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Aflibercept

AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye

Abstract

Aflibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human IgG_1. Aflibercept is in clinical development with Regeneron Pharmaceuticals and sanofi-aventis for the treatment of cancer, while Regeneron and Bayer are developing the agent for eye disorders. Aflibercept binds to all VEGF-A isoforms as well as placental growth factor (PIGF), thereby preventing these factors from stimulating angiogenesis. Blockade of VEGF can also prevent blood vessel formation and vasuclar leakage associated with wet age-related macular degeneration (AMD). Aflibercept is a member of Regeneron's proprietary family of 'Trap' product candidates that catch, hold and block (i.e. trap) certain harmful cytokines or growth factors.

Regeneron and Bayer HealthCare entered into a collaboration agreement in October 2006 to develop and commercialize aflibercept for the treatment of eye disorders outside the US. The companies will share equally in profits from this market, while Regeneron will retain exclusive commercialization rights and profits from sales in the US.[1]

Regeneron and sanofi-aventis amended their aflibercept collaboration agreement to include Japan. Under the terms of the amended agreement, reported in December 2005, the two companies will jointly develop and commercialize aflibercept worldwide in all indications, except for intraocular delivery to the eye. sanofi-aventis paid $US25 million to Regeneron for the inclusion of Japan and will pay milestone payments linked to Japanese regulatory approvals, plus royalties on Japanese sales. sanofi-aventis will lead Japanese development and will pay all development costs; however, Regeneron will repay 50% of these expenses out of profits generated through the commercialization of aflibercept.[2]

sanofi-aventis reaffirmed its commitment to the aflibercept programme in oncology in January 2005, while the exclusive rights to develop and commercialize the agent for eye diseases through local delivery systems reverted to Regeneron. A $US25 million clinical development milestone payment to Regeneron was also triggered in connection with this agreement.[3]

Aventis (now sanofi-aventis) and Regeneron entered into a global (excluding Japan) agreement in September 2003 to jointly develop and commercialize aflibercept. Under the terms of the agreement, Aventis was to pay Regeneron $US125 million and fund development costs. An additional early clinical milestone payment of $US25 million was also outlined in the agreement. The two companies will share promotional rights equally, and profits globally. Aventis will also pay Regeneron up to $US360 million at identified milestones related to the receipt of marketing approvals for up to eight indications in Europe and the

US. The companies initially agreed to jointly develop aflibercept in oncology, ophthalmology and possibly in other indications.[4]

Originally, aflibercept was being developed under a research and development alliance between Regeneron and Procter & Gamble. However, in 2000 this agreement was restructured and Regeneron regained all rights.

An NCI-sponsored phase II trial (NCT00407654) of aflibercept, involving 80 patients with previously treated metastatic colorectal cancer, is also underway in the US and Canada. The trial was initiated in October 2006 and is evaluating the efficacy of aflibercept in this patient group, as measured by objective tumour response and progression-free survival at 4 months.

In September 2006, a phase II trial in 82 patients with locally advanced, unresectable or metastatic gynaecological soft tissue sarcoma was initiated by NCI and Regeneron in the US and Canada. This ongoing trial (NCT00390234) will evaluate the efficacy of aflibercept, as measured by progression-free survival and tumour response rate.

Regeneron and sanofi-aventis are conducting a phase II trial of intravenously (IV) administered aflibercept in patients with advanced ovarian cancer who have recurrent symptomatic malignant ascites (SMA). The trial (NCT00327444) began in July 2006 and was continuing to recruit a total of 54 patients at centres in the US, Canada, India and the EU (Austria, Belgium, Hungary, Spain and the UK) in April 2007.

In October 2006, the companies initiated a second small phase II trial of aflibercept (NCT00396591) in 15 patients with malignant ascites associated with ovarian cancer. The study will assess the efficacy, safety, pharmacokinetics and immunogenicity of aflibercept IV given every 2 weeks in the US and EU (Italy and Sweden) and was recruiting patients in May 2007.

