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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

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

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

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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