ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 01/09/2013

Grantor: CDER IND/IDE Number: BB-IND 9948 Serial Number: 129

AVE0005 (VEGF Trap) in Patients With Recurrent Symptomatic Malignant Ascites

This study has been completed.

Sponsor:	Sanofi
Collaborators:	Regeneron Pharmaceuticals
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00396591

Purpose

The primary objective of this study was to compare the time between paracenteses before and after administration of Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) in ovarian cancer participants with symptomatic malignant ascites.

The secondary objectives were to further assess efficacy and safety of Aflibercept treatment, and the exploratory objectives were to assess pharmacokinetics, immunogenicity and health-related quality of life.

Condition	Intervention	Phase
Ovarian Neoplasms	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®)	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: A Multicenter, Open-label, Single-arm Study of the Efficacy and Safety of Intravenous AVE0005 (VEGF Trap) Administered Every 2 Weeks in Advanced Ovarian Cancer Patients With Recurrent Symptomatic Malignant Ascites

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Percentage of Participants With a Repeat Paracentesis Response (RPR) [Time Frame: up to 2 years post-registration] [Designated as safety issue: No]

RPR was defined as at least a two-fold increase in the time to repeat paracentesis (TRP) as compared to the average duration of the 2 intervals between the 3 most recent paracenteses prior to study registration (ie, the baseline interval of paracentesis). Percentage of participants with a repeat paracentesis response were the number of participants with RPR / number of total participants * 100.

Secondary Outcome Measures:

- Time to Repeat Paracentesis (TRP) [Time Frame: up to 6 months from registration] [Designated as safety issue: No]
  TRP is the number of days between the date of registration and the date of the first postregistration paracentesis. Median TRP was estimated from Kaplan-Meier curves. For participants who did not undergo a postregistration paracentesis while on study, TRP was censored at the end of the treatment period (last dose + 1 cycle), at the last visit known without repeat paracentesis, at 6 months postregistration, or at death, whichever was earlier.
- 60-day Frequency of Paracentesis (FOP) [Time Frame: up to 60 days post-registration] [Designated as safety issue: No]
  FOP was the total number of paracenteses performed within the first 60 days postregistration. For participants who had withdrawn after registration but prior to the 60-day cutoff date, the withdrawal would have been regarded as a paracentesis event and the 60-day FOP normalized and calculated as the nearest integer of the value corresponding to 60 × number of paracenteses / x, where x represents the number of days on study.
- Progression-free Survival (PFS) Time [Time Frame: up to 6 months post-registration] [Designated as safety issue: No]
  According to the Response Evaluation Criteria in Solid Tumors [RECIST], progression was at least a 20% increase in the sum of the longest diameter (LD) of tumors, compared to smallest sum LD recorded since treatment started, or the appearance of one or more new tumors. PFS time was interval from the date of registration to the date of tumor progression or death from any cause, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots. If participants were alive and progression-free at 6 months postregistration, they were censored for PFS.
- Overall Survival (OS) Time [Time Frame: up to 6 months post-registration] [Designated as safety issue: No]
  OS time was the time interval between the date of registration to the date of death from any cause. Median OS was estimated from Kaplan-Meier curves. Participants who died after efficacy data cutoff date (6 months postregistration) were censored at the data cutoff date.
- Number of Participants With a Positive Anti-drug Antibody Response [Time Frame: up to 60 days after the last dose of treatment] [Designated as safety issue: No]
  Anti-drug antibodies in participant's serum were measured using 2 different methods - an Enzyme Linked Immunosorbent Assay (ELISA) in which the lower limit of detection (LLOD) was 238.4 ng/mL; and - an Electrochemiluminescence-based, Bridging Assay in which the validated LLOD was about 5.4 ng/mL in the absence of aflibercept and about 25.2 ng/mL in the presence of 20 µg/mL of aflibercept. Participants with detectable anti-drug antibodies by either method were considered to have a positive anti-drug antibody response.
- Safety - Number of Participants With Adverse Events (AE) [Time Frame: up to 60 days after last dose of treatment (approximately 2 years), or until TEAE was resolved or stabilized] [Designated as safety issue: Yes]
  All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 60 days after the last administration of study treatment, were recorded, and followed until resolution or stabilization. The number of participants with all treatment emergent adverse events (TEAE), serious adverse events (SAE), TEAE leading to death, and TEAE leading to permanent treatment discontinuation are reported.

Enrollment: 16
Study Start Date: October 2006
Primary Completion Date: November 2008
Study Completion Date: November 2008

Arms	Assigned Interventions
Experimental: Aflibercept Participants with advanced ovarian epithelial cancer (including fallopian tube and primary peritoneal adenocarcinoma)	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4.0 mg/kg administered intravenously (IV) once every 2 weeks

Arms	Assigned Interventions
treated with Aflibercept every 2 weeks until a criterion for treatment discontinuation was met	

Detailed Description:

The study consisted of:

- A 30-day screening phase prior to Day 1
- Day 1 registration and pre-treatment paracentesis
- Aflibercept administration within 1-day of registration
- Two-week study treatment cycles (for efficacy data, the cut-off date was 6 months post-registration
- A 60-day post-treatment follow-up phase

During the study, participants were treated with Aflibercept study treatment through the duration of the study unless they met one the following criteria for discontinuation:

- Participant (or legal representative) chose to withdraw from treatment
- The investigator or sponsor thought that continuation of the study would be detrimental to the participants well-being
- Participant had intercurrent illness that prevented further administration of investigational product (IP)
- Participant had more than 2 IP dose reductions
- Participant had unacceptable adverse events (AEs)
- Participant had arterial thromboembolic events, including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, new onset angina, or worsening of preexisting angina
- Participant required surgical intervention for intestinal obstruction or gastrointestinal perforation

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Participants that met the following criteria were eligible.

Inclusion Criteria:

- Symptomatic malignant ascites resulting from advanced ovarian epithelial cancer (including fallopian tube and primary peritoneal adenocarcinoma) that required at least 3 previous therapeutic paracenteses at a frequency of 1 to 4 paracenteses per month for management.
- Platinum resistant disease defined by relapse or progression of disease during or after treatment, or drug intolerance.
- Topotecan- and/or liposomal doxorubicin-resistant disease defined by relapse or progression of disease during or after treatment, or drug intolerance.

Exclusion Criteria:

- Peritoneovenous or other type of shunt that was placed for the management of ascites

- Prior treatment with a VEGF or VEGF receptor inhibitor
- Uncontrolled hypertension

The above information is not intended to contain all considerations relevant to participation in a clinical trial.

Contacts and Locations

Locations

United States, New Jersey
sanofi-aventis administrative office
Bridgewater, New Jersey, United States, 08807
Italy
sanofi-aventis administrative office
Milano, Italy
Sweden
sanofi-aventis administrative office
Bromma, Sweden

Investigators

Study Director:	ICD	sanofi-aventis

More Information

Responsible Party:	Sanofi
Study ID Numbers:	ARD6772 EUDRACT: 2006-000604-16
Health Authority:	United States: Food and Drug Administration Italy: Ethics Committee Sweden: Medical Products Agency

Study Results

Participant Flow

Recruitment Details	17 participants were screened for this study, of which 16 participants were enrolled.

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Overall Study

	Aflibercept
Started	16
Completed	0
Not Completed	16
Disease Progression	13
Adverse Event	2
Participant request	1

Baseline Characteristics

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Baseline Measures

	Aflibercept
Number of Participants	16
Age, Continuous [units: years] Mean (Standard Deviation)	59.3 (8.9)
Age, Customized [units: participants]	
<65 years	11
>=65 years	5
Gender, Male/Female [units: participants]	
Female	16
Male	0
Race/Ethnicity, Customized Caucasian [units: Participants]	16
Primary tumor site - Ovaries	16

	Aflibercept
[units: Participants]	
Time since initial cancer diagnosis [units: Years] Mean (Standard Deviation)	2.8 (1.7)
Histology [units: Participants]	
Serous	9
Endometrioid	3
Clear cell (mesonephroid)	1
Other	1
Missing data	2
Histology grade [units: Participants]	
Unknown	5
Moderately differentiated	1
Poorly differentiated	10
Prior anticancer surgeries, [units: Participants]	
No	1
Yes	15
Baseline interval of paracentesis [1] [units: days] Mean (Standard Deviation)	16.5 (7.8)
Eastern Cooperative Oncology Group (ECOG) performance status score [2] [units: participants]	
ECOG Score = 0	3
ECOG Score = 1	10
ECOG Score = 2	3

[1] Average of the two paracentesis intervals prior to the Day 1 paracentesis before registration.

[2] The ECOG score assesses how the disease affects a participant's daily living abilities. It ranges from 0-5, with 0 being the best and 5 being the worst outcome. "0" reflects a fully active participant, able to carry on all pre-disease performance without restriction. "1" reflects a participant restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. "2" reflects an ambulatory participant, who is up and about more than 50% of waking hours, and capable of all self-care but unable to carry out any work activities.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With a Repeat Paracentesis Response (RPR)
Measure Description	RPR was defined as at least a two-fold increase in the time to repeat paracentesis (TRP) as compared to the average duration of the 2 intervals between the 3 most recent paracenteses prior to study registration (ie, the baseline interval of paracentesis). Percentage of participants with a repeat paracentesis response were the number of participants with RPR / number of total participants * 100.
Time Frame	up to 2 years post-registration
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	16
Percentage of Participants With a Repeat Paracentesis Response (RPR) [units: percentage of participants] Number (95% Confidence Interval)	62.5 (35.43 to 84.80)

2. Secondary Outcome Measure:

Measure Title	Time to Repeat Paracentesis (TRP)
Measure Description	TRP is the number of days between the date of registration and the date of the first postregistration paracentesis. Median TRP was estimated from Kaplan-Meier curves. For participants who did not undergo a postregistration paracentesis while on study, TRP was censored at the end of the treatment period (last dose + 1 cycle), at the last visit known without repeat paracentesis, at 6 months postregistration, or at death, whichever was earlier.
Time Frame	up to 6 months from registration
Safety Issue?	No

Analysis Population Description

All participants were analyzed. 8 had one or more paracentesis events. Participants with no paracentesis events were censored at the end of the treatment period (last dose + 1 cycle).

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	16
Number of Paracentesis (>/= 1 per participant) Analyzed	8
Time to Repeat Paracentesis (TRP) [units: days] Median (95% Confidence Interval)	76.0 (64.0 to 178.0)

3. Secondary Outcome Measure:

Measure Title	60-day Frequency of Paracentesis (FOP)
Measure Description	FOP was the total number of paracenteses performed within the first 60 days postregistration. For participants who had withdrawn after registration but prior to the 60-day cutoff date, the withdrawal would have been regarded as a paracentesis event and the 60-day FOP normalized and calculated as the nearest integer of the value corresponding to 60 × number of paracenteses / x, where x represents the number of days on study.
Time Frame	up to 60 days post-registration
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	16
60-day Frequency of Paracentesis (FOP) [units: paracenteses] Mean (Standard Deviation)	1.5 (1.6)

4. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time
Measure Description	According to the Response Evaluation Criteria in Solid Tumors [RECIST], progression was at least a 20% increase in the sum of the longest diameter (LD) of tumors, compared to smallest sum LD recorded since treatment started, or the appearance of one or more new tumors. PFS time was interval from the date of registration to the date of tumor progression or death from any cause, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots. If participants were alive and progression-free at 6 months postregistration, they were censored for PFS.
Time Frame	up to 6 months post-registration
Safety Issue?	No

Analysis Population Description
Participants with a PFS event (tumor progression or death) were analyzed.

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	12
Progression-free Survival (PFS) Time [units: days] Median (95% Confidence Interval)	59.5 (41.0 to 83.0)

5. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	OS time was the time interval between the date of registration to the date of death from any cause. Median OS was estimated from Kaplan-Meier curves. Participants who died after efficacy data cutoff date (6 months postregistration) were censored at the data cutoff date.
Time Frame	up to 6 months post-registration
Safety Issue?	No

Analysis Population Description

All participants were analyzed. 5 participants who died after efficacy data cutoff date (6 months postregistration) were censored at the data cutoff date.

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	16
Number of Events (Death) Analyzed	11
Overall Survival (OS) Time [units: days] Median (95% Confidence Interval)	92.0 (58.0 to NA) [1]

[1] Not calculable as some participants were still alive at the cut-off date.

6. Secondary Outcome Measure:

Measure Title	Number of Participants With a Positive Anti-drug Antibody Response
Measure Description	Anti-drug antibodies in participant's serum were measured using 2 different methods • an Enzyme Linked Immunosorbent Assay (ELISA) in which the lower limit of detection (LLOD) was 238.4 ng/mL; and • an Electrochemiluminescence-based, Bridging Assay in which the validated LLOD was about 5.4 ng/mL in the absence of aflibercept and about 25.2 ng/mL in the presence of 20 µg/mL of aflibercept. Participants with detectable anti-drug antibodies by either method were considered to have a positive anti-drug antibody response.
Time Frame	up to 60 days after the last dose of treatment
Safety Issue?	No

Analysis Population Description

Participants who received at least part of 1 dose of aflibercept and had evaluable blood samples

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	11
Number of Participants With a Positive Anti-drug Antibody Response [units: participants]	0

7. Secondary Outcome Measure:

Measure Title	Safety - Number of Participants With Adverse Events (AE)
Measure Description	All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 60 days after the last administration of study treatment, were recorded, and followed until resolution or stabilization. The number of participants with all treatment emergent adverse events (TEAE), serious adverse events (SAE), TEAE leading to death, and TEAE leading to permanent treatment discontinuation are reported.
Time Frame	up to 60 days after last dose of treatment (approximately 2 years), or until TEAE was resolved or stabilized

Safety Issue?	Yes

Analysis Population Description

All participants who received at least part of 1 dose of the study treatment.

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Measured Values

	Aflibercept
Number of Participants Analyzed	16
Safety - Number of Participants With Adverse Events (AE) [units: participants]	
With at least one TEAE	16
With at least one serious TEAE	15
With a TEAE leading to death	8
With a TEAE resulting in discontinuation	2

Reported Adverse Events

Time Frame	From treatment initiation to January 30, 2009
Additional Description	[Not specified]

Reporting Groups

	Description
Aflibercept	Participants with advanced ovarian epithelial cancer treated with 4.0 mg/kg Aflibercept every 2 weeks until a criterion for treatment discontinuation was met

Serious Adverse Events

	Aflibercept
	Affected/At Risk (%)
Total	15/16 (93.75%)
Blood and lymphatic system disorders	
Anaemia [A] *	1/16 (6.25%)
Cardiac disorders	
Tachyarrhythmia [A] *	1/16 (6.25%)
Gastrointestinal disorders	
Abdominal pain [A] *	1/16 (6.25%)
Intestinal obstruction [A] *	5/16 (31.25%)
Intestinal perforation [A] *	1/16 (6.25%)
Large intestinal obstruction [A] *	1/16 (6.25%)
Nausea [A] *	2/16 (12.5%)
Small intestinal obstruction [A] *	1/16 (6.25%)
Vomiting [A] *	4/16 (25%)
General disorders	
Disease progression [A] *	4/16 (25%)
General physical health deterioration [A] *	1/16 (6.25%)
Infections and infestations	
Gastroenteritis [A] *	1/16 (6.25%)
Metabolism and nutrition disorders	
Dehydration [A] *	1/16 (6.25%)
Nervous system disorders	
Cognitive disorder [A] *	1/16 (6.25%)
Respiratory, thoracic and mediastinal disorders	

	Aflibercept
	Affected/At Risk (%)
Hydropneumothorax [A] *	1/16 (6.25%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 11.1

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept
	Affected/At Risk (%)
Total	16/16 (100%)
Blood and lymphatic system disorders	
Anaemia [A] *	1/16 (6.25%)
Lymphadenitis [A] *	1/16 (6.25%)
Cardiac disorders	
Tachyarrhythmia [A] *	1/16 (6.25%)
Eye disorders	
Conjunctivitis [A] *	1/16 (6.25%)
Gastrointestinal disorders	
Abdominal distension [A] *	2/16 (12.5%)
Abdominal pain [A] *	6/16 (37.5%)
Abdominal pain upper [A] *	2/16 (12.5%)
Colitis [A] *	1/16 (6.25%)
Constipation [A] *	3/16 (18.75%)
Diarrhoea [A] *	2/16 (12.5%)
Dyspepsia [A] *	1/16 (6.25%)
Gastritis [A] *	1/16 (6.25%)

	Aflibercept
	Affected/At Risk (%)
Gastrooesophageal reflux disease [A] *	1/16 (6.25%)
Intestinal obstruction [A] *	1/16 (6.25%)
Intestinal perforation [A] *	1/16 (6.25%)
Nausea [A] *	6/16 (37.5%)
Oesophagitis [A] *	1/16 (6.25%)
Subileus [A] *	1/16 (6.25%)
Toothache [A] *	1/16 (6.25%)
Vomiting [A] *	8/16 (50%)
General disorders	
Asthenia [A] *	5/16 (31.25%)
Disease progression [A] *	5/16 (31.25%)
Early satiety [A] *	2/16 (12.5%)
Fatigue [A] *	4/16 (25%)
General physical health deterioration [A] *	1/16 (6.25%)
Mucosal inflammation [A] *	1/16 (6.25%)
Oedema peripheral [A] *	3/16 (18.75%)
Pain [A] *	2/16 (12.5%)
Pyrexia [A] *	1/16 (6.25%)
Hepatobiliary disorders	
Hepatic failure [A] *	1/16 (6.25%)
Infections and infestations	
Gastroenteritis [A] *	2/16 (12.5%)

	Aflibercept
	Affected/At Risk (%)
Nasopharyngitis [A] *	1/16 (6.25%)
Rhinitis [A] *	1/16 (6.25%)
Tooth infection [A] *	1/16 (6.25%)
Urinary tract infection [A] *	1/16 (6.25%)
Investigations	
Cardiac murmur [A] *	1/16 (6.25%)
Urine output decreased [A] *	1/16 (6.25%)
Urine output increased [A] *	1/16 (6.25%)
Weight decreased [A] *	2/16 (12.5%)
Metabolism and nutrition disorders	
Anorexia [A] *	5/16 (31.25%)
Decreased appetite [A] *	1/16 (6.25%)
Dehydration [A] *	2/16 (12.5%)
Hypokalaemia [A] *	1/16 (6.25%)
Hyponatraemia [A] *	2/16 (12.5%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	2/16 (12.5%)
Back pain [A] *	3/16 (18.75%)
Musculoskeletal pain [A] *	1/16 (6.25%)
Neck pain [A] *	1/16 (6.25%)
Nervous system disorders	
Dizziness [A] *	1/16 (6.25%)
Dysgeusia [A] *	1/16 (6.25%)

	Aflibercept
	Affected/At Risk (%)
Headache [A] *	3/16 (18.75%)
Neuropathy peripheral [A] *	1/16 (6.25%)
Peripheral sensory neuropathy [A] *	1/16 (6.25%)
Psychiatric disorders	
Insomnia [A] *	2/16 (12.5%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	1/16 (6.25%)
Dysphonia [A] *	3/16 (18.75%)
Pleural effusion [A] *	1/16 (6.25%)
Sinus congestion [A] *	1/16 (6.25%)
Skin and subcutaneous tissue disorders	
Alopecia [A] *	1/16 (6.25%)
Hyperhidrosis [A] *	1/16 (6.25%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	1/16 (6.25%)
Rash [A] *	2/16 (12.5%)
Skin exfoliation [A] *	1/16 (6.25%)
Vascular disorders	
Hypertension [A] *	7/16 (43.75%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 11.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The investigator has the right to independently publish study results from his site after a multicenter publication, or 12 months after the completion of the study by all sites. He must provide the sponsor a copy of any such publication derived from the study for review and comment at least 45 days (20 for abstracts) in advance of any submission for publication. The Sponsor may request for the publication to be delayed for a limited time, not to exceed 90 days to preserve its proprietary rights.

Results Point of Contact:

Name/Official Title: Trial Transparency Team
Organization: sanofi-aventis
Phone:
Email: Contact-Us@sanofi.com