Clinical trial results:
A randomised, double-blind, placebo-controlled, parallel-design, multi-centre study to investigate the efficacy to reduce chemotherapy-induced neutropenia (CIN), effects on the haematopoietic system, safety and pharmacokinetics of Myelo001 in patients receiving adjuvant or neoadjuvant chemotherapy for the treatment of breast cancer

Summary

EudraCT number	2015-003610-25
Trial protocol	DE
Global end of trial date	20 November 2017

Results information

Result version number	v1 (current)
This version publication date	05 December 2018
First version publication date	05 December 2018

Trial information

Trial identification

Sponsor protocol code	CT-MT001-2-2015-1

Additional study identifiers

ISRCTN number	ISRCTN10853057
ClinicalTrials.gov id (NCT number)	NCT02692742
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Myelo Therapeutics GmbH
Sponsor organisation address	Kastanienallee 56, Berlin, Germany, 10119
Public contact	Clinical Project Management, Myelo Therapeutics GmbH, clinicaltrials@myelotherapeutics.com
Scientific contact	Clinical Project Management, Myelo Therapeutics GmbH, clinicaltrials@myelotherapeutics.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	20 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2017
Global end of trial reached?	Yes
Global end of trial date	20 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of repeated doses of Myelo001 100 mg tablets taken once per day (QD) per os (p.o.) to reduce chemotherapy induced neutropenia (CIN) in patients receiving chemotherapy for the treatment of breast cancer

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) and that are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (ICH E6) and applicable local regulatory requirements and laws.
The clinical study protocol and informed consent forms were reviewed and approved by an Independent Ethics Committee (IEC).
Safety assessments used in this study included standard measurements that are used routinely in clinical studies of investigational drugs, such as assessment of AEs, physical examinations, vital signs, ECGs, and clinical laboratory evaluations.
A Data Safety Monitoring Board (DSMB) evaluated patients' safety in scheduled intervals.

Background therapy:

Neoadjuvant or adjuvant standard of care poly-chemotherapy regimen containing anthracyclines in combination with cyclophosphamide (CP) defined as EC standard regimen (with or without treatment with taxanes afterwards) served as inclusion criterion. The EC standard regimen the patient needed to be assigned for prior to being informed about the trial was Epirubicin (E) combined with CP: Epirubicin 90 mg/m² BSA (body surface area) + CP 600 mg/m² BSA q21d (every 21 days). Permitted taxane treatments after EC standard regime were paclitaxel (P) and docetaxel (D).

Evidence for comparator:

In this phase 2a trial, Myelo001 was compared to placebo only.

Actual start date of recruitment	01 March 2016
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	Germany: 137
Worldwide total number of subjects	137
EEA total number of subjects	137

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)	108
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at multiple trial sites in Germany. Patients were recruited from March 2016 to September 2017.

Pre-assignment

Screening details:

145 patients consented to participate. 1 patient withdraw consent prior to screening. 3 patients were not eligible to participate in the study, because inclusion criterion 8 was not met (Haematologic, laboratory and chemistry thresholds at baseline). 4 patients declined participation in the study after screening. 137 patients were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Myelo001

Arm description:

Patients received Myelo001 (100 mg) once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).
The first batch of the investigational medicinal product (IMP) was exchanged with an exchange IMP batch after 49 patients were randomized.
Altogether, 67 patients were treated with Myelo001. Of these, 26 patients were treated with Myelo001 tablets (#216) of the initial IMP batch and are referred in post-hoc analyses as subgroup Myelo001 IMP Batch 1. The other 41 patients were treated with Myelo001 tablets (#416) of the exchange IMP batch and are referred as subgroup Myelo001 IMP Batch 2.
After no positive treatment effect was evident from the main study results (per protocol set: 65 patients treated with Myelo001), the sponsor authorized further statistical analyses of the effects of the two sets of batches.
The statistical analyses were identical for main and subgroups.

Arm type	Experimental
Investigational medicinal product name	Myelo001 tablet (100 mg)
Investigational medicinal product code	
Other name	Imidazolyl ethanamide pentandioic acid, Vitaglutam, Dicarbamin, Dicarbamine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients took Myelo001 (100 mg), one tablet orally daily around the same time in the morning. Intake started 5 days prior to the first chemotherapy treatment cycle and was continued until 3 days prior to the second chemotherapy cycle. Based on the standard schedule of the epirubicin/cyclophosphamide chemotherapy selected for this trial, investigational medicinal product intake was 23 days. If the start of the second chemotherapy cycle was delayed, the investigator could decide to prolong Myelo001 treatment to a maximum intake duration of 28 days.

Arm title	Placebo

Arm description:

Patients received matching placebo once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).
The first batch of the investigational medicinal product (IMP) was exchanged with an exchange IMP batch after 49 patients were randomized.

Altogether, 67 patients were treated with placebo. Of these, 23 patients were treated with placebo tablets (#116) of the initial IMP batch and are referred in post-hoc analyses as subgroup Placebo IMP Batch 1. The other 44 patients were treated with placebo tablets (#316) of the exchange IMP batch and are referred as subgroup Placebo IMP Batch 2.
After no positive treatment effect was evident from the main study results (per protocol set: 65 patients treated with placebo), the sponsor authorized further statistical analyses of the effects of the two sets of batches.
The statistical analyses were identical for main and subgroups.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients took matching placebo, one tablet orally daily around the same time in the morning. Intake started 5 days prior to the first chemotherapy treatment cycle and was continued until 3 days prior to the second chemotherapy cycle. Based on the standard schedule of the epirubicin/cyclophosphamide chemotherapy selected for this trial, investigational medicinal product (IMP) intake was 23 days. If the start of the second chemotherapy cycle was delayed, the investigator could decide to prolong IMP intake to a maximum intake duration of 28 days.

Number of subjects in period 1	Myelo001	Placebo
Started	68	69
Completed	63	65
Not completed	5	4
Consent withdrawn by subject	4	2
Physician decision	-	2
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Myelo001

Reporting group description:

Patients received Myelo001 (100 mg) once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).
The first batch of the investigational medicinal product (IMP) was exchanged with an exchange IMP batch after 49 patients were randomized.
Altogether, 67 patients were treated with Myelo001. Of these, 26 patients were treated with Myelo001 tablets (#216) of the initial IMP batch and are referred in post-hoc analyses as subgroup Myelo001 IMP Batch 1. The other 41 patients were treated with Myelo001 tablets (#416) of the exchange IMP batch and are referred as subgroup Myelo001 IMP Batch 2.
After no positive treatment effect was evident from the main study results (per protocol set: 65 patients treated with Myelo001), the sponsor authorized further statistical analyses of the effects of the two sets of batches.
The statistical analyses were identical for main and subgroups.

Reporting group title	Placebo

Reporting group description:

Patients received matching placebo once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).
The first batch of the investigational medicinal product (IMP) was exchanged with an exchange IMP batch after 49 patients were randomized.
Altogether, 67 patients were treated with placebo. Of these, 23 patients were treated with placebo tablets (#116) of the initial IMP batch and are referred in post-hoc analyses as subgroup Placebo IMP Batch 1. The other 44 patients were treated with placebo tablets (#316) of the exchange IMP batch and are referred as subgroup Placebo IMP Batch 2.
After no positive treatment effect was evident from the main study results (per protocol set: 65 patients treated with placebo), the sponsor authorized further statistical analyses of the effects of the two sets of batches.
The statistical analyses were identical for main and subgroups.

Reporting group values	Myelo001	Placebo	Total
Number of subjects	68	69	137
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
arithmetic mean (standard deviation)			
Units: years			
arithmetic mean	54.4	55.5	
standard deviation	± 10.51	± 10.61	-
Gender categorical			
Units: Subjects			
Female	68	69	137

Male	0	0	0

End points

End points reporting groups

Reporting group title	Myelo001

Reporting group description:

Patients received Myelo001 (100 mg) once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).
The first batch of the investigational medicinal product (IMP) was exchanged with an exchange IMP batch after 49 patients were randomized.
Altogether, 67 patients were treated with Myelo001. Of these, 26 patients were treated with Myelo001 tablets (#216) of the initial IMP batch and are referred in post-hoc analyses as subgroup Myelo001 IMP Batch 1. The other 41 patients were treated with Myelo001 tablets (#416) of the exchange IMP batch and are referred as subgroup Myelo001 IMP Batch 2.
After no positive treatment effect was evident from the main study results (per protocol set: 65 patients treated with Myelo001), the sponsor authorized further statistical analyses of the effects of the two sets of batches.
The statistical analyses were identical for main and subgroups.

Reporting group title	Placebo

Reporting group description:

Patients received matching placebo once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).
The first batch of the investigational medicinal product (IMP) was exchanged with an exchange IMP batch after 49 patients were randomized.
Altogether, 67 patients were treated with placebo. Of these, 23 patients were treated with placebo tablets (#116) of the initial IMP batch and are referred in post-hoc analyses as subgroup Placebo IMP Batch 1. The other 44 patients were treated with placebo tablets (#316) of the exchange IMP batch and are referred as subgroup Placebo IMP Batch 2.
After no positive treatment effect was evident from the main study results (per protocol set: 65 patients treated with placebo), the sponsor authorized further statistical analyses of the effects of the two sets of batches.
The statistical analyses were identical for main and subgroups.

Subject analysis set title	Myelo001 (IMP Batch 1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients of the per protocol set receiving Myelo001 of investigational medicinal product (IMP) batch 1.
The results of post-hoc analyses for ANC related endpoints revealed a strong batch effect and a significant interaction between IMP batch and treatment ($p < 0.03$) for all three primary / co-primary endpoints.

Subject analysis set title	Placebo (IMP Batch 1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients of the per protocol set receiving placebo of investigational medicinal product (IMP) batch 1.
The results of post-hoc analyses for ANC related endpoints revealed a strong batch effect and a significant interaction between IMP batch and treatment ($p < 0.03$) for all three primary / co-primary endpoints.

Subject analysis set title	Myelo001 (IMP Batch 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients of the per protocol set receiving Myelo001 of investigational medicinal product (IMP) batch 2.
The results of post-hoc analyses for ANC related endpoints revealed a strong batch effect and a significant interaction between IMP batch and treatment ($p < 0.03$) for all three primary / co-primary endpoints.

Subject analysis set title	Placebo (IMP Batch 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients of the per protocol set receiving placebo of investigational medicinal product (IMP) batch 2.
The results of post-hoc analyses for ANC related endpoints revealed a strong batch effect and a significant interaction between IMP batch and treatment ($p < 0.03$) for all three primary / co-primary endpoints.

Primary: Threshold area over the curve (AOC1) of absolute neutrophil count (ANC) in the study period of d1/c1 to d22/c1

End point title	Threshold area over the curve (AOC1) of absolute neutrophil count (ANC) in the study period of d1/c1 to d22/c1

End point description:

Area below the threshold line [ANC 2.0x10exp9/L classified as grade 1 neutropenia according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] and above the individual ANC trajectory in the study period of d1/c1 to d22/c1.

End point type	Primary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[1]	65[2]	24[3]	23[4]
Units: (ANC/nL)*days				
least squares mean (confidence interval 95%)	13.562 (12.601 to 14.522)	13.989 (13.041 to 14.936)	11.993 (10.486 to 13.501)	14.281 (12.737 to 15.824)

Notes:

[1] - per protocol set (PPS)

[2] - per protocol set (PPS)

[3] - per protocol set (PPS)

[4] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[5]	42[6]		
Units: (ANC/nL)*days				
least squares mean (confidence interval 95%)	14.683 (13.520 to 15.847)	13.761 (12.634 to 14.889)		

Notes:

[5] - per protocol set (PPS)

[6] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of AOC1 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 v Placebo

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5242
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0304
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)
Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2533
Method	ANCOVA

Primary: Threshold area over the curve (AOC3) of absolute neutrophil count (ANC) in the study period of d1/c1 to d22/c1

End point title	Threshold area over the curve (AOC3) of absolute neutrophil count (ANC) in the study period of d1/c1 to d22/c1

End point description:

• co-primary endpoint:
Area below the threshold line [ANC 1.0x10exp9/L classified as grade 3 neutropenia according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] and above the individual ANC trajectory, in the study period of d1/c1 to d22/c1.

End point type	Primary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[7]	65[8]	24[9]	23[10]
Units: (ANC/nL)*days				
least squares mean (confidence interval 95%)	4.093 (3.565 to 4.621)	4.284 (3.763 to 4.805)	3.367 (2.549 to 4.184)	4.615 (3.778 to 5.452)

Notes:

[7] - per protocol set (PPS)

[8] - per protocol set (PPS)

[9] - per protocol set (PPS)

[10] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[11]	42[12]		
Units: (ANC/nL)*days				
least squares mean (confidence interval 95%)	4.636 (3.996 to 5.275)	4.080 (3.460 to 4.700)		

Notes:

[11] - per protocol set (PPS)

[12] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of AOC3 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6042
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC3 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)

Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0293
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC3 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)
Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2107
Method	ANCOVA

Primary: Duration of ANC < 1.0x10exp9/L classified as grade 3 neutropenia in the study period of d1/c1 to d22/c1

End point title	Duration of ANC < 1.0x10exp9/L classified as grade 3 neutropenia in the study period of d1/c1 to d22/c1

End point description:

• co-primary endpoint:
Duration of ANC < 1.0x10exp9/L classified as grade 3 neutropenia [according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] in the study period of d1/c1 to d22/c1

End point type	Primary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[13]	65[14]	24[15]	23[16]
Units: days				
least squares mean (confidence interval 95%)	7.403 (6.837 to 7.969)	7.824 (7.265 to 8.382)	6.343 (5.434 to 7.253)	7.923 (6.992 to 8.854)

Notes:

[13] - per protocol set (PPS)

[14] - per protocol set (PPS)

[15] - per protocol set (PPS)

[16] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[17]	42[18]		
Units: days				
least squares mean (confidence interval 95%)	8.121 (7.461 to 8.781)	7.703 (7.063 to 8.342)		

Notes:

[17] - per protocol set (PPS)

[18] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of duration of AOC3 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2879
Method	ANCOVA

Statistical analysis title	ANCOVA of duration of AOC3 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA

Statistical analysis title	ANCOVA of duration of AOC3 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) neutrophil counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)

Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.36
Method	ANCOVA

Secondary: Threshold area over the curve (AOC1) of lymphocytes in the study period of d1/c1 to d22/c1

End point title	Threshold area over the curve (AOC1) of lymphocytes in the study period of d1/c1 to d22/c1

End point description:

Area below the threshold line [classified as grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] and above the individual absolute lymphocyte count trajectory in the study period of d1/c1-d22/c1.

End point type	Secondary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[19]	65[20]	24[21]	23[22]
Units: (lymphocytes/nL)*days				
least squares mean (confidence interval 95%)	1.548 (1.148 to 1.948)	1.712 (1.318 to 2.107)	1.283 (0.518 to 2.048)	2.061 (1.278 to 2.843)

Notes:

[19] - per protocol set (PPS)

[20] - per protocol set (PPS)

[21] - per protocol set (PPS)

[22] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[23]	42[24]		
Units: (lymphocytes/nL)*days				
least squares mean (confidence interval 95%)	1.689 (1.211 to 2.166)	1.465 (1.004 to 1.927)		

Notes:

[23] - per protocol set (PPS)

[24] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of AOC1 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) lymphocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means

(Myelo001 minus placebo).

Comparison groups	Placebo v Myelo001
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5561
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) lymphocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1423
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) lymphocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)
Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4981
Method	ANCOVA

Secondary: Threshold area over the curve (AOC1) of leukocytes in the study period of d1/c1 to d22/c1

End point title	Threshold area over the curve (AOC1) of leukocytes in the study period of d1/c1 to d22/c1

End point description:

Area below the threshold line [classified as grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] and above the individual absolute leukocyte count trajectory in the study period of d1/c1 to d22/c1.

End point type	Secondary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[25]	65[26]	24[27]	23[28]
Units: (leucocytes/nL)*days				
least squares mean (confidence interval 95%)	19.503 (17.789 to 21.218)	20.670 (18.979 to 22.362)	17.237 (14.494 to 19.979)	21.950 (19.145 to 24.754)

Notes:

[25] - per protocol set (PPS)

[26] - per protocol set (PPS)

[27] - per protocol set (PPS)

[28] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[29]	42[30]		
Units: (leucocytes/nL)*days				
least squares mean (confidence interval 95%)	21.110 (18.914 to 23.305)	20.016 (17.887 to 22.144)		

Notes:

[29] - per protocol set (PPS)

[30] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of AOC1 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) leukocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3304
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) leukocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)

Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0149
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) leukocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)
Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.472
Method	ANCOVA

Secondary: Threshold area over the curve (AOC1) of thrombocytes in the study period d1/c1 to d22/c1

End point title	Threshold area over the curve (AOC1) of thrombocytes in the study period d1/c1 to d22/c1

End point description:

Area below the threshold line [classified as grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] and above the individual absolute thrombocyte count trajectory in the study period d1/c1 to d22/c1.

End point type	Secondary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[31]	65[32]	24[33]	23[34]
Units: (thrombocytes/nL)*days				
least squares mean (confidence interval 95%)	114.613 (73.830 to 155.396)	89.216 (48.771 to 129.660)	55.726 (-3.667 to 115.119)	96.190 (35.498 to 156.883)

Notes:

[31] - per protocol set (PPS)

[32] - per protocol set (PPS)

[33] - per protocol set (PPS)

[34] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[35]	42[36]		
Units: (thrombocytes/nL)*days				
least squares mean (confidence interval 95%)	145.684 (89.143 to 202.224)	84.114 (29.310 to 138.918)		

Notes:

[35] - per protocol set (PPS)

[36] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of AOC1 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) thrombocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) thrombocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3323
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) thrombocyte counts as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)

Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1173
Method	ANCOVA

Secondary: Proportion of patients developing febrile neutropenia in the study period of d1/c1 to d22/c1

End point title	Proportion of patients developing febrile neutropenia in the study period of d1/c1 to d22/c1

End point description:

Proportion of patients developing febrile neutropenia [body temperature ≥38.3°C (single tympanic or oral measurement) and ANC ≤0.5x10exp9/L (Grade 4 according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010)]

End point type	Secondary

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	64	63	23	21
Units: subjects	1	1	1	0

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	42		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Threshold area over the curve (AOC1) of Hemoglobin in the study period of d1/c1 to d22/c1

End point title	Threshold area over the curve (AOC1) of Hemoglobin in the study period of d1/c1 to d22/c1

End point description:

Area below the threshold line [classified as grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE), v4.03, 2010] and above the individual hemoglobin value trajectory in the study period d1/c1 to d22/c1.

End point type	Other pre-specified

End point timeframe:

day 1 to day 22 of chemotherapy cycle 1

End point values	Myelo001	Placebo	Myelo001 (IMP Batch 1)	Placebo (IMP Batch 1)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65[37]	65[38]	24[39]	23[40]
Units: days*(g/dL)				
least squares mean (confidence interval 95%)	1.462 (0.426 to 2.498)	1.970 (0.948 to 2.992)	2.173 (-0.125 to 4.471)	3.106 (0.756 to 5.455)

Notes:

[37] - per protocol set (PPS)

[38] - per protocol set (PPS)

[39] - per protocol set (PPS)

[40] - per protocol set (PPS)

End point values	Myelo001 (IMP Batch 2)	Placebo (IMP Batch 2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[41]	42[42]		
Units: days*(g/dL)				
least squares mean (confidence interval 95%)	0.989 (0.163 to 1.815)	1.436 (0.637 to 2.236)		

Notes:

[41] - per protocol set (PPS)

[42] - per protocol set (PPS)

Statistical analyses

Statistical analysis title	ANCOVA of AOC1 (total)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) hemoglobin as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4824
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 1)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) hemoglobin as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 1) v Placebo (IMP Batch 1)
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5508
Method	ANCOVA

Statistical analysis title	ANCOVA of AOC1 (IMP Batch 2)

Statistical analysis description:

Analysis-of-covariance model (ANCOVA) with treatment and region as fixed effects and baseline (before first IMP or placebo administration) hemoglobin as covariate. Point estimates (LS Means) were calculated for each treatment group and a two-sided 95% confidence interval based on the t-distribution and the residual error of the model was computed for the difference between treatment means (Myelo001 minus placebo).

Comparison groups	Myelo001 (IMP Batch 2) v Placebo (IMP Batch 2)
Number of subjects included in analysis	83
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4335
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Visit 1 (Screening visit) up to the start of the application of the third chemotherapy cycle, i.e. until Visit 12 (End-of-study visit).

Adverse event reporting additional description:

134 patients were included into the safety analysis set (SAS). During the full trial period, in total 1014 adverse events were reported for the patients of the SAS. Of the adverse event total, 684 (67.5%) were assessed by the investigators as toxicity event related to the background treatment with anti-cancer chemotherapy drugs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Myelo001

Reporting group description:

Patients received Myelo001 (100 mg) once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).

Reporting group title	Placebo

Reporting group description:

Patients received matching placebo once daily orally for scheduled 23 days from 5 days prior to the first chemotherapy cycle until 3 days prior to the second chemotherapy cycle (epirubicin/cyclophosphamide).

Serious adverse events	Myelo001	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 67 (7.46%)	6 / 67 (8.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Poor peripheral circulation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Myocardial infarction			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (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			
Neutropenia			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
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			
Erythema			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Myelo001	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 67 (100.00%)	66 / 67 (98.51%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Haemodynamic instability			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	3 / 67 (4.48%)	4 / 67 (5.97%)	
occurrences (all)	3	4	
Hypertension			
subjects affected / exposed	7 / 67 (10.45%)	6 / 67 (8.96%)	
occurrences (all)	7	6	
Hypotension			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Phlebitis			

subjects affected / exposed	2 / 67 (2.99%)	0 / 67 (0.00%)	
occurrences (all)	2	0	
Poor peripheral circulation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 67 (1.49%)	3 / 67 (4.48%)	
occurrences (all)	1	3	
Catheter site pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	2	2	
Fatigue			
subjects affected / exposed	27 / 67 (40.30%)	26 / 67 (38.81%)	
occurrences (all)	29	29	
Feeling cold			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	2	
General physical health deterioration			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Hypothermia			
subjects affected / exposed	6 / 67 (8.96%)	10 / 67 (14.93%)	
occurrences (all)	10	20	
Implant site irritation			

subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	2	
Implant site pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness			
subjects affected / exposed	1 / 67 (1.49%)	3 / 67 (4.48%)	
occurrences (all)	1	3	
Mucosal inflammation			
subjects affected / exposed	13 / 67 (19.40%)	15 / 67 (22.39%)	
occurrences (all)	13	15	
Oedema			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 67 (2.99%)	1 / 67 (1.49%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			
Breast inflammation			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Dysmenorrhoea			

subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 67 (1.49%)	3 / 67 (4.48%)	
occurrences (all)	1	4	
Dysphonia			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	2 / 67 (2.99%)	1 / 67 (1.49%)	
occurrences (all)	2	1	
Hiccups			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Nasal septum disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 67 (4.48%)	11 / 67 (16.42%)	
occurrences (all)	3	11	
Pulmonary hypertension			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Throat irritation			

subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	2 / 67 (2.99%)	3 / 67 (4.48%)	
occurrences (all)	3	3	
Mental disorder			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	2	
Restlessness			
subjects affected / exposed	2 / 67 (2.99%)	0 / 67 (0.00%)	
occurrences (all)	2	0	
Sleep disorder			
subjects affected / exposed	0 / 67 (0.00%)	3 / 67 (4.48%)	
occurrences (all)	0	3	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Bile duct pressure			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	5 / 67 (7.46%)	6 / 67 (8.96%)	
occurrences (all)	5	7	
Heart rate increased			

subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Mean cell volume abnormal			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Monocyte count decreased			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Red blood cell count decreased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
White blood cells urine positive			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Drug-induced liver injury			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Infusion site thrombosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Myocardial infarction			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Palpitations			

subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Sinus tachycardia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	7 / 67 (10.45%)	10 / 67 (14.93%)	
occurrences (all)	7	12	
Dysgeusia			
subjects affected / exposed	4 / 67 (5.97%)	2 / 67 (2.99%)	
occurrences (all)	4	2	
Head discomfort			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	16 / 67 (23.88%)	19 / 67 (28.36%)	
occurrences (all)	20	22	
Neuropathy peripheral			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Polyneuropathy			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Poor quality sleep			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 67 (1.49%)	4 / 67 (5.97%)	
occurrences (all)	1	4	
Febrile neutropenia			
subjects affected / exposed	2 / 67 (2.99%)	1 / 67 (1.49%)	
occurrences (all)	2	1	
Leukocytosis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	55 / 67 (82.09%)	56 / 67 (83.58%)	
occurrences (all)	62	60	
Lymphadenopathy			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Lymphocytopenia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	63 / 67 (94.03%)	65 / 67 (97.01%)	
occurrences (all)	77	80	
Thrombocytopenia			
subjects affected / exposed	4 / 67 (5.97%)	1 / 67 (1.49%)	
occurrences (all)	4	1	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	2	
Tinnitus			

subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	
Vertigo			
subjects affected / exposed	8 / 67 (11.94%)	6 / 67 (8.96%)	
occurrences (all)	10	7	
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 67 (2.99%)	0 / 67 (0.00%)	
occurrences (all)	2	0	
Eye swelling			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	2 / 67 (2.99%)	2 / 67 (2.99%)	
occurrences (all)	3	2	
Abdominal pain upper			
subjects affected / exposed	3 / 67 (4.48%)	8 / 67 (11.94%)	
occurrences (all)	3	9	
Constipation			
subjects affected / exposed	18 / 67 (26.87%)	16 / 67 (23.88%)	
occurrences (all)	19	16	
Diarrhoea			
subjects affected / exposed	5 / 67 (7.46%)	9 / 67 (13.43%)	
occurrences (all)	5	10	
Dry mouth			
subjects affected / exposed	1 / 67 (1.49%)	3 / 67 (4.48%)	
occurrences (all)	1	5	
Duodenitis			

subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	
Eructation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	
Hiatus hernia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	37 / 67 (55.22%)	31 / 67 (46.27%)	
occurrences (all)	40	38	
Oesophagitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	2 / 67 (2.99%)	3 / 67 (4.48%)	
occurrences (all)	2	3	
Vomiting			

subjects affected / exposed	4 / 67 (5.97%)	7 / 67 (10.45%)	
occurrences (all)	4	7	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	37 / 67 (55.22%)	44 / 67 (65.67%)	
occurrences (all)	37	45	
dermatitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	2	2	
Erythema multiforme			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 67 (0.00%)	
occurrences (all)	5	0	
Miliaria			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Nail discolouration			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Nail disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	

Pain of skin			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	3	
Skin erosion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Urinary incontinence			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 67 (1.49%)	3 / 67 (4.48%)	
occurrences (all)	1	3	
Back pain			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Bone pain			
subjects affected / exposed	2 / 67 (2.99%)	1 / 67 (1.49%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	0 / 67 (0.00%)	3 / 67 (4.48%)	
occurrences (all)	0	3	
Muscular weakness			

subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Osteolysis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	3 / 67 (4.48%)	2 / 67 (2.99%)	
occurrences (all)	3	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	
Device related infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	

Oral candidiasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Tooth infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	3 / 67 (4.48%)	1 / 67 (1.49%)	
occurrences (all)	4	1	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 67 (4.48%)	2 / 67 (2.99%)	
occurrences (all)	3	2	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	

Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	2 / 67 (2.99%)	4 / 67 (5.97%)	
occurrences (all)	2	4	
Hypocalcaemia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2016	In the process of implementing the clinical trial a few changes to the protocol became necessary to add precision and facilitate the per protocol conduct of the trial. The overall trial design remained unchanged. Notable changes included: • Permission to draw the blood sample a day earlier for baseline assessment and urine pregnancy testing as an alternative to analysis in serum • Change of visit schedule allowing shifts by +/- 1 day for certain study visits • Permission to substitute the baseline serum pregnancy test for an equivalent urine pregnancy test (local lab only) • Clarification that the use of (low-dose) dexamethasone for antiemetic use does not fall under the exclusion criteria and definition of maximum dose to achieve an equilibrium of the hematopoietic influence of dexamethasone • Adjustment of laboratory sample volumes to maximum amounts required by the two permitted systems • Consistency in the text that adverse events are followed up from first (screening) to last visit (EOS)
17 August 2017	Changes are mainly related to the statistical analyses and endpoint section. No procedure for the patient or investigators were changed. The most important changes include: • Revision of primary endpoint(s): Two co-primary endpoints were added • Revision of primary statistical test procedure • Addition of secondary endpoints • Sample size adjustment based on revised statistical procedure • Revised definition of the analysis sets (Revised Full Analysis Set and Per Protocol Set) Importantly, all protocol changes did not entail any procedural or interventional changes, but deepen or expand the analysis of the data generated from existing study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported