Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With Nab-Paclitaxel Plus Gemcitabine Compared With Placebo Plus Nab-Paclitaxel and Gemcitabine in Subjects With Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma

Summary

EudraCT number	2015-004068-13
Trial protocol	LV HU BE GB LT DE DK NL ES FR HR IT
Global end of trial date	04 November 2019

Results information

Result version number	v1 (current)
This version publication date	04 March 2021
First version publication date	04 March 2021

Trial information

Trial identification

Sponsor protocol code	HALO-109-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02715804
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Halozyme Therapeutics
Sponsor organisation address	11388 Sorrento Valley Road, San Diego, United States, 92191
Public contact	VP, Medical, Regulatory and Drug Safety, Halozyme Therapeutics, 001 8587948889, medinfo@halozyme.com
Scientific contact	VP, Medical, Regulatory and Drug Safety, Halozyme Therapeutics, 001 8587948889, medinfo@halozyme.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2019
Global end of trial reached?	Yes
Global end of trial date	04 November 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to compare the efficacy and safety of PEGylated Recombinant Human Hyaluronidase (PEGPH20) combined with nab-paclitaxel plus gemcitabine (PAG treatment), compared with placebo combined with nab-paclitaxel plus gemcitabine (AG treatment), in participants with hyaluronan (HA)-high Stage IV previously untreated pancreatic ductal adenocarcinoma (PDA).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council on Harmonisation (ICH) guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 44
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Korea, Republic of: 30
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Lithuania: 6
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 185

Country: Number of subjects enrolled	Belgium: 10
Worldwide total number of subjects	492
EEA total number of subjects	195

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	250
From 65 to 84 years	240
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 492 participants were enrolled from 14 March 2016 through 26 December 2018 in 20 countries.

Pre-assignment

Screening details:

A total of 492 participants were enrolled and randomized in 2:1 ratio to received either PAG (PEGPH20 + Nab-paclitaxel + Gemcitabine) or AG (Placebo + Nab-paclitaxel + Gemcitabine).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine

Arm description:

Participants received 3.0 micrograms/kilogram (µg/kg) PEGPH20 as an intravenous (IV) infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisted of 4 weeks [Week 4 of every cycle was a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 milligrams/square meter (mg/m^2) nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 150.1 weeks).

Arm type	Experimental
Investigational medicinal product name	PEGylated Recombinant Human Hyaluronidase (PEGPH20)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PEGPH20 was administered as per the dose and schedule specified in the arm description.

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel was administered as per the dose and schedule specified in the arm description.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar®
Pharmaceutical forms	Powder for infusion, Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as per the dose and schedule specified in the arm description.

Arm title	AG: Placebo + nab-Paclitaxel + Gemcitabine

Arm description:

Participants received placebo matching to PEGPH20 as an IV infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisting of 4 weeks [Week 4 of every cycle will be a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 mg/m^2 nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 83.9 weeks).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo for PEGPH20 was administered as per schedule specified in the arm description.

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel was administered as per the dose and schedule specified in the arm description.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar®
Pharmaceutical forms	Concentrate for concentrate for solution for infusion, Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as per the dose and schedule specified in the arm description.

Number of subjects in period 1	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine
Started	327	165
Received at least 1 dose of study drug	323	158
Safety population	325	156
Completed	98	52
Not completed	229	113
Adverse event, serious fatal	222	106
Consent withdrawn by subject	5	4
Other than specified	2	3

Baseline characteristics

Reporting groups	
Reporting group title	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine
Reporting group description:	
Participants received 3.0 micrograms/kilogram (µg/kg) PEGPH20 as an intravenous (IV) infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisted of 4 weeks [Week 4 of every cycle was a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 milligrams/square meter (mg/m^2) nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 150.1 weeks).	
Reporting group title	AG: Placebo + nab-Paclitaxel + Gemcitabine
Reporting group description:	
Participants received placebo matching to PEGPH20 as an IV infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisting of 4 weeks [Week 4 of every cycle will be a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 mg/m^2 nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 83.9 weeks).	

Reporting group values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine	Total
Number of subjects	327	165	492
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	158	92	250
From 65-84 years	168	72	240
85 years and over	1	1	2
Age Continuous Units: years			
arithmetic mean	63.8	62.3	
standard deviation	± 9.62	± 9.50	-
Sex: Female, Male Units: participants			
Female	147	85	232
Male	180	80	260
Race/Ethnicity, Customized Units: Subjects			
White/Caucasian	266	126	392
Black or African American	11	5	16
Asian	33	24	57
Other	17	10	27
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	24	11	35
Not Hispanic or Latino	267	138	405
Unknown or Not Reported	36	16	52

End points

End points reporting groups

Reporting group title	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine

Reporting group description:

Participants received 3.0 micrograms/kilogram (µg/kg) PEGPH20 as an intravenous (IV) infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisted of 4 weeks [Week 4 of every cycle was a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 milligrams/square meter (mg/m^2) nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 150.1 weeks).

Reporting group title	AG: Placebo + nab-Paclitaxel + Gemcitabine

Reporting group description:

Participants received placebo matching to PEGPH20 as an IV infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisting of 4 weeks [Week 4 of every cycle will be a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 mg/m^2 nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 83.9 weeks).

Primary: Overall Survival

End point title	Overall Survival[1]

End point description:

Overall survival was defined as the time from randomization until death from any cause. Overall survival was analyzed using Kaplan-Meier methods. Intent-to-treat (ITT) population included all randomized participants.

End point type	Primary

End point timeframe:

From randomization until death from any cause (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses not applicable for this endpoint.

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	165		
Units: months				
median (confidence interval 95%)	11.2 (10.3 to 12.3)	11.5 (9.0 to 12.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS: time from randomization until first occurrence of radiological disease progression, as determined by blinded Central Imaging Vendor (CIV) based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, or death from any cause during treatment period. Disease progression was defined as at least a 20 percent (%) increase in sum of diameters of target lesions, taking as reference the smallest sum on study thus far, nadir (this included baseline sum if that was the smallest on study); Sum must also demonstrate an absolute increase of at least 5 millimeters (mm); Appearance of 1 or more new lesions; Unequivocal progression of existing non-target lesions. Surviving participants without disease progression were censored for PFS analysis at the date of last evaluable postbaseline tumor assessment. Surviving participants without any postbaseline disease assessment were censored on Day 1. PFS was estimated using Kaplan-Meier method. ITT population: all randomized participants.

End point type	Secondary

End point timeframe:

From the date of randomization until disease progression or death from any cause (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	165		
Units: months				
median (confidence interval 95%)	7.1 (5.5 to 7.4)	7.1 (4.8 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR): Percentage of Participants With Objective Response

End point title	Objective Response Rate (ORR): Percentage of Participants With Objective Response

End point description:

ORR was defined as percentage of participants who achieved either a complete response (CR) or partial response (PR) as determined by the blinded CIV based on RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions; Any pathological or non-pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

From the date of randomization until CR or PR (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	165		
Units: percentage of participants				
number (confidence interval 95%)	47.1 (41.6 to 52.7)	36.4 (29.0 to 44.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR: time from the first objective response of CR or PR until disease progression (as determined by the blinded CIV based on RECIST version 1.1) or death within 14 days of last dose of study treatment or randomization. CR: disappearance of all target and non-target lesions; Any pathological or non-pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Disease progression: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study thus far, the sum must also demonstrate an absolute increase of at least 5 mm, or appearance of one or more new lesions; and unequivocal progression of existing non-target lesions. DOR was analyzed using Kaplan-Meier methods. ITT population: all randomized participants. 'Number of participants analyzed' = participants with objective response.

End point type	Secondary

End point timeframe:

From date of first objective response (CR or PR) until date of first disease progression (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	60		
Units: months				
median (confidence interval 95%)	6.1 (5.5 to 7.8)	7.4 (5.3 to 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (AEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (AEs)

End point description:

AE: any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious adverse event (SAE): an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent AEs: AEs that begin or worsen in severity during or after participant's first dose of study treatment and no later than 30 days after the date of last dose of study treatment and/or any treatment-related AE regardless of onset date. AEs included both SAEs and non-serious AEs. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. Safety population included all participants who received at least 1 dose of study drug, and analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

From administration of first dose of study drug up to 30 days after last dose of study drug (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	156		
Units: participants	325	156		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Worst Post-Baseline Hematology and Chemistry (Clinical Laboratory Parameters) Severity Grade During the Study

End point title	Number of Participants With Worst Post-Baseline Hematology and Chemistry (Clinical Laboratory Parameters) Severity Grade During the Study

End point description:

Severity grades (per CTCAE Version 4.03): Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening. Grade 0 indicates evaluable lab records but not fall into any CTCAE grade for certain CTCAE term. A worst postbaseline grade shift was defined as the worst change that occurred at any measured timepoint during study. Hematology abnormalities: anemia, lymphocyte (Ly) count decreased, Ly count increased, neutropenia, thrombocytopenia, and leukopenia. Chemistry abnormalities: hypoalbuminemia, alkaline phosphatase increased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hyperbilirubinemia, hypo- and hypercalcemia, creatinine increased, hypo- and hyperglycaemia, hypo- and hyperkalemia, hypo- and hypermagnesemia, hypo- and hypernatremia. Safety population: all participants who received at least 1 dose of study drug, and analyzed according to treatment they actually received. ‘n’= participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

From administration of first dose of study drug up to 30 days after last dose of study drug (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	156		
Units: participants				
Anemia: Grade 0 (n=321,155)	6	3		
Anemia: Grade 1 (n=321,155)	84	41		
Anemia: Grade 2 (n=321,155)	164	74		
Anemia: Grade 3 (n=321,155)	67	37		
Anemia: Grade 4 (n=321,155)	0	0		
Lymphocyte count decreased: Grade 0 (n=321,155)	33	17		
Lymphocyte count decreased: Grade 1 (n=321,155)	83	46		
Lymphocyte count decreased: Grade 2 (n=321,155)	102	46		
Lymphocyte count decreased: Grade 3 (n=321,155)	90	40		
Lymphocyte count decreased: Grade 4 (n=321,155)	13	6		
Lymphocyte count increased: Grade 0 (n=321,155)	302	150		
Lymphocyte count increased: Grade 1 (n=321,155)	0	0		
Lymphocyte count increased: Grade 2 (n=321,155)	19	5		
Lymphocyte count increased: Grade 3 (n=321,155)	0	0		
Lymphocyte count increased: Grade 4 (n=321,155)	0	0		
Neutropenia: Grade 0 (n=321,155)	85	31		
Neutropenia: Grade 1 (n=321,155)	27	11		
Neutropenia: Grade 2 (n=321,155)	57	30		
Neutropenia: Grade 3 (n=321,155)	98	48		
Neutropenia: Grade 4 (n=321,155)	54	35		
Thrombocytopenia: Grade 0 (n=322,155)	52	32		
Thrombocytopenia: Grade 1 (n=322,155)	134	63		
Thrombocytopenia: Grade 2 (n=322,155)	76	36		
Thrombocytopenia: Grade 3 (n=322,155)	51	20		
Thrombocytopenia: Grade 4 (n=322,155)	9	4		
Leukopenia: Grade 0 (n=321,155)	74	32		
Leukopenia: Grade 1 (n=321,155)	30	15		
Leukopenia: Grade 2 (n=321,155)	100	43		
Leukopenia: Grade 3 (n=321,155)	87	51		
Leukopenia: Grade 4 (n=321,155)	30	14		
Hypoalbuminemia (Albumin): Grade 0 (n=318,155)	19	46		
Hypoalbuminemia (Albumin): Grade 1 (n=318,155)	102	62		
Hypoalbuminemia (Albumin): Grade 2 (n=318,155)	185	44		

Hypoalbuminemia (Albumin): Grade 3 (n=318,155)	12	3		
Hypoalbuminemia (Albumin): Grade 4 (n=318,155)	0	0		
Alkaline phosphatase increased:Grade 0 (n=318,155)	135	57		
Alkaline phosphatase increased:Grade 1 (n=318,155)	114	62		
Alkaline phosphatase increased:Grade 2 (n=318,155)	50	26		
Alkaline phosphatase increased:Grade 3 (n=318,155)	19	10		
Alkaline phosphatase increased:Grade 4 (n=318,155)	0	0		
ALT increased: Grade 0 (n=318,155)	69	33		
ALT increased: Grade 1 (n=318,155)	155	72		
ALT increased: Grade 2 (n=318,155)	43	32		
ALT increased: Grade 3 (n=318,155)	51	17		
ALT increased: Grade 4 (n=318,155)	0	1		
AST increased: Grade 0 (n=319,155)	77	28		
AST increased: Grade 1 (n=319,155)	168	96		
AST increased: Grade 2 (n=319,155)	49	17		
AST increased: Grade 3 (n=319,155)	25	13		
AST increased: Grade 4 (n=319,155)	0	1		
Hyperbilirubinemia: Grade 0 (n=319,155)	237	125		
Hyperbilirubinemia: Grade 1 (n=319,155)	36	9		
Hyperbilirubinemia: Grade 2 (n=319,155)	31	15		
Hyperbilirubinemia: Grade 3 (n=319,155)	12	6		
Hyperbilirubinemia: Grade 4 (n=319,155)	3	0		
Hypocalcemia (calcium): Grade 0 (n=318,155)	224	119		
Hypocalcemia (calcium): Grade 1 (n=318,155)	68	30		
Hypocalcemia (calcium): Grade 2 (n=318,155)	22	6		
Hypocalcemia (calcium): Grade 3 (n=318,155)	4	0		
Hypocalcemia (calcium): Grade 4 (n=318,155)	0	0		
Hypercalcemia (calcium): Grade 0 (n=318,155)	278	148		
Hypercalcemia (calcium): Grade 1 (n=318,155)	34	6		
Hypercalcemia (calcium): Grade 2 (n=318,155)	3	0		
Hypercalcemia (calcium): Grade 3 (n=318,155)	3	1		
Hypercalcemia (calcium): Grade 4 (n=318,155)	0	0		
Creatinine increased: Grade 0 (n=318,155)	267	135		
Creatinine increased: Grade 1 (n=318,155)	45	16		
Creatinine increased: Grade 2 (n=318,155)	6	4		

Creatinine increased: Grade 3 (n=318,155)	0	0		
Creatinine increased: Grade 4 (n=318,155)	0	0		
Hypoglycemia (glucose): Grade 0 (n=320,155)	292	140		
Hypoglycemia (glucose): Grade 1 (n=320,155)	17	9		
Hypoglycemia (glucose): Grade 2 (n=320,155)	7	1		
Hypoglycemia (glucose): Grade 3 (n=320,155)	3	1		
Hypoglycemia (glucose): Grade 4 (n=320,155)	1	4		
Hyperglycemia (glucose): Grade 0 (n=320,155)	31	24		
Hyperglycemia (glucose): Grade 1 (n=320,155)	90	45		
Hyperglycemia (glucose): Grade 2 (n=320,155)	119	44		
Hyperglycemia (glucose): Grade 3 (n=320,155)	76	40		
Hyperglycemia (glucose): Grade 4 (n=320,155)	4	2		
Hypokalemia (potassium): Grade 0 (n=319,155)	202	104		
Hypokalemia (potassium): Grade 1 (n=319,155)	89	38		
Hypokalemia (potassium): Grade 2 (n=319,155)	0	0		
Hypokalemia (potassium): Grade 3 (n=319,155)	24	11		
Hypokalemia (potassium): Grade 4 (n=319,155)	4	2		
Hyperkalemia (potassium): Grade 0 (n=319,155)	245	122		
Hyperkalemia (potassium): Grade 1 (n=319,155)	44	19		
Hyperkalemia (potassium): Grade 2 (n=319,155)	21	11		
Hyperkalemia (potassium): Grade 3 (n=319,155)	7	3		
Hyperkalemia (potassium): Grade 4 (n=319,155)	2	0		
Hypomagnesemia (magnesium): Grade 0 (n=318,154)	209	113		
Hypomagnesemia (magnesium): Grade 1 (n=318,154)	95	36		
Hypomagnesemia (magnesium): Grade 2 (n=318,154)	9	5		
Hypomagnesemia (magnesium): Grade 3 (n=318,154)	4	0		
Hypomagnesemia (magnesium): Grade 4 (n=318,154)	1	0		
Hypermagnesemia (magnesium): Grade 0 (n=318,154)	306	150		
Hypermagnesemia (magnesium): Grade 1 (n=318,154)	8	4		
Hypermagnesemia (magnesium): Grade 2 (n=318,154)	0	0		
Hypermagnesemia (magnesium): Grade 3 (n=318,154)	4	0		

Hypermagnesemia (magnesium): Grade 4 (n=318,154)	0	0		
Hyponatremia (sodium): Grade 0 (n=318,155)	96	49		
Hyponatremia (sodium): Grade 1 (n=318,155)	167	85		
Hyponatremia (sodium): Grade 2 (n=318,155)	0	0		
Hyponatremia (sodium): Grade 3 (n=318,155)	54	21		
Hyponatremia (sodium): Grade 4 (n=318,155)	1	0		
Hypernatremia (sodium): Grade 0 (n=318,155)	308	153		
Hypernatremia (sodium): Grade 1 (n=318,155)	9	2		
Hypernatremia (sodium): Grade 2 (n=318,155)	0	0		
Hypernatremia (sodium): Grade 3 (n=318,155)	0	0		
Hypernatremia (sodium): Grade 4 (n=318,155)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Abnormalities in Electrocardiogram (ECG)

End point title	Number of Participants With Clinically Significant Abnormalities in Electrocardiogram (ECG)

End point description:

ECGs including clinical significance was evaluated by the Investigator. Criteria for clinical significance were as per investigator's discretion. Safety population included all participants who received at least 1 dose of study drug, and analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

From administration of first dose of study drug up to 30 days after last dose of study drug (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	156		
Units: participants	8	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Abnormalities in Vital Signs

End point title	Number of Participants With Clinically Significant Abnormalities in Vital Signs

End point description:

Vital signs included measurement of blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), heart rate, and body weight. Criteria for clinical significance abnormalities were: Heart rate: <50 beats per minute (bpm), >120 bpm, >=30 bpm increase from baseline, >=30 bpm decrease from baseline. SBP: >140 millimeters of mercury (mmHg) and increase from baseline >20 mmHg, >180 mmHg, <90 mmHg and decrease from baseline >10 mmHg. DBP: >90 mmHg and increase from baseline >20 mmHg, >105 mmHg, <60 mmHg and decrease from baseline >10 mmHg. Change in weight: >=5% increase from baseline, >=5% decrease from baseline. Safety population included all participants who received at least 1 dose of study drug, and analyzed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

From administration of first dose of study drug up to 30 days after last dose of study drug (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

End point values	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	AG: Placebo + nab-Paclitaxel + Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325	156		
Units: participants				
Heart rate: <50 bpm	7	4		
Heart rate: >120 bpm	47	13		
Heart rate: >=30 bpm increase from baseline	102	26		
Heart rate: >=30 bpm decrease from baseline	38	19		
SBP: >140 mmHg and increase from baseline >20 mmHg	75	37		
SBP: >180 mmHg	6	4		
SBP: <90 mmHg and decrease from baseline >10 mmHg	60	17		
DBP: >90 mmHg and increase from baseline >20 mmHg	21	10		
DBP: >105 mmHg	8	6		
DBP: <60 mmHg and decrease from baseline >10 mmHg	142	56		
Change in weight: >=5% increase from baseline	85	52		
Change in weight: >=5% decrease from baseline	151	57		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From administration of first dose of study drug up to 30 days after last dose of study drug (maximum exposure: 150.1 weeks for PAG, and 83.9 weeks for AG)

Adverse event reporting additional description:

3 participants randomized to AG received PAG, hence included in PAG arm for safety and 1 randomized to PAG but received AG, hence included in AG arm. Number of participants affected per preferred term is reported for number of occurrences (all), and deaths and occurrences related to treatment reported as 0 because this data was not summarized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	AG: Placebo + nab-Paclitaxel + Gemcitabine

Reporting group description:

Participants received placebo matching to PEGPH20 as an IV infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisting of 4 weeks [Week 4 of every cycle will be a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 mg/m^2 nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 83.9 weeks).

Reporting group title	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine

Reporting group description:

Participants received 3.0 µg/kg PEGPH20 as an IV infusion, twice weekly for Weeks 1 to 3 of Cycle 1 (each cycle consisted of 4 weeks [Week 4 of every cycle was a rest week with no treatment]), then once weekly for Weeks 1 to 3 of Cycle 2 and beyond in combination with 125 mg/m^2 nab-paclitaxel as an IV infusion and 1000 mg/m^2 gemcitabine as an IV infusion, once weekly for Weeks 1 to 3 of all treatment cycles. Treatment was continued until disease progression, unacceptable toxicity, death, or withdrawal of consent (Maximum exposure: 150.1 weeks).

Serious adverse events	AG: Placebo + nab-Paclitaxel + Gemcitabine	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 156 (51.28%)	187 / 325 (57.54%)	
number of deaths (all causes)	106	222	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 156 (1.92%)	8 / 325 (2.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 156 (0.00%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 156 (0.00%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	8 / 156 (5.13%)	23 / 325 (7.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 156 (1.28%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 156 (0.64%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 156 (0.00%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 156 (0.00%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst	Additional description: This is a gender-specific AE. Only female participants were at risk.		
subjects affected / exposed[1]	1 / 85 (1.18%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 156 (1.92%)	5 / 325 (1.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 156 (0.00%)	7 / 325 (2.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 156 (0.64%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 156 (0.64%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 156 (0.64%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 156 (0.64%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 156 (1.28%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Interstitial lung disease			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary cavitation			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 156 (0.64%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Platelet count decreased			
subjects affected / exposed	2 / 156 (1.28%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin K decreased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 156 (0.00%)	8 / 325 (2.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 156 (1.28%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 156 (0.00%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexopathy			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 156 (6.41%)	16 / 325 (4.92%)	
occurrences causally related to treatment / all	0 / 10	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 156 (1.92%)	9 / 325 (2.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 156 (2.56%)	8 / 325 (2.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 156 (0.64%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	2 / 156 (1.28%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 156 (4.49%)	13 / 325 (4.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	6 / 156 (3.85%)	10 / 325 (3.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 156 (3.21%)	9 / 325 (2.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 156 (1.92%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 156 (1.92%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 156 (1.28%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	5 / 325 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 156 (0.00%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 156 (0.64%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			

subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula of small intestine			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal ulcer			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	6 / 156 (3.85%)	8 / 325 (2.46%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 156 (0.00%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 156 (1.28%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	2 / 156 (1.28%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vein thrombosis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 156 (0.00%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine flow decreased			

subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rhabdomyolysis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	4 / 156 (2.56%)	22 / 325 (6.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 156 (3.85%)	10 / 325 (3.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 156 (1.28%)	8 / 325 (2.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 156 (0.64%)	6 / 325 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 156 (0.64%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 156 (0.64%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 156 (0.64%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 156 (1.28%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 156 (1.28%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 156 (0.64%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 156 (0.00%)	2 / 325 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 156 (1.92%)	5 / 325 (1.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 156 (1.28%)	5 / 325 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 156 (0.64%)	4 / 325 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 156 (0.64%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 156 (0.64%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 156 (0.00%)	3 / 325 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 156 (0.00%)	1 / 325 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a gender-specific AE. Only female participants were at risk.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AG: Placebo + nab-Paclitaxel + Gemcitabine	PAG: PEGPH20 + nab-Paclitaxel + Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 156 (46.79%)	198 / 325 (60.92%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	20 / 156 (12.82%)	46 / 325 (14.15%)	
occurrences (all)	20	46	
Hypertension			
subjects affected / exposed	12 / 156 (7.69%)	23 / 325 (7.08%)	
occurrences (all)	12	23	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	52 / 156 (33.33%)	198 / 325 (60.92%)	
occurrences (all)	52	198	
Fatigue			
subjects affected / exposed	70 / 156 (44.87%)	162 / 325 (49.85%)	
occurrences (all)	70	162	
Pyrexia			
subjects affected / exposed	49 / 156 (31.41%)	94 / 325 (28.92%)	
occurrences (all)	49	94	
Asthenia			
subjects affected / exposed	36 / 156 (23.08%)	74 / 325 (22.77%)	
occurrences (all)	36	74	
Chills			
subjects affected / exposed	10 / 156 (6.41%)	25 / 325 (7.69%)	
occurrences (all)	10	25	
Mucosal inflammation			
subjects affected / exposed	7 / 156 (4.49%)	23 / 325 (7.08%)	
occurrences (all)	7	23	
Peripheral swelling			
subjects affected / exposed	9 / 156 (5.77%)	7 / 325 (2.15%)	
occurrences (all)	9	7	

Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	7 / 156 (4.49%)	48 / 325 (14.77%)	
occurrences (all)	7	48	
Dyspnoea			
subjects affected / exposed	17 / 156 (10.90%)	48 / 325 (14.77%)	
occurrences (all)	17	48	
Cough			
subjects affected / exposed	22 / 156 (14.10%)	46 / 325 (14.15%)	
occurrences (all)	22	46	
Epistaxis			
subjects affected / exposed	16 / 156 (10.26%)	43 / 325 (13.23%)	
occurrences (all)	16	43	
Hiccups			
subjects affected / exposed	15 / 156 (9.62%)	21 / 325 (6.46%)	
occurrences (all)	15	21	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 156 (10.90%)	61 / 325 (18.77%)	
occurrences (all)	17	61	
Depression			
subjects affected / exposed	11 / 156 (7.05%)	22 / 325 (6.77%)	
occurrences (all)	11	22	
Anxiety			
subjects affected / exposed	11 / 156 (7.05%)	20 / 325 (6.15%)	
occurrences (all)	11	20	
Investigations			
Platelet count decreased			
subjects affected / exposed	36 / 156 (23.08%)	73 / 325 (22.46%)	
occurrences (all)	36	73	
Weight decreased			
subjects affected / exposed	14 / 156 (8.97%)	57 / 325 (17.54%)	
occurrences (all)	14	57	
Neutrophil count decreased			
subjects affected / exposed	39 / 156 (25.00%)	55 / 325 (16.92%)	
occurrences (all)	39	55	

Alanine aminotransferase increased			
subjects affected / exposed	25 / 156 (16.03%)	51 / 325 (15.69%)	
occurrences (all)	25	51	
White blood cell count decreased			
subjects affected / exposed	23 / 156 (14.74%)	44 / 325 (13.54%)	
occurrences (all)	23	44	
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 156 (10.90%)	34 / 325 (10.46%)	
occurrences (all)	17	34	
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 156 (5.13%)	16 / 325 (4.92%)	
occurrences (all)	8	16	
Blood bilirubin increased			
subjects affected / exposed	11 / 156 (7.05%)	13 / 325 (4.00%)	
occurrences (all)	11	13	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 156 (2.56%)	19 / 325 (5.85%)	
occurrences (all)	4	19	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	24 / 156 (15.38%)	64 / 325 (19.69%)	
occurrences (all)	24	64	
Dysgeusia			
subjects affected / exposed	25 / 156 (16.03%)	53 / 325 (16.31%)	
occurrences (all)	25	53	
Dizziness			
subjects affected / exposed	24 / 156 (15.38%)	46 / 325 (14.15%)	
occurrences (all)	24	46	
Peripheral sensory neuropathy			
subjects affected / exposed	27 / 156 (17.31%)	42 / 325 (12.92%)	
occurrences (all)	27	42	
Headache			
subjects affected / exposed	20 / 156 (12.82%)	33 / 325 (10.15%)	
occurrences (all)	20	33	
Paraesthesia			

subjects affected / exposed	17 / 156 (10.90%)	25 / 325 (7.69%)	
occurrences (all)	17	25	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	70 / 156 (44.87%)	139 / 325 (42.77%)	
occurrences (all)	70	139	
Neutropenia			
subjects affected / exposed	51 / 156 (32.69%)	106 / 325 (32.62%)	
occurrences (all)	51	106	
Thrombocytopenia			
subjects affected / exposed	32 / 156 (20.51%)	90 / 325 (27.69%)	
occurrences (all)	32	90	
Leukopenia			
subjects affected / exposed	15 / 156 (9.62%)	28 / 325 (8.62%)	
occurrences (all)	15	28	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	68 / 156 (43.59%)	149 / 325 (45.85%)	
occurrences (all)	68	149	
Diarrhoea			
subjects affected / exposed	73 / 156 (46.79%)	148 / 325 (45.54%)	
occurrences (all)	73	148	
Vomiting			
subjects affected / exposed	38 / 156 (24.36%)	100 / 325 (30.77%)	
occurrences (all)	38	100	
Constipation			
subjects affected / exposed	58 / 156 (37.18%)	85 / 325 (26.15%)	
occurrences (all)	58	85	
Abdominal pain			
subjects affected / exposed	43 / 156 (27.56%)	80 / 325 (24.62%)	
occurrences (all)	43	80	
Stomatitis			
subjects affected / exposed	9 / 156 (5.77%)	34 / 325 (10.46%)	
occurrences (all)	9	34	
Abdominal pain upper			

subjects affected / exposed	11 / 156 (7.05%)	23 / 325 (7.08%)	
occurrences (all)	11	23	
Dry mouth			
subjects affected / exposed	9 / 156 (5.77%)	22 / 325 (6.77%)	
occurrences (all)	9	22	
Dyspepsia			
subjects affected / exposed	10 / 156 (6.41%)	22 / 325 (6.77%)	
occurrences (all)	10	22	
Abdominal distension			
subjects affected / exposed	5 / 156 (3.21%)	19 / 325 (5.85%)	
occurrences (all)	5	19	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	59 / 156 (37.82%)	110 / 325 (33.85%)	
occurrences (all)	59	110	
Rash			
subjects affected / exposed	17 / 156 (10.90%)	28 / 325 (8.62%)	
occurrences (all)	17	28	
Dry skin			
subjects affected / exposed	8 / 156 (5.13%)	19 / 325 (5.85%)	
occurrences (all)	8	19	
Pruritus			
subjects affected / exposed	10 / 156 (6.41%)	19 / 325 (5.85%)	
occurrences (all)	10	19	
Erythema			
subjects affected / exposed	10 / 156 (6.41%)	14 / 325 (4.31%)	
occurrences (all)	10	14	
Rash maculo-papular			
subjects affected / exposed	10 / 156 (6.41%)	11 / 325 (3.38%)	
occurrences (all)	10	11	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	15 / 156 (9.62%)	166 / 325 (51.08%)	
occurrences (all)	15	166	
Myalgia			

subjects affected / exposed	22 / 156 (14.10%)	92 / 325 (28.31%)	
occurrences (all)	22	92	
Arthralgia			
subjects affected / exposed	18 / 156 (11.54%)	63 / 325 (19.38%)	
occurrences (all)	18	63	
Back pain			
subjects affected / exposed	20 / 156 (12.82%)	35 / 325 (10.77%)	
occurrences (all)	20	35	
Pain in extremity			
subjects affected / exposed	16 / 156 (10.26%)	24 / 325 (7.38%)	
occurrences (all)	16	24	
Muscular weakness			
subjects affected / exposed	9 / 156 (5.77%)	16 / 325 (4.92%)	
occurrences (all)	9	16	
Musculoskeletal pain			
subjects affected / exposed	8 / 156 (5.13%)	14 / 325 (4.31%)	
occurrences (all)	8	14	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 156 (7.05%)	28 / 325 (8.62%)	
occurrences (all)	11	28	
Upper respiratory tract infection			
subjects affected / exposed	11 / 156 (7.05%)	18 / 325 (5.54%)	
occurrences (all)	11	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 156 (26.92%)	106 / 325 (32.62%)	
occurrences (all)	42	106	
Hypokalaemia			
subjects affected / exposed	23 / 156 (14.74%)	51 / 325 (15.69%)	
occurrences (all)	23	51	
Hypoalbuminaemia			
subjects affected / exposed	11 / 156 (7.05%)	48 / 325 (14.77%)	
occurrences (all)	11	48	
Dehydration			

subjects affected / exposed	8 / 156 (5.13%)	37 / 325 (11.38%)	
occurrences (all)	8	37	
Hyponatraemia			
subjects affected / exposed	10 / 156 (6.41%)	37 / 325 (11.38%)	
occurrences (all)	10	37	
Hyperglycaemia			
subjects affected / exposed	16 / 156 (10.26%)	30 / 325 (9.23%)	
occurrences (all)	16	30	
Hypocalcaemia			
subjects affected / exposed	4 / 156 (2.56%)	22 / 325 (6.77%)	
occurrences (all)	4	22	
Hypomagnesaemia			
subjects affected / exposed	10 / 156 (6.41%)	20 / 325 (6.15%)	
occurrences (all)	10	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2015	• The inclusion exclusion criteria were updated. • The frequency of coagulation tests was reduced from every treatment cycle to baseline and time of disease progression, in alignment with current medical practice. • Clarified that enoxaparin treatment should be stopped when the participant was permanently removed from the study treatment. • Indicated that hyaluronan (HA) testing at screening need not be performed prior to any invasive screening procedures. • Clarified that if the scan results were not received by the site before the next cycle began, study medication treatment was to continue until results were received and disease progression was confirmed by the CIV. • Moved the sample for assessment of PEGPH20 pharmacokinetics (PK) from Day 8 to Day 4 of Cycle 1, to allow for capturing trough concentrations more accurately. • Removed Day 22 visit of all cycles to reduce procedure/visit burden on participants.• Made biomarker sampling adjustments, including removal of serum and urine samples, addition of plasma samples (Days 2, 4, 8, and 11 of Cycle 1; and Days 1 and 8 of Cycle 2 and every other cycle thereafter; and End of Treatment visit), and added one pharmacogenetic whole blood sample collection to Cycle 1 Day 1. • Clarified language about tumor biopsy tissue samples, including change in timing of optional tumor biopsy from Day 22 of Cycle 1 to collection upon progression, revised scope of analysis for tumor samples to include dysregulation in tumor-relevant pathways, added a subsection on pharmacogenetic analysis, and clarified scope of analysis of plasma samples to reflect the types of biomarkers that may be analyzed; and clarified future use of samples. • Added End of Study definition to conform to European Union (EU) regulatory requirements as follows: The end of the study is defined by the final OS analysis. • Added information on pancreatic cancer statistics globally and in the EU, to be consistent with the global nature of the study.
10 December 2015	• The inclusion exclusion criteria were updated. • Added monthly pregnancy tests on Day 1 of Cycle 2 and all cycles thereafter for women of childbearing potential (WOCBP) • Added Contraception, with details about the required duration of contraception and the recommended highly effective methods of contraception for WOCBP and male participants • Added single 12-lead ECGs on Day 1 of Cycles 2 through 6 as recommended in the Abraxane® summary of product characteristics (SmPC) for vigilant monitoring for occurrence of cardiac events • Added references to the SmPCs for Abraxane® and Gemzar® as appropriate in the protocol. Recommendations were included regarding dose recommendations and modifications guidelines and toxicity management guidelines (including recommendations addressing posterior reversible encephalopathy syndrome and capillary leak syndrome). • Excluded Concomitant Medication and Study Restrictions, to prohibit live vaccines during the study and for 4 weeks following the last study treatment administration, add cautionary language regarding the use of palliative radiotherapy as per the EU Gemzar® SmPC, and add cautionary language regarding concomitant administration of medicines known to inhibit or induce either cytochrome P2C8 (CYP2C8) or cytochrome P3A4 (CYP3A4), as the metabolism of paclitaxel is catalyzed in part by these enzymes • Clarified that SAEs, thromboembolic (TE) events, and pregnancies must be reported immediately and no later than within 24 hours of awareness • Clarified language on unblinding of treatment assignments in emergency situations • Added language specifying that the Sponsor would determine if SAEs were suspected unexpected serious adverse reactions (SUSARs) and if so would expedite reporting of any SUSARs to Regulatory Authorities.

27 February 2017	• The inclusion exclusion criteria were updated. • Extended enrollment beyond 420 participants up to a maximum of 570 total participants before completion of interim efficacy analysis; removed projected timeline for target number of PFS and OS events • Clarified that if the final PFS at the interim was significant at the alpha level of 0.01, then the alpha of 0.01 assigned to the final PFS at the interim would passed to the final OS so that the final OS analysis would be conducted at the significance level of 0.05; otherwise, the final OS analysis would be conducted at the significance level of 0.04 • Decreased maximum number of OS events for the adaptive sample size increase from 495 to 450 to account for potential loss to follow up for OS • In the analysis of the PFS and OS efficacy endpoints, Efron's method of handling ties was added to pre-specify the details for hazard ratio and 95% confidence interval (CI) estimation in the Cox proportional hazard model • Removed modified intent-to-treat (mITT) population • Extended Screening Period duration to 28 days • Permitted participant eligibility according to the Investigator's determination of measurable disease, removed requirement for blinded CIV confirmation • Increased frequency of information collection to monthly during the Long Term Follow Up Period • Investigators required to review the latest CIV report for tumor assessments before determining that the participant had unambiguous clinical progression (in the absence of radiological confirmation) and should no longer receive study treatment.
23 April 2018	• Clarified inclusion criteria tumor tissue requirements for histological or cytological confirmation of pancreatic ductal adenocarcinoma (PDA) and for HA determination based on standard clinical practice and on the recognition that some limited samples obtained by and labeled as fine needle aspirates up to Protocol Amendment 3 actually contained adequate tumor architecture for HA determination • Added an interim OS efficacy claim at the significance level of 0.001 when at least 165 (50%) OS events (deaths) had occurred. The overall alpha level for OS was controlled by subtracting alpha of 0.001 for the final OS. If a compelling OS benefit was observed at the interim analysis (IA), it could become unethical to continue placebo treatment. In this scenario, the data monitoring committee (DMC) could recommend an OS benefit claim with potential cross-over treatment based on the totality of the data and ethical considerations • Decreased the bar for futility stop by adding the unfavorable zone to the futility zone so that the study could be stopped for futility when the interim OS data fell into the futility zone or unfavorable zone only if PFS failed to achieve statistical significance at the IA. Assuming the correlation between PFS and OS, if PFS failed to achieve statistical significance at the IA and interim OS fell in the unfavorable zone, the likelihood to have a positive OS at the end of the study would be substantially decreased. In such a situation, the study should have had a higher probability to stop for futility to allow participants the opportunity for treatment with only AG or other treatment options • Deleted enrollment projections added in Amendment 3 based on enrollment rates at that time.
10 January 2019	PFS was changed from a primary objective/endpoint to a secondary objective/endpoint • Previously planned interim efficacy analysis for final PFS and interim OS was removed • Conduct of the final OS analysis was designated to occur after 330 deaths had occurred in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the negative study outcome, development of PEGPH20 was terminated.

Notes: