ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 04/25/2016

ClinicalTrials.gov ID: NCT00451906

Study Identification

Unique Protocol ID:	MO19390
Brief Title:	A Study of Avastin (Bevacizumab) in Combination With Platinum-Containing Chemotherapy in Patients With Advanced or Recurrent Non-Squamous Cell Lung Cancer.
Official Title:	Open-label Study of Bevacizumab (AVASTIN®) in Combination With Platinum-containing Chemotherapy as First-line Treatment of Patients With Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer
Secondary IDs:	

Study Status

Record Verification:	April 2016
Overall Status:	Completed
Study Start:	August 2006
Primary Completion:	June 2009 [Actual]
Study Completion:	June 2009 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 293/2006 Board Name: Ethik-Kommission der Medizinischen Universitat Wien und des allgemeinen Krankenhauses der Stadt Wien Board Affiliation: Unknown Phone: +43 1 404002147 Email: ethik-kom@meduniwien.ac.at
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Austria: Ministry of Health

Study Description

Brief Summary:	This single arm study will assess the safety and efficacy of Avastin combined with platinum-containing chemotherapy regimens in patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC). Avastin will be given as first-line treatment in combination with platinum-based chemotherapy or in combination with any standard of care NSCLC first-line chemotherapy used in line with the licensed national prescribing information. Eligible patients will receive Avastin (15mg/kg iv on day 1 of each 3 week cycle) concomitantly with chemotherapy. Avastin treatment will continue after completion of chemotherapy cycles until disease progression, and the target sample size is 500+ individuals.
Detailed Description:	

Conditions

Conditions:	Non-Squamous Non-Small Cell Lung Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 4
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	N/A

Endpoint Classification: Safety/Efficacy Study

Enrollment: 2252 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Bevacizumab + Chemotherapy Participants with advanced or recurrent NSCLC will be administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab will be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy.	Drug: Platinum-based chemotherapy As prescribed Drug: Bevacizumab [Avastin] 15 mg/kg IV on Day 1 of each 3 week cycle

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- adult patients, >=18 years of age;
- histologically or cytologically documented inoperable, locally advanced (stage III), metastatic (stage IV) or recurrent NSCLC other than squamous cell (tumors of mixed histology should be categorized by the predominant cell type);
- ECOG PS status 0-2;
- life expectancy >= 12weeks;
- adequate renal, liver and hematological function.

Exclusion Criteria:

- mixed, non-small and small cell tumors, or mixed adenosquamous carcinomas with a predominant squamous component;
- hemoptysis (>=1/2 teaspoon of bright red blood) in previous 3 months;
- evidence of tumor invading major blood vessels on imaging;
- evidence of CNS metastases, even if previously treated.

- major surgery (including open biopsy), significant traumatic injury within 28 days prior to enrolment, or anticipation of need for major surgery during study treatment;
- prior chemotherapy for stage IIIb/IV disease.

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: Austria
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Wels, Austria, 4600

Zams, Austria, 6511

Innsbruck, Austria, 6020

Kufstein, Austria, 6330

Vöcklabruck, Austria, 4840

Wien, Austria, 1130

Bludesch, Austria, 6712

Salzburg, Austria, 5020

Natters, Austria, 6161

Wien, Austria, 1140

St Veit An Der Glan, Austria, 9300

Graz, Austria, 8036

Linz, Austria, 4020

Knittelfeld, Austria, 8720

Linz, Austria, 4010

Wien, Austria, 1145

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Eindhoven, Netherlands, 5623 EJ

Helmond, Netherlands, 5700 AB

Zwolle, Netherlands, 8011 JW

Groningen, Netherlands, 9728 NZ

Haarlem, Netherlands, 2035 RC

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Tampere, Finland, 33520

Paimio, Finland, 21540

Pori, Finland, 28500

Germany
Minden, Germany, 32423

Villingen-Schwenningen, Germany, 78045

Neuruppin, Germany, 16816

Essen, Germany, 45147

Nürnberg, Germany, 90419

Löwenstein, Germany, 74245

Wiesbaden, Germany, 65199

Hannover, Germany, 30169

Göttingen, Germany, 37075

Wuerselen, Germany, 52146

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Taipei, Taiwan, 112

Taipei, Taiwan, 100

Taoyuan, Taiwan, 333

Taichung, Taiwan, 407

Tainan, Taiwan, 704

Germany

Leipzig, Germany, 04207

Augsburg, Germany, 86150

Muenchen, Germany, 80336

Magdeburg, Germany, 39120

Kiel, Germany, 24116

Bonn, Germany, 53113

Hamburg, Germany, 22081

Karlsruhe, Germany, 76137

Leer, Germany, 26789

Grosshansdorf, Germany, 22927

Oldenburg, Germany, 26121

Berlin, Germany, 12200

Köln, Germany, 50677

Bad Berka, Germany, 99437

Halle (Saale), Germany, 06120

Mainz, Germany, 55131

Gerlingen, Germany, 70839

Rostock, Germany, 18057

Gauting, Germany, 82131

Erlangen, Germany, 91054

Ulm, Germany, 89081

Treuenbrietzen, Germany, 14929

Donaustauf, Germany, 93093

Wolfsburg, Germany, 38440

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Manizales, Colombia

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Budapest, Hungary, 1529

Germany
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Elche, Alicante, Spain, 03202

Valencia, Valencia, Spain, 41014

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Madrid, Madrid, Spain, 28040

Madrid, Madrid, Spain, 28002

Madrid, Madrid, Spain, 28046

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Madrid, Madrid, Spain, 28035

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Bordeaux, France, 33076

Marseille, France, 13273

Toulouse, France, 31400

Strasbourg, France, 67085

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Setubal, Portugal, 2910-446

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Toulouse, France, 31052

Beziers, France, 34525

Valenciennes, France, 59300

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Guangzhou, China, 510080

Guangzhou, China, 510060

Beijing, China, 100021

Beijing, China, 100730

Russian Federation
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Russian Federation

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Coswig, Germany, 01640

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Ankara, Turkey, 06530

Izmir, Turkey, 35100

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Besancon, France, 75015

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Bogota, Colombia

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Jerusalem, Israel, 91031

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Tel Aviv, Israel, 64239

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Warszawa, Poland, 02-781

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Iceland
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Israel
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Mataro, Barcelona, Spain, 08304

Barcelona, Barcelona, Spain, 08907

Manresa, Barcelona, Spain, 08243

Alcorcon, Madrid, Spain, 28922

La Laguna, Tenerife, Spain, 38320

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Sassari, Sardegna, Italy, 07100

Netherlands
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France
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Germany
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China
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Russian Federation
Kislino, Kursk Region, Russian Federation, 305035

Egypt
Cairo, Egypt, 11737

France
Caen, France, 14076

Turkey
Gaziantep, Turkey, 27310

Italy
Forli, Emilia-Romagna, Italy, 47100

Bologna, Umbria, Italy, 6132

Australia
Sydney, New South Wales, Australia, 2077

Austria
Feldkirch, Austria, 6807

Poland
Warszawa, Poland, 04-394

Hong Kong
Hong Kong, Hong Kong

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	This study was conducted at 384 sites in 39 countries from 21 August 2006 to 30 June 2009.
Pre-Assignment Details	A total of 2252 participants were enrolled into the study, of which 2172 received the study drug. A total of 80 randomized participants did not receive study drug.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Overall Study

	Bevacizumab + Chemotherapy
Started	2252
Completed	13
Not Completed	2239
Adverse Event	515
Lost to Follow-up	31
Withdrawal by Subject	111
Protocol Violation	21
Progressive disease	1328
Termination of the study	108
Other Reasons	121
Did not complete final visit	4

Baseline Characteristics

Analysis Population Description

Baseline characteristics were described for the intent-to-treat (ITT) population, which included all participants with at least one valid post-baseline (Day -28 to -1) assessment.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Baseline Measures

	Bevacizumab + Chemotherapy
Number of Participants	2172
Age, Continuous [units: years] Mean (Standard Deviation)	58.8 (10.3)
Gender, Male/Female [units: Number of participants]	
Female	866
Male	1306

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Adverse Events of Special Interest
Measure Description	Participants with adverse events (AEs) of special interest (hypertension, proteinuria, wound healing complications, gastrointestinal perforation, arterial and venous thromboembolic events, hemoptysis, Central Nervous System (CNS) bleeding, other hemorrhage events and congestive heart failure) were reported.
Time Frame	Up to 3 years
Safety Issue?	No

Analysis Population Description

The ITT population included all participants with at least one valid post-baseline (Day -28 to -1) assessment.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Measured Values

	Bevacizumab + Chemotherapy
Number of Participants Analyzed	2172
Number of Participants With Adverse Events of Special Interest [units: participants]	
Hypertension	687
Proteinuria	672
Wound healing complication	26
Gastrointestinal perforation	30
Arterial/Venous thromboembolic events	274
Hemoptysis	176
CNS bleeding	7
Other hemorrhage events	744
Congestive heart failure	17

2. Primary Outcome Measure:

Measure Title	Number of Participants With Serious Adverse Events Related to Bevacizumab
Measure Description	Participants with serious adverse events (SAEs) related to bevacizumab were reported for the duration of the study.
Time Frame	Up to 3 years

Safety Issue?	No

Analysis Population Description

The ITT population included all participants with at least one valid post-baseline (Day -28 to -1) assessment.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Measured Values

	Bevacizumab + Chemotherapy
Number of Participants Analyzed	2172
Number of Participants With Serious Adverse Events Related to Bevacizumab [units: participants]	283

3. Secondary Outcome Measure:

Measure Title	Duration of Overall Survival
Measure Description	Overall survival time was defined as time between first bevacizumab administration and date of death, irrespective of the cause of death. Participants for whom no death was captured on the clinical database were censored at the most recent date they were known to be alive.
Time Frame	Up to 3 years
Safety Issue?	No

Analysis Population Description

The ITT population included all participants with at least one valid post-baseline (Day -28 to -1) assessment. Participants available at the time of assessment were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Measured Values

	Bevacizumab + Chemotherapy
Number of Participants Analyzed	1258
Duration of Overall Survival [units: Months] Median (95% Confidence Interval)	14.6 (13.8 to 15.3)

4. Secondary Outcome Measure:

Measure Title	Time to Disease Progression
Measure Description	Time to disease progression was defined as time between first bevacizumab administration and date of first occurrence of progressive disease. Participants who had not progressed at the time of study completion (including participants who died before progressive disease) or who were lost to follow-up were censored at the last bevacizumab administration date. Progressive disease is defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Time to disease progression was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.
Time Frame	Up to 3 years
Safety Issue?	No

Analysis Population Description

The ITT population was considered for analysis, which included all participants with at least one valid post-baseline (Day -28 to -1) assessment. Participants available at the time of assessment were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Measured Values

	Bevacizumab + Chemotherapy
Number of Participants Analyzed	1501
Time to Disease Progression [units: Months] Median (95% Confidence Interval)	7.8 (7.5 to 8.1)

5. Secondary Outcome Measure:

Measure Title	Number of Participants With Central Nervous System Bleeding
Measure Description	The incidence of central nervous system (CNS) bleeding was reported for participants who developed CNS metastases during the study period and who did not have Computed Tomography (CT) or magnetic resonance imaging (MRI) techniques of the head performed at baseline.
Time Frame	Up to 3 years
Safety Issue?	No

Analysis Population Description

The ITT population was used for analysis, which included all participants with at least one valid post-baseline (Day -28 to -1) assessment. n = number of participants available at the time of assessment who were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Measured Values

	Bevacizumab + Chemotherapy
Number of Participants Analyzed	367
Number of Participants With Central Nervous System Bleeding [units: participants]	
With CNS metastases (n = 281)	12
Without CT/MRI scans (n = 367)	16

Reported Adverse Events

Time Frame	Up to 3 years
Additional Description	The ITT population was used for the safety analysis, which included all participants who had been treated with bevacizumab and chemotherapy at least once.

Reporting Groups

	Description
Bevacizumab + Chemotherapy	Eligible participants with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) were administered bevacizumab infusions at a dose of 7.5 milligram per kilogram (mg/kg) or 15 mg/kg (investigator's choice) on Day 1 and then every 3 weeks, intravenously (IV) for a maximum of 6 cycles in combination with the standard of care NSCLC first-line chemotherapy in line with the licensed national prescribing information, during the treatment period. The initial dose of bevacizumab was to be administered following chemotherapy; all subsequent doses could be given before or after chemotherapy. After the end of chemotherapy participants without disease progression could continue bevacizumab as maintenance therapy until confirmed disease progression, unacceptable toxicity or participant consent withdrawal. Participants were followed-up through a final-visit (28 days after last bevacizumab infusion) and then every 3 months until death.

Serious Adverse Events

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Total	834/2212 (37.7%)
Blood and lymphatic system disorders	
Anaemia [A] †	36/2212 (1.63%)
Anaemia haemolytic autoimmune [A] †	1/2212 (0.05%)
Febrile bone marrow aplasia [A] †	5/2212 (0.23%)
Febrile neutropenia [A] †	52/2212 (2.35%)
Leukopenia [A] †	10/2212 (0.45%)
Neutropenia [A] †	84/2212 (3.8%)
Pancytopenia [A] †	11/2212 (0.5%)
Thrombocythaemia [A] †	1/2212 (0.05%)
Thrombocytopenia [A] †	44/2212 (1.99%)
Cardiac disorders	
Acute coronary syndrome [A] †	1/2212 (0.05%)
Acute myocardial infarction [A] †	2/2212 (0.09%)
Angina unstable [A] †	2/2212 (0.09%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Arrhythmia [A] †	1/2212 (0.05%)
Atrial fibrillation [A] †	8/2212 (0.36%)
Atrial flutter [A] †	1/2212 (0.05%)
Bradycardia [A] †	1/2212 (0.05%)
Cardiac arrest [A] †	2/2212 (0.09%)
Cardiac disorder [A] †	1/2212 (0.05%)
Cardiac failure [A] †	4/2212 (0.18%)
Cardiac failure congestive [A] †	4/2212 (0.18%)
Cardiac flutter [A] †	1/2212 (0.05%)
Cardiac tamponade [A] †	1/2212 (0.05%)
Cardio-respiratory arrest [A] †	3/2212 (0.14%)
Cardiogenic shock [A] †	1/2212 (0.05%)
Cardiomyopathy [A] †	1/2212 (0.05%)
Cardiopulmonary failure [A] †	1/2212 (0.05%)
Coronary artery disease [A] †	1/2212 (0.05%)
Left ventricular failure [A] †	1/2212 (0.05%)
Myocardial infarction [A] †	17/2212 (0.77%)
Myocardial ischaemia [A] †	4/2212 (0.18%)
Pericardial effusion [A] †	1/2212 (0.05%)
Pericarditis [A] †	2/2212 (0.09%)
Tachyarrhythmia [A] †	1/2212 (0.05%)
Tachycardia [A] †	2/2212 (0.09%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Ear and labyrinth disorders	
Tympanic membrane disorder [A] †	1/2212 (0.05%)
Eye disorders	
Angle closure glaucoma [A] †	1/2212 (0.05%)
Optic ischaemic neuropathy [A] †	1/2212 (0.05%)
Retinal vein thrombosis [A] †	1/2212 (0.05%)
Visual acuity reduced [A] †	1/2212 (0.05%)
Visual disturbance [A] †	1/2212 (0.05%)
Gastrointestinal disorders	
Abdominal pain [A] †	13/2212 (0.59%)
Abdominal pain upper [A] †	3/2212 (0.14%)
Anal fistula [A] †	1/2212 (0.05%)
Anal stenosis [A] †	1/2212 (0.05%)
Anal ulcer [A] †	1/2212 (0.05%)
Appendicitis perforated [A] †	2/2212 (0.09%)
Colitis [A] †	3/2212 (0.14%)
Colitis ischaemic [A] †	2/2212 (0.09%)
Constipation [A] †	12/2212 (0.54%)
Diarrhoea [A] †	18/2212 (0.81%)
Diverticular perforation [A] †	3/2212 (0.14%)
Duodenal ulcer [A] †	1/2212 (0.05%)
Duodenal ulcer haemorrhage [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Dysphagia [A] †	2/2212 (0.09%)
Enteritis [A] †	1/2212 (0.05%)
Faeces discoloured [A] †	1/2212 (0.05%)
Gastric haemorrhage [A] †	1/2212 (0.05%)
Gastric ulcer [A] †	1/2212 (0.05%)
Gastric ulcer haemorrhage [A] †	1/2212 (0.05%)
Gastritis [A] †	1/2212 (0.05%)
Gastrointestinal disorder [A] †	1/2212 (0.05%)
Gastrointestinal haemorrhage [A] †	8/2212 (0.36%)
Gastrointestinal perforation [A] †	9/2212 (0.41%)
Gingival disorder [A] †	1/2212 (0.05%)
Glossodynia [A] †	1/2212 (0.05%)
Haematemesis [A] †	3/2212 (0.14%)
Haemorrhoids [A] †	2/2212 (0.09%)
Ileus [A] †	4/2212 (0.18%)
Ileus paralytic [A] †	1/2212 (0.05%)
Intestinal obstruction [A] †	2/2212 (0.09%)
Intestinal perforation [A] †	2/2212 (0.09%)
Jejunal perforation [A] †	1/2212 (0.05%)
Large intestine perforation [A] †	7/2212 (0.32%)
Lower gastrointestinal haemorrhage [A] †	1/2212 (0.05%)
Mechanical ileus [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Nausea [A] †	25/2212 (1.13%)
Oesophagitis [A] †	1/2212 (0.05%)
Pancreatitis acute [A] †	1/2212 (0.05%)
Peptic ulcer perforation [A] †	1/2212 (0.05%)
Peritonitis [A] †	3/2212 (0.14%)
Rectal haemorrhage [A] †	7/2212 (0.32%)
Small intestinal perforation [A] †	3/2212 (0.14%)
Stomatitis [A] †	1/2212 (0.05%)
Subileus [A] †	3/2212 (0.14%)
Upper gastrointestinal haemorrhage [A] †	2/2212 (0.09%)
Vomiting [A] †	26/2212 (1.18%)
General disorders	
Aplasia [A] †	1/2212 (0.05%)
Asthenia [A] †	2/2212 (0.09%)
Catheter thrombosis [A] †	4/2212 (0.18%)
Chest pain [A] †	19/2212 (0.86%)
Chills [A] †	1/2212 (0.05%)
Cyst rupture [A] †	1/2212 (0.05%)
Death [A] †	14/2212 (0.63%)
Extravasation [A] †	1/2212 (0.05%)
Fatigue [A] †	19/2212 (0.86%)
Feeling abnormal [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Gait disturbance [A] †	1/2212 (0.05%)
General physical health deterioration [A] †	13/2212 (0.59%)
Hyperpyrexia [A] †	1/2212 (0.05%)
Ill-defined disorder [A] †	2/2212 (0.09%)
Impaired healing [A] †	1/2212 (0.05%)
Infusion related reaction [A] †	1/2212 (0.05%)
Mucosal inflammation [A] †	1/2212 (0.05%)
Multi-organ failure [A] †	1/2212 (0.05%)
Pain [A] †	3/2212 (0.14%)
Performance status decreased [A] †	2/2212 (0.09%)
Pyrexia [A] †	37/2212 (1.67%)
Sudden death [A] †	4/2212 (0.18%)
Hepatobiliary disorders	
Alcoholic liver disease [A] †	1/2212 (0.05%)
Bile duct stone [A] †	1/2212 (0.05%)
Cholecystitis [A] †	2/2212 (0.09%)
Cholecystitis acute [A] †	1/2212 (0.05%)
Cholelithiasis [A] †	1/2212 (0.05%)
Cholestasis [A] †	3/2212 (0.14%)
Hepatic failure [A] †	2/2212 (0.09%)
Hepatitis acute [A] †	1/2212 (0.05%)
Hepatorenal syndrome [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Jaundice [A] †	2/2212 (0.09%)
Immune system disorders	
Drug hypersensitivity [A] †	1/2212 (0.05%)
Hypersensitivity [A] †	2/2212 (0.09%)
Infections and infestations	
Abscess [A] †	3/2212 (0.14%)
Abscess bacterial [A] †	1/2212 (0.05%)
Anal abscess [A] †	4/2212 (0.18%)
Anal infection [A] †	1/2212 (0.05%)
Appendicitis [A] †	1/2212 (0.05%)
Bronchitis [A] †	2/2212 (0.09%)
Bronchopneumonia [A] †	2/2212 (0.09%)
Candidiasis [A] †	1/2212 (0.05%)
Catheter related infection [A] †	2/2212 (0.09%)
Catheter site infection [A] †	2/2212 (0.09%)
Cellulitis [A] †	2/2212 (0.09%)
Central line infection [A] †	3/2212 (0.14%)
Clostridial infection [A] †	2/2212 (0.09%)
Device related infection [A] †	2/2212 (0.09%)
Diverticulitis [A] †	2/2212 (0.09%)
Empyema [A] †	6/2212 (0.27%)
Enterocolitis infectious [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Erysipelas [A] †	1/2212 (0.05%)
Febrile infection [A] †	1/2212 (0.05%)
Gastroenteritis [A] †	6/2212 (0.27%)
Herpes zoster [A] †	1/2212 (0.05%)
Infection [A] †	7/2212 (0.32%)
Lobar pneumonia [A] †	1/2212 (0.05%)
Lower respiratory tract infection [A] †	2/2212 (0.09%)
Lung abscess [A] †	1/2212 (0.05%)
Lung infection [A] †	5/2212 (0.23%)
Mumps [A] †	1/2212 (0.05%)
Nasopharyngitis [A] †	1/2212 (0.05%)
Neutropenic infection [A] †	1/2212 (0.05%)
Neutropenic sepsis [A] †	2/2212 (0.09%)
Not Codable [A] [1] †	1/2212 (0.05%)
Penile abscess [A] †	1/2212 (0.05%)
Peridiverticular abscess [A] †	1/2212 (0.05%)
Perirectal abscess [A] †	2/2212 (0.09%)
Pneumonia [A] †	52/2212 (2.35%)
Pneumonia necrotising [A] †	1/2212 (0.05%)
Pneumonia primary atypical [A] †	1/2212 (0.05%)
Psoas abscess [A] †	1/2212 (0.05%)
Pyopneumothorax [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Respiratory tract infection [A] †	10/2212 (0.45%)
Sepsis [A] †	8/2212 (0.36%)
Septic shock [A] †	4/2212 (0.18%)
Sinusitis [A] †	2/2212 (0.09%)
Staphylococcal infection [A] †	1/2212 (0.05%)
Superinfection [A] †	1/2212 (0.05%)
Tonsillitis [A] †	1/2212 (0.05%)
Upper respiratory tract infection [A] †	4/2212 (0.18%)
Urinary tract infection [A] †	4/2212 (0.18%)
Urosepsis [A] †	1/2212 (0.05%)
Viral infection [A] †	2/2212 (0.09%)
Viral skin infection [A] †	1/2212 (0.05%)
Injury, poisoning and procedural complications	
Accidental overdose [A] †	1/2212 (0.05%)
Alcohol poisoning [A] †	1/2212 (0.05%)
Allergic transfusion reaction [A] †	1/2212 (0.05%)
Ankle fracture [A] †	1/2212 (0.05%)
Bone fissure [A] †	1/2212 (0.05%)
Femur fracture [A] †	2/2212 (0.09%)
Incision site haemorrhage [A] †	1/2212 (0.05%)
Overdose [A] †	1/2212 (0.05%)
Post procedural haemorrhage [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Postoperative thoracic procedure complication [A] †	1/2212 (0.05%)
Radiation oesophagitis [A] †	1/2212 (0.05%)
Rib fracture [A] †	1/2212 (0.05%)
Wound [A] †	1/2212 (0.05%)
Wound dehiscence [A] †	1/2212 (0.05%)
Investigations	
Activated partial thromboplastin time prolonged [A] †	1/2212 (0.05%)
Aspiration bronchial [A] †	1/2212 (0.05%)
Blood bilirubin increased [A] †	1/2212 (0.05%)
Blood creatinine increased [A] †	9/2212 (0.41%)
Blood potassium decreased [A] †	1/2212 (0.05%)
C-reactive protein increased [A] †	3/2212 (0.14%)
Creatinine renal clearance decreased [A] †	1/2212 (0.05%)
Gamma-glutamyltransferase increased [A] †	1/2212 (0.05%)
Haematology test abnormal [A] †	1/2212 (0.05%)
Haemoglobin decreased [A] †	5/2212 (0.23%)
Neutrophil count decreased [A] †	9/2212 (0.41%)
Platelet count decreased [A] †	11/2212 (0.5%)
Transaminases abnormal [A] †	1/2212 (0.05%)
Weight decreased [A] †	1/2212 (0.05%)
White blood cell count decreased [A] †	8/2212 (0.36%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Metabolism and nutrition disorders	
Anorexia [A] †	4/2212 (0.18%)
Cachexia [A] †	3/2212 (0.14%)
Dehydration [A] †	9/2212 (0.41%)
Electrolyte imbalance [A] †	1/2212 (0.05%)
Hypercalcaemia [A] †	5/2212 (0.23%)
Hypercreatininaemia [A] †	2/2212 (0.09%)
Hyperglycaemia [A] †	2/2212 (0.09%)
Hypoalbuminaemia [A] †	1/2212 (0.05%)
Hypokalaemia [A] †	3/2212 (0.14%)
Hyponatraemia [A] †	3/2212 (0.14%)
Hypoproteinaemia [A] †	1/2212 (0.05%)
Starvation [A] †	1/2212 (0.05%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] †	3/2212 (0.14%)
Arthritis [A] †	2/2212 (0.09%)
Back pain [A] †	5/2212 (0.23%)
Bone pain [A] †	5/2212 (0.23%)
Fistula [A] †	1/2212 (0.05%)
Muscle haemorrhage [A] †	1/2212 (0.05%)
Muscular weakness [A] †	2/2212 (0.09%)
Musculoskeletal chest pain [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Musculoskeletal pain [A] †	1/2212 (0.05%)
Osteolysis [A] †	1/2212 (0.05%)
Pain in extremity [A] †	2/2212 (0.09%)
Pathological fracture [A] †	2/2212 (0.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Bladder cancer [A] †	1/2212 (0.05%)
Bladder neoplasm [A] †	1/2212 (0.05%)
Colon cancer [A] †	1/2212 (0.05%)
Infected neoplasm [A] †	2/2212 (0.09%)
Lung neoplasm [A] †	1/2212 (0.05%)
Metastases to bone [A] †	1/2212 (0.05%)
Metastases to meninges [A] †	1/2212 (0.05%)
Metastatic pain [A] †	1/2212 (0.05%)
Paraneoplastic syndrome [A] †	3/2212 (0.14%)
Tumour haemorrhage [A] †	1/2212 (0.05%)
Nervous system disorders	
Aphonia [A] †	1/2212 (0.05%)
Autonomic nervous system imbalance [A] *	1/2212 (0.05%)
Brain stem infarction [A] †	1/2212 (0.05%)
Cerebral haematoma [A] †	1/2212 (0.05%)
Cerebral haemorrhage [A] †	2/2212 (0.09%)
Cerebral infarction [A] †	4/2212 (0.18%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Cerebral ischaemia [A] †	4/2212 (0.18%)
Cerebral microangiopathy [A] †	1/2212 (0.05%)
Cerebrovascular accident [A] †	7/2212 (0.32%)
Coma [A] †	1/2212 (0.05%)
Convulsion [A] †	6/2212 (0.27%)
Dizziness [A] †	2/2212 (0.09%)
Encephalopathy [A] †	1/2212 (0.05%)
Epilepsy [A] †	2/2212 (0.09%)
Headache [A] †	8/2212 (0.36%)
Hemiparesis [A] †	1/2212 (0.05%)
Hydrocephalus [A] †	1/2212 (0.05%)
Hypertensive encephalopathy [A] †	1/2212 (0.05%)
Intracranial aneurysm [A] †	1/2212 (0.05%)
Ischaemic stroke [A] †	1/2212 (0.05%)
Lacunar infarction [A] †	1/2212 (0.05%)
Leukoencephalopathy [A] †	2/2212 (0.09%)
Nervous system disorder [A] †	2/2212 (0.09%)
Neuralgia [A] †	2/2212 (0.09%)
Neuropathy peripheral [A] †	1/2212 (0.05%)
Optic neuritis [A] †	1/2212 (0.05%)
Peroneal nerve palsy [A] †	1/2212 (0.05%)
Polyneuropathy [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Presyncope [A] †	1/2212 (0.05%)
Sciatica [A] †	1/2212 (0.05%)
Status epilepticus [A] †	1/2212 (0.05%)
Syncope [A] †	11/2212 (0.5%)
Toxic encephalopathy [A] †	1/2212 (0.05%)
Transient ischaemic attack [A] †	1/2212 (0.05%)
Psychiatric disorders	
Confusional state [A] †	7/2212 (0.32%)
Emotional disorder [A] †	1/2212 (0.05%)
Renal and urinary disorders	
Haematuria [A] †	1/2212 (0.05%)
Nephritic syndrome [A] †	1/2212 (0.05%)
Nephrolithiasis [A] †	2/2212 (0.09%)
Nephrotic syndrome [A] †	3/2212 (0.14%)
Proteinuria [A] †	3/2212 (0.14%)
Renal failure [A] †	11/2212 (0.5%)
Renal failure acute [A] *	8/2212 (0.36%)
Renal haemorrhage [A] †	1/2212 (0.05%)
Renal impairment [A] †	1/2212 (0.05%)
Urinary retention [A] †	1/2212 (0.05%)
Reproductive system and breast disorders	
Benign prostatic hyperplasia [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Pelvic pain [A] †	1/2212 (0.05%)
Respiratory, thoracic and mediastinal disorders	
Acute pulmonary oedema [A] †	1/2212 (0.05%)
Acute respiratory failure [A] †	1/2212 (0.05%)
Alveolitis [A] †	1/2212 (0.05%)
Bronchopleural fistula [A] †	1/2212 (0.05%)
Bronchospasm [A] †	1/2212 (0.05%)
Chronic obstructive pulmonary disease [A] †	1/2212 (0.05%)
Dysphonia [A] †	1/2212 (0.05%)
Dyspnoea [A] †	32/2212 (1.45%)
Epistaxis [A] †	21/2212 (0.95%)
Haemoptysis [A] †	18/2212 (0.81%)
Haemothorax [A] †	2/2212 (0.09%)
Hydropneumothorax [A] †	1/2212 (0.05%)
Interstitial lung disease [A] †	1/2212 (0.05%)
Lung disorder [A] †	4/2212 (0.18%)
Lung infiltration [A] †	1/2212 (0.05%)
Pharyngolaryngeal pain [A] †	2/2212 (0.09%)
Pleural effusion [A] †	5/2212 (0.23%)
Pleuritic pain [A] †	1/2212 (0.05%)
Pneumonitis [A] †	2/2212 (0.09%)
Pneumothorax [A] †	12/2212 (0.54%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Pulmonary congestion [A] †	1/2212 (0.05%)
Pulmonary embolism [A] †	55/2212 (2.49%)
Pulmonary haemorrhage [A] †	4/2212 (0.18%)
Pulmonary infarction [A] †	1/2212 (0.05%)
Pulmonary thrombosis [A] †	1/2212 (0.05%)
Pulmonary venous thrombosis [A] †	1/2212 (0.05%)
Respiratory distress [A] †	2/2212 (0.09%)
Respiratory failure [A] †	5/2212 (0.23%)
Thoracic haemorrhage [A] †	1/2212 (0.05%)
Skin and subcutaneous tissue disorders	
Angioedema [A] †	1/2212 (0.05%)
Drug eruption [A] †	1/2212 (0.05%)
Leukocytoclastic vasculitis [A] †	1/2212 (0.05%)
Rash [A] †	1/2212 (0.05%)
Skin lesion [A] †	1/2212 (0.05%)
Skin ulcer [A] †	2/2212 (0.09%)
Skin ulcer haemorrhage [A] †	1/2212 (0.05%)
Stevens-johnson syndrome [A] †	1/2212 (0.05%)
Surgical and medical procedures	
Astringent therapy [A] †	1/2212 (0.05%)
Catheter placement [A] †	1/2212 (0.05%)
Knee operation [A] †	1/2212 (0.05%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Lung lobectomy [A] †	1/2212 (0.05%)
Pleurodesis [A] †	1/2212 (0.05%)
Tumour excision [A] †	1/2212 (0.05%)
Vascular disorders	
Aortic aneurysm [A] †	1/2212 (0.05%)
Capillary leak syndrome [A] †	1/2212 (0.05%)
Deep vein thrombosis [A] †	29/2212 (1.31%)
Embolism [A] †	3/2212 (0.14%)
Embolism venous [A] †	1/2212 (0.05%)
Haemorrhage [A] †	2/2212 (0.09%)
Hypertension [A] †	9/2212 (0.41%)
Hypertensive crisis [A] †	4/2212 (0.18%)
Infarction [A] †	1/2212 (0.05%)
Jugular vein thrombosis [A] †	2/2212 (0.09%)
Orthostatic hypotension [A] †	1/2212 (0.05%)
Peripheral arterial occlusive disease [A] †	1/2212 (0.05%)
Peripheral ischaemia [A] †	2/2212 (0.09%)
Peripheral vascular disorder [A] †	1/2212 (0.05%)
Phlebitis superficial [A] †	1/2212 (0.05%)
Shock [A] †	1/2212 (0.05%)
Subclavian vein thrombosis [A] †	2/2212 (0.09%)
Thrombosis [A] †	7/2212 (0.32%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Vena cava thrombosis [A] †	1/2212 (0.05%)
Venous insufficiency [A] †	1/2212 (0.05%)
Venous thrombosis [A] †	3/2212 (0.14%)
Venous thrombosis limb [A] †	2/2212 (0.09%)

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.1)

[1] Neutropenia Due to Respiratory Infection

Other Adverse Events

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

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Total	1982/2212 (89.6%)
Gastrointestinal disorders	
Constipation [A] †	423/2212 (19.12%)
Diarrhoea [A] †	347/2212 (15.69%)
Nausea [A] †	827/2212 (37.39%)
Stomatitis [A] †	260/2212 (11.75%)
Vomiting [A] †	516/2212 (23.33%)
General disorders	
Chest pain [A] †	224/2212 (10.13%)
Fatigue [A] †	893/2212 (40.37%)
Pyrexia [A] †	263/2212 (11.89%)
Investigations	
Alanine aminotransferase increased [A] †	159/2212 (7.19%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Aspartate aminotransferase increased [A] †	141/2212 (6.37%)
Blood creatinine increased [A] †	186/2212 (8.41%)
Gamma-glutamyltransferase increased [A] †	121/2212 (5.47%)
Haemoglobin decreased [A] †	788/2212 (35.62%)
Neutrophil count decreased [A] †	696/2212 (31.46%)
Platelet count decreased [A] †	573/2212 (25.9%)
Protein urine present [A] †	111/2212 (5.02%)
White blood cell count decreased [A] †	623/2212 (28.16%)
Metabolism and nutrition disorders	
Anorexia [A] †	462/2212 (20.89%)
Hyperglycaemia [A] †	122/2212 (5.52%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] †	182/2212 (8.23%)
Back pain [A] †	219/2212 (9.9%)
Musculoskeletal pain [A] †	134/2212 (6.06%)
Myalgia [A] †	135/2212 (6.1%)
Pain in extremity [A] †	189/2212 (8.54%)
Nervous system disorders	
Dizziness [A] †	128/2212 (5.79%)
Headache [A] †	309/2212 (13.97%)
Neuropathy [A] †	179/2212 (8.09%)
Psychiatric disorders	
Insomnia [A] †	112/2212 (5.06%)

	Bevacizumab + Chemotherapy
	Affected/At Risk (%)
Renal and urinary disorders	
Proteinuria [A] †	568/2212 (25.68%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] †	328/2212 (14.83%)
Dysphonia [A] †	130/2212 (5.88%)
Dyspnoea [A] †	279/2212 (12.61%)
Epistaxis [A] †	589/2212 (26.63%)
Haemoptysis [A] †	167/2212 (7.55%)
Skin and subcutaneous tissue disorders	
Alopecia [A] †	526/2212 (23.78%)
Rash [A] †	167/2212 (7.55%)
Vascular disorders	
Hypertension [A] †	680/2212 (30.74%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (10.1)

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 Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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