Regeneron and sanofi-aventis are also conducting a single-agent phase II study of aflibercept in non-small-cell lung adenocarcinoma (NSCLA). The open-label, single-arm study (NCT00284141) has completed enrolment of approximately 100 patients with platinum- and erlotinib-resistant, locally advanced or metastatic NSCLA to receive aflibercept (4.0 mg/kg IV) in the US, France and Canada. Results from the first 37 evaluable patients have been reported showing aflibercept was generally well tolerated and two partial reponses were noted.[5,6]

Regeneron has completed an open-label phase I trial in patients with solid tumours and non-Hodgkin's lymphoma (NHL) at three sites in the US. The study enrolled 38 patients with incurable, relapsed or refractory solid tumours who received subcutaneous injections. In total, the trial enrolled patients with 15 different types of cancer who were treated with seven subcutaneous doses of aflibercept over 10 weeks. In June 2004, Regeneron presented results from this study showing that the aflibercept was well tolerated and had a good safety profile. The maximum tolerated dose was not established. The company has not conducted any further trials in this indication with aflibercept as a monotherapy, although the NCI has ongoing trials of aflibercept in patients with solid tumours and NHL (e.g. NCT0008283).[7]

In May 2005, Regeneron announced initiation of a phase I safety and tolerability study with aflibercept in combination with the FOLFOX-4 regimen (oxaliplatin, 5-fluorouracil and leucovorin) in patients with advanced solid tumours. As at

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August 2006, the maximum tolerated dose had not been reached and dose-escalation was continuing in this study.[8,9]

The NCI/Regeneron trial in patients with metastatic or unresectable kidney cancer began in September 2007 with continued recruitment in April 2008. This trial (NCT00357760) is anticipated to recruit 120 patients in the US to evaluate the efficacy of two doses of aflibercept.

Regeneron and Bayer inititiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007. The non-inferiority, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) study will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and 2.0 mg at an 8-week dosing interval, compared with 0.5 mg ranibizumab administered every 4 weeks. The randomized, double-blind trial will be conducted at more than 200 centres throughout the US and Canada, pursuant to a Special Protocol Assessment (SPA) issued by the the US FDA. Patients will continue to be treated and followed for an additional year, after the first year of treatment. The VIEW 1 study is the first in a phase III global development programme in wet AMD, which is expected to be conducted in the US, Europe and other nations. Regeneron received a $US20 million milestone payment from Bayer HealthCare in August 2007 following dosing of the first patient.[10,11]

A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008. The VIEW 2 trial will enrol approximately 1200 patients from the EU, Asia Pacific, Japan and Latin America. This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. The primary endpoint will be the proportion of patients treated with aflibercept who maintain vision at the end of 1 year compared with ranibizumab patients.[12,13]

Regeneron has completed a 12-week, phase II trial in patients with wet AMD, to evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens. Two patient groups received monthly doses of 0.5 or 2.0 mg, and three groups received quarterly doses of 0.5, 2.0 or 4.0 mg (baseline and week 12). Analysis of data demonstrated that all five doses of aflibercept met the primary study endpoint of a statistically significant reduction in retinal thickness after 12 weeks and 32 weeks of treatment compared with baseline. The study commenced in April 2006 and enrolled 157 patients at sites in the US. Preliminary phase I trial results in 21 patients have also been presented.[14-16]

Additionally, Regeneron has conducted a phase I trial of aflibercept in five patients with diabetic macular oedema (DME) in the US. Results presented in May 2007 indicated that a single 4 mg injection resulted in a marked decrease in mean central retinal thickness and mean macular volume throughout the 6-week observation period. The VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events.[17] Regeneron plans to conduct advanced studies of the VEGF Trap-Eye in DME.

Previously, sanofi-aventis and Regeneron had been collaborating on the development of aflibercept for eye diseases through local delivery systems. However, the exclusive rights to develop and commercialize aflibercept for eye diseases

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through local delivery systems reverted to Regeneron in January 2005. Additionally, Regeneron chose to pursue intravitreal inection as a route of administration, instead of systemic delivery.[18]

Results from an earlier phase I trial assessing the safety and tolerability of intravenous infusions of aflibercept in patients with wet AMD have been reported. Preliminary results from the trial showed that the efficacy endpoint was met. Furthermore, systemic delivery of aflibercept was associated with a dose-dependent increase in blood pressure.[19]

Table I. Features and properties

CAS number	862111-32-8
WHO ATC code	A10X (Other Drugs Used in Diabetes) S01X (Other Ophthalmologicals) L01 (Antineoplastic Agents)
EphMRA ATC code	A10X (Other Drugs Used in Diabetes) S1X (Other Ophthalmologicals) L1 (Antineoplastics)
Originator	Regeneron Pharmaceuticals: USA
Licensee companies	Bayer HealthCare: world; sanofi-aventis: world
Highest development phase	Phase III (World)
Properties	
Mechanism of action	Vascular endothelial growth factor A antagonists
Pharmacodynamics	Halts new blood vessel growth and stopped leakage from existing blood vessels in mice; inhibits VEGF and abolishes mature, pre-existing vasculature of tumours in mice; inhibits development of ascites and decreases tumour burden in animal models of ovarian cancer
Route	IV

1. Profile

1.1 Pharmacokinetics

Clinical studies: Preliminary results of an open-label, phase I trial of a single dose of subcutaneous VEGF Trap (25, 50, 100 or 200 μg/kg) followed 4 weeks later by six weekly doses in patients with solid tumours or lymphoma showed that VEGF Trap binds to VEGF in plasma and has an apparent elimination half-life ($t_{1/2}$) of ≈17 days.[20]

Results of a phase I, open-label, dose-escalation trial of 38 patients with relapsed or refractory solid tumours showed that VEGF Trap has a long $t_{1/2}$ and binds to both VEGF 121 and VEGF 165 in patient plasma. Plasma VEGF Trap levels that were associated with antitumour activity in animal models were approached in patients receiving the two highest dose groups or 800 μg/kg once or twice weekly. In the trial patients received one or two initial doses of VEGF Trap followed 4 weeks later by six weekly or twice-weekly doses. Seven dose groups were evaluated in the trial ranging from 25 to 800 μg/kg weekly or 800 μg/kg twice weekly. Values for t_{max}, C_{max}, $t_{1/2}$, AUC_{28} and CL/F were 84 ± 60 hours, 3 ± 1 μg/mL, 25.3 ± 9.3 days, 1304 ± 256 μg • h/mL and 0.4 ± 0.1 mL/h/kg, respectively.[21]

1.2 Adverse Events

Solid tumours: Results of a phase I, open-label, dose-escalation trial of VEGF Trap in 38 patients with relapsed or refractory solid tumours showed that the drug had a good safety profile and was well tolerated overall. The maximum tolerated dose was not reached in the study, which reached the highest planned dose level of 800 μg/kg twice weekly. The majority of adverse events reported were grade 1 or

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Table II. Drug development history

May 2000	Preclinical development for Cancer in the US (Unknown route)
Nov 2001	Phase-I for Non-Hodgkin's lymphoma in the US (Unknown route)
Nov 2001	Phase-I for Solid tumours in the US (Unknown route)
Jun 2003	Prein Age-related macular degeneration in the US (IV)
Jun 2003	Prein Eye disorders in the US (Intravitreous)
Jun 2003	Prein Wilms' tumour in the US (Intraperitoneal)
Sep 2003	Aflibercept has been licensed to Aventis worldwide (excluding Japan)
Mar 2004	Phase-I in Age-related macular degeneration in the US (IV)
Apr 2004	Regeneron has initiated enrolment in a phase I trial for cancer in the US
Aug 2004	Aventis has merged with Sanofi-Synthelabo to form sanofi-aventis
Feb 2005	Aflibercept received Fast Track designation for Malignant ascites [IV] in the US
Feb 2005	Discontinued – Phase-I for Age-related macular degeneration in the US (IV-infusion)
May 2005	Regeneron has initiated the safety and tolerability study with VEGF Trap in combination with the FOLFOX-4 regimen (oxaliplatin, 5-fluorouracil and folinic acid) in patients with advanced tumours
May 2005	Phase-I in Solid tumours in the US (IV)
Jul 2005	Phase-I in Age-related macular degeneration in the US (Intravitreous)
Jul 2005	Prein Eye disorders in the US (Intravitreous)
Dec 2005	Regeneron has licensed aflibercept to sanofi-aventis in Japan
Dec 2005	Phase-II in Non-small cell lung cancer in France (IV)
Dec 2005	Phase-II in Non-small cell lung cancer in Canada (IV)
Dec 2005	Phase-II in Non-small cell lung cancer in the US (IV)
May 2006	Phase-I in Diabetic macular oedema in the US (Intravitreous)
May 2006	Phase-II in Age-related macular degeneration in the US (Intravitreous)
Jun 2006	Phase-II in Ovarian cancer in the US (IV)
Jun 2006	Phase-II in Ovarian cancer in Australia (IV)
Jun 2006	Phase-II in Ovarian cancer in Canada (IV)
Jun 2006	Phase-II in Ovarian cancer in Europe (IV)
Jul 2006	Phase-II/III in Malignant ascites in India (IV)
Jul 2006	Phase-II/III in Malignant ascites in the US (IV)
Jul 2006	Phase-II/III in Malignant ascites in Canada (IV)
Jul 2006	Phase-II/III in Malignant ascites in Europe (IV)
Aug 2006	Phase-II in Glioma in the US (IV)
Sep 2006	Phase-II in Sarcoma in Canada (IV)
Sep 2006	Phase-II in Sarcoma in the US (IV)
Oct 2006	Aflibercept has been licensed to Bayer HealthCare for the treatment of eye disorders
Oct 2006	Phase-II in Colorectal cancer in Canada (IV)
Oct 2006	Regeneron and sanofi-aventis initiate enrolment in a second phase II trial in Malignant ascites in the EU and US
Oct 2006	Phase-II in Colorectal cancer in the US (IV)
Nov 2006	Phase-II in Bladder cancer in the USA (IV)
Dec 2006	Phase-II in Multiple myeloma in the US (IV)
Jan 2007	Phase-II in Gynaecological cancer in the US (IV)
Jan 2007	Phase-II in Breast cancer in the US (IV)

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Table II. Contd

Mar 2007	Interim results from a phase II clinical trial in wet Age-related macular degeneration added to the Eye Disorders therapeutic trials section
Mar 2007	Phase-I in Cancer in Japan (IV)
Jun 2007	Final results from a phase I clinical trial in patients with diabetic macular oedema added to the adverse events and Eye Disorders therapeutic trials sections
Jun 2007	Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO-2007) added to the adverse events and Cancer therapeutic trials sections
Jun 2007	Phase-II in Malignant melanoma in the US (IV)
Jul 2007	Suspended – Phase-II for Colorectal cancer in Canada (IV)
Jul 2007	Suspended – Phase-II for Colorectal cancer in the US (IV)
Aug 2007	Phase-III in Age-related macular degeneration in the US (Intravitreous)
Aug 2007	Regeneron initiates patient dosing in a phase III trial for Age-related macular degeneration in the US
Aug 2007	Phase-III in Prostate cancer in the US (IV)
Aug 2007	Phase-III in Prostate cancer in Canada (IV)
Aug 2007	Phase-III in Prostate cancer in European Union (IV)
Aug 2007	Phase-III in Prostate cancer in Switzerland (IV)
Aug 2007	Phase-III in Prostate cancer in South Africa (IV)
Aug 2007	Phase-III in Prostate cancer in South America (IV)
Aug 2007	Phase-III in Prostate cancer in Asia (IV)
Aug 2007	Phase-III in Non-small cell lung cancer in the US (IV)
Aug 2007	Phase-III in Non-small cell lung cancer in France (IV)
Aug 2007	Phase-III in Prostate cancer in Australia (IV)
Oct 2007	Results from a phase II clinical trial in age-related macular degeneration added to the Eye Disorders therapeutic trials section
Dec 2007	Phase-III in Pancreatic cancer in World (IV)
Dec 2007	Phase-III in Colorectal cancer in World (IV)
Dec 2007	Phase-III in Non-small cell lung cancer in World (IV)
Dec 2007	Phase-III in Prostate cancer in World (IV)
Dec 2007	Suspended – Phase-II for Breast cancer in the US (IV)
Apr 2008	Interim efficacy data from a phase II trial in wet AMD released by Regeneron
May 2008	Bayer and Regeneron initiates enrolment in the VIEW 2 trial for Age-related macular degeneration in EU, Asia Pacific, Japan, and Latin America

2, including fatigue, nausea and vomiting. Observed grade 3 and 4 adverse events that were potentially drug related were grade 3 leukopenia, afebrile neutropenia and proteinuria, and grade 3 and 4 thromboembolic events including a transient cerebral ischaemia and a pulmonary embolism. Dose-related adverse events included hypertension and grade 1 hoarseness and anorexia. All patients who discontinued participation in the extension study withdrew due to disease progression, except one patient who developed grade 3 hypertension and proteinuria and was withdrawn after 22 weeks.[21]

The VEGF Trap administered intravenously every 2 weeks was generally well tolerated in a phase I, open-label, dose-ascending study in 27 patients with advanced solid tumours. The maximum tolerated dose has not been reached. The most frequently reported adverse events included fatigue, pain and constipation. The majority of adverse events were mild to moderate by nature. Occasional adverse events, including hypertension, were manageable and reversible. There were no anti-VEGF Trap antibodies detected.[9]

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1.3 Pharmacodynamics

1.3.1 Cancer

Preclinical studies: VEGF Trap inhibited VEGF and destroyed mature, pre-existing vasculature in nude mice bearing established Wilms' tumour (SK-NEP-1) xenografts. This could provide an alternative therapeutic option for patients with bulky, metastatic cancers. Destruction of blood vessels was followed by marked tumour regression that included regression of lung micrometastases. The size of pulmonary metastases was significantly smaller in the lungs of VEGF Trap-treated animals compared with controls. These observations indicated that VEGF inhibition by VEGF Trap had interrupted cell signalling of the endothelial-vascular wall essential for the protection of tumours from apoptosis. Thus, it was concluded that even low levels of VEGF could be critical to the integrity of blood vessels and the maintenance of even the smallest tumour masses.[22]

VEGF Trap inhibited the development of ascites and decreased tumour burden in animal models of ovarian cancer. Findings indicated that VEGF Trap's activity was facilitated by inhibition of tumour angiogenesis as well as reduction in vascular permeability. In the first model, SKOV-3 ovarian carcinoma cells were engineered to overexpress VEGF (SKOV-VEGF) and then injected into the peritoneum of female nude mice. The animals were then administered subcutaneous (SC) VEGF Trap 25 mg/kg or control solution twice weekly until they had lost >10% of bodyweight or had persistent ascites. In the second model, OVCAR-3 ovarian cancer cells were injected into the peritoneum of athymic Balb/C nude mice. Fourteen days later, twice-weekly treatment with subcutaneous VEGF Trap 25 mg/kg or control solution was initiated and continued for 5 weeks. Ascites developed considerably earlier in control animals injected with SKOV-VEGF cells, compared with those injected with unaltered SKOV-3 cells. In contrast, the majority of mice administered VEGF Trap did not develop ascites, and those that did develop ascites had much lower volumes of fluid, compared with controls, according to the researchers. The mean volume of ascites in the OVCAR-3 model was also significantly lower in the VEGF Trap group, compared with controls. In fact, VEGF Trap completely inhibited the development of measurable ascites. Furthermore, tumour burden was reduced by 56% in the VEGF Trap group, compared with the controls.[23]

1.3.2 Eye Disorders

Preclinical studies: Administration of VEGF Trap (either subcutaneously or directly into the eye) resulted in significantly less new blood vessel growth, and also blocked leaking of blood vessels usually caused by VEGF, in two groups of mice. In the first group, mice with laser-induced rupture of Bruch's membrane received a single intravitreous injection of VEGF Trap. In the second group, mice genetically engineered to express VEGF in the retina received subcutaneous injections of VEGF Trap. No adverse effects were observed in these studies.[24]

1.4 Therapeutic Trials

1.4.1 Cancer

Ovarian cancer: Preliminary results of an open-label, phase I trial of a single dose of subcutaneous aflibercept (25, 50, 100 or 200 μg/kg) followed 4 weeks later by six weekly doses in patients with solid tumours or lymphoma (n = 14 treated to date) showed stable disease in patients with renal cell carcinoma (up to 15 weeks) and colon cancer.[20]

Preliminary efficacy data of the aflibercept administered intravenously every 2 weeks showed the reduction of tumour size and prolonged stable disease in some patients. A partial response with disappearance of ascites has been achieved in one patient, two patients had minor responses, and a stable disease was maintained in one patient for more than 11 months.[9]

1.4.2 Eye Disorders

Age-related macular degeneration (AMD): At 32 weeks, the 157 patients receiving either 0.5 or 2.0 mg followed by as-needed (PRN) dosing achieved mean improvements in visual acuity of 8.0 and 10.1 letters, respectively, and mean decreases in retinal thickness of 141 and 162 microns, respectively.

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While PRN dosing also maintained the improvements versus baseline following a fixed dosing regimen (quarterly dosing at baseline and week 12), the results achieved were generally not as robust as those achieved with initial fixed monthly dosing. After the last fixed-dose administration at week 12, patients from all dose groups required on average only one additional injection over the following 20 weeks to maintain visual acuity gain achieved. Fifty-five percent of patients receiving 2.0 mg monthly for 12 weeks did not require any additional treatment throughout the next 20-week PRN dosing period.[14]

Preliminary results from a phase I trial in 20 patients with wet AMD have shown rapid, substantial and prolonged (≥4 weeks) reductions in retinal thickness with single-dose intravitreal injections of VEGF Trap. Ninety-five percent of patients had stabilization or improvement in visual acuity.[16,25]

Preliminary results from a phase I trial in 25 patients with advanced AMD showed a statistically significant decrease in excess retinal thickness with VEGF Trap (0.3, 1.0 and 3.0 mg/kg) compared with placebo.[19]

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