.55 µg/L at steady state; and AUC of 5238 µg.h/mL rising to

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<sup>14</sup> Can Cutsem E *et al.* Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomised Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. *J Clinical Oncology* 2012; 30 (28): 3499-3506.

<sup>15</sup> that is, with median co-variate values; for example co-variates for the final model of clearance included creatinine clearance, albumin and weight amongst others; NB the evaluator considered that dose adjustment for renal failure would not be required.

6306 µg.h/mL at steady state (all based on the population PK model in POH0265). These values were broadly consistent with those seen in the PK analysis of patients in VELOUR.

No metabolism studies were conducted, with the sponsor expecting degradation of aflibercept and the VEGF : aflibercept complex to small peptides and individual amino acids.

Clearance was dose-dependent at lower doses but stable over the 3-7 mg/kg dose range. This non-linearity was explained by target-mediated drug disposition, resulting from saturable binding of free aflibercept to endogenous VEGF. Thus, “once endogenous VEGF binding sites are fully occupied then free aflibercept undergoes non-saturable clearance presumably *via* catabolism”. The sponsor suggests that the dominant elimination pathway is saturable binding to VEGF (followed by internalisation), with the other elimination pathway being non-saturable elimination from the central compartment.

Typical clearance values for free aflibercept were 5-fold higher than for bound aflibercept. Estimated terminal half-life of bound aflibercept was approximately 25 days.

Studies suggested that at  $\geq 2$  mg/kg, there was enough free aflibercept to bind all endogenous VEGF, and that bound aflibercept levels are limited by VEGF levels.

Bound aflibercept steady state trough concentrations were reached after 1-2 months, with high inter-individual variability, but in POH0265, 81% of  $C_{\text{trough,ss}}$  was reached after the first dose. Bound aflibercept is stated to be pharmacologically inert.

The recommended dose regimen (4 mg/kg q2w) was supported by study of the free / bound aflibercept ratio (maintaining a ratio  $>1$ , it was argued, would maintain endogenous VEGF concentrations below levels seen in healthy subjects).

The following specific issues were identified:

- No formal PK study in hepatic impairment was submitted. Results from VELOUR suggested mild and moderate impairment did not affect free aflibercept PK. There were limited data for moderate and severe impairment.
- No formal PK study in renal impairment was submitted. In POH0265, free aflibercept clearance fell with increasing renal impairment, but systemic exposure was not markedly affected. The sponsor maintains that “since high molecular weight proteins are not cleared by [renal elimination], renal elimination of aflibercept is expected to be minimal”. Perhaps a confounding factor influences clearance and is associated with renal function. No patients in VELOUR had severe renal impairment.
- In VELOUR, exposure to free aflibercept increased with body weight, and clearance decreased, despite dosing according to weight. AUC was 29% higher in  $>100$  kg patients than in 50-100 kg patients (analysis of AEs by weight raised no concerns).
- With combination treatments (that is, aflibercept plus other agents), relative to treatment with aflibercept alone, there was higher exposure to bound aflibercept.

The effect of concomitant aflibercept on PK of multiple other anti-cancer agents was studied using historical comparison. There was a suggestion that clearance of gemcitabine was lower with concomitant aflibercept, though this is an exploratory finding.

## Pharmacodynamics

Studies PDY6655 (blood pressure), PDY6656 (blood pressure) and TES10897 (QT interval) provided PD data. The evaluator discounted PDY6656 as it was not placebo-controlled and lacked a 4 mg/kg arm. Relevant results are considered under ‘Safety’ below.

## Efficacy

The 4 mg/kg dose used in VELOUR was determined in a Phase I study (TCD6118) of 2, 4, 5 and 6 mg/kg doses in patients with solid tumours. The evaluator considered that the optimum dose has not been characterised.

### Study EFC10262 (VELOUR)

VELOUR was a Phase III, randomised, double-blind, placebo-controlled trial in adult patients with MCRC being treated with irinotecan / 5-FU / leucovorin (FOLFIRI) following disease progression while on or after completion of treatment with an oxaliplatin-based regimen. Inclusion and exclusion criteria are detailed in the CER; notably, patients were not eligible if certain anti-VEGF class events were present at baseline. Enrolment started in 11/2007 and finished in 3/2010; the data cut-off was in 2/2011.

The evaluator notes that comparison of aflibercept + FOLFIRI with bevacizumab + FOLFIRI would be clinically relevant, but accepts the sponsor's argument that data did not support this choice of comparator regimen at the time the study was started.

Patients received aflibercept or placebo infused IV over 1 h, followed immediately by the FOLFIRI regimen (within the FOLFIRI regimen, l-leucovorin 200 mg/m<sup>2</sup> was an alternative to dl-leucovorin 400 mg/m<sup>2</sup>). This was repeated every two weeks, until disease progression, unacceptable toxicity, patient refusal or investigator's decision to stop. Premedications routinely included atropine for cholinergic adverse events (AEs), anti-emetics and granulocyte colony stimulating factor (G-CSF).

A total of 1226 subjects were randomised (1:1) to receive placebo (n=614) or aflibercept (n=612); this ITT population was the primary population for efficacy analysis. Stratification was based on prior use of bevacizumab and Eastern cooperative oncology group (ECOG) performance status (0 versus 1 versus 2; most had a performance status of 0 or 1<sup>16</sup>). Median numbers of infusions (and range) are described in Table 13.

**Table 13. VELOUR. Median numbers (and range) of infusions.**

	Placebo + FOLFIRI	Aflibercept + FOLFIRI
Placebo or aflibercept	8 (1-67)	7 (1-35)
Irinotecan	8 (1-67)	9 (1-50)
5-fluorouracil (5-FU)	8 (1-67)	9 (1-50)

There were imbalances in the proportion of subjects with cycle delays and dose modifications across arms, for placebo / aflibercept, irinotecan and 5-fluorouracil. The lower median number of aflibercept infusions is accounted for by a higher frequency of dose reductions and omissions and permanent discontinuations due to AEs in the aflibercept arm.

Study arms were well-balanced in terms of demographics and baseline disease characteristics; the median age was 61 years and the median time from first diagnosis to randomisation was 14.3 months. About 57% of subjects had baseline ECOG performance status of 0 and only about 30% had prior bevacizumab use. Prior chemotherapy was well-

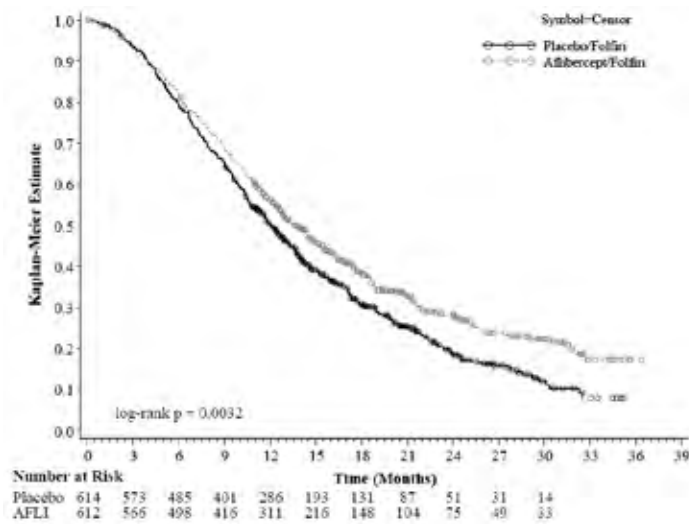
<sup>16</sup> See Appendix B of the Attached CER extract for a details of the performance scale.

balanced; almost all had received oxaliplatin with a fluoropyrimidine, and in most oxaliplatin was to treat metastatic/ advanced disease.

### **Overall survival (OS)**

The primary endpoint was OS. Results for the primary endpoint are shown in Figure 4 and Table 14:

**Figure 4. OS (months). Kaplan-Meier curves by treatment group; ITT population**





**Table 14. Efficacy results for Study EFC10262 (VELOUR) in second line treatment of metastatic colorectal cancer. Overall survival analysis (months); ITT population.**

Time to Event or Censoring	Placebo/Folfini (N=614)	Aflibercept/Folfini (N=612)
Overall		
Number of death events, n/N(%)	460/614 (74.9%)	403/612 (65.8%)
25% quantile overall survival (95.34% CI) (months)	6.83 (6.144 to 7.589)	7.62 (6.571 to 8.476)
Median overall survival (95.34% CI) (months)	<b>12.06 (11.072 to 13.109)</b>	<b>13.50 (12.517 to 14.949)</b>
75% quantile overall survival (95.34% CI) (months)	21.03 (18.924 to 22.801)	25.59 (22.012 to 31.704)
Number of patients at risk		
3 months	573	566
6 months	485	498
9 months	401	416
12 months	286	311
18 months	131	148
24 months	51	75
27 months	31	49
30 months	14	33
Survival probability (95.34% CI)		
3 months	0.935 (0.915 to 0.955)	0.931 (0.911 to 0.951)
6 months	0.791 (0.759 to 0.824)	0.819 (0.788 to 0.850)
9 months	0.654 (0.616 to 0.692)	0.687 (0.650 to 0.725)
12 months	0.503 (0.462 to 0.543)	0.561 (0.521 to 0.602)
18 months	0.309 (0.269 to 0.348)	0.385 (0.343 to 0.427)
24 months	0.187 (0.149 to 0.225)	0.280 (0.237 to 0.324)
27 months	0.158 (0.120 to 0.196)	0.238 (0.194 to 0.283)
30 months	0.120 (0.080 to 0.160)	0.223 (0.178 to 0.268)
Stratified Log-Rank test p-value <sup>a</sup>		
vs Placebo/Folfini	-	<b>0.0032</b>
Stratified Hazard ratio (95.34% CI) <sup>a</sup>		
vs Placebo/Folfini	-	<b>0.817 (0.713 to 0.937)</b>

Cutoff date = 7 FEBRUARY 2011

Median follow-up time = 22.28 in months

<sup>a</sup>: 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.

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Median OS in the placebo arm was 12.1 months and in the aflibercept arm 13.5 months (HR 0.817, 95.34% CI 0.713-0.937).

The sponsor notes<sup>17</sup> that “the objective of subgroup analyses in the study was to assess the consistency of the treatment effect across subgroups” and also that “the study was not powered to demonstrate a statistically significant treatment effect in a particular subgroup”. In unadjusted sub-group analysis, there is an indication of an inconsistent treatment effect across subgroups defined by ECOG status, with the ECOG 0 subgroup results favouring aflibercept, the ECOG 1 subgroup results similar across arms, and the ECOG 2 subgroup results favouring placebo (there, median OS was 4.4 months in the placebo arm and 2.8 months in the aflibercept arm). A test for heterogeneity of treatment effects was negative<sup>18</sup>; this was taken to support “a consistent effect of treatment across subgroups” (however given the actual results, this negative test for heterogeneity does not seem to be strong evidence for a consistent treatment effect). It is accepted that these are exploratory results and that the ECOG 2 stratum was small (27/1226); also, this pattern was not repeated for PFS data. The sponsor discusses ECOG 0-1 results but not ECOG 2 results in the Clinical Trials section of the draft PI, but in light of the above this is probably reasonable.

<sup>17</sup> Letter to TGA dated 14 September 2012; notification of errors or omissions

<sup>18</sup> Interaction test from the Cox proportional hazard model including the factor, treatment effect and treatment by factor interaction; p=0.5668

In 264 subjects with a “rectosigmoid or other” primary tumour location (that is, not colon; not rectum), the HR was 1.039; the interaction of treatment with primary tumour location did not reach statistical significance. Given similar benefit of aflibercept in patients with a primary tumour location of colon and of rectum, and the lack of an analogous PFS finding, this result can reasonably be attributed to chance.

In subjects with liver metastases only, the aflibercept benefit on OS was more pronounced.

Overall survival may, in general terms, be influenced by effective treatments received after study drug discontinuation. Post-study anti-cancer treatment was balanced across arms.

### ***Progression-free survival (PFS)***

Progression free survival was generally based on independent, blinded third-party review by the IRC. Median PFS was 4.7 months for placebo versus 6.9 months for aflibercept (HR 0.758, 99.99% CI 0.578 to 0.995); this was based on interim analysis in May 2010. Results for this endpoint are shown in Table 15. Subgroup analyses of PFS was performed. Again in subjects with liver metastases only, the aflibercept benefit was more pronounced.

**Table 15. Progression-free survival (months); assessed by the independent review committee (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 <sup>a</sup>	0.00007	
Stratified HR (99.99% CI) <sup>a</sup>	0.758 (CI: 99.99%: 0.578 to 0.995)	

Cut-off date = 06 May 2010.

<sup>a</sup> Stratified on ECOG Performance Status (0 versus 1 versus 2) and Prior Bevacizumab (yes versus no) according to IVRS.

Significance threshold is set to 0.0001.

### ***Objective response rate (ORR)***

ORR was analysed in the “evaluable patient population” with IRC assessment. An overall response was seen in 11.1% (placebo) versus 19.8% (aflibercept), although the only two patients with a complete response were in the placebo arm.

### ***Quality of life***

Quality of life was not assessed, which the Delegate considers a deficiency.

### ***Exposure-efficacy modelling in VELOUR***

Overall survival was correlated with decreased free aflibercept clearance and with increased free aflibercept C<sub>max</sub> and exposure (AUC). An increase in free aflibercept AUC of 1000 µg.h/mL was associated with a 13% increase in the survival hazard rate. Similar results were observed for progression-free survival.

The correlation persisted after addition of endogenous VEGF at baseline as a covariate. The finding is difficult to interpret: systemic exposure to aflibercept over time would be related to changing VEGF (and other target molecule) levels after baseline, which could

reflect altered tumour or patient characteristics that might influence survival in their own right.

### **Other efficacy evidence**

The CER includes a discussion of Phase I dose-ranging study TCD6118, and the sponsor has provided a description of efficacy outcomes amongst 42 heavily pre-treated MCRC patients given various doses of aflibercept in combination with fluorouracil, leucovorin and irinotecan. There was no Phase II study of combination therapy.

Other studies supportive of safety had efficacy data for indications other than that proposed (for example, ovarian cancer, non small-cell lung cancer, pancreatic cancer, non-Hodgkin lymphoma).

### **Safety**

#### *Exposure*

2073 patients were exposed to aflibercept in Phase I, II and III trials integrated into a safety database (including VELOUR); the general cut-off date for safety analysis in these subjects was 7<sup>th</sup> February 2011.

Pivotal safety data were from VELOUR, where the safety population was 605 (placebo; median 8 infusions, range 1-67; median duration of exposure 18 weeks) and 611 (aflibercept; median 7 infusions, range 1-35; median duration of exposure 17.9 weeks).

Emphasis in the clinical evaluation of safety was on Phase III data (VELOUR, VANILLA, VITAL). Exposure in VANILLA and VITAL is described in the CER.

Additional safety data from 7 ongoing Sanofi and Regenero studies and 16 NCI sponsored studies were mentioned by the clinical evaluator, producing a grand total of 3759 exposed patients as of 28<sup>th</sup> July 2011.

#### *Overview (VELOUR)*

The following is an overview of safety outcomes in VELOUR's safety population:

**Table 16. Overview of safety outcomes in VELOUR's safety population.**

<b>n(%)</b>	<b>Placebo/Folfiri (N=605)</b>	<b>Aflibercept/Folfiri (N=611)</b>
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 <sup>a</sup>	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

Aflibercept was associated with an increased incidence of most of the common AEs, notably dysphonia (25.4% versus 3.3%), proteinuria (10.3% versus 1.5%<sup>19</sup>), hypertension (41.2% versus 10.7%), epistaxis (27.7% versus 7.4%), skin hyperpigmentation (8.2% versus 2.8%), palmar-plantar erythrodysesthesia syndrome (11.0% versus 4.3%), headache (22.3% versus 8.8%), weight decreased (31.9% versus 14.4%; more common in those ≥65 yrs of age), stomatitis (50.1% versus 32.9%) and diarrhoea (69.2% versus 56.5%).

<sup>19</sup> For proteinuria, inclusion of lab abnormalities produces frequencies of 62.2% (aflibercept) versus 40.7% (placebo)

The difference in permanent treatment discontinuation rates between aflibercept and placebo was taken to indicate that dose delay and modification were not always successful approaches to managing AEs.

Anti-VEGF class events were well described, and the following table presents a selection of these events for the VELOUR safety population, summarised by risk ratio:

**Table 17. Selected anti-VEGF class events for the VELOUR safety population, summarised by risk ratio.**

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

Results of a meta-analysis for AEs of special interest (incorporating VELOUR, VANILLA and VITAL) were also provided.

#### Deaths

In VELOUR's aflibercept arm, 403/611 subjects had died by the data cut-off (66.0%), versus 452/605 placebo subjects (75.7%). In the aflibercept arm, 14/611 subjects (2.3%) died due to AEs, versus 4/605 in the placebo arm. This suggests that while aflibercept adds appreciably to anticancer treatment-related mortality, at the population level for this indication there is a net survival benefit.

In VANILLA (metastatic pancreatic cancer), there were more deaths in the aflibercept arm (74.1%) than the placebo arm (65.7%). With the exception of 4 deaths from haemorrhage in the aflibercept arm (1 cerebral, 3 gastrointestinal), the impression was that the imbalance was efficacy-related.

In VITAL (NSCLC), deaths occurred in about 75% in each arm (aflibercept and placebo). Neutropenic sepsis was the cause of death in 5 aflibercept patients and no placebo patients.

#### Hypertension

Hypertension is an anti-VEGF class effect. According to the nonclinical evaluation report: "In addition to its function as a vascular growth factor, VEGF is involved in the regulation of blood pressure by modulating available nitric oxide and prostacyclin levels to promote vasodilatation".

Study PDY6655 confirmed that aflibercept increases blood pressure. The placebo-corrected increase in 24 h mean systolic blood pressure with the 4 mg/kg dose peaked at +14.5 mmHg at week 2. There was a dose effect. The effect on blood pressure waned over time in this study, but was present at day 44. Other results suggested an indirect effect on

the renin-angiotensin-aldosterone system. Heart rate fell. There were no effects on endothelial or renal function as measured by serum or urinary biomarkers, but inter-subject variability was high.

In VELOUR, hypertension was an AE in 41.2% (aflibercept) versus 10.7% (placebo); Grade 3+ hypertension was reported in 19.1% versus 1.5%. Most "Grade 3 or worse" events were Grade 3 (requiring >1 drug or more intensive therapy than before). The proportion of subjects with outlying systolic and diastolic hypertension across arms is noted. Hypertension was a frequent cause of aflibercept discontinuation (in 2.3% of patients, versus no placebo patients), as well as a common cause of cycle delay and dose modification.

The sponsor summarised cases of reversible posterior leukoencephalopathy syndrome (RPLS) reported to 28.7.2011. Frequency was approximately 0.5% across 3759 subjects given aflibercept (17 subjects, 13 of whom were female, and with a median age of 59 years). Mean cycle at diagnosis was 4.8. There was recovery in 12/17 cases, after a mean of approximately 2 weeks. In 6/17, doses of 5-6 mg/kg were used. Common presentations were altered mental status, seizures and headache. There were no reports in VELOUR.

Cardiac dysfunction was reported in 2 aflibercept subjects in VELOUR, and no placebo subjects; there was a similar picture in VANILLA and VITAL. Any link to hypertension is unclear.

#### *QT prolongation*

Study TES10897 suggested to the clinical evaluator that aflibercept is unlikely to prolong the QT interval significantly.

#### *Haemorrhage*

Haemorrhage is an anti-VEGF class effect. Haemorrhage was reported in 37.8% (aflibercept) versus 19.0% (placebo); epistaxis accounted for much of this. Haemorrhage of Grade 3+ was reported in 2.9% versus 1.7%. There was a fatal duodenal ulcer bleed in an aflibercept patient; in other studies there have been 15 fatal haemorrhagic events. Of relevance for epistaxis, the nasal cavity was a target of toxicity in cynomolgus monkeys.

#### *Proteinuria*

Proteinuria is a class effect of agents targeting the VEGF pathway. Proteinuria was reported in 62.7% of aflibercept patients and 40.7% of placebo patients; Grade  $\geq 3$  events were reported in 7.9% versus 1.2% respectively. Proteinuria (including nephrotic syndrome) was a common cause of aflibercept discontinuation (in 1.7% of patients, versus no placebo patients), cycle delay (3.4% versus 1.2%) and dose modification. It was generally first reported early during treatment (for example, for 62.9% of aflibercept patients, within the first 3 cycles). Despite the frequency of proteinuria, there was no strong signal of associated renal impairment (for example, renal failure events were reported in 2.9% of aflibercept and 2.1% of placebo patients).

#### *Diarrhoea and stomatitis*

In VELOUR, Grade 3+ diarrhoea was an AE in 19.3% (aflibercept) versus 7.8% (placebo). Dehydration was a fatal AE within 30 days of study treatment in 2 aflibercept patients. An aflibercept-related fatality from hypovolaemic shock was related to diarrhoea and vomiting. A similar picture is painted in reporting of serious AEs for diarrhoea (and dehydration). Diarrhoea was a common cause of aflibercept discontinuation (in 2.3% of patients, versus 0.7% of placebo patients), as well as a common cause of cycle delay and dose modification. Severe diarrhoea and severe dehydration were more common in those  $\geq 65$  yrs of age.

In VELOUR, stomatitis was an AE in 50.1% versus 32.9%, and Grade 3+ stomatitis in 12.8% versus 4.6%. It caused cycle delay (in 8.5% versus 3.1%) and dose modification.

### *Fistulae and gastrointestinal perforation*

In VELOUR, 3 placebo patients and 9 aflibercept patients had a fistula (GI or non-GI origin). In 8/9 patients, primary tumours were rectum or rectosigmoid. Events resolved in most cases after corrective surgery. In VELOUR, arms were balanced for gastrointestinal perforation, but across the 3 Phase III studies frequencies were 0.3% for placebo and 0.8% for aflibercept (with perforation leading to multiple fatalities).

### *Thromboembolism*

Arterial thromboembolism was reported in 2.6% (aflibercept) versus 1.5% (placebo) in VELOUR, and a similar outcome was seen in VANILLA (but not VITAL). Venous thromboembolism was reported in 9.3% versus 7.3% (but was less common with aflibercept than placebo in VANILLA and VITAL). Within Venous thromboembolism events was pulmonary embolism (4.7% versus 3.5%), including a fatal event.

### *Blood cell counts*

There was a slight increase in the frequency of neutropenia and thrombocytopenia in the aflibercept arm. Despite the apparently modest increased frequency of neutropenia in the aflibercept arm, the frequency of neutropenic complications was at least twice that of the placebo arm; there were two deaths due to neutropenic infection in the aflibercept arm and one in the placebo arm. This is consistent with a possible effect on neutrophil function or other unmeasured impact on the immune system.

There was a decrease in the incidence of anaemia in the aflibercept arm, consistent with erythrocytosis (red cell count was not reported). An increase in hepatic erythropoietin production has been reported with good blockade of VEGF signalling.<sup>20</sup> Ideally the sponsor should describe the rate and extent of clinically relevant rises in haemoglobin (particularly since dehydration may also occur with aflibercept (see above) and there was an increased incidence of venous, and arterial, thrombosis in the aflibercept arm of VELOUR<sup>21</sup>).

### *Hepatic and renal toxicity*

There was no major imbalance between aflibercept and comparators regarding liver toxicity, although in VANILLA there were more reports of hyperbilirubinaemia leading to discontinuation or dose delay / modification in the aflibercept arm.

There was no major imbalance between aflibercept and comparators regarding abnormalities in creatinine clearance, although there were more renal failure events with aflibercept than with placebo (2.9% versus 2.1%, with most such events apparently secondary to dehydration, sepsis or obstructive uropathy).

### *Dysphonia*

Dysphonia was described as due to VEGF blockade. The nasal cavity was a target of toxicity in monkeys given systemic aflibercept. There was atrophy / loss of septum and / or turbinates, associated with necrotising inflammation. Whether alteration in the nasal cavity itself could cause dysphonia, or whether similar effects extend into the larynx / vocal folds, is unclear. Anti-VEGF drugs have been described based on study of 5 patients as causing laryngeal mucosal pathology akin to that seen in the nasal mucosa.<sup>22</sup> Dysphonia is described as commonly reported in the post-market setting for bevacizumab.

<sup>20</sup> Tam BYY *et al.* VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. *Nature Medicine* 2006;12 (7):793-800. [There was induction of hepatic *Epo* transcription.]

<sup>21</sup> Schreijer AJ *et al.* High hematocrit as a risk factor for venous thrombosis. Cause or innocent bystander? *Haematologica* 2010;95 (2):182-184.

<sup>22</sup> Hartl DM *et al.* Dysphonia induced by vascular endothelium growth factor / vascular endothelium growth factor receptor inhibitors. *Invest New Drugs* 2010; 28:884-886.

### *Immunogenicity*

Many placebo arm subjects had baseline positive results for anti-aflibercept antibodies, suggestive of assay cross-reactivity. Across all clinical studies, neutralising antibodies were seen in 17/1671 aflibercept subjects (1.3%) versus 0.2% of placebo subjects (2/1105). The key issue of whether anti-aflibercept antibodies or neutralising antibodies had a functional impact was not addressed with data, according to the clinical evaluator.

### *Safety-exposure modelling*

Hypertension in cycles 1 and 2 correlated with free aflibercept C<sub>max</sub> and AUC. Exposure to free aflibercept at cycles 1 and 2 was negatively correlated with proteinuria Grade  $\geq 2$  in cycles 1 and 2 (an increase in exposure of 2000  $\mu\text{g}\cdot\text{h}/\text{mL}$  corresponding to a 51% decrease in the odds of experiencing proteinuria). Haemorrhage correlated with free aflibercept AUC, an increase in exposure of 1000  $\mu\text{g}\cdot\text{h}/\text{mL}$  corresponding to a 19% increase in the odds of haemorrhage.

### *Drug interactions*

Despite no PK evidence of drug interactions, dose modifications of irinotecan and fluorouracil were required in 37.2% and 39.1% of patients in the aflibercept arm, versus 22.6% and 21.7% for placebo, respectively. This was often due to diarrhoea, stomatitis, neutropenia, hypertension or proteinuria. Addition of aflibercept to FOLFIRI resulted in increased frequency of AEs characteristic of FOLFIRI, for example, diarrhoea, neutropenia and stomatitis.

### **Population PK data evaluation**

Evaluators of the population-PK aspects of this submission concluded that the proposed dosing regimen is supported by presented population-PK studies.

### **Clinical evaluator's recommendation**

The clinical evaluator has recommended rejection of the application.

### **Risk management plan**

Routine pharmacovigilance and risk minimisation activities are proposed for ongoing safety concerns. The RMP evaluator accepted this proposition.

### **Risk-benefit analysis**

### **Delegate considerations**

#### ***Efficacy***

The clinical evaluator states that "results are considered to be clinically insignificant, based on the survival parameters used to calculate the sample size". The Delegate considers that OS results are statistically and clinically significant, in the context of available treatments. Sample size criteria are used to design an adequately powered study. In the Delegate's view, the minimum clinically significant difference in OS may differ from the parameters used to calculate sample size.

There is only one randomised, controlled study to support efficacy. The TGA's guidance on applications with one pivotal study states that "*the minimum requirement is generally one controlled study with statistically compelling and clinically relevant results*". Section III.2 of this guideline notes characteristics of acceptable single pivotal studies. The Delegate's view is that VELOUR can be considered an acceptable single pivotal study.

### **Indications**

Based on National Comprehensive Cancer Network (USA) guidelines for chemotherapy of advanced / metastatic colorectal cancer (Version 3.2013, Colon Cancer): “oxaliplatin-containing” regimens include FOLFOX (leucovorin, fluorouracil, oxaliplatin) variants but would also include CapeOX (bevacizumab may be used in conjunction with these regimens) and FOLFOXIRI; “irinotecan-fluoropyrimidine-based chemotherapy” includes FOLFIRI (leucovorin, fluorouracil, irinotecan) and FOLFIRI in conjunction with biologicals (bevacizumab, cetuximab or panitumumab).<sup>23</sup>

The CER summarises prior chemotherapy in VELOUR but does not drill down beyond use of “oxaliplatin + fluoropyrimidine” to whether FOLFOX, CapeOX, FOLFOXIRI or some other [chemotherapy] variant was used.

In VELOUR, aflibercept was used with FOLFIRI. The proposed indication is broader, in that a recognised “irinotecan-fluoropyrimidine-based chemotherapy” might be taken to include FOLFIRI in conjunction with biologicals, or irinotecan plus capecitabine. This would not be supported by evidence from VELOUR.

### **Proposed action**

The Delegate proposed to approve the application with the indication proposed by the sponsor.

The Delegate proposed the following condition of registration:

- implementation of the RMP identified as the EU Risk Management Plan Version 1.0 (dated 18 October 2011) and the ASA Version 1.0 (March 2012), and any subsequent versions approved by the TGA’s Office of Product Review.

Regarding the RMP evaluator’s query about osteonecrosis, the sponsor’s justification (provided to the TGA prior to this overview being finalised) is accepted. The sponsor is asked to re-consider this issue early (and amend the PI accordingly) if any post-marketing signal of disproportionately high reporting is received (especially if cases are not associated with bisphosphonate use).

The Delegate’s additional comments and proposed revisions to the PI are beyond the scope of this AusPAR.

### **Advice requested from ACPM**

The Delegate sought general advice on this application from the ACPM, and in particular requested the committee consider the value of either adding an explanatory sentence to the indication (for example, “For second line treatment for metastatic colorectal cancer, there are clinical trial data to support use of aflibercept in combination with FOLFIRI, but none to support use in combination with other irinotecan-fluoropyrimidine-based regimens”) or referring directly to FOLFIRI (compare with the US indication).

### **Response from sponsor**

The sponsor’s comments on matters for which ACPM is sought, as outlined in the Delegate’s overview are presented below.

<sup>23</sup> EviQ also notes XELIRI (capecitabine and irinotecan) as a treatment of mCRC in patients with a performance status of 0-1 where treatment with FOLFIRI is not suitable or practical. EviQ sits within the Cancer Services and Information Division at the Cancer Institute NSW.



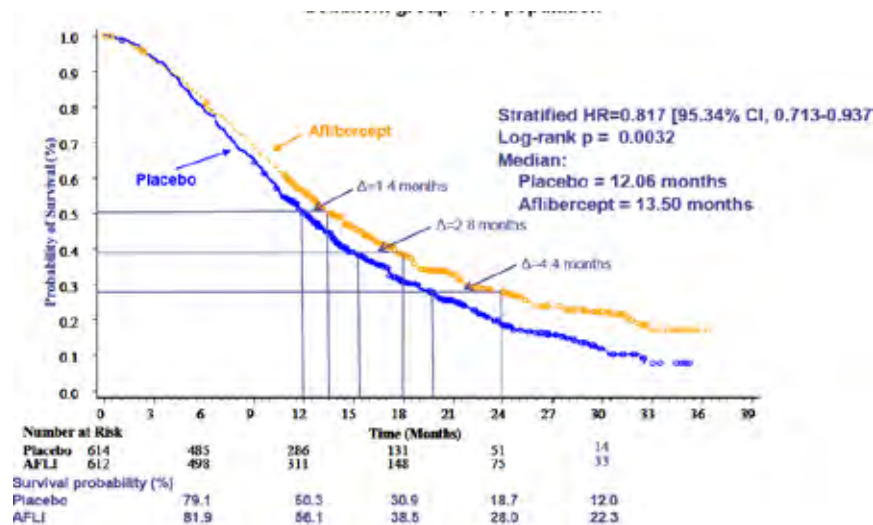
### Benefit/Risk assessment

Patients with MCRC who have progressed following an oxaliplatin-based treatment regimen have few therapeutic options. The sponsor endorses the Delegate's recommendation to approve Zaltrap for use in this indication which will address an unmet clinical need. It should be noted that aflibercept was approved in combination with FOLFIRI by the FDA on August, 3, 2012 and the use of aflibercept in combination with FOLFIRI in this patient setting has also been included in the National Comprehensive Cancer Network (NCCN) guidelines which are widely recognised and referenced in Australian clinical practice. In the EU, a positive CHMP Opinion was issued in November 2012 to recommend approval.

To further support the Delegate's positive opinion, key elements of the benefit/risk assessment for aflibercept in MCRC are summarised below.

- A clinically and statistically significant improvement of OS in patients treated with aflibercept and FOLFIRI over patients treated with placebo and FOLFIRI was demonstrated in the VELOUR clinical study
  - The estimated median OS in the placebo arm was 12.06 months (95.34% CI: 11.072 to 13.109), compared to 13.50 months (95.34% CI: 12.517 to 14.949) in the aflibercept arm.
  - The Kaplan-Meier survival curves continue to separate past the median time point indicating that the magnitude of the aflibercept treatment effect is increasing over time (see Figure 5)
  - The robustness and internal consistency of the OS results were observed in several sensitivity analyses, and in all of the key pre-specified subgroups.
  - Aflibercept also demonstrated a statistically and clinically significant improvement in progression-free survival of 2.23 months (HR 0.758, p=0.00007) and overall response rate (19.8% versus 11.1%, p=0.0001), both of which are clinically important endpoints in MCRC.
- None of the three biologically targeted products (bevacizumab, cetuximab and panitumumab) currently approved for use in Australia for second line MCRC has demonstrated a statistically significant improvement in OS in combination with FOLFIRI.

**Figure 5. EFC10262 (MCRC / VELOUR) study - Overall survival (months) - Kaplan-Meier curves by treatment group - ITT population**



- The safety profile of aflibercept plus FOLFIRI comprises toxicities that oncologic specialists are familiar with and are adept at managing. The AEs are either due to:
  - common potential anti-VEGF class effects including hypertension, proteinuria and haemorrhage and less frequent adverse events such as gastro-intestinal perforation, and fistula formation
  - an enhancement of FOLFIRI-related adverse events due to addition of aflibercept such as diarrhoea stomatitis, infection, neutropenic complications aesthetic conditions and hematologic adverse events.
- The toxicities observed in VELOUR did not lead to a reduced cumulative exposure to chemotherapy in the aflibercept treatment arm when compared to the placebo arm and did not preclude patients from receiving further systemic anti-cancer treatment.

Following study treatment discontinuation, a similar number of patients in both treatment groups went on to receive additional anti-cancer therapy.

- Overall, 59.5% of patients in the aflibercept plus FOLFIRI treatment group received further systemic anti-cancer therapy, including further irinotecan in 28.4% of the patients and fluoropyrimidine in 36.4% of the patients

In conclusion, aflibercept plus FOLFIRI is the only regimen to demonstrate a significant and clinically meaningful OS and PFS advantage in MCRC, with a assessment, in an indication with a high unmet medical need where patients have few therapeutic options.

### **Indication**

The sponsor fully endorses the Delegate's opinion that the VELOUR clinical trial is an acceptable single pivotal study to support the proposed indication and most importantly, the OS results are both statistically and clinically significant, in the context of available treatments.

The sponsor agrees with the recommendation of the Delegate to approve the application for aflibercept for the indication given below.

*'Zaltrap, in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.'*

The indication statement proposed for Zaltrap is aligned with that in the approved PI for Avastin (bevacizumab) which falls within the same drug class as aflibercept. Full details on the clinical trial design of VELOUR is described in the *Clinical Trials* section of the PI and adequately informs clinicians that the clinical data was generated using a combination with the FOLFIRI regimen.

The sponsor also provided comments on recommended revisions to the PI. Details of these are beyond the scope of this AusPAR.

### **Risk management plan**

The Delegate has indicated that the proposed condition of registration include:

- EU RMP v1.0 dated 18 October 2011 and the ASA version 1.0 dated March 2012

An updated ASA version 1.1 has been submitted to the TGA and a further update is included with this response to reflect the latest EU-RMP and the EU SmPC. The sponsor suggested the conditions of registration should therefore refer to:

- EU RMP v1.3 dated 15 November 2012 and ASA version 1.2 dated January 2013

In relation to osteonecrosis mentioned in the Delegate's overview, an assurance is provided that if any post-marketing signals of disproportionately high reporting is

received (especially if cases are not associated with bisphosphate use), osteonecrosis will be reconsidered early and if necessary the PI will be amended accordingly.

### **Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality considered these products to have an overall positive benefit-risk profile for the following indication:

*Aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen*

The ACPM advised that the PI must include an explanatory sentence explaining that for second line treatment for metastatic colorectal cancer, there is clinical trial data only supporting the use of aflibercept in combination with FOLFIRI but not with other irinotecan-fluoropyrimidine-based or other biological agent regimens.

In making this recommendation the ACPM noted the statistical significance of OS efficacy; however, discussed the clinical significance of limited increase in survival demonstrated.

In addition, the ACPM expressed concern that Quality of Life outcomes were not measured as a defined outcome in the studies and advised that this is a matter of critical importance for all products where extension of life is an end point.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and agreed that these documents accurately reflect the toxicity, side effect and safety concerns for these products for prescribers and consumers, together with the aforementioned outcomes from the data.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Zaltrap/Aflitiv/Lidaveg concentrated injection vial containing aflibercept *rch* 4 mg/100 mL and 8 mg/200 mL for intravenous infusion, indicated for:

*Zaltrap/Aflitiv/Lidaveg in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.*

*[See CLINICAL TRIALS for results of ZALTRAP/AFLITIV/LIDAVEG in combination with FOLFIRI. Other combinations have not been evaluated.]*

### **Specific conditions of registration applying to these therapeutic goods**

The implementation in Australia of the aflibercept RMP Aus-RMP Version 1.2 (dated Jan 2013, DLP 07/02/2011) and Australian specific annex v1.2 (dated Jan 2013) and any future updates as agreed with the TGA and its Office of Product Review.

## **Attachment 1. Product Information**

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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