ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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Study of the Effect of Intravenous AVE0005 (VEGF Trap) in Advanced Ovarian Cancer 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:	NCT00327444

Purpose

This study was designed to characterize the effect of aflibercept in participants with advanced chemoresistant ovarian cancer.

Primary objective: Compare the effect of aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) to placebo treatment on repeat paracentesis in symptomatic malignant ascites in participants with advanced ovarian cancer

Secondary objectives: Safety, tolerability, paracentesis-related parameters, participant-reported outcome.

Condition	Intervention	Phase
Ovarian Neoplasms Ascites	Drug: aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) Drug: Placebo	Phase 2/ Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-arm Study of the Effect of Intravenous Aflibercept Administered Every 2 Weeks in Advanced Ovarian Cancer Patients With Recurrent Symptomatic Malignant Ascites

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Time to Repeat Paracentesis (TRP) [Time Frame: From Day 1 up to 6 months from randomization] [Designated as safety issue: No]
  TRP was defined as the number of days between the date of randomization and the date of the first post-randomization paracentesis. For participants who did not undergo a postrandomization paracentesis on study, TRP was calculated from randomization to the end of the double-blind treatment period.

Secondary Outcome Measures:

- Area Under the Curve (AUC) for Participant Assessed Ascites Impact Measure (AIM) [Time Frame: From Day 1 up to 60 days from randomization to the first postrandomization paracentesis] [Designated as safety issue: No]
  AIM 4 symptoms (abdominal discomfort, abdominal bloating, abdominal pain, and ability to move normally) are scored from 0 to 5, where higher scores represent worst outcomes. An AIM total score ranges from 0-20. A plot for (The AIM questionnaire total score - Baseline score) versus time were generated. AIM AUC represents the overall improvement (scored positive) if the area is below the baseline value or worsening (scored negative) if the area is above the baseline. AIM AUC for a participant is the sum of individual areas representing improvement (+) or worsening (-).
- 60-Day Frequency of Paracentesis (FOP) [Time Frame: From Day 1 up to 60 days from randomization] [Designated as safety issue: No]
  60-Day FOP was defined as the total number of paracenteses performed within the first 60 days after randomization during the double blind treatment period.
- Plasma Levels of Free and VEGF-bound Aflibercept [Time Frame: Following every biweekly treatment administration up to 60 days after treatment discontinuation] [Designated as safety issue: No]
  Free aflibercept and VEGF-bound aflibercept plasma concentrations were measured by separate enzyme-linked immunosorbent assay (ELISA). The limit of quantitation of free aflibercept was 15.6 ng/mL, and of VEGF-bound aflibercept was 43.9 ng/mL. Peak free aflibercept was estimated at the end of Cycle 1 (C1) administration. The median free and VEGF-bound trough concentrations were determined for each participant beyond Cycle 3 (C3), then mean values were estimated from these median values.

Enrollment: 58
Study Start Date: July 2006
Primary Completion Date: October 2009
Study Completion Date: October 2009

Arms	Assigned Interventions
Placebo Comparator: Placebo Participants with advanced ovarian cancer administered placebo in the double-blind (DB) period. In the open-label (OL) period, participants had the option to receive aflibercept or be withdrawn from the study.	Drug: Placebo Placebo was administered intravenously (IV) over 1 hour once every 2 weeks in the DB period. Drug: aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4.0 mg/kg aflibercept was administered intravenously (IV) over 1 hour once every 2 weeks in the OL period.
Experimental: Aflibercept Participants with advanced ovarian cancer administered aflibercept in the double-blind (DB) period.	Drug: aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4.0 mg/kg aflibercept was administered intravenously (IV) over 1 hour once every 2 weeks in the DB period.

Arms	Assigned Interventions
In the open-label (OL) period, participants had the option to continue to receive aflibercept or be withdrawn from the study.	Drug: aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4.0 mg/kg aflibercept was administered intravenously (IV) over 1 hour once every 2 weeks in the OL period.

Detailed Description:

The study included:

- A Thirty (30)-day screening phase
- The double blind treatment period for a minimum of 60 days. Day 1 of the double-blind treatment period was defined as the date of the qualifying paracentesis (ie, withdrawal of >= 1 Liter of ascitic fluid). Participants were randomized after adequate recovery from the qualifying paracentesis (The first dose was administered on Day 1 or Day 2).
- The optional open-label extension (until treatment discontinuation criteria were met)
- A posttreatment follow-up phase lasting 60 days.

Criteria for discontinuation included:

1. Participant or his legally authorized representative request discontinuation
2. In the Investigator's opinion, continuation of treatment would be detrimental to the participant's well being, such as disease progression, unacceptable toxicity, noncompliance, or logistical considerations
3. Sponsor request
4. Intercurrent illness that prevented further administration of investigational product(IP)
5. More than 2 IP dose reductions
6. Unacceptable adverse events (AE) not manageable by symptomatic therapy, dose delay, or dose modification
7. Arterial thromboembolic events, including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, new onset or worsening of preexisting angina
8. Radiographic evidence of intestinal obstruction (for example, dilated loops of bowel accompanied by air-fluid levels) or gastrointestinal perforation (for example, presence of extraluminal gas) requiring surgical intervention

Eligibility

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

Criteria

Participants who met the following criteria were eligible to participate in this study.

Inclusion Criteria:

- Advanced ovarian epithelial cancer, treated with paracentesis
- Platinum-resistant, and topotecan-resistant and/or liposomal doxorubicin-resistant disease;
- Eastern Cooperative Oncology Group (ECOG) performance status =< 2.

Exclusion Criteria:

- Pseudomyxoma peritonei or peritoneal mesothelioma;
- Transudative ascites;
- Peritoneovenous or other shunt placed for malignant ascites management;
- Recent (<6 months) cardiovascular event (pulmonary embolus, myocardial infarction, stroke) or gastrointestinal disease (ulcer, hepatic cirrhosis);
- Known brain metastases;
- Uncontrolled hypertension;
- Recent treatment with chemotherapy, surgery or radiotherapy;
- Prior treatment with VEGF or VEGFR inhibitor.

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
Austria
sanofi-aventis administrative office
Vienna, Austria
Belgium
sanofi-aventis administrative office
Diegem, Belgium
Canada
sanofi-aventis administrative office
Laval, Canada
Hungary
sanofi-aventis administrative office
Budapest, Hungary
India
sanofi-aventis administrative office
Mumbai, India
Israel
sanofi-aventis administrative office
Natanya, Israel
Spain
sanofi-aventis administrative office
Barcelona, Spain
United Kingdom
sanofi-aventis administrative office
Guildford Surrey, United Kingdom

Investigators

Principal Investigator:	Walter GOTLIEB	Director of Gynecologic Oncology and Colposcopy Associate Professor of Oncology, McGill University - Montreal - Quebec Canada

More Information

Responsible Party:	Sanofi
Study ID Numbers:	EFC6125 EudraCT : 2005-005026-31 AVE0005A /3001
Health Authority:	United States: Food and Drug Administration Canada: Health Canada

Study Results

Participant Flow

Recruitment Details	Fifty-eight (58) participants from a total of 23 sites in 7 countries were enrolled in the study.
Pre-Assignment Details	55 were randomized (started population). 3 participants were not randomized but they were treated, and permanently withdrawn from the study due to disease progression (1 participant), fatal disease progression (1 participant) and a treatment emergent adverse event (1 participant).

Reporting Groups

	Description
Placebo	Participants with advanced ovarian cancer administered placebo intravenously, once every two weeks in the DB period and 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.
Aflibercept	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period and the OL period.

Double Blind Treatment (DB) Period

	Placebo	Aflibercept
Started	26	29
SAFETY	25 [1]	30 [2]
Completed	0	0

	Placebo	Aflibercept
Not Completed	26	29
Disease progression	10	13
Adverse Event	5	5
Subject request	0	1
Withdrew DB and continued to OL	11	10

[1] Excludes one participant from the Placebo arm who received aflibercept in error in the DB period.
[2] Includes 1 from Placebo who received aflibercept in DB period

Open Label Treatment (OL) Period

	Placebo	Aflibercept
Started	11	10
ONGOING TREATMENT	1	0
Completed	0 [1]	0 [1]
Not Completed	11	10
Disease progression	8	7
Adverse Event	2	2
Worsening dyspnea	0	1
Ongoing Treatment	1	0

[1] All participants were treated till they met treatment discontinuation criteria

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants with advanced ovarian cancer administered placebo intravenously, once every two weeks in the DB period and 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.
Aflibercept	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period and the OL period.

Baseline Measures

	Placebo	Aflibercept	Total
Number of Participants	26	29	55
Age, Customized [1] [units: participants]			
< 35 years	0	1	1
>=35 to <45 years	5	1	6
>=45 to <55 years	10	7	17
>=55 to <65 years	4	11	15
>=65 to <75 years	6	7	13
>=75 years	1	2	3
Gender, Male/Female [units: participants]			
Female	26	29	55
Male	0	0	0
Race/Ethnicity, Customized [units: participants]			
Caucasian	19	22	41
Black	1	0	1
Asian, Oriental	6	7	13

[1] Baseline characteristics are reported for the randomized population

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Time to Repeat Paracentesis (TRP)
Measure Description	TRP was defined as the number of days between the date of randomization and the date of the first post-randomization paracentesis. For participants who did not undergo a postrandomization paracentesis on study, TRP was calculated from randomization to the end of the double-blind treatment period.
Time Frame	From Day 1 up to 6 months from randomization

Safety Issue?	No

Analysis Population Description

The intent-to-treat (ITT) population - all participants who were randomized in the study.

Reporting Groups

	Description
Placebo	Participants with advanced ovarian cancer administered placebo intravenously, once every two weeks in the DB period and 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.
Aflibercept	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period and the OL period.

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	26	29
Time to Repeat Paracentesis (TRP) [units: days] Least Squares Mean (Standard Error)	23.3 (7.70)	55.1 (7.25)

Statistical Analysis 1 for Time to Repeat Paracentesis (TRP)

Statistical Analysis Overview	Comparison Groups	Placebo, Aflibercept
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0019
	Comments	Estimated using Wilcoxon rank-sum test with stratification of baseline paracentesis (=<2 weeks versus >2 weeks) at randomization.
	Method	ANOVA
	Comments	Estimated from ANOVA model with stratification of baseline paracentesis (=<2 weeks versus >2 weeks).

Method of Estimation	Estimation Parameter	Other [Least squares (LS) Mean difference]
	Estimated Value	31.8

	Confidence Interval	(2-Sided) 95% 10.56 to 53.05
	Parameter Dispersion	Type: Standard Error of the mean Value: 10.59
	Estimation Comments	The LS mean difference is estimated for aflibercept versus placebo (aflibercept-placebo).

2. Secondary Outcome Measure:

Measure Title	Area Under the Curve (AUC) for Participant Assessed Ascites Impact Measure (AIM)
Measure Description	AIM 4 symptoms (abdominal discomfort, abdominal bloating, abdominal pain, and ability to move normally) are scored from 0 to 5, where higher scores represent worst outcomes. An AIM total score ranges from 0-20. A plot for (The AIM questionnaire total score - Baseline score) versus time were generated. AIM AUC represents the overall improvement (scored positive) if the area is below the baseline value or worsening (scored negative) if the area is above the baseline. AIM AUC for a participant is the sum of individual areas representing improvement (+) or worsening (-).
Time Frame	From Day 1 up to 60 days from randomization to the first postrandomization paracentesis
Safety Issue?	No

Analysis Population Description

The intent-to-treat (ITT) population - all participants who were randomized in the study, and had evaluable AIM scores.

Reporting Groups

	Description
Placebo	Participants with advanced ovarian cancer administered placebo intravenously, once every two weeks in the DB period and 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.
Aflibercept	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period and the OL period.

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	15	16
Area Under the Curve (AUC) for Participant Assessed Ascites Impact Measure (AIM) [units: (units on a 4-symptom scale)*day] Least Squares Mean (Standard Error)	29.8 (148.07)	405.3 (143.21)

Statistical Analysis 1 for Area Under the Curve (AUC) for Participant Assessed Ascites Impact Measure (AIM)

Statistical Analysis Overview	Comparison Groups	Placebo, Aflibercept
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0160
	Comments	Estimated using Wilcoxon rank-sum test with stratification of baseline paracentesis (=<2 weeks versus >2 weeks) at randomization.
	Method	ANOVA
	Comments	Estimated from ANOVA model with stratification of baseline paracentesis (=<2 weeks versus >2 weeks).

Method of Estimation	Estimation Parameter	Other [Least squares (LS) Mean difference]
	Estimated Value	375.5
	Confidence Interval	(2-Sided) 95% -46.48 to 797.42
	Parameter Dispersion	Type: Standard Error of the mean Value: 205.99
	Estimation Comments	The LS mean difference was estimated for aflibercept versus placebo (aflibercept-placebo).

3. Secondary Outcome Measure:

Measure Title	60-Day Frequency of Paracentesis (FOP)
Measure Description	60-Day FOP was defined as the total number of paracenteses performed within the first 60 days after randomization during the double blind treatment period.
Time Frame	From Day 1 up to 60 days from randomization
Safety Issue?	No

Analysis Population Description

The intent-to-treat (ITT) population - all participants who were randomized in the study.

Reporting Groups

	Description
Placebo	Participants with advanced ovarian cancer administered placebo intravenously, once every two weeks in the DB period and 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.
Aflibercept	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period and the OL period.

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	26	29
60-Day Frequency of Paracentesis (FOP) [units: paracentesis] Least Squares Mean (Standard Error)	5.1 (0.69)	2.7 (0.65)

Statistical Analysis 1 for 60-Day Frequency of Paracentesis (FOP)

Statistical Analysis Overview	Comparison Groups	Placebo, Aflibercept
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0035
	Comments	Estimated using Wilcoxon rank-sum test with stratification of baseline paracentesis (=<2 weeks versus >2 weeks) at randomization.
	Method	ANOVA
	Comments	Estimated from ANOVA model with stratification of baseline paracentesis (=<2 weeks versus >2 weeks).

Method of Estimation	Estimation Parameter	Other [Least squares (LS) Mean difference]
	Estimated Value	-2.4
	Confidence Interval	(2-Sided) 95% -4.33 to -0.54
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.94

	Estimation Comments	The LS mean difference is estimated for aflibercept versus placebo (aflibercept-placebo).

4. Secondary Outcome Measure:

Measure Title	Plasma Levels of Free and VEGF-bound Aflibercept
Measure Description	Free aflibercept and VEGF-bound aflibercept plasma concentrations were measured by separate enzyme-linked immunosorbent assay (ELISA). The limit of quantitation of free aflibercept was 15.6 ng/mL, and of VEGF-bound aflibercept was 43.9 ng/mL. Peak free aflibercept was estimated at the end of Cycle 1 (C1) administration. The median free and VEGF-bound trough concentrations were determined for each participant beyond Cycle 3 (C3), then mean values were estimated from these median values.
Time Frame	Following every biweekly treatment administration up to 60 days after treatment discontinuation
Safety Issue?	No

Analysis Population Description

The analysis was performed using the safety population with evaluable blood samples. 42 participants were evaluated.

Reporting Groups

	Description
Double Blind (DB) Period	Participants with advanced ovarian cancer administered placebo or 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period.
Open-Label (OL) Period	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.

Measured Values

	Double Blind (DB) Period	Open-Label (OL) Period
Number of Participants Analyzed	30	21
Plasma Levels of Free and VEGF-bound Aflibercept [units: µg/mL] Mean (Standard Deviation)		
Peak Free Aflibercept (C1) (N=20, N=15)	69.8 (29.7)	62.1 (29.5)
Trough Free Aflibercept (Beyond C3) (N=15, N=19)	5.33 (3.67)	5.10 (5.29)
Trough Bound Aflibercept (Beyond C3) (N=16, N=17)	3.02 (1.29)	3.49 (1.48)

Reported Adverse Events

Time Frame	From treatment initiation to October 30, 2009
Additional Description	Adverse events were collected and reported per arm only as there was no washout period between the double-blind and open label treatment periods.

Reporting Groups

	Description
Placebo	Participants with advanced ovarian cancer administered placebo intravenously, once every two weeks in the DB period and 4.0 mg/kg aflibercept intravenously, once every two weeks in the OL period.
Aflibercept	Participants with advanced ovarian cancer administered 4.0 mg/kg aflibercept intravenously, once every two weeks in the DB period and the OL period.

Serious Adverse Events

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Total	18/25 (72%)	27/30 (90%)
Blood and lymphatic system disorders		
Anaemia [A]	1/25 (4%)	0/30 (0%)
Febrile neutropenia [A]	1/25 (4%)	0/30 (0%)
Pancytopenia [A]	1/25 (4%)	0/30 (0%)
Cardiac disorders		
Cardiopulmonary failure [A]	0/25 (0%)	1/30 (3.33%)
Pericardial effusion [A]	1/25 (4%)	0/30 (0%)
Gastrointestinal disorders		
Abdominal pain [A]	0/25 (0%)	3/30 (10%)
Ascites [A]	2/25 (8%)	1/30 (3.33%)
Colonic fistula [A]	1/25 (4%)	0/30 (0%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Diarrhoea [A]	0/25 (0%)	2/30 (6.67%)
Gastric ulcer haemorrhage [A]	1/25 (4%)	0/30 (0%)
Intestinal obstruction [A]	2/25 (8%)	0/30 (0%)
Intestinal perforation [A]	0/25 (0%)	1/30 (3.33%)
Large intestinal obstruction [A]	0/25 (0%)	1/30 (3.33%)
Large intestine perforation [A]	0/25 (0%)	1/30 (3.33%)
Nausea [A]	0/25 (0%)	2/30 (6.67%)
Obstruction gastric [A]	0/25 (0%)	1/30 (3.33%)
Small intestinal obstruction [A]	1/25 (4%)	3/30 (10%)
Small intestinal perforation [A]	0/25 (0%)	1/30 (3.33%)
Vomiting [A]	3/25 (12%)	6/30 (20%)
General disorders		
Asthenia [A]	0/25 (0%)	1/30 (3.33%)
Death [A]	0/25 (0%)	1/30 (3.33%)
Disease progression [A]	8/25 (32%)	10/30 (33.33%)
Fatigue [A]	2/25 (8%)	0/30 (0%)
Multi-organ failure [A]	1/25 (4%)	0/30 (0%)
Oedema peripheral [A]	1/25 (4%)	0/30 (0%)
Pain [A]	0/25 (0%)	1/30 (3.33%)
Pyrexia [A]	1/25 (4%)	0/30 (0%)
Hepatobiliary disorders		
Bile duct obstruction [A]	0/25 (0%)	1/30 (3.33%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Infections and infestations		
Abscess [A]	1/25 (4%)	0/30 (0%)
Fungal skin infection [A]	0/25 (0%)	1/30 (3.33%)
Pneumonia [A]	0/25 (0%)	1/30 (3.33%)
Sepsis [A]	1/25 (4%)	1/30 (3.33%)
Upper respiratory tract infection [A]	0/25 (0%)	1/30 (3.33%)
Injury, poisoning and procedural complications		
Hip fracture [A]	1/25 (4%)	0/30 (0%)
Investigations		
Blood electrolytes abnormal [A]	0/25 (0%)	1/30 (3.33%)
Metabolism and nutrition disorders		
Anorexia [A]	1/25 (4%)	0/30 (0%)
Dehydration [A]	4/25 (16%)	4/30 (13.33%)
Failure to thrive [A]	0/25 (0%)	1/30 (3.33%)
Hypoglycaemia [A]	1/25 (4%)	0/30 (0%)
Nervous system disorders		
Headache [A]	0/25 (0%)	1/30 (3.33%)
Psychiatric disorders		
Confusional state [A]	0/25 (0%)	1/30 (3.33%)
Renal and urinary disorders		
Renal failure acute [A]	1/25 (4%)	0/30 (0%)
Respiratory, thoracic and mediastinal disorders		
Aspiration [A]	1/25 (4%)	0/30 (0%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Dyspnoea [A]	1/25 (4%)	6/30 (20%)
Pleural effusion [A]	0/25 (0%)	1/30 (3.33%)
Pleuritic pain [A]	0/25 (0%)	1/30 (3.33%)
Pneumonia aspiration [A]	0/25 (0%)	1/30 (3.33%)
Pulmonary embolism [A]	0/25 (0%)	1/30 (3.33%)
Respiratory distress [A]	2/25 (8%)	1/30 (3.33%)
Vascular disorders		
Hypertension [A]	0/25 (0%)	1/30 (3.33%)
Hypotension [A]	0/25 (0%)	1/30 (3.33%)

A Term from vocabulary, MedDRA 12.0

Other Adverse Events

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

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Total	22/25 (88%)	28/30 (93.33%)
Blood and lymphatic system disorders		
Anaemia [A]	4/25 (16%)	3/30 (10%)
Cardiac disorders		
Tachycardia [A]	1/25 (4%)	2/30 (6.67%)
Gastrointestinal disorders		
Abdominal distension [A]	2/25 (8%)	5/30 (16.67%)
Abdominal pain [A]	5/25 (20%)	5/30 (16.67%)
Abdominal pain upper [A]	1/25 (4%)	6/30 (20%)
Constipation [A]	3/25 (12%)	5/30 (16.67%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Diarrhoea [A]	5/25 (20%)	12/30 (40%)
Dyspepsia [A]	2/25 (8%)	5/30 (16.67%)
Nausea [A]	9/25 (36%)	11/30 (36.67%)
Oral pain [A]	0/25 (0%)	2/30 (6.67%)
Stomatitis [A]	2/25 (8%)	1/30 (3.33%)
Vomiting [A]	13/25 (52%)	19/30 (63.33%)
General disorders		
Asthenia [A]	3/25 (12%)	7/30 (23.33%)
Chest pain [A]	0/25 (0%)	2/30 (6.67%)
Fatigue [A]	14/25 (56%)	10/30 (33.33%)
Gait disturbance [A]	1/25 (4%)	2/30 (6.67%)
Mucosal inflammation [A]	0/25 (0%)	2/30 (6.67%)
Oedema peripheral [A]	10/25 (40%)	11/30 (36.67%)
Pyrexia [A]	2/25 (8%)	3/30 (10%)
Infections and infestations		
Nasopharyngitis [A]	0/25 (0%)	2/30 (6.67%)
Pneumonia [A]	0/25 (0%)	3/30 (10%)
Upper respiratory tract infection [A]	0/25 (0%)	2/30 (6.67%)
Urinary tract infection [A]	4/25 (16%)	1/30 (3.33%)
Investigations		
Weight decreased [A]	0/25 (0%)	5/30 (16.67%)
Metabolism and nutrition disorders		
Anorexia [A]	9/25 (36%)	8/30 (26.67%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Dehydration [A]	2/25 (8%)	4/30 (13.33%)
Hypoalbuminaemia [A]	1/25 (4%)	2/30 (6.67%)
Hypocalcaemia [A]	0/25 (0%)	3/30 (10%)
Hypomagnesaemia [A]	0/25 (0%)	2/30 (6.67%)
Hyponatraemia [A]	2/25 (8%)	2/30 (6.67%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A]	3/25 (12%)	0/30 (0%)
Back pain [A]	4/25 (16%)	7/30 (23.33%)
Muscle spasms [A]	2/25 (8%)	3/30 (10%)
Muscular weakness [A]	2/25 (8%)	3/30 (10%)
Myalgia [A]	3/25 (12%)	2/30 (6.67%)
Pain in extremity [A]	2/25 (8%)	2/30 (6.67%)
Nervous system disorders		
Dizziness [A]	1/25 (4%)	2/30 (6.67%)
Dysgeusia [A]	1/25 (4%)	2/30 (6.67%)
Headache [A]	1/25 (4%)	7/30 (23.33%)
Psychiatric disorders		
Confusional state [A]	0/25 (0%)	2/30 (6.67%)
Insomnia [A]	0/25 (0%)	2/30 (6.67%)
Renal and urinary disorders		
Dysuria [A]	2/25 (8%)	1/30 (3.33%)
Pollakiuria [A]	0/25 (0%)	3/30 (10%)
Proteinuria [A]	1/25 (4%)	4/30 (13.33%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders		
Cough [A]	3/25 (12%)	8/30 (26.67%)
Dysphonia [A]	1/25 (4%)	7/30 (23.33%)
Dyspnoea [A]	9/25 (36%)	6/30 (20%)
Dyspnoea exertional [A]	0/25 (0%)	3/30 (10%)
Epistaxis [A]	0/25 (0%)	2/30 (6.67%)
Oropharyngeal pain [A]	0/25 (0%)	3/30 (10%)
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome [A]	0/25 (0%)	2/30 (6.67%)
Petechiae [A]	0/25 (0%)	2/30 (6.67%)
Pruritus [A]	0/25 (0%)	3/30 (10%)
Rash [A]	2/25 (8%)	4/30 (13.33%)
Vascular disorders		
Hypertension [A]	3/25 (12%)	4/30 (13.33%)
Hypotension [A]	2/25 (8%)	2/30 (6.67%)

A Term from vocabulary, MedDRA 12.0

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 shall have 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 days) in advance of any submission, and delay publication till the approval of the publication is given in writing by the Sponsor (not to exceed ninety days).

Results Point of Contact:

